CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

210259Orig1s006
210259Orig1s007

Trade Name:	CALQUENCE capsules
Generic or Proper Name:	acalabrutinib
Sponsor:	AstraZeneca UK Limited c/o Acerta Pharma
Approval Date:	November 21, 2019
Indication:	For the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

CENTER FOR DRUG EVALUATION AND RESEARCH

210259Orig1s006
210259Orig1s007

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210259Orig1s006
210259Orig1s007

APPROVAL LETTER

NDA 210259/S-006
NDA 210259/S-007

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT

AstraZeneca UK Limited
c/o Acerta Pharma
Attention: Amanda Roodhouse
Director, Regulatory Science
121 Oyster Point Blvd
South San Francisco, CA 94080

Dear Ms. Roodhouse:

Please refer to your supplemental new drug applications (sNDAs) dated September 24, 2019, received September 24, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for CALQUENCE (acalabrutinib) capsules.

These Prior Approval supplemental new drug applications provide for the use of CALQUENCE for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Prescribing Information and Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also, within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submission dated September 24, 2019, containing the final report for the following postmarketing requirement listed in the October 31, 2017, accelerated approval letter for NDA 210259.

PMR 3291-3 Conduct a clinical pharmacokinetic trial to determine an appropriate safe dose of acalabrutinib in patients with severe hepatic impairment. This trial should be designed and conducted in accordance with the FDA Guidance for Industry entitled "*Pharmacokinetics in Patients with Impaired Hepatic*

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

We have reviewed your submission and conclude that the above requirement was fulfilled.

We remind you that there is a postmarketing requirement listed in the October 31, 2017, accelerated approval letter that is still open.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jennifer Lee, Senior Regulatory Health Project Manager, at (240) 402-4622.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210259Orig1s006
210259Orig1s007

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CALQUENCE safely and effectively. See full prescribing information for CALQUENCE.

CALQUENCE® (acalabrutinib) capsules, for oral use
Initial U.S. Approval: 2017

---------- RECENT MAJOR CHANGES ----------

Indications and Usage (1.2)	11/2019
Dosage and Administration (2.2)	11/2019

---------- INDICATIONS AND USAGE ----------

CALQUENCE is a kinase inhibitor indicated for the treatment of adult patients with:

- Mantle cell lymphoma (MCL) who have received at least one prior therapy. (1 1)
  This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.1, 14.1)
- Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). (1.2)

---------- DOSAGE AND ADMINISTRATION ----------

- Recommended dose is 100 mg orally approximately every 12 hours; swallow whole with water and with or without food. (2.1)
- Advise patients not to break, open, or chew capsules. (2.1)
- Manage toxicities using treatment interruption, dose reduction, or discontinuation. (2.2)
- Avoid CALQUENCE in patients with severe hepatic impairment (2.2, 8.6)

---------- DOSAGE FORMS AND STRENGTHS ----------

Capsules: 100 mg. (3)

---------- CONTRAINDICATIONS ----------

None. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Serious and Opportunistic Infections: Monitor for signs and symptoms of infection and treat promptly. (5.1)
- Hemorrhage: Monitor for bleeding and manage appropriately. (5.2)
- Cytopenias: Monitor complete blood counts regularly. (5.3)
- Second Primary Malignancies: Other malignancies have occurred, including skin cancers and other solid tumors. Advise patients to use sun protection. (5.4)
- Atrial Fibrillation and Flutter: Monitor for symptoms of arrhythmias and manage. (5.5)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (incidence ≥ 30%) were: anemia, neutropenia, upper respiratory tract infection, thrombocytopenia, headache, diarrhea, and musculoskeletal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

- CYP3A Inhibitors: Avoid co-administration with strong CYP3A inhibitors. Dose adjustments may be recommended. (2.3, 7, 12.3)
- CYP3A Inducers: Avoid co-administration with strong CYP3A inducers. Dose adjustments may be recommended. (2.3, 7, 12.3)
- Gastric Acid Reducing Agents: Avoid co-administration with proton pump inhibitors (PPIs). Stagger dosing with H2-receptor antagonists and antacids. (2.4, 7, 12.3)

---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: May cause fetal harm and dystocia (8.1)
- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Mantle Cell Lymphoma

CALQUENCE is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.1)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

1.2 Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

CALQUENCE is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

CALQUENCE as Monotherapy

For patients with MCL, CLL, or SLL, the recommended dose of CALQUENCE is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity.

CALQUENCE in Combination with Obinutuzumab

For patients with previously untreated CLL or SLL, the recommended dose of CALQUENCE is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity. Start CALQUENCE at Cycle 1 (each cycle is 28 days). Start obinutuzumab at Cycle 2 for a total of 6 cycles and refer to the obinutuzumab prescribing information for recommended dosing. Administer CALQUENCE prior to obinutuzumab when given on the same day.

Advise patients to swallow capsule whole with water. Advise patients not to open, break or chew the capsules. CALQUENCE may be taken with or without food. If a dose of CALQUENCE is missed by more than 3 hours, it should be skipped and the next dose should be taken at its regularly scheduled time. Extra capsules of CALQUENCE should not be taken to make up for a missed dose.

2.2 Recommended Dosage for Hepatic Impairment

Avoid administration of CALQUENCE in patients with severe hepatic impairment.

Dose modifications are not required for patients with mild or moderate hepatic impairment *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

2.3 Recommended Dosage for Drug Interactions

Dose Modifications for Use with CYP3A Inhibitors or Inducers

These are described in Table 1 *[see Drug Interactions (7)]*.

Table 1: Recommended Dose Modifications for Use with CYP3A Inhibitors or Inducers

CYP3A	Co-administered Drug	Recommended CALQUENCE use
Inhibition	Strong CYP3A inhibitor	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for up to seven days), interrupt CALQUENCE.
	Moderate CYP3A inhibitor	100 mg once daily.
Induction	Strong CYP3A inducer	Avoid concomitant use. If these inducers cannot be avoided, increase CALQUENCE dose to 200 mg approximately every 12 hours.

Concomitant Use with Gastric Acid Reducing Agents

Proton Pump Inhibitors: Avoid concomitant use *[see Drug Interactions (7)]*.

H2-Receptor Antagonists: Take CALQUENCE 2 hours before taking a H2-receptor antagonist *[see Drug Interactions (7)]*.

Antacids: Separate dosing by at least 2 hours *[see Drug Interactions (7)]*.

2.4 Dose Modifications for Adverse Reactions

Recommended dose modifications of CALQUENCE for Grade 3 or greater adverse reactions are provided in Table 2.

Table 2: Recommended Dose Modifications for Adverse Reactions

Event	**Adverse Reaction Occurrence**	**Dose Modification** (Starting dose = 100 mg approximately every 12 hours)
Grade 3 or greater non-hematologic toxicities, Grade 3 thrombocytopenia with bleeding, Grade 4 thrombocytopenia	First and Second	Interrupt CALQUENCE. Once toxicity has resolved to Grade 1 or baseline level, CALQUENCE may be resumed at 100 mg approximately every 12 hours.

Event	Adverse Reaction Occurrence	Dose Modification (Starting dose = 100 mg approximately every 12 hours)
or Grade 4 neutropenia lasting longer than 7 days	Third	Interrupt CALQUENCE. Once toxicity has resolved to Grade 1 or baseline level, CALQUENCE may be resumed at a reduced frequency of 100 mg once daily.
	Fourth	Discontinue CALQUENCE.

Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

Refer to the obinutuzumab prescribing information for management of obinutuzumab toxicities.

3 DOSAGE FORMS AND STRENGTHS

100 mg capsules.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Serious and Opportunistic Infections

Fatal and serious infections, including opportunistic infections, have occurred in patients with hematologic malignancies treated with CALQUENCE.

Serious or Grade 3 or higher infections (bacterial, viral, or fungal) occurred in 19% of 1029 patients exposed to CALQUENCE in clinical trials, most often due to respiratory tract infections (11% of all patients, including pneumonia in 6%). These infections predominantly occurred in the absence of Grade 3 or 4 neutropenia, with neutropenic infection reported in 1.9% of all patients. Opportunistic infections in recipients of CALQUENCE have included, but are not limited to, hepatitis B virus reactivation, fungal pneumonia, *Pneumocystis jiroveci* pneumonia, Epstein-Barr virus reactivation, cytomegalovirus, and progressive multifocal leukoencephalopathy (PML). Consider prophylaxis in patients who are at increased risk for opportunistic infections. Monitor patients for signs and symptoms of infection and treat promptly.

5.2 Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients with hematologic malignancies treated with CALQUENCE. Major hemorrhage (serious or Grade 3 or higher bleeding or any central nervous system bleeding) occurred in 3.0% of patients, with fatal hemorrhage occurring in 0.1% of 1029 patients exposed to CALQUENCE in clinical trials. Bleeding events of any grade, excluding bruising and petechiae, occurred in 22% of patients.

Use of antithrombotic agents concomitantly with CALQUENCE may further increase the risk of hemorrhage. In clinical trials, major hemorrhage occurred in 2.7% of patients taking CALQUENCE without antithrombotic agents and 3.6% of patients taking CALQUENCE with antithrombotic agents. Consider the risks and benefits of antithrombotic agents when co-administered with CALQUENCE. Monitor patients for signs of bleeding.

Consider the benefit-risk of withholding CALQUENCE for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

5.3 Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (23%), anemia (8%), thrombocytopenia (7%), and lymphopenia (7%), developed in patients with hematologic malignancies treated with CALQUENCE. Grade 4 neutropenia developed in 12% of patients. Monitor complete blood counts regularly during treatment. Interrupt treatment, reduce the dose, or discontinue treatment as warranted *[see Dose Modifications for Adverse Reactions (2.4)]*.

5.4 Second Primary Malignancies

Second primary malignancies, including skin cancers and other solid tumors, occurred in 12% of 1029 patients exposed to CALQUENCE in clinical trials. The most frequent second primary malignancy was skin cancer, reported in 6% of patients. Monitor patients for skin cancers and advise protection from sun exposure.

5.5 Atrial Fibrillation and Flutter

Grade 3 atrial fibrillation or flutter occurred in 1.1% of 1029 patients treated with CALQUENCE, with all grades of atrial fibrillation or flutter reported in 4.1% of all patients. The risk may be increased in patients with cardiac risk factors, hypertension, previous arrhythmias, and acute infection. Monitor for symptoms of arrhythmia (e.g., palpitations, dizziness, syncope, dyspnea) and manage as appropriate.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Serious and Opportunistic Infections *[see Warnings and Precautions (5.1)]*
- Hemorrhage *[see Warnings and Precautions (5.2)]*
- Cytopenias *[see Warnings and Precautions (5.3)]*
- Second Primary Malignancies *[see Warnings and Precautions (5.4)]*
- Atrial Fibrillation and Flutter *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

As clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the Warnings and Precautions reflect exposure to CALQUENCE 100 mg approximately every 12 hours in 1029 patients with hematologic malignancies. Treatment includes CALQUENCE monotherapy in 820 patients in 6 trials, and CALQUENCE with obinutuzumab in 209 patients in 2 trials. Among these recipients of CALQUENCE, 88% were exposed for at least 6 months and 79% were exposed for at least one year. In this pooled safety population, adverse reactions in ≥ 30% of 1029 patients were anemia, neutropenia, upper respiratory tract infection, thrombocytopenia, headache, diarrhea, and musculoskeletal pain.

Mantle Cell Lymphoma

The safety data described in this section reflect exposure to CALQUENCE (100 mg approximately every 12 hours) in 124 patients with previously treated MCL in Trial LY-004 *[see Clinical Studies (14.1)]*. The median duration of treatment with CALQUENCE was 16.6 (range: 0.1 to 26.6) months. A total of 91 (73.4%) patients were treated with CALQUENCE for ≥ 6 months and 74 (59.7%) patients were treated for ≥ 1 year.

The most common adverse reactions (≥ 20%) of any grade were anemia, thrombocytopenia, headache, neutropenia, diarrhea, fatigue, myalgia, and bruising. Grade 1 severity for the non-hematologic, most common events were as follows: headache (25%), diarrhea (16%), fatigue (20%), myalgia (15%), and bruising (19%). The most common Grade ≥ 3 non-hematological adverse reaction (reported in at least 2% of patients) was diarrhea.

Dose reductions and discontinuation due to any adverse reaction were reported in 1.6% and 6.5% of patients, respectively.

Tables 3 and 4 present the frequency category of adverse reactions observed in patients with MCL treated with CALQUENCE.

Table 3: Non-Hematologic Adverse Reactions in ≥ 5% (All Grades) of Patients with MCL in Trial LY-004

Body System Adverse Reactions*	CALQUENCE Monotherapy N=124	
	All Grades (%)	Grade ≥ 3 (%)
Nervous system disorders		
Headache	39	1.6
Gastrointestinal disorders		
Diarrhea	31	3.2
Nausea	19	0.8
Abdominal pain	15	1.6
Constipation	15	-
Vomiting	13	1.6
General disorders		
Fatigue	28	0.8
Musculoskeletal and connective tissue disorders		
Myalgia	21	0.8
Skin and subcutaneous tissue disorders		
Bruising[a]	21	-

Body System Adverse Reactions*	CALQUENCE Monotherapy N=124	
	All Grades (%)	Grade ≥ 3 (%)
Rash[b]	18	0.8
Vascular disorders		
Hemorrhage[c]	8	0.8
Respiratory, thoracic and mediastinal disorders		
Epistaxis	6	-

*Per NCI CTCAE version 4.03.
[a] Bruising: Includes all terms containing 'bruise,' 'contusion,' 'petechiae,' or 'ecchymosis'
[b] Rash: Includes all terms containing 'rash'
[c] Hemorrhage: Includes all terms containing 'hemorrhage' or 'hematoma'

Table 4: Hematologic Adverse Reactions Reported in ≥ 20% of Patients with MCL in Trial LY-004

Hematologic Adverse Reactions*	CALQUENCE Monotherapy N=124	
	All Grades (%)	Grade ≥ 3 (%)
Hemoglobin decreased	46	10
Platelets decreased	44	12
Neutrophils decreased	36	15

*Per NCI CTCAE version 4.03; based on laboratory measurements and adverse reactions.

Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 4.8% of patients.

Chronic Lymphocytic Leukemia

The safety data described below reflect exposure to CALQUENCE (100 mg approximately every 12 hours, with or without obinutuzumab) in 511 patients with CLL from two randomized controlled clinical trials *[see Clinical Studies (14.2)]*.

The most common adverse reactions (≥ 30%) of any grade in patients with CLL were anemia, neutropenia, thrombocytopenia, headache, upper respiratory tract infection, and diarrhea.

ELEVATE-TN
The safety of CALQUENCE plus obinutuzumab (CALQUENCE+G), CALQUENCE monotherapy, and obinutuzumab plus chlorambucil (GClb) was evaluated in a randomized, multicenter, open-label, actively controlled trial in 526 patients with previously untreated CLL *[see Clinical Studies (14.2)]*.

Patients randomized to the CALQUENCE+G arm were treated with CALQUENCE and obinutuzumab in combination for six cycles, then with CALQUENCE as monotherapy until disease progression or unacceptable toxicity. Patients initiated obinutuzumab on Day 1 of Cycle 2, continuing for a total of 6 cycles. Patient randomized to CALQUENCE monotherapy received CALQUENCE approximately every 12 hours until disease progression or unacceptable toxicity. The trial required age ≥ 65 years of age or 18 to < 65 years of age with a total Cumulative Illness Rating Scale (CIRS) > 6 or creatinine clearance of 30 to 69 mL/min, hepatic transaminases ≤ 3 times upper limit of normal (ULN) and total bilirubin ≤ 1.5 times ULN, and allowed patients to receive antithrombotic agents other than warfarin or equivalent vitamin K antagonists.

During randomized treatment, the median duration of exposure to CALQUENCE in the CALQUENCE+G and CALQUENCE monotherapy arms was 27.7 months (range 0.3 to 40 months), with 95% and 92% and 89% and 86% of patients with at least 6 months and 12 months of exposure, respectively. In the obinutuzumab and chlorambucil arm the median number of cycles was 6 with 84% of patients receiving at least 6 cycles of obinutuzumab, 70% of patients received at least 6 cycles of chlorambucil. Eighty-five percent of patients in the CALQUENCE+G arm received at least 6 cycles of obinutuzumab.

In the CALQUENCE+G and CALQUENCE monotherapy arms, fatal adverse reactions that occurred in the absence of disease progression and with onset within 30 days of the last study treatment were reported in 2% for each treatment arm, most often from infection. Serious adverse reactions were reported in 39% of patients in the CALQUENCE+G arm and 32% in the CALQUENCE monotherapy arm, most often due to events of pneumonia (2.8% to 7%).

In the CALQUENCE+G arm, adverse reactions led to treatment discontinuation in 11% of patients and a dose reduction of CALQUENCE in 7% of patients. In the CALQUENCE monotherapy arm, adverse reactions led to discontinuation in 10% and dose reduction in 4% of patients.

Tables 5 and 6 presents adverse reactions and laboratory abnormalities identified in the ELEVATE-TN trial.

Table 5: Common Adverse Reactions (≥ 15% Any Grade) with CALQUENCE in Patients with CLL (ELEVATE-TN)

Body System Adverse Reaction*	CALQUENCE plus Obinutuzumab N=178		CALQUENCE Monotherapy N=179		Obinutuzumab plus Chlorambucil N=169	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Infections						
Infection†	69	22‡	65	14‡	46	13‡
Upper respiratory tract infection[a]	39	2.8	35	0	17	1.2
Lower respiratory tract infection[b]	24	8	18	4.5	7	1.8
Urinary tract infection	15	1.7	15	2.8	5	0.6
Blood and lymphatic system disorders§						
Neutropenia[c]	53	37	23	13	78	50
Anemia[d]	52	12	53	10	54	14
Thrombocytopenia[e]	51	12	32	3.4	61	16
Lymphocytosis[f]	12	11	16	15	0.6	0.6
Nervous system disorders						
Headache	40	1.1	39	1.1	12	0
Dizziness	20	0	12	0	7	0
Gastrointestinal disorders						
Diarrhea	39	4.5	35	0.6	21	1.8
Nausea	20	0	22	0	31	0
Musculoskeletal and connective tissue disorders						

Body System Adverse Reaction*	CALQUENCE plus Obinutuzumab N=178		CALQUENCE Monotherapy N=179		Obinutuzumab plus Chlorambucil N=169	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Musculoskeletal pain[g]	37	2.2	32	1.1	16	2.4
Arthralgia	22	1.1	16	0.6	4.7	1.2
General disorders and administration site conditions						
Fatigue[h]	34	2.2	23	1.1	24	1.2
Skin and subcutaneous tissue disorders						
Bruising[i]	31	0	21	0	5	0
Rash[j]	26	2.2	25	0.6	9	0.6
Vascular disorders						
Hemorrhage[k]	20	1.7	20	1.7	6	0

*Per NCI CTCAE version 4.03

† Includes any adverse reactions involving infection or febrile neutropenia

‡ Includes 3 fatal cases in the CALQUENCE plus obinutuzumab arm, 3 fatal cases in the CALQUENCE monotherapy arm and 1 fatal case in the obinutuzumab plus chlorambucil arm

§ Derived from adverse reaction and laboratory data

[a] Upper respiratory tract infection, nasopharyngitis and sinusitis

[b] Includes pneumonia, lower respiratory tract infection, bronchitis, bronchiolitis, tracheitis, and lung infection

[c] Includes neutropenia, neutrophil count decreased, and related laboratory data

[d] Includes anemia, red blood cell count decreased, and related laboratory data

[e] Includes thrombocytopenia, platelet count decreased, and related laboratory data

[f] Includes lymphocytosis, lymphocyte count increased, and related laboratory data

[g] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity and spinal pain

[h] Includes asthenia, fatigue, and lethargy

[i] Includes bruise, contusion, and ecchymosis

[j] Includes rash, dermatitis, and other related terms

[k] Includes hemorrhage, hematoma, hemoptysis, hematuria, menorrhagia, hemarthrosis, and epistaxis

Other clinically relevant adverse reactions (all grades incidence < 15%) in recipients of CALQUENCE (CALQUENCE in combination with obinutuzumab and monotherapy) included:

- *Neoplasms:* second primary malignancy (10%), non-melanoma skin cancer (5%)
- *Cardiac disorders:* atrial fibrillation or flutter (3.6%), hypertension (5%)
- *Infection:* herpesvirus infection (6%)

Table 6: Select Non-Hematologic Laboratory Abnormalities (≥ 15% Any Grade), New or Worsening from Baseline in Patients Receiving CALQUENCE (ELEVATE-TN)

Laboratory Abnormality[*,a]	CALQUENCE plus Obinutuzumab N=178		CALQUENCE Monotherapy N=179		Obinutuzumab plus Chlorambucil N=169	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Uric acid increase	29	29	22	22	37	37
ALT increase	30	7	20	1.1	36	6
AST increase	38	5	17	0.6	60	8
Bilirubin increase	13	0.6	15	0.6	11	0.6

[*]Per NCI CTCAE version 4.03

[a] Excludes electrolytes

Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 3.9% and 2.8% of patients in the CALQUENCE combination arm and monotherapy arm, respectively.

ASCEND

The safety of CALQUENCE in patients with relapsed or refractory CLL was evaluated in a randomized, open-label study (ASCEND) *[see Clinical Studies (14.2)]*. The trial enrolled patients with relapsed or refractory CLL after at least one prior therapy and required hepatic transaminases ≤ 2 times upper limit of normal (ULN), total bilirubin ≤ 1.5 times ULN, and an estimated creatinine clearance ≥ 30 mL/min. The trial excluded patients having an absolute neutrophil count < 500/μL, platelet count < 30,000/μL, prothrombin time or activated partial thromboplastin time > 2 times ULN, significant cardiovascular disease, or a requirement for strong CYP3A inhibitors or inducers. Patients were allowed to receive antithrombotic agents other than warfarin or equivalent vitamin K antagonist.

In ASCEND, 154 patients received CALQUENCE (100 mg approximately every 12 hours until disease progression or unacceptable toxicity), 118 received idelalisib (150 mg approximately every 12 hours until disease progression or unacceptable toxicity) with up to 8 infusions of a rituximab product, and 35 received up to 6 cycles of bendamustine and a rituximab product. The median age overall was 68 years (range: 32-90); 67% were male; 92% were white; and 88% had an ECOG performance status of 0 or 1.

In the CALQUENCE arm, serious adverse reactions occurred in 29% of patients. Serious adverse reactions in > 5% of patients who received CALQUENCE included lower respiratory tract infection (6%). Fatal adverse reactions within 30 days of the last dose of CALQUENCE occurred in 2.6% of patients, including from second primary malignancies and infection.

In recipients of CALQUENCE, permanent discontinuation due to an adverse reaction occurred in 10% of patients, most frequently due to second primary malignancies followed by infection. Adverse reactions led to dosage interruptions of CALQUENCE in 34% of patients, most often due to respiratory tract infections followed by neutropenia, and dose reduction in 3.9% of patients.

Selected adverse reactions are described in Table 7 and non-hematologic laboratory abnormalities are described in Table 8. These tables reflect exposure to CALQUENCE with median duration of 15.7

months with 94% of patients on treatment for greater than 6 months and 86% of patients on treatment for greater than 12 months. The median duration of exposure to idelalisib was 11.5 months with 72% of patients on treatment for greater than 6 months and 48% of patients on treatment for greater than 12 months. Eighty-three percent of patients completed 6 cycles of bendamustine and rituximab product.

Table 7: Common Adverse Reactions (≥ 15% Any Grade) with CALQUENCE in Patients with CLL (ASCEND)

Body System Adverse Reaction*	CALQUENCE N=154		Idelalisib plus Rituximab Product N=118		Bendamustine plus Rituximab Product N=35	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Infections						
Infection†	56	15‡	65	28‡	49	11
Upper respiratory tract infection[a]	29	1.9	26	3.4	17	2.9
Lower respiratory tract infection[b]	23	6	26	15	14	6
Blood and lymphatic system disorders§						
Neutropenia[c]	48	23	79	53	80	40
Anemia[d]	47	15	45	8	57	17
Thrombocytopenia[e]	33	6	41	13	54	6
Lymphocytosis[f]	26	19	23	18	2.9	2.9
Nervous system disorders						
Headache	22	0.6	6	0	0	0
Gastrointestinal disorders						
Diarrhea[g]	18	1.3	49	25	14	0
Vascular disorders						
Hemorrhage[h]	16	1.3	5	1.7	6	2.9
General disorders						
Fatigue[i]	15	1.9	13	0.8	31	6
Musculoskeletal and connective tissue disorders						
Musculoskeletal pain[j]	15	1.3	15	1.7	2.9	0

* Per NCI CTCAE version 4.03

† Includes any adverse reactions involving infection or febrile neutropenia

‡ Includes 1 fatal case in the CALQUENCE monotherapy arm and 1 fatal case in the Idelalisib plus Rituximab arm

§ Derived from adverse reaction and laboratory data

[a] Upper respiratory tract infection, rhinitis and nasopharyngitis

[b] Includes pneumonia, lower respiratory tract infection, bronchitis, bronchiolitis, tracheitis, and lung infection.

[c] Includes neutropenia, neutrophil count decreased, and related laboratory data

[d] Includes anemia, red blood cell decreased, and related laboratory data

[e] Includes thrombocytopenia, platelet count decreased, and related laboratory data

[f] Includes lymphocytosis, lymphocyte count increased and related laboratory data

[g] Includes colitis, diarrhea, and enterocolitis

[h] Includes hemorrhage, hematoma, hemoptysis, hematuria, menorrhagia, hemarthrosis, and epistaxis

[i] Includes asthenia, fatigue, and lethargy

[j] Includes back pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal discomfort, pain in extremity, myalgia, spinal pain and bone pain

Other clinically relevant adverse reactions (all grades incidence < 15%) in recipients of CALQUENCE included:

- *Skin and subcutaneous disorders*: bruising (10%), rash (9%)
- *Neoplasms*: second primary malignancy (12%), non-melanoma skin cancer (6%)
- *Musculoskeletal and connective tissue disorders*: arthralgia (8%)
- *Cardiac disorders*: atrial fibrillation or flutter (5%), hypertension (3.2%)
- *Infection*: herpesvirus infection (4.5%)

Table 8: Select Non-Hematologic Laboratory Abnormalities (≥ 10% Any Grade), New or Worsening from Baseline in Patients Receiving CALQUENCE (ASCEND)

Laboratory Abnormality [a]	CALQUENCE N=154		Idelalisib plus Rituximab Product N=118		Bendamustine plus Rituximab Product N=35	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Uric acid increase	15	15	11	11	23	23
ALT increase	15	1.9	59	23	26	2.9
AST increase	13	0.6	48	13	31	2.9
Bilirubin increase	13	1.3	16	1.7	26	11

Per NCI CTCAE version 5

[a] Excludes electrolytes

Increases in creatinine to 1.5 to 3 times ULN occurred in 1.3% of patients who received CALQUENCE.

7 DRUG INTERACTIONS

Strong CYP3A Inhibitors	
Clinical Impact	• Co-administration of CALQUENCE with a strong CYP3A inhibitor (itraconazole) increased acalabrutinib plasma concentrations *[see Clinical Pharmacology (12.3)]*. • Increased acalabrutinib concentrations may result in increased toxicity.
Prevention or Management	• Avoid co-administration of strong CYP3A inhibitors with CALQUENCE. • Alternatively, if the inhibitor will be used short-term, interrupt CALQUENCE *[see Recommended Dosage for Drug Interactions (2.3)]*.
Moderate CYP3A Inhibitors	

Clinical Impact	• Co-administration of CALQUENCE with a moderate CYP3A inhibitor may increase acalabrutinib plasma concentrations *[see Clinical Pharmacology (12.3)]*. • Increased acalabrutinib concentrations may result in increased toxicity.	
Prevention or Management	• When CALQUENCE is co-administered with moderate CYP3A inhibitors, reduce acalabrutinib dose to 100 mg once daily.	
Strong CYP3A Inducers		
Clinical Impact	• Co-administration of CALQUENCE with a strong CYP3A inducer (rifampin) decreased acalabrutinib plasma concentrations *[see Clinical Pharmacology (12.3)]*. • Decreased acalabrutinib concentrations may reduce CALQUENCE activity.	
Prevention or Management	• Avoid co-administration of strong CYP3A inducers with CALQUENCE. • If a strong CYP3A inducer cannot be avoided, increase the acalabrutinib dose to 200 mg approximately every 12 hours.	
Gastric Acid Reducing Agents		
Clinical Impact	• Co-administration of CALQUENCE with a proton pump inhibitor, H2-receptor antagonist, or antacid may decrease acalabrutinib plasma concentrations *[see Clinical Pharmacology (12.3)]*. • Decreased acalabrutinib concentrations may reduce CALQUENCE activity. • If treatment with a gastric acid reducing agent is required, consider using a H2-receptor antagonist (e.g., ranitidine or famotidine) or an antacid (e.g., calcium carbonate).	
Prevention or Management	Antacids	Separate dosing by at least 2 hours *[see Recommended Dosage for Drug Interactions (2.3)]*.
	H2-receptor antagonists	Take CALQUENCE 2 hours before taking the H2-receptor antagonist *[see Recommended Dosage for Drug Interactions (2.3)]*.
	Proton pump inhibitors	Avoid co-administration. Due to the long-lasting effect of proton pump inhibitors, separation of doses may not eliminate the interaction with CALQUENCE.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals, CALQUENCE may cause fetal harm and dystocia when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of acalabrutinib to animals during organogenesis resulted in dystocia in rats and reduced fetal growth in rabbits at maternal exposures (AUC) 2 times exposures in patients at the recommended dose of 100 mg approximately every 12 hours (*see Data*). Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In a combined fertility and embryo-fetal development study in female rats, acalabrutinib was administered orally at doses up to 200 mg/kg/day starting 14 days prior to mating through gestational day [GD] 17. No effects on embryo-fetal development and survival were observed. The AUC at 200 mg/kg/day in pregnant rats was approximately 9-times the AUC in patients at the recommended dose of 100 mg approximately every 12 hours. The presence of acalabrutinib and its active metabolite were confirmed in fetal rat plasma.

In an embryo-fetal development study in rabbits, pregnant animals were administered acalabrutinib orally at doses up to 200 mg/kg/day during the period of organogenesis (from GD 6-18). Administration of acalabrutinib at doses ≥ 100 mg/kg/day produced maternal toxicity and 100 mg/kg/day resulted in decreased fetal body weights and delayed skeletal ossification. The AUC at 100 mg/kg/day in pregnant rabbits was approximately 2-times the AUC in patients at 100 mg approximately every 12 hours.

In a pre- and postnatal development study in rats, acalabrutinib was administered orally to pregnant animals during organogenesis, parturition and lactation, at doses of 50, 100, and 150 mg/kg/day. Dystocia (prolonged or difficult labor) and mortality of offspring were observed at doses ≥ 100 mg/kg/day. The AUC at 100 mg/kg/day in pregnant rats was approximately 2-times the AUC in patients at 100 mg approximately every 12 hours. Underdeveloped renal papilla was also observed in F1 generation offspring at 150 mg/kg/day with an AUC approximately 5-times the AUC in patients at 100 mg approximately every 12 hours.

8.2 Lactation

Risk Summary

No data are available regarding the presence of acalabrutinib or its active metabolite in human milk, its effects on the breastfed child, or on milk production. Acalabrutinib and its active metabolite were present in the milk of lactating rats. Due to the potential for adverse reactions in a breastfed child from CALQUENCE, advise lactating women not to breastfeed while taking CALQUENCE and for at least 2 weeks after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy

Pregnancy testing is recommended for females of reproductive potential prior to initiating CALQUENCE therapy.

Contraception

Females

CALQUENCE may cause embryo-fetal harm and dystocia when administered to pregnant women *[see Use in Specific Populations (8.1)]*. Advise female patients of reproductive potential to use effective contraception during treatment with CALQUENCE and for at least 1 week following the last dose of CALQUENCE. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

8.4 Pediatric Use

The safety and efficacy of CALQUENCE in pediatric patients have not been established.

8.5 Geriatric Use

Of the 929 patients with CLL or MCL in clinical trials of CALQUENCE, 68% were 65 years of age or older, and 24% were 75 years of age or older. Among patients 65 years of age or older, 59% had Grade 3 or higher adverse reactions and 39% had serious adverse reactions. Among patients younger than age 65, 45% had Grade 3 or higher adverse reactions and 25% had serious adverse reactions. No clinically relevant differences in efficacy were observed between patients ≥ 65 years and younger.

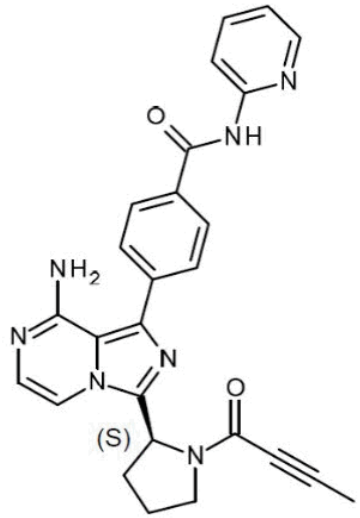
8.6 Hepatic Impairment

Avoid administration of CALQUENCE in patients with severe hepatic impairment. The safety of CALQUENCE has not been evaluated in patients with moderate or severe hepatic impairment *[see Recommended Dosage for Hepatic Impairment (2.2)* and *Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

CALQUENCE (acalabrutinib) is an inhibitor of Bruton tyrosine kinase (BTK). The molecular formula for acalabrutinib is $C_{26}H_{23}N_7O_2$, and the molecular weight is 465.51. The chemical name is 4-{8-amino-3-[(2S)-1-(but-2-ynoyl)pyrrolidin-2-yl]imidazo[1,5-a]pyrazin-1-yl)}-N-(pyridine-2-yl)benzamide.

The chemical structure of acalabrutinib is shown below:



Acalabrutinib is a white to yellow powder with pH-dependent solubility. It is freely soluble in water at pH values below 3 and practically insoluble at pH values above 6.

CALQUENCE capsules for oral administration contains 100 mg acalabrutinib and the following inactive ingredients: silicified microcrystalline cellulose, partially pregelatinized starch, magnesium stearate, and sodium starch glycolate. The capsule shell contains gelatin, titanium dioxide, yellow iron oxide, FD&C Blue 2 and is imprinted with edible black ink.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Acalabrutinib is a small-molecule inhibitor of BTK. Acalabrutinib and its active metabolite, ACP-5862, form a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B cell antigen receptor (BCR) and cytokine receptor pathways. In B cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. In nonclinical studies, acalabrutinib inhibited BTK-mediated activation of downstream signaling proteins CD86 and CD69 and inhibited malignant B-cell proliferation and tumor growth in mouse xenograft models.

12.2 Pharmacodynamics

In patients with B-cell malignancies dosed with 100 mg approximately every 12 hours, median steady state BTK occupancy of ≥ 95% in peripheral blood was maintained over 12 hours, resulting in inactivation of BTK throughout the recommended dosing interval.

Cardiac Electrophysiology

The effect of acalabrutinib on the QTc interval was evaluated in a randomized, double-blind, double-dummy, placebo- and positive-controlled, 4-way crossover thorough QTc study in 48 healthy adult subjects. Administration of a single dose of acalabrutinib that is the 4-fold maximum recommended single dose did not prolong the QTc interval to any clinically relevant extent (i.e., ≥ 10 ms).

12.3 Pharmacokinetics

Acalabrutinib exhibits dose-proportionality, and both acalabrutinib and its active metabolite, ACP-5862, exposures increase with dose across a dose range of 75 to 250 mg (0.75 to 2.5 times the approved recommended single dose) in patients with B-cell malignancies. At the recommended dose of 100 mg twice daily, the geometric mean (% coefficient of variation [CV]) daily area under the plasma drug concentration over time curve (AUC_{24h}) and maximum plasma concentration (C_{max}) for acalabrutinib were 1843 (38%) ng•h/mL and 563 (29%) ng/mL, respectively, and for ACP-5862 were 3947 (43%) ng•h/mL and 451 (52%) ng/mL, respectively.

Absorption

The geometric mean absolute bioavailability of acalabrutinib was 25%. Median [min, max] time to peak acalabrutinib plasma concentrations (T_{max}) was 0.9 [0.5, 1.9] hours, and 1.6 [0.9, 2.7] hour for ACP-5862.

Effect of Food

In healthy subjects, administration of a single 75 mg dose of acalabrutinib (0.75 times the approved recommended single dose) with a high-fat, high-calorie meal (approximately 918 calories, 59 grams carbohydrate, 59 grams fat, and 39 grams protein) did not affect the mean AUC as compared to dosing under fasted conditions. Resulting C_{max} decreased by 73% and T_{max} was delayed 1-2 hours.

Distribution

Reversible binding to human plasma protein was 97.5% for acalabrutinib and 98.6% for ACP-5862. The in vitro mean blood-to-plasma ratio was 0.8 for acalabrutinib and 0.7 for ACP-5862. The geometric mean (% CV) steady-state volume of distribution (V_{ss}) was approximately 101 (52%) L for acalabrutinib and 67 (32%) L for ACP-5862.

Elimination

The geometric mean (% CV) terminal elimination half-life ($t_{1/2}$) was 1 (59%) hour for acalabrutinib and 3.5 (24%) hours for ACP-5862. The geometric mean (%CV) apparent oral clearance (CL/F) was 71 (35%) L/hr for acalabrutinib and 13 (42%) L/hr for ACP-5862.

Metabolism

Acalabrutinib is predominantly metabolized by CYP3A enzymes, and to a minor extent, by glutathione conjugation and amide hydrolysis, based on in vitro studies. ACP-5862 was identified as the major active metabolite in plasma with a geometric mean exposure (AUC) that was approximately 2- to 3-fold higher than the exposure of acalabrutinib. ACP-5862 is approximately 50% less potent than acalabrutinib with regard to BTK inhibition.

Excretion

Following administration of a single 100 mg radiolabeled acalabrutinib dose in healthy subjects, 84% of the dose was recovered in the feces and 12% of the dose was recovered in the urine, with less than 2% of the dose excreted as unchanged acalabrutinib in urine and feces.

Specific Populations

Age, Race, and Body Weight

Age (32 to 90 years), sex, race (Caucasian, African American), and body weight (40 to 149 kg) did not have clinically meaningful effects on the PK of acalabrutinib and its active metabolite, ACP-5862.

Renal Impairment

No clinically relevant PK difference was observed in patients with mild or moderate renal impairment (eGFR $\geq$ 30 mL/min/1.73m^2, as estimated by MDRD (modification of diet in renal disease equation)). Acalabrutinib PK has not been evaluated in patients with severe renal impairment (eGFR < 29 mL/min/1.73m^2, MDRD) or renal impairment requiring dialysis.

Hepatic Impairment

The AUC of acalabrutinib increased 1.9-fold in subjects with mild hepatic impairment (Child-Pugh class A), 1.5-fold in subjects with moderate hepatic impairment (Child-Pugh class B) and 5.3-fold in subjects with severe hepatic impairment (Child-Pugh class C) compared to subjects with normal liver function. No clinically relevant PK difference in ACP-5862 was observed in subjects with severe hepatic impairment (Child-Pugh Class C) compared to subjects with normal liver function. No clinically relevant PK differences in acalabrutinib and ACP-5862 were observed in patients with mild or moderate hepatic impairment (total bilirubin less and equal to upper limit of normal [ULN] and AST greater than ULN, or total bilirubin greater than ULN and any AST) relative to patients with normal hepatic function (total bilirubin and AST within ULN).

Drug Interaction Studies

Effect of CYP3A Inhibitors on Acalabrutinib

Co-administration with a strong CYP3A inhibitor (200 mg itraconazole once daily for 5 days) increased the acalabrutinib C_{max} by 3.9-fold and AUC by 5.1-fold in healthy subjects.

Physiologically based pharmacokinetic (PBPK) simulations with acalabrutinib and moderate CYP3A inhibitors (erythromycin, fluconazole, diltiazem) showed that co-administration increased acalabrutinib C_{max} and AUC approximately 2- to 3-fold.

Effect of CYP3A Inducers on Acalabrutinib

Co-administration with a strong CYP3A inducer (600 mg rifampin once daily for 9 days) decreased acalabrutinib C_{max} by 68% and AUC by 77% in healthy subjects.

Gastric Acid Reducing Agents

Acalabrutinib solubility decreases with increasing pH. Co-administration with an antacid (1 g calcium carbonate) decreased acalabrutinib AUC by 53% in healthy subjects. Co-administration with a proton pump inhibitor (40 mg omeprazole for 5 days) decreased acalabrutinib AUC by 43%.

In Vitro Studies

Metabolic Pathways

Acalabrutinib is a weak inhibitor of CYP3A4/5, CYP2C8 and CYP2C9, but does not inhibit CYP1A2, CYP2B6, CYP2C19, CYP2D6, UGT1A1, and UGT2B7. ACP-5862 is a weak inhibitor of CYP2C8, CYP2C9 and CYP2C19, but does not inhibit CYP1A2, CYP2B6, CYP2D6, CYP3A4/5, UGT1A1, and UGT2B7.

Acalabrutinib is a weak inducer of CYP1A2, CYP2B6 and CYP3A4; ACP-5862 weakly induces CYP3A4.

Based on in vitro data and PBPK modeling, no interaction with CYP substrates is expected at clinically relevant concentrations.

Drug Transporter Systems

Acalabrutinib and its active metabolite, ACP-5862, are substrates of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Acalabrutinib is not a substrate of renal uptake transporters OAT1, OAT3, and OCT2, or hepatic transporters OATP1B1, and OATP1B3. ACP-5862 is not a substrate of OATP1B1 or OATP1B3.

Acalabrutinib and ACP-5862 do not inhibit P-gp, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, and MATE2-K at clinically relevant concentrations.

Acalabrutinib may increase exposure to co-administered BCRP substrates (e.g., methotrexate) by inhibition of intestinal BCRP. ACP-5862 does not inhibit BCRP at clinically relevant concentrations. Acalabrutinib does not inhibit MATE1, while ACP-5862 may increase exposure to co-administered MATE1 substrates (e.g., metformin) by inhibition of MATE1.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with acalabrutinib.

Acalabrutinib was not mutagenic in an in vitro bacterial reverse mutation (AMES) assay or clastogenic in an in vitro human lymphocyte chromosomal aberration assay or in an in vivo rat bone marrow micronucleus assay.

In a fertility study in rats, there were no effects of acalabrutinib on fertility in male rats at exposures 11-times, or in female rats at exposures 9-times the AUC observed in patients at the recommended dose of 100 mg twice daily.

14 CLINICAL STUDIES

14.1 Mantle Cell Lymphoma

The efficacy of CALQUENCE was based upon Trial LY-004 titled "An Open-label, Phase 2 Study of ACP-196 in Subjects with Mantle Cell Lymphoma" (NCT02213926). Trial LY-004 enrolled a total of 124 patients with MCL who had received at least one prior therapy.

The median age was 68 (range 42 to 90) years, 80% were male, and 74% were Caucasian. At baseline, 93% of patients had an ECOG performance status of 0 or 1. The median time since diagnosis was 46.3 months and the median number of prior treatments was 2 (range 1 to 5), including 18% with prior stem cell transplant. Patients who received prior treatment with BTK inhibitors were excluded. The most common prior regimens were CHOP-based (52%) and ARA-C (34%). At baseline, 37% of patients had at least one tumor with a longest diameter ≥ 5 cm, 73% had extra nodal involvement including 51% with bone marrow involvement. The simplified MIPI score (which includes age, ECOG score, and baseline lactate dehydrogenase and white cell count) was intermediate in 44% and high in 17% of patients.

CALQUENCE was administered orally at 100 mg approximately every 12 hours until disease progression or unacceptable toxicity. The median dose intensity was 98.5%. The major efficacy outcome of Trial LY-004 was overall response rate and the median follow-up was 15.2 months.

Table 9: Efficacy Results in Patients with MCL in Trial LY-004

	Investigator Assessed N=124	**Independent Review Committee (IRC) Assessed N=124**
Overall Response Rate (ORR)*		
ORR (%) [95% CI]	81 [73, 87]	80 [72, 87]
Complete Response (%) [95% CI]	40 [31, 49]	40 [31, 49]
Partial Response (%) [95% CI]	41 [32, 50]	40 [32, 50]
Duration of Response (DoR)		
Median DoR in months [range]	NE [1+ to 20+]	NE [0+ to 20+]

*Per 2014 Lugano Classification.
CI= Confidence Interval; NE=Not Estimable; + indicates censored observations.

The median time to best response was 1.9 months.

Lymphocytosis

Upon initiation of CALQUENCE, a temporary increase in lymphocyte counts (defined as absolute lymphocyte count (ALC) increased ≥ 50% from baseline and a post baseline assessment ≥ 5 x 10^9) in 31.5% of patients in Trial LY-004. The median time to onset of lymphocytosis was 1.1 weeks and the median duration of lymphocytosis was 6.7 weeks.

14.2 Chronic Lymphocytic Leukemia

The efficacy of CALQUENCE in patients with CLL was demonstrated in two randomized, controlled trials. The indication for CALQUENCE includes patients with SLL because it is the same disease.

ELEVATE-TN

The efficacy of CALQUENCE was evaluated in the ELEVATE-TN trial, a randomized, multicenter, open-label, actively controlled, 3 arm trial of CALQUENCE in combination with obinutuzumab, CALQUENCE monotherapy, and obinutuzumab in combination with chlorambucil in 535 patients with previously untreated chronic lymphocytic leukemia (NCT02475681). Patients 65 years of age or older or between 18 and 65 years of age with a total Cumulative Illness Rating Scale (CIRS) > 6 or creatinine clearance of 30 to 69 mL/min were enrolled. The trial also required hepatic transaminases ≤3 times upper limit of normal (ULN) and total bilirubin ≤1.5 times ULN, and excluded patients with Richter's transformation.

Patients were randomized in a 1:1:1 ratio into 3 arms to receive:

- CALQUENCE plus obinutuzumab (CALQUENCE+G): CALQUENCE 100 mg was administered approximately every 12 hours starting on Cycle 1 Day 1 until disease progression or unacceptable toxicity. Obinutuzumab was administered starting on Cycle 2 Day 1 for a maximum of 6 treatment cycles. Obinutuzumab 1000 mg was administered on Days 1 and 2 (100 mg on Day 1 and 900 mg on

Day 2), 8 and 15 of Cycle 2 followed by 1000 mg on Day 1 of Cycles 3 up to 7. Each cycle was 28 days.

- CALQUENCE monotherapy: CALQUENCE 100 mg was administered approximately every 12 hours until disease progression or unacceptable toxicity.
- Obinutuzumab plus chlorambucil (GClb): Obinutuzumab and chlorambucil were administered for a maximum of 6 treatment cycles. Obinutuzumab 1000 mg was administered intravenously on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of Cycle 1 followed by 1000 mg on Day 1 of Cycles 2 to 6. Chlorambucil 0.5 mg/kg was administered orally on Days 1 and 15 of Cycles 1 to 6. Each cycle was 28 days.

Randomization was stratified by 17p deletion mutation status, ECOG performance status (0 or 1 versus 2), and geographic region. A total of 535 patients were randomized, 179 to CALQUENCE+G, 179 to CALQUENCE monotherapy, and 177 to GClb. The overall median age was 70 years (range: 41 to 91 years), 47% had Rai stage III or IV disease, 14% had 17p deletion or TP53 mutation, 63% of patients had an unmutated IGVH, and 18% had 11q deletion. Baseline demographic and disease characteristics were similar between treatment arms.

Efficacy was based on progression-free survival (PFS) as assessed by an Independent Review Committee (IRC). The median duration of follow-up was 28.3 months (range: 0.0 to 40.8 months). Efficacy results are presented in Table 10. The Kaplan-Meier curves for PFS are shown in Figure 1.

Table 10. Efficacy Results per IRC in Patients with CLL -- ITT population (ELEVATE-TN)

	CALQUENCE plus Obinutuzumab N=179	**CALQUENCE Monotherapy N=179**	**Obinutuzumab plus Chlorambucil N=177**
Progression-Free Survival [a]			
Number of events (%)	14 (8)	26 (15)	93 (53)
PD, n (%)	9 (5)	20 (11)	82 (46)
Death events, n (%)	5 (3)	6 (3)	11 (6)
Median (95% CI), months [b]	NE	NE (34, NE)	22.6 (20, 28)
HR[c] (95% CI)	0.10 (0.06, 0.17)	0.20 (0.13, 0.30)	-
p-value [d]	< 0.0001	< 0.0001	-
Overall Response Rate[a] (CR + CRi + nPR + PR)			
ORR, n (%)	168 (94)	153 (86)	139 (79)
(95% CI)	(89, 97)	(80, 90)	(72, 84)
p-value [e]	< 0.0001	0.0763	-
CR, n (%)	23 (13)	1 (1)	8 (5)
CRi, n (%)	1 (1)	0	0
nPR, n (%)	1 (1)	2 (1)	3 (2)
PR, n (%)	143 (80)	150 (84)	128 (72)

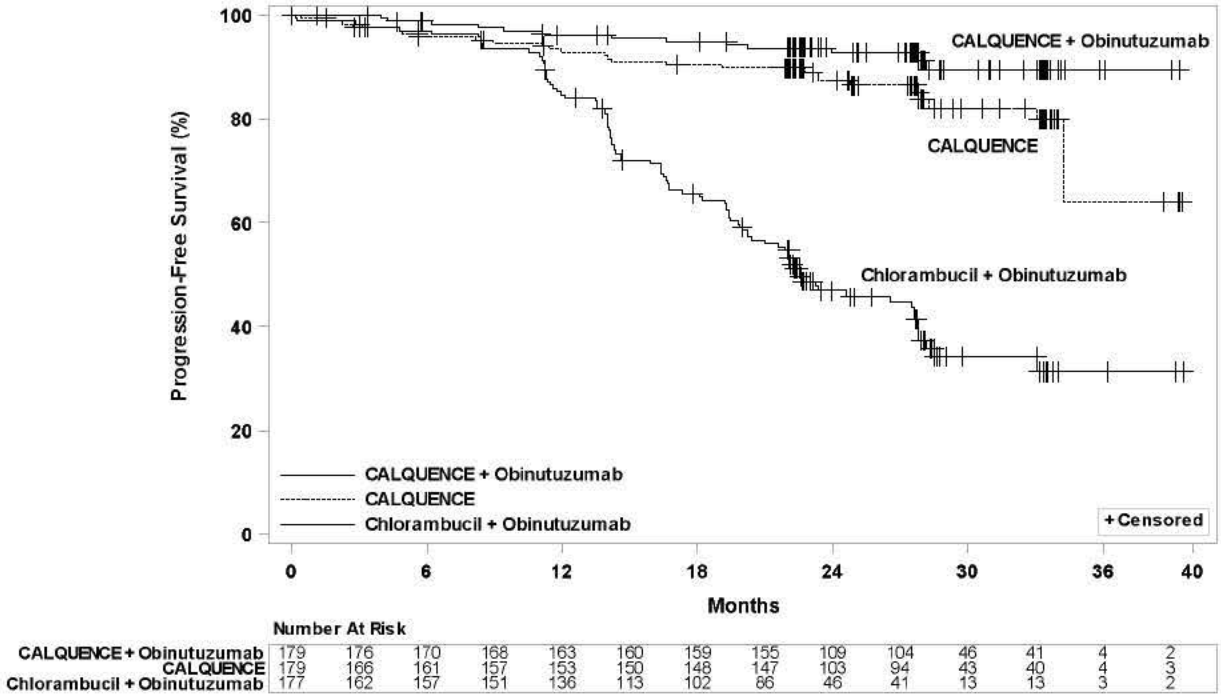
ITT=intent-to-treat; CI=confidence interval; HR=hazard ratio; NE=not estimable; CR=complete response; CRi=complete response with incomplete blood count recovery; nPR=nodular partial response; PR=partial response.

[a] Per 2008 International Workshop on CLL (IWCLL) criteria.

[b] Kaplan-Meier estimate.

[c] Based on a stratified Cox-Proportional-Hazards model. Both hazard ratios are compared with the obinutuzumab and chlorambucil arm.
[d] Based on a stratified log-rank test, with an alpha level of 0.012 derived from alpha spending function by the O'Brien-Fleming method.
[e] Based on a stratified Cochran–Mantel–Haenszel test, for the comparison with the obinutuzumab and chlorambucil arm.

Figure 1: Kaplan-Meier Curve of IRC-Assessed PFS in Patients with CLL in ELEVATE-TN



Number At Risk

CALQUENCE + Obinutuzumab	179	176	170	168	163	160	159	155	109	104	46	41	4	2
CALQUENCE	179	166	161	157	153	150	148	147	103	94	43	40	4	3
Chlorambucil + Obinutuzumab	177	162	157	151	136	113	102	86	46	41	13	13	3	2

With a median follow-up of 28.3 months, median overall survival was not reached in any arm, with fewer than 10% of patients experiencing an event.

ASCEND

The efficacy of CALQUENCE in patients with relapsed or refractory CLL was based upon a multicenter, randomized, open-label trial (ASCEND; NCT02970318). The trial enrolled 310 patients with relapsed or refractory CLL after at least 1 prior systemic therapy. The trial excluded patients with transformed disease, prolymphocytic leukemia, or previous treatment with venetoclax, a Bruton tyrosine kinase inhibitor, or a phosphoinositide-3 kinase inhibitor.

Patients were randomized in a 1:1 ratio to receive either:

- CALQUENCE 100 mg approximately every 12 hours until disease progression or unacceptable toxicity, or
- Investigator's choice:

- Idelalisib plus a rituximab product (IR): Idelalisib 150 mg orally approximately every 12 hours until disease progression or unacceptable toxicity, in combination with 8 infusions of a rituximab product (375 mg/m^2 intravenously on Day 1 of Cycle 1, followed by 500 mg/m^2 every 2 weeks for 4 doses and then every 4 weeks for 3 doses), with a 28-day cycle length.

- Bendamustine plus a rituximab product (BR): Bendamustine 70 mg/m^2 intravenously (Day 1 and 2 of each 28-day cycle), in combination with a rituximab product (375 mg/m^2 intravenously on Day 1 of Cycle 1, then 500 mg/m^2 on Day 1 of subsequent cycles), for up to 6 cycles.

Randomization was stratified by 17p deletion mutation status, ECOG performance status (0 or 1 versus 2), and number of prior therapies (1 to 3 versus ≥ 4). Of 310 patients total, 155 were assigned to CALQUENCE monotherapy, 119 to IR, and 36 to BR. The median age overall was 67 years (range: 32 to 90 years), 42% had Rai stage III or IV disease, 28% had 17p deletion or TP53 mutation, 78% of patients had an unmutated IGVH, and 27% had a 11q deletion. The CALQUENCE arm had a median of 1 prior therapy (range 1-8), with 47% having at least 2 prior therapies. The investigator's choice arm had a median of 2 prior therapies (range 1-10), with 57% having at least 2 prior therapies.

In the CALQUENCE arm, the median treatment duration was 15.7 months, with 94% of patients treated for at least 6 months and 86% of patients treated for at least 1 year. In the investigator's choice arm, the median treatment duration was 8.4 months, with 59% of patients treated for at least 6 months and 37% treated for at least 1 year.

Efficacy was based on PFS as assessed by an IRC, with a median follow-up of 16.1 months (range 0.03 to 22.4 months). Efficacy results are presented in Table 11. The Kaplan-Meier curve for PFS is shown in Figure 2. There was no statistically significant difference in overall response rates between the two treatment arms.

Table 11: Efficacy Results per IRC in Patients with Relapsed or Refractory CLL – ITT Population (ASCEND)

	CALQUENCE Monotherapy N=155	**Investigator's Choice of Idelalisib + Rituximab Product or Bendamustine + Rituximab Product N=155**
Progression-Free Survival [a]		
Number of events, n (%)	27 (17)	68 (44)
Disease progression, n	19	59
Death, n	8	9
Median (95% CI), months [b]	NE (NE, NE)	16.5 (14.0, 17.1)
HR (95% CI) [c]	0.31 (0.20, 0.49)	
P-value [d]	< 0.0001	
Overall Response Rate (CR + CRi + nPR + PR) [a, e]		
ORR, n (%) [e]	126 (81)	117 (75)
(95% CI)	(74, 87)	(68, 82)
CR, n (%)	0	2 (1)
CRi, n (%)	0	0

	CALQUENCE Monotherapy N=155	Investigator's Choice of Idelalisib + Rituximab Product or Bendamustine + Rituximab Product N=155
nPR, n (%)	0	0
PR, n (%)	126 (81)	115 (74)

ITT=intent-to-treat; CI=confidence interval; HR=hazard ratio; NE=not estimable; CR=complete response; CRi=complete response with incomplete blood count recovery; nPR=nodular partial response; PR=partial response

[a] Per 2008 IWCLL criteria.

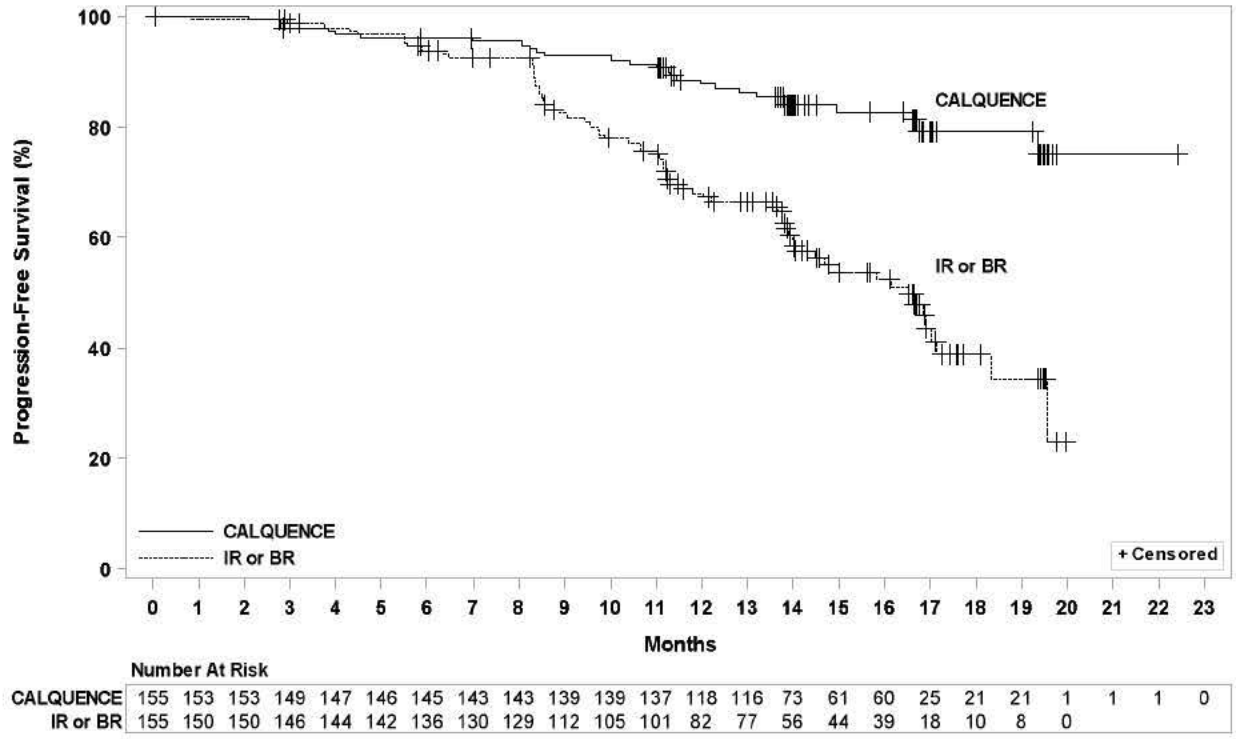
[b] Kaplan-Meier estimate

[c] Based on a stratified Cox-Proportional-Hazards model

[d] Based on a stratified Log-rank test. The pre-specified type I error rate (α) for this interim analysis is 0.012 derived from a Lan-DeMets alpha spending function with O'Brien-Fleming boundary

[e] Through a hierarchical testing procedure, the difference in ORR was not statistically significant, based on a Cochran-Mantel Haenzel test with adjustment for randomization stratification factors.

Figure 2: Kaplan-Meier Curve of IRC-Assessed PFS in Patients with CLL in ASCEND



With a median follow up of 16.1 months, median overall survival was not reached in either arm, with fewer than 11% of patients experiencing an event.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Pack Size	Contents	NDC Number
60-count bottle	Bottle containing 60 capsules 100 mg, hard gelatin capsules with yellow body and blue cap, marked in black ink with 'ACA 100 mg'	0310-0512-60

Storage

Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Serious and Opportunistic Infections
Inform patients of the possibility of serious infection and to report signs or symptoms suggestive of infection *[see Warnings and Precautions (5.1)]*.

Hemorrhage
Inform patients to report signs or symptoms of bleeding. Inform patients that CALQUENCE may need to be interrupted for major surgeries *[see Warnings and Precautions (5.2)]*.

Cytopenias
Inform patients that they will need periodic blood tests to check blood counts during treatment with CALQUENCE *[see Warnings and Precautions (5.3)]*.

Second Primary Malignancies
Inform patients that other malignancies have been reported in patients who have been treated with CALQUENCE, including skin cancer and other solid tumors. Advise patients to use sun protection *[see Warnings and Precautions (5.4)]*.

Atrial Fibrillation and Flutter
Counsel patients to report any signs of palpitations, dizziness, fainting, chest discomfort, and shortness of breath *[see Warnings and Precautions (5.5)]*.

Pregnancy Complication
CALQUENCE may cause fetal harm and dystocia. Advise women to avoid becoming pregnant during treatment and for at least 1 week after the last dose of CALQUENCE *[see Use in Specific Populations (8.3)]*.

Lactation
Advise females not to breastfeed during treatment with CALQUENCE and for at least 2 weeks after the final dose *[see Use in Specific Populations (8.2)]*.

Dosing Instructions

Instruct patients to take CALQUENCE orally twice daily, about 12 hours apart. CALQUENCE may be taken with or without food. Advise patients that CALQUENCE capsules should be swallowed whole with a glass of water, without being opened, broken, or chewed *[see Dosage and Administration (2.1)]*.

Missed Dose

Advise patients that if they miss a dose of CALQUENCE, they may still take it up to 3 hours after the time they would normally take it. If more than 3 hours have elapsed, they should be instructed to skip that dose and take their next dose of CALQUENCE at the usual time. Warn patients they should not take extra capsules to make up for the dose that they missed *[see Dosage and Administration (2.1)]*.

Drug Interactions

Advise patients to inform their healthcare providers of all concomitant medications, including over-the-counter medications, vitamins and herbal products *[see Drug Interactions (7)]*.

Distributed by:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

PATIENT INFORMATION
CALQUENCE® (KAL-kwens)
(acalabrutinib)
Capsules

What is CALQUENCE?

CALQUENCE is a prescription medicine used to treat adults with:

- Mantle cell lymphoma (MCL) who have received at least one prior treatment for their cancer.
- Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

It is not known if CALQUENCE is safe and effective in children.

Before taking CALQUENCE, tell your healthcare provider about all of your medical conditions, including if you:

- have had recent surgery or plan to have surgery. Your healthcare provider may stop CALQUENCE for any planned medical, surgical, or dental procedure.
- have bleeding problems.
- have or had heart rhythm problems.
- have an infection.
- have or had liver problems, including hepatitis B virus (HBV) infection.
- are pregnant or plan to become pregnant. CALQUENCE may harm your unborn baby and problems during childbirth (dystocia).
    - If you are able to become pregnant, your healthcare provider may do a pregnancy test before you start treatment with CALQUENCE
    - Females who are able to become pregnant should use effective birth control (contraception) during treatment with CALQUENCE and for at least 1 week after the last dose of CALQUENCE.
- are breastfeeding or plan to breastfeed. It is not known if CALQUENCE passes into your breast milk. Do not breastfeed during treatment with CALQUENCE and for at least 2 weeks after your final dose of CALQUENCE.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking CALQUENCE with certain other medications may affect how CALQUENCE works and can cause side effects. Especially tell your healthcare provider if you take a blood thinner medicine.

How should I take CALQUENCE?

- Take CALQUENCE exactly as your healthcare provider tells you to take it.
- Do not change your dose or stop taking CALQUENCE unless your healthcare provider tells you to.
- Your healthcare provider may tell you to decrease your dose, temporarily stop, or completely stop taking CALQUENCE if you develop certain side effects.
- Take CALQUENCE 2 times a day (about 12 hours apart).
- Take CALQUENCE with or without food.
- Swallow CALQUENCE capsules whole with a glass of water. Do not open, break, or chew capsules.
- If you need to take an antacid medicine, take it either 2 hours before or 2 hours after you take CALQUENCE.
- If you need to take certain other medicines called acid reducers (H-2 receptor blockers), take CALQUENCE 2 hours before the acid reducer medicine.
- If you miss a dose of CALQUENCE, take it as soon as you remember. If it is more than 3 hours past your usual dosing time, skip the missed dose and take your next dose of CALQUENCE at your regularly scheduled time. Do not take an extra dose to make up for a missed dose.

What are the possible side effects of CALQUENCE?
CALQUENCE may cause serious side effects, including:

- **Serious infections** can happen during treatment with CALQUENCE and may lead to death. Your healthcare provider may prescribe certain medicines if you have an increased risk of getting infections. Tell your healthcare provider right away if you have any signs or symptoms of an infection, including fever, chills, or flu-like symptoms.
- **Bleeding problems (hemorrhage)** can happen during treatment with CALQUENCE and can be serious and may lead to death. Your risk of bleeding may increase if you are also taking a blood thinner medicine. Tell your healthcare provider if you have any signs or symptoms of bleeding, including:
  - blood in your stools or black stools (looks like tar)
  - pink or brown urine
  - unexpected bleeding, or bleeding that is severe or you cannot control
  - vomit blood or vomit that looks like coffee grounds
  - cough up blood or blood clots
  - dizziness
  - weakness
  - confusion
  - changes in your speech
  - headache that lasts a long time
  - bruising or red or purple skin marks
- **Decrease in blood cell counts.** Decreased blood counts (white blood cells, platelets, and red blood cells) are common with CALQUENCE, but can also be severe. Your healthcare provider should do blood tests to check your blood counts regularly during treatment with CALQUENCE.
- **Second primary cancers.** New cancers have happened in people during treatment with CALQUENCE, including cancers of the skin or other organs. Your healthcare provider will check you for skin cancers during treatment with CALQUENCE. Use sun protection when you are outside in sunlight.
- **Heart rhythm problems (atrial fibrillation and atrial flutter)** have happened in people treated with CALQUENCE. Tell your healthcare provider if you have any of the following signs or symptoms:
  - fast or irregular heartbeat
  - dizziness
  - feeling faint
  - chest discomfort
  - shortness of breath

The most common side effects of CALQUENCE include:

• headache • diarrhea • muscle and joint pain	• upper respiratory tract infection • bruising

These are not all of the possible side effects of CALQUENCE.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CALQUENCE?

- Store CALQUENCE at room temperature between 68°F to 77°F (20°C to 25°C).

Keep CALQUENCE and all medicines out of the reach of children.

General information about the safe and effective use of CALQUENCE.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use CALQUENCE for a condition for which it was not prescribed. Do not give CALQUENCE to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for more information about CALQUENCE that is written for health professionals.

What are the ingredients in CALQUENCE?

Active ingredient: acalabrutinib
Inactive ingredients: silicified microcrystalline cellulose, pregelatinized starch, magnesium stearate, and sodium starch glycolate.
Capsule shell contains: gelatin, titanium dioxide, yellow iron oxide, FD&C Blue 2, and black ink.

Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

For more information, go to www.CALQUENCE.com or call 1-800-236-9933.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 11/2019

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ALBERT B DEISSEROTH
11/21/2019 08:58:53 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210259Orig1s006
210259Orig1s007

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "The Applicant's Description" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the Regulatory Authorities.

Application Type	Supplemental NDA
Application Number	NDA 210259/S-006
Priority or Standard	Priority
Submit Date	August 5, August 24, and September 24, 2019
Received Date	September 24, 2019
PDUFA Goal Date	March 24, 2020
Division/Office	Division of Hematology Products/OHOP
Review Completion Date	November 20, 2019
Established Name	Acalabrutinib
Trade Name	CALQUENCE
Pharmacologic Class	Kinase inhibitor
Code name	ACP-196
Applicant	AstraZeneca UK Limited
Formulation	Capsule
Dosing Regimen	100 mg orally approximately every 12 hours
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s)	Treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)

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Reviewers of Multi-Disciplinary Review and Evaluation

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Health Canada Review Team for Assessment Aid

Lead Reviewer	(b) (6)
Clinical Reviewer (Clinical Pharmacology)	
Clinical Reviewer	
Non-Clinical Reviewer	

Therapeutic Goods Administration (Australia) Review Team for Assessment Aid

Clinical Reviewer (Senior Medical Advisor Haematology Clinical Evaluation Unit 6)	(b) (6)
Non-Clinical Reviewer	
Co-lead Risk Management Evaluation Unit	

Glossary

ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
ALC	absolute lymphocyte count
AR	adverse reaction
BCR	B-cell receptor
BID	twice daily
BR	bendamustine+rituximab
BTK	Bruton tyrosine kinase inhibitor
Combo	combination therapy
CRi	complete response with incomplete blood count recovery
CSR	clinical study report
DOR	duration of response
ECI	event of clinical interest
eGFR	estimated glomerular filtration rate
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
HemMalig	hematologic malignancy
HI	hepatic impairment
HR	hazard ratio
IC	investigator's choice
IGHV	immunoglobulin heavy-chain variable
IR	idelalisib+rituximab
IRC	Independent Review Committee
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
IXRS	interactive voice/web response system
KM	Kaplan-Meier
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
Mono	monotherapy
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NCCN	National Comprehensive Cancer Network
NE	not estimable
nPR	nodular partial remission
OL	open-label

ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PI	prescribing information
PI3K	phosphoinositide-3 kinase
PK	pharmacokinetics
PR-L	partial response with lymphocytosis
PRO	patient reported outcome
PT	preferred term
R/R	relapsed or refractory
RS	Richter's syndrome
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	system organ class
SPM	second primary malignancy
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
TN	treatment-naïve
TTNT	time to next treatment
WM	Waldenström macroglobulinemia

1 Executive Summary

1.1. Product Introduction

The FDA review team recommends regular approval of acalabrutinib (Calquence) for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Acalabrutinib, an orally administered Bruton tyrosine kinase (BTK) inhibitor, currently has accelerated approval for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. The present supplement provides for an indication for acalabrutinib for patients with relapsed or refractory CLL or SLL after at least one prior therapy. The recommended dosing of acalabrutinib in either setting is 100 mg orally approximately every 12 hours, continued until disease progression or unacceptable toxicity.

A concurrently submitted supplement (NDA 210259 S-007) provides for an indication for acalabrutinib as a single agent or in combination with obinutuzumab for patients with previously untreated CLL or SLL. The recommended indication statement for patients with CLL or SLL is based on the totality of data from these two supplements.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Efficacy in relapsed or refractory CLL is based on progression-free survival (PFS), as determined by an independent review committee (IRC), in ASCEND (ACE-CL-309), a randomized, open-label phase 3 trial comparing acalabrutinib monotherapy at the intended dosing to investigator's choice (IC) of idelalisib plus rituximab (IR) or bendamustine plus rituximab (BR). The trial enrolled 310 patients with relapsed or refractory CLL after at least one prior systemic therapy, with 155 assigned to acalabrutinib, 119 to IR, and 36 to BR. On prespecified interim analysis, with a median follow-up of 16.1 months, the hazard ratio (HR) for IRC-assessed PFS (acalabrutinib/IC) was 0.31 (95% CI: 0.20, 0.49), with a p-value of <0.0001 (stratified log-rank test). At the time of analysis, the median PFS had not been reached in the acalabrutinib arm. There was no statistically significant difference in overall response rate (ORR) between the two treatment arms.

The significant PFS benefit with acalabrutinib in this randomized, actively-controlled trial constitutes substantial evidence of effectiveness in patients with relapsed or refractory CLL. Because SLL represents the same disease process as CLL, the FDA review team recommends to extend the efficacy and safety outcomes to patients with relapsed or refractory SLL.

1.3. Benefit-Risk Assessment

FDA's Benefit-Risk Summary and Assessment

Efficacy: Efficacy in the relapsed or refractory (rel/ref) setting is based on ASCEND, a multicenter, open-label trial of 510 patients with rel/ref CLL after at least 1 prior therapy, who were randomized in a 1:1 fashion to acalabrutinib (100 mg ~Q12H continuously until disease progression or unacceptable toxicity), or investigator's choice (IC) of idelalisib + rituximab (idelalisib continuously with up to 8 rituximab infusions) or up to 6 cycles of bendamustine + rituximab (BR). The primary endpoint was PFS per IRC. The treatment arms were balanced with the exception of median number of prior therapies (1 in the acalabrutinib arm, 2 in the IC arm). The median age overall was 67 years, 42% had Rai stage III or IV disease, 28% had 17p deletion or TP53 mutation, and 78% had an unmutated IGHV. The median treatment duration was 2-fold longer in the acalabrutinib arm (15.7 months) than the IC arm (8.4 months), with ~50% of patients on IR discontinuing treatment due to AEs.

On prespecified interim analysis, with a median follow-up of 16.1 months, the acalabrutinib arm had a statistically significantly improved PFS, with a HR (acalabrutinib/IC) of 0.31 (95% CI: 0.20, 0.49; p <0.0001). The median PFS had not been reached in the acalabrutinib arm and was 16.5 months (95% CI, 14.0, 17.1) in the IC arm. There was no statistically significant difference in the key secondary endpoint of IRC-assessed overall response rate (ORR); ORR was 81% (95% CI: 74, 87) in the acalabrutinib arm with no CR/CRi, and 75% (95% CI: 68, 82) in the IC arm with 1% CR/CRi. Overall survival data were immature.

The superior PFS in the acalabrutinib arm, without improvement in response rate, is attributable in part to the substantially longer duration of exposure to acalabrutinib than to the IC regimens. The longer exposure to acalabrutinib reflects the more tolerable safety profile compared to IR, coupled with the fixed duration of BR.

Safety: Safety is based on ASCEND, coupled with an expanded safety analysis of 1029 patients with hematologic malignancies who received acalabrutinib 100 mg ~Q12H with or without obinutuzumab. In ASCEND, 154 patients received acalabrutinib (100 mg ~Q12H continuously until disease progression or unacceptable toxicity), 118 received idelalisib continuously with up to 8 rituximab infusions, and 35 received up to 6 cycles of BR. In the acalabrutinib arm, serious adverse events (SAEs) occurred in 29% (fatal AEs within 30 days of last dose, 2.6%). AEs led to acalabrutinib interruption in 34%, dose reduction in 3.9%, and permanent discontinuation in 10%. The most common AEs (≥ 30%) with acalabrutinib were neutropenia, anemia, and thrombocytopenia. Other common TEAEs (incidence ≥ 15%) included upper and lower respiratory tract infections, lymphocytosis, headache, diarrhea, musculoskeletal pain, bleeding, and fatigue.

Similarly, in the expanded safety analysis (N = 1029), the most common treatment-emergent AEs (≥ 30%) were anemia, neutropenia, upper respiratory tract infection, thrombocytopenia, headache, diarrhea, and musculoskeletal pain. Events of clinical interest evaluated in this expanded population included serious or grade ≥ 3 infections (19%, most often respiratory tract infections) including opportunistic infections; bleeding (any grade 22%; major hemorrhage

3.2%); cytopenias including grade 3 or 4 neutropenia (23%; 12% grade 4), anemia (8%), thrombocytopenia (7%), and lymphopenia (7%); second primary malignancies (SPM; 12%, most often nonmelanoma skin cancer); and atrial fibrillation or flutter (4.1%). In ASCEND, recipients of acalabrutinib had a higher incidence of SPM than recipeints of IC.

Overall benefit-risk assessment: In patients with relapsed or refractory CLL after at least one prior systemic therapy, acalabrutinib has a favorable benefit-risk balance.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• CLL is a generally incurable malignancy, and relapse is near universal. • With successive treatment regimens, many patients have diminished response rates and shorter response duration. Patients with high-risk cytogenetic features have an especially poor prognosis.	• CLL is serious and life-threatening.
Current Treatment Options	• Available therapy for relapsed or refractory (rel/ref) CLL includes chemotherapy or chemo-immunotherapy, monoclonal anti-CD20 antibodies, ibrutinib, venetoclax, and PI3K inhibitors (duvelisib, idelalisib). Nevertheless, CLL almost invariably relapses or progress despite these agents, and some agents, most notably the PI3K inhibitors, have significant toxicities leading to treatment discontinuation.	• Effective, yet tolerable, treatment options are needed for the intended population, including chemotherapy-free regimens.
Benefit	• In ASCEND, 355 patients with rel/ref CLL after at least 1 prior therapy were randomized 1:1 to acalabrutinib or investigator's choice (IC) of idelalisib + rituximab or bendamustine + rituximab. • PFS per IRC was superior in the acalabrutinib arm compared to IC (HR 0.31; 95% CI: 0.20, 0.49; p <0.0001). The treatment arms had similar ORRs (81% and 75%, respectively).	• Based on PFS, there is substantial evidence of effectiveness of acalabrutinib in rel/ref CLL.
Risk and Risk Management	• In ASCEND, the most common AEs (incidence ≥ 30%) with acalabrutinib were neutropenia, anemia, and thrombocytopenia. Other common AEs (incidence ≥ 15%) included upper respiratory tract infection, lymphocytosis, headache, diarrhea, musculoskeletal pain, bleeding, and fatigue. • Events of clinical interest with acalabrutinib include serious and opportunistic infections; bleeding; grade 3-4 cytopenias; SPMs; and atrial fibrillation or flutter.	• The overall safety profile in patients with rel/ref CLL is similar to safety profile described previously in mantle cell lymphoma. • The risks are acceptable in patients with rel/ref CLL who have an indication for treatment.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

X	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as			8.1.2
			X	Patient reported outcome (PRO)	
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

X _____
Cross-Disciplinary Team Leader

X _____
Clinical Reviewer

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Chronic lymphocytic leukemia (CLL) is a malignancy of B cells that predominantly affects an elderly population. It is the most prevalent form of adult leukemia, with an age-adjusted incidence of 3.3–6.4 per 100,000 person-years and a median age at diagnosis of 70 years (Noone et al. 2018). The diagnosis of CLL is established using peripheral blood and immunophenotyping and requires a minimum of $5x10^9$ monoclonal B cells that co-express the surface antigens CD5, CD19, CD20, and CD23. While patients with early disease have not been shown to have a survival advantage with early treatment, most patients will eventually require therapy for their disease with the onset of symptoms or cytopenias. Treatment of CLL is therefore often deferred in asymptomatic patients with early-stage disease and initiated once there is evidence for progressive or symptomatic/active disease as defined by International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines (Hallek et al. 2008, Hallek et al. 2018a). Despite the relatively long life expectancy for early stage disease, CLL remains an incurable disease.

In the frontline setting, the treatment approach is determined by several key factors which include prognostic molecular markers such as cytogenetic abnormalities and mutational status of the B-cell receptor (BCR) immunoglobulin heavy-chain variable (*IGHV*) genes, age, and comorbidities. In patients without high-risk cytogenetics—for example, 17p deletion or *TP53* mutation—chemoimmunotherapy remains a standard of care as frontline therapy (NCCN 2019; Eichhorst et al. 2015). While fludarabine-based chemoimmunotherapy is standard for treatment-naive younger/fitter patients with CLL, the therapy for older patients or patients with comorbidities is less well defined. Chlorambucil has now long been a standard frontline treatment for CLL for elderly patients and patients with comorbidities regardless of age (Han et al. 1973; Knospe and Loeb 1980; Eichhorst et al. 2009). Subsequently the addition of anti-CD20 monoclonal antibodies to chlorambucil was demonstrated to prolong survival in elderly patients with comorbidities.

Chemoimmunotherapy has less favorable outcomes in patients who have high risk cytogenetics such as deletions in the long arm of chromosome 11 (11q deletion) or in the short arm of chromosome 17 (17p deletion). These patients may prove to be refractory to therapy and/or experience short remission durations and rapid progression of disease (Hallek et al. 2010, Hillmen et al. 2007). The development of novel molecularly targeted agents, particularly the Bruton tyrosine kinase (BTK) inhibitor ibrutinib, the phosphoinositide-3 kinase (PI3K)δ inhibitor idelalisib, and the apoptosis regulator BCL-2 antagonist venetoclax, have transformed the treatment paradigm for patients with CLL, particularly for those with high-risk disease who have inferior outcomes with chemotherapy-based regimens. These agents have demonstrated

compelling efficacy in subjects with high-risk CLL, with generally favorable safety profiles and a typically low incidence of myelosuppression (Mato et al. 2018a; Mato et al. 2018b; Moreno et al. 2019; O'Brien et al. 2016; Roberts et al. 2016; Seymour et al. 2018; Sharman et al. 2019; Shanafelt et al. 2018; Stilgenbauer et al, 2016; UK CLL Forum 2016).

Although chemoimmunotherapy yields response and potentially long progression-free survival (PFS), CLL remains incurable with relapse inevitable and most patients requiring multiple lines of therapy. Therapeutic choice after relapse requires the evaluation of the intensity of the previous therapies, the duration of response to those therapies, and patient comorbidities.

Standard therapeutic options for relapsed or refractory (R/R) CLL include combination chemoimmunotherapy regimens with bendamustine+rituximab (BR) and idelalisib+rituximab (IR) (Eichhorst et al. 2015; NCCN 2019; Hallek et al. 2018b; Fischer et al. 2011; Cheson et al. 2010; Furman et al. 2014). National Comprehensive Cancer Network (NCCN) guidelines recommend chemoimmunotherapy, including BR, as third-line treatment for R/R CLL but do not recommend it for patients with 17p deletion. European Society for Medical Oncology (ESMO) guidelines also do not recommend BR for patients with 17p deletion or TP53 mutation. They do, however, recommend repeating first-line chemoimmunotherapy (including BR) if relapse or progression occurred at least 24-36 months after initial chemoimmunotherapy. Although a viable option in the elderly population, BR is associated with hematologic toxicity and infections.

Novel regiments with targeted agents such as ibrutinib, idelalisib, and venetoclax are listed as treatment options for R/R CLL irrespective of 17p deletion or TP53 mutation in the NCCN and ESMO guidelines. The development of targeted therapies against B cell markers/antigens or against components of the BCR signaling pathway such as ibrutinib and idelalisib have demonstrated efficacy in CLL with less toxicity compared to chemoimmunotherapy (Wiestner 2015).

The BTK inhibitor ibrutinib is approved in previously untreated and R/R CLL settings (ibrutinib US prescribing information and SmPC 2019) based on superior clinical outcomes compared with standard treatment approaches, but ibrutinib has a distinct toxicity profile that may lead to therapy discontinuation (Burger et al. 2015; Byrd et al. 2013; Woyach et al. 2014). Therapy with other agents targeting the BCR signaling pathway such as the PI3Kδ inhibitor idelalisib has demonstrated efficacy but is also associated with clinically important safety risks, including hepatotoxicity, severe diarrhea or colitis, pneumonitis, severe cutaneous reactions, and intestinal perforation (idelalisib US prescribing information and SmPC 2018). Given the safety profile of these BCR pathway inhibitors, an unmet need exists for therapeutic agents which are better tolerated, potentially improving the benefit risk ratio.

Acalabrutinib is being evaluated in the R/R CLL patient population as monotherapy versus the combination of IR or BR in the ongoing Phase 3 pivotal Study ASCEND (ACE-CL-309), entitled, "A Randomized, Multicenter, Open-Label, Phase 3 Study of Acalabrutinib (ACP-196) Versus

Investigator's Choice of Either Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukemia" (NCT02970318). The primary endpoint of the study is PFS (defined as the time from randomization until disease progression or death from any cause) as assessed by the Independent Review Committee (IRC) per IWCLL 2008 criteria, with incorporation of the clarification for treatment-related lymphocytosis (Cheson 2012).

Regulatory Authorities Assessment:
We agree with the Applicant's overall assessment of the condition.

2.2. Analysis of Current Treatment Options

Table 1 Summary of NCCN Preferred Regimens for Relapsed or Refractory (R/R) Chronic Lymphocytic Leukemia

Product(s) Name	Relevant Indication	Year of Approval And Type of Approval [1]	Dosing/ Adminis-tration	Efficacy Information	Important Safety and Tolerability Issues[2]	Other Comments
FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]						
Small molecules						
Ibrutinib	Treatment of patients with CLL who have received at least 1 prior therapy	2014/ accelerated approval	420 mg taken orally once daily	Multicenter, open-label trial of previously treated patients (N=48). The ORR was 58.3% (95% CI: 43.2%, 72.4%), all partial responses. None of the patients achieved CR. The DOR ranged from 5.6 to 24.2+ months. The median DOR was not reached.	Hemorrhage, infections, myelosuppression, renal toxicity, second primary malignancies, including skin cancers and other carcinomas and embryo-fetal toxicity	
Ibrutinib	Treatment of patients with CLL/SLL	2016/full approval	420 mg taken orally once daily	Randomized, multicenter, open-label Phase 3 study of Ibrutinib versus ofatumumab in patients with previously treated CLL or SLL (N=391). The median follow-up in the trial was 9.4 months. Patients who received ibrutinib had a 78% reduction in the risk of disease progression or death compared with those in the ofatumumab group. At 12 months of follow-up, 90% of patients in the ibrutinib group were still alive, compared with 81% of patients in the ofatumumab group. The reduction in the risk of death was 57% for those who received ibrutinib. The IRC-assessed response in the ibrutinib arm was 43% versus 4% in the ofatumumab group.	Hemorrhage, infections, cytopenias, atrial fibrillation, hypertension, second primary malignancies including skin cancers and other carcinomas, tumor lysis syndrome and embryo-fetal toxicity	

Product(s) Name	Relevant Indication	Year of Approval And Type of Approval [1]	Dosing/ Adminis-tration	Efficacy Information	Important Safety and Tolerability Issues[2]	Other Comments
Duvelisib	Treatment of adult patients with relapsed or refractory CLL or SLL after at least 2 prior therapies	2018/ full approval	25 mg taken orally twice daily	Multicenter, open-label trial comparing Duvelisib versus ofatumumab in 319 adult patients with CLL (N=312) or SLL (N=7) after at least 1 prior therapy. Approval was based on efficacy and safety analysis of patients with at least 2 prior lines of therapy, as the benefit-risk appeared greater in this more heavily pretreated population compared to the overall trial population. Among 196 patients receiving at least 2 prior therapies (95 randomized to duvelisib, 101 randomized to ofatumumab), the median IRC-assessed PFS per was 16.4 months in the duvelisib arm and 9.1 months in the ofatumumab arm (HR of 0.40; SE 0.2). The ORR per IRC was 78% and 39% for the duvelisib and ofatumumab arms, respectively (39% difference, SE 6.5%).	Hepatotoxicity, neutropenia and embryo-fetal toxicity	
Venetoclax	Treatment of patients with CLL with 17p deletion, as detected by an FDA-approved test, who have received at least 1 prior therapy.	2017/ accelerated approval	20 mg once daily for 7 days, taken orally, followed by a weekly ramp-up dosing schedule to 400 mg	Open-label, single-arm, multicenter clinical trial of CLL patients with 17p deletion (N=106) who had received at least one prior therapy. In the study, 17p deletion was confirmed in peripheral blood specimens from patients using Vysis CLL FISH Probe Kit, which is FDA approved for selection of patients for VENCLEXTA treatment. The median time on treatment at the time of evaluation was 12.1 months. The efficacy was	Tumor lysis syndrome (TLS), neutropenia, immunization and embryo-fetal toxicity	

Product(s) Name	Relevant Indication	Year of Approval And Type of Approval [1]	Dosing/ Adminis-tration	Efficacy Information	Important Safety and Tolerability Issues[2]	Other Comments
				evaluated by IRC-assessed ORR. ORR was 85%. The median time to first response was 0.8 months. Median DOR had not been reached with approximately 12 months median follow-up.		
Combination therapy						
Venetoclax	in combination with Rituximab- for the treatment of patients with CLL or SLL, with or without 17p deletion, who have received at least 1 prior therapy.	2018/full approval	20 mg once daily for 7 days, taken orally, followed by a weekly ramp-up dosing schedule to 400 mg administer rituximab after the 5-week ramp-up schedule with Venetoclax	Open-label, international, multicenter Phase 3 trial including R/R CLL patients who had previously received between 1 and 3 lines of therapy with at least 1 chemotherapy regimen (N=389). These patients were randomly assigned to rituximab plus either venetoclax (n=194) or bendamustine (n=195). Efficacy was based on IRC-assessed PFS. The combination of venetoclax plus rituximab lowered the risk of disease progression or death by 83% in comparison with bendamustine plus rituximab in patients with R/R CLL.	TLS, neutropenia, immunization and embryo-fetal toxicity	
Idelalisib	in combination with Rituximab, for treatment of patients with relapsed CLL for whom rituximab alone would be	2014/full approval	150 mg taken orally twice daily (BID)	Randomized, double-blind, placebo-controlled study in patients with relapsed CLL (N=220) who required treatment and were unable to tolerate standard chemoimmunotherapy due to coexisting medical conditions. Treatment with idelalisib plus rituximab (median duration	Severe cutaneous reactions, anaphylaxis, neutropenia, embryo-fetal toxicity	

Product(s) Name	Relevant Indication	Year of Approval And Type of Approval [1]	Dosing/ Adminis-tration	Efficacy Information	Important Safety and Tolerability Issues[2]	Other Comments
	considered appropriate therapy due to other co-morbidities.			of therapy, 3.8 months; range, 0.3 to 16+ months) led to a significantly improved median PFS time compared with placebo plus rituximab (median time not reached vs. 5.5 months; HR= 0.15; 95% CI, 0.08 to 0.28). The 12-month OS rate was 92% in the idelalisib plus rituximab arm compared with 80% in the placebo plus rituximab arm (HR=0.28; 95% CI, 0.09 to 0.86).		

BID=twice daily; CI=confidence interval; CLL=chronic lymphocytic leukemia; CR=complete response; DOR=duration of response; HR=hazard ratio; IRC=Independent Review Committee; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; R/R=relapsed/refractory; SE=standard error; SLL=small lymphocytic lymphoma; TLS=tumor lysis syndrome.

1**:** Accelerated approval or full approval

2: Important Safety and Tolerability Issues include "Warnings and Precautions" from the originally approved labels

The Applicant's Position:

CLL is a serious and life-threatening condition for which there is currently no known cure. There is a high unmet medical need for treatments which control the disease and, importantly, do not significantly add to the burden of morbidity and risk of mortality already experienced by patients with this incurable condition. ASCEND (ACE-CL-309), a study in R/R CLL subjects, demonstrated that acalabrutinib has a statistically significant and clinically meaningful difference in PFS compared to combination standard of care therapies. Acalabrutinib is well tolerated by the majority of subjects, with very few treatment discontinuations or dose reductions due to adverse events (AEs). These data suggest acalabrutinib provides substantial improvement over currently available therapies and an important treatment option for patients with CLL.

In addition, the safety and tolerability of acalabrutinib in ASCEND was consistent with the known safety profile of acalabrutinib. Acalabrutinib may provide a new tolerable and effective chemo-free treatment option to CLL patients.

Regulatory Authorities Assessment:

We agree with the description of current treatment options. The data support the statement that acalabrutinib provides substantial improvement in PFS over two available therapies (idelalsib+rituximab and bendamustine+rituximab) in the relapsed/refractory CLL setting, providing a chemotherapy-free option. However, the efficacy and safety of acalabrutinib relative to other available therapies such as venetoclax, the PI3K inhibitor duvelisib, and ibrutinib has not been evaluated.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
Acalabrutinib was first approved by the United States Food and Drug Administration (FDA) on 31 October 2017 under accelerated approval for New Drug Application (NDA) 210259 for the treatment of adult patients with MCL who have received at least one prior therapy at a dosage of 100 mg twice daily (BID).

Regulatory Authorities Assessment:
Regulatory authorities agree. The MCL indication is the only approved indication for acalabrutinib.

3.2. Summary of Presubmission/Submission Regulatory ActivityThe Applicant's Position:

A summary of key interactions with the FDA regarding acalabrutinib development and ASCEND (ACE-CL-309), the pivotal study for this sNDA, is provided in Table 2.

Table 2 Major regulatory milestones for acalabrutinib development in relation to ASCEND (ACE-CL-309)

Date	Milestone and Details
27 Dec 2013	IND 118717 for treatment of B-cell malignancies activated (ACE-CL-001)
13 May 2015	Orphan Drug Designation granted for acalabrutinib for treatment of CLL
13 Jun 2017	NDA 210259 submitted for acalabrutinib for adult patients with MCL who have received at least one prior therapy
31 July 2017	BTD granted for acalabrutinib for treatment of MCL
31 Oct 2017	Acalabrutinib NDA 210259 approved under accelerated approval for adult patients with MCL who have received at least one prior therapy
23 May 2018	Type C Meeting, Agency approved the statistical analysis plans for the ASCEND interim analysis, and agreed that ongoing/completed toxicology studies are sufficient to support and sNDA for CLL
01 Feb 2019	Type C Written Responses, Agency approved the proposed format and content of sNDA for ASCEND and advised additional analyses to compliment the proposed safety pooling strategy
11 Apr 2019	FDA agreement of Sponsor's amended safety pooling strategy
07 Jun 2019	TC meeting to discuss ELEVATE-TN and ASCEND topline data and timeline for sNDAs
19 Jun 2019	BTD request submitted for acalabrutinib for CLL indications
12 Aug 2019	BTD granted for acalabrutinib monotherapy for treatment of adult patients with CLL

Regulatory Authorities Assessment:
Regulatory authorities agree with the description of major milestones. This supplement, involving acalabrutinib in the setting of relapsed or refractory CLL, was submitted concurrently with NDA210259 S-007, involving acalabrutinib in the setting of previously untreated CLL. For both supplements, the Applicant agreed to participate in:

- Project Orbis involving collaborative NDA review by FDA, the Australian Therapeutic

Good Administration, and Health Canada

- The Real-Time Oncology Review (RTOR) pilot. After negotiation of submission timelines, two RTOR presubmissions were received on 5 Aug 2019 and 26 Aug 2019, with final components received 24 Sept 2019.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI was not consulted for this supplement. In the concurrently submitted sNDA (NDA 210259-S007) involving previously untreated CLL, OSI did not identify significant issues in the Applicant's oversight and clinical trial monitoring of the pivotal trial, ELEVATE-TN.

4.2. Product Quality

Not applicable, as this sNDA does not contain CMC-related changes.

4.3. Clinical Microbiology

Not applicable

4.4. Devices and Companion Diagnostic Issues

Not applicable

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Regulatory Authorities Assessment:
The Applicant updated animal:human safety margins to reflect the clinical exposure at the recommended dose in CLL patients and added the finding of dystocia in rats to Section 8.1 of the label. The Applicant submitted the pilot and GLP pre- and postnatal development studies to support the labeling changes, which were reviewed by the FDA. In the pilot pre- and postnatal development study in rats, acalabrutinib was administered by oral gavage at doses of 0, 100, 200, or 300 mg/kg/day once daily from Gestational Day (GD) 6 through Lactation Day (LD) 12. In the GLP pre- and postnatal development study in rats, acalabrutinib was administered by oral gavage at doses of 0, 50, 100, or 150 mg/kg/day from GD 6 through LD 20, and then F1 generation pups were followed to assess the developmental milestones from weaning through mating. The following findings from these studies will be included in the label: dystocia (prolonged/ difficult labor with or without a normal developing fetus lodged in the vaginal canal), underdeveloped renal papilla in F_1 generation pups observed in both studies, and mortality in F1 generation pups observed in the GLP study.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:
Reference is made to original acalabrutinib NDA 210259 submitted on 13 June 2017 and approved on 31 October 2017. The nonclinical pharmacology/toxicology profile for acalabrutinib has not changed and results support the treatment of patients with CLL with the intended therapeutic dose regimen of 100 mg BID.

Regulatory Authorities Assessment:
FDA disagrees with the Applicant's position. In the newly submitted pilot and GLP pre- and postnatal development studies, there were mortalities at 300 mg/kg in the pilot study and at doses ≥ 100 mg/kg in the GLP study due to fetal dystocia. Additionally, at doses ≥ 200 mg/kg in the pilot study, there were dams found dead with the cause of death undetermined since microscopic examination was limited in these animals to the kidneys. At the time when the fertility and embryo-fetal development study was reviewed for the original application, the maternal mortality at 200 mg/kg due to fetal dystocia was at very low incidence and not considered test article-related. In light of multiple studies showing dose-dependent dystocia, this finding is included in current labeling under Use in Specific Populations and 8.1; and, in 8.3 and 17 to advise females of reproductive potential to use effective contraception and to avoid pregnancy during treatment with acalaburtinib and for 1 week after the final dose. Also to be included are underdeveloped renal papilla in F1 pups and mortality in two F1 males (on Days 68 and 71 with red discoloration of the lungs or thymus) at ≥ 150 and 100 mg/kg, respectively.

5.3. Pharmacology

Primary pharmacology

Regulatory Authorities Assessment:
No new pharmacology data was submitted or is in need of review in the current submission.

Secondary Pharmacology

Data:
No new information is provided in the current submission.

The Applicant's Position:
Not applicable

Regulatory Authorities Assessment:
Regulatory authorities agree with the Applicant.

Safety Pharmacology

Data:
No new information is provided in the current submission.

The Applicant's Position:
Not applicable

Regulatory Authorities Assessment:
Regulatory authorities agree with the Applicant.

5.4. ADME/PK

Data:
No new information is provided in the current submission.

The Applicant's Position:
Not applicable.

Regulatory Authorities Assessment:
Regulatory authorities agree with the Applicant.

5.5. Toxicology

5.5.1. General Toxicology

Data:
No new information is provided in the current submission.

The Applicant's Position:
Not applicable

Regulatory Authorities Assessment:
Regulatory authorities agree with the Applicant.

General toxicology; additional studies
Data:
No new information is provided in the current submission.

The Applicant's Position:
Not applicable

Regulatory Authorities Assessment:
Regulatory authorities agree with the Applicant.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)
Data:
No new information is provided in the current submission.

The Applicant's Position:
Not applicable

Regulatory Authorities Assessment:
Regulatory authorities agree with the Applicant.

In Vitro Assays in Mammalian Cells
Data:
No new information is provided in the current submission.

The Applicant's Position:
Not applicable

Regulatory Authorities Assessment:
Regulatory authorities agree with the Applicant.

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)
Data:
No new information is provided in the current submission.

The Applicant's Position:
Not applicable.

Regulatory Authorities Assessment:
Regulatory authorities agree with the Applicant.

Other Genetic Toxicity Studies *(For API only; does not refer to impurities)*
Data
No new information is provided in the current submission.

The Applicant's Position:
Not applicable.

Regulatory Authorities Assessment:
Regulatory authorities agree with the Applicant.

5.5.3. Carcinogenicity

Data:
No new information is provided in the current submission.

The Applicant's Position:
Not applicable

Regulatory Authorities Assessment:
Regulatory authorities agree with the Applicant.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Data:
See Section Prenatal and Postnatal development below.

The Applicant's Position:
See Section Prenatal and Postnatal development below.

Regulatory Authorities Assessment:
Regulatory authorities agree with the Applicant.

Embryo-Fetal Development

Data:
No new information is provided in the current submission.

The Applicant's Position:
Not applicable

Regulatory Authorities Assessment:
Regulatory authorities agree with the Applicant.

Prenatal and Postnatal Development

Data:
The study reports for the following two reproductive and toxicology studies are included in the sNDA submission:

- 2219-109 - A Pilot Pre- and Postnatal Development Toxicity Study in Rats
- 2219-111 - A Study of Toxic effects on Pre- and Postnatal Development, Including Maternal Function in Rats

2219-109 / A Pilot Pre- and Postnatal Development Toxicity Study in Rats
Key Study Findings:

- No effects of ACP-196 were noted on survival of P females at 100 mg/kg/day.
- Based on these findings, a high dose level of 150 mg/kg/day was considered appropriate for the definitive pre- and postnatal developmental toxicity study in rats.

2219-111 - A Study of Toxic effects on Pre- and Postnatal Development, Including Maternal Function in Rats
Key Study Findings:

- No-observed-adverse-effect level (NOAEL) for P females was considered to be 50 mg/kg/day, with a corresponding $AUC_{(0-t)}$ on LD 20 of 1420 hr*ng/mL, based on the low incidence of dystocia observed at dose levels ≥100 mg/kg/day.
- In the F1 animals, the NOAEL for survival, growth, and physical and functional development was considered 150 mg/kg/day.

The Applicant's Position:
The results of the reproductive toxicity studies conducted to date with acalabrutinib did not identify specific risks to fertility and embryofetal development.

Regulatory Authorities Assessment:
Regulatory authorities agree with the Applicant that there are no new specific risks to fertility and embryofetal development. However, it is noted that the animal: safety margins are now down to 2-fold due to new clinical exposure data. Considering the variation in exposure in both animals and humans, the safety margins may be even less in some patients. Further, the pharmacologically active ACP-5862 metabolite levels in patients are 2 times higher than acalabrutinib; however, metabolite levels in maternal and fetal plasma in rats are much lower than acalabrutinib and were not measured in rabbits, suggesting that some of the developmental and reproductive toxicities may be underpredicted in animals. The submitted data also reveals a new pregnancy complication risk for dystocia and F1 generation toxicity and mortality that was not previously included in the label. See data below for more information.

Study title/ number: ACP-196: A PILOT PRE- AND POSTNATAL DEVELOPMENTAL TOXICITY STUDY IN RATS/ 2219-109

Key Study Findings

- Acalabrutinib (ACP-196)-related mortality due to dystocia was observed at 300 mg/kg. Dams were found dead at doses ≥ 200 mg/kg/day, with some of the same macroscopic and microscopic findings as the dam with dystocia. A definitive cause of death could not be determined for animals found dead since microscopic examination was limited to the kidneys.
- Fetal toxicity, including underdeveloped renal papilla was observed in the presence of maternal toxicity at 200 mg/kg/day.
- On GD17, ACP-5862 metabolite levels in maternal plasma were ~0.5x acalabrutinib levels. On GD 18, acalabrutinib fetal plasma levels were ~0.5x maternal plasma levels. ACP-5862 plasma fetal plasma levels were 2 to 4% of maternal levels.
- Despite high maternal plasma and milk concentrations during lactation, very little (less than 1% of maternal plasma concentrations) acalabrutinib was detected in pup plasma during the lactation phase. The metabolite ACP-5862 was detected in pup plasma at levels less than 5% of maternal plasma levels.

Conducting laboratory and location:	(b) (4)
GLP compliance:	No

Methods

Dose and frequency of dosing:	0, 100, 200, or 300 mg/kg/day from GD 6 through LD 12

Route of administration:	Oral gavage
Formulation/Vehicle:	[redacted] (w:v) and [redacted] (w:v) in NANOpure Diamond Ultrapure water
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	6/sex/group; only females were dosed
Satellite groups:	Toxicokinetics (TK): 8 females/group (acalabrutinib treatment groups); 4 females/group (controls) taken 0.5, 1, 3, 9, and 24 hours postdose on GD 6 and 17; 1 hour postdose on GD18 (fetal plasma levels were also determined); and 1 and 3 hours postdose on LD 12 (maternal milk and pup plasma levels were also measured 3 hours postdose on LD12).
Study design:	Pregnant females (F0 dams) were administered acalabrutinib once daily from GD 6 through LD 12; females were allowed to deliver the F1 litters and rear the F1 pups until LD12 to evaluate the effects on the F0 dams and F1 generation pups; standardization of litter size (culling) to 8 pups/litter (4/sex when possible), occurred on postnatal day (PND) 4.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

<table>
<tr><th>Generation</th><th colspan="4">Major Findings</th></tr>
<tr><td>F0 Dams</td><td colspan="4"></td></tr>
<tr><td>Mortality</td><td colspan="4">Dams with Early Mortalities:
<table>
<tr><th>Dose</th><th>Disposition</th><th>Day</th><th>Cause of Death, Macroscopic and Microscopic (kidneys only) Findings</th></tr>
<tr><td>200</td><td>Found dead</td><td>GD 24</td><td>Undetermined*; macroscopic findings of red (pelvis) or tan (medulla) discoloration in the kidneys, red discoloration of the lung with mainstem bronchi, red discoloration and edema of the thymus, yellow (color of test compound) fluid within the thoracic and abdominal cavities, and yellow and red discoloration and edema of the pancreas; microscopic findings of moderate degree of kidney tubular degeneration/necrosis.</td></tr>
<tr><td>300</td><td>Found dead, pregnant</td><td>GD 22</td><td>Undetermined*; macroscopic findings of red discoloration of the adrenal glands and red (pelvis) discoloration of the kidneys; microscopic findings of moderate kidney tubular degeneration/ necrosis.</td></tr>
<tr><td></td><td>Euthanized in extremis,</td><td>GD 23</td><td>Dystocia with clinical signs of hunched posture and activity decreased; macroscopic findings of yellow discoloration of the kidneys, liver, and skin, enlarged and</td></tr>
</table></td></tr>
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<table>
<tr><td></td><td>
<table>
<tr><td></td><td>incomplete delivery</td><td></td><td>black discoloration of renal lymph node, black discoloration of ovaries; microscopic findings of moderate kidney tubular degeneration/necrosis.</td></tr>
</table>
* a definitive cause of death could not be determined for animals found dead since microscopic examination was limited to the kidneys. Doses are in mg/kg/day.
</td></tr>
<tr><td>Clinical Signs and Body Weight</td><td>300 mg/kg/day: Bent tail was observed on LD 10-12 in 1/6 females.
≥ 100 mg/kg/day: Salivation was observed on GD 17-22 at all doses in animals with and without early mortality (1/6, 3/6, and 3/6 dams at 100, 200, and 300 mg/kg/day, respectively) and during the lactation phase in 1 to 4 animals per acalabrutinib treatment group. Mean body weight changes were generally transient and/or did not demonstrate a dose response.</td></tr>
<tr><td>Necropsy Findings (macroscopic)</td><td>300 mg/kg/day: Mild enlargement of the mandibular lymph node in 1/6 females.
≥ 100 mg/kg/day: Minimal to moderate red discoloration of the mandibular lymph node in 5/6, 3/5, and 1/4 females at 100, 200, and 300 mg/kg/day, respectively, and mild to moderate red discoloration of the renal lymph node in 2/6, 2/5, and 0/4 (1/2 with early mortality) females at 100, 200, and 300 mg/kg/day, respectively. Per protocol, no microscopic examination was performed on tissues from animals that survived to the terminal necropsy.</td></tr>
<tr><td>Concentrations in maternal, fetal and pup plasma; and maternal milk</td><td><u>Acalabrutinib</u>
Maternal Tmax (hr): 0.5
Maternal T1/2 (hr): 2 (3 for ACP-5862)

<u>Maternal Plasma TK on GD17</u>
<table>
<tr><th>Dose (mg/kg/day)</th><th>Cmax (ng/mL)</th><th>AUC_{0-t} (hr*ng/mL)</th></tr>
<tr><td>100</td><td>2520</td><td>9260</td></tr>
<tr><td>200</td><td>7060</td><td>17900</td></tr>
<tr><td>300</td><td>10100</td><td>26300</td></tr>
</table>
On GD17, maternal ACP-5862 AUC values were 55, 57, and 46% of 100, 200, and 300 mg/kg/day acalabrutinib values; Cmax values were 61, 42, and 34%, respectively.

On GD 18, mean fetal plasma acalabrutinib concentrations were lower than in maternal plasma. The mean acalabrutinib fetal plasma levels were ~40 to 50% of maternal levels. Mean fetal ACP-5862 plasma concentrations were 2 to 4% of maternal plasma concentrations.

Concentrations of acalabrutinib and ACP-5862 were higher in maternal milk than plasma. Maximum pup concentrations of acalabrutinib and ACP-5862 were less than 1 and <5% of maternal plasma levels (see original multidisciplinary review).</td></tr>
<tr><td>F1 Generation</td><td></td></tr>
<tr><td>F1 mortality</td><td>There were no acalabrutinib-related mortalities other than the litter of the dam with dystocia.</td></tr>
<tr><td>F1 clinical observations</td><td>200 mg/kg/day: Eight pups were thin and cold to the touch from one dam (who lost 24 g of body weight and had reduced food consumption (this female also had clinical signs of salivation) over lactation days 0 to 10 at 200 mg/kg/day. The dam also had macroscopic findings of moderate tan kidney discolortation, and mild to moderate red discoloration of the mandibular and renal lymph nodes.</td></tr>
<tr><td>F1 body weight</td><td>Unremarkable</td></tr>
</table>

<table>
<tr><td>F1 Necropsy Findings</td><td>There were no test article-related microscopic findings in pups from dams that survived to scheduled necropsy.

Fetal Observations in Dams with Early Mortality:
<table>
<tr><th>Dose</th><th>Dam Disposition</th><th>Day</th><th>Fetal Macroscopic Findings</th></tr>
<tr><td>200</td><td>Found dead</td><td>GD 24</td><td>Dam delivered 13 pups that had macroscopic findings of underdeveloped renal papilla (generally bilateral).</td></tr>
<tr><td>300</td><td>Found dead, pregnant</td><td>GD 22</td><td>Dam died pregnant with no information available on her pups other than “normal developing implant”.</td></tr>
<tr><td></td><td>Euthanized in extremis, incomplete delivery</td><td>GD 23</td><td>Macroscopic observations were within normal limits for the 8 pups that survived birth.</td></tr>
</table>
Doses are in mg/kg/day.</td></tr>
</table>

Study title/ number: ACP-196: A STUDY OF TOXIC EFFECTS ON PRE- AND POSTNATAL DEVELOPMENT, INCLUDING MATERNAL FUNCTION IN RATS/ 2219-111

Key Study Findings

- No-observed-adverse-effect level (NOAEL) for acalabrutinib (ACP-196) in pregnant females and F1 animals was considered to be 50 mg/kg/day, with a corresponding AUC(0-t) on LD 20 of 1420 hr*ng/mL. The NOAEL is based on the low, but consistently observed accoss studies, incidence of dystocia observed in dams and underdeveloped renal papilla and mortality (with red discoloration of the lung or thymus) in F1 offspring at dose levels ≥ 100 mg/kg/day.
- There was variability (large standard deviation) in maternal plasma levels of acalabrutinib.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 50, 100, or 150 mg/kg/day from GD 6 through LD 20

Route of administration: Oral gavage

Formulation/Vehicle: (b) (4) (w:v) and (b) (4) (w:v) in NANOpure Diamond Ultrapure water

Species/Strain: Rat/Sprague-Dawley

Number/Sex/Group: 25/sex/group; only females were dosed

Satellite groups: None. Blood samples were collected from the first 6 females/group at 0.5, 1, 3, 9, and 24 hours postdose on LD20.

Study design: Pregnant females (F0 dams) were administered acalabrutinib once daily from GD 6 through LD 20; females were allowed to deliver the F1 litters and rear the F1 pups to weaning on LD/PND 21 to evaluate the effects on the F0 dams and F1 generation pups through weaning; standardization of litter size (culling) to 8 pups/litter (4/sex when possible), occurred on PND 4; F1 pups evaluated on LD 2 for static righting reflex and pinna detachment, on LD 11 for cliff aversion, LD 13 for eye opening, LD 16 for air drop righting reflex, LD 21 for neuropharmacological evalulation outlined by Irwin, and PND 22 for auditory response. On PND 28 a maximum of 25 males and 25 females per group were selected to continue on the study for assessment of sexual maturation and behavioral or reproductive performance (PND 28 for vaginial opening, PND 35 for preputial separation, motor activity and Functional Observational Battery (FOB) Observations, and learning and memory assessments). These F1 animals were mated (at least 80 days old) and uterine parameters were evaluated with necrospsy on GD 13.

Deviation from study protocol affecting interpretation of results: No

Observations and Results

<table>
<tr><th>Generation</th><th>Major Findings</th></tr>
<tr><td>F0 Dams</td><td></td></tr>
<tr><td>Mortality</td><td>Unscheduled mortalities:
<table>
<tr><th>Dose</th><th>Disposition</th><th>Day</th><th>Cause of Death, Macroscopic (Maternal) Findings</th></tr>
<tr><td>100</td><td>Euthanized pregnant in extremis</td><td>GD 22</td><td>Dystocia with swelling of the vulva and anogenital region, purple skin discoloration in anogenital region, piloerection; developing fetus lodged in the vaginal canal and mild pelvic dilation of the kidneys.</td></tr>
<tr><td>150</td><td>Euthanized pregnant in extremis</td><td>GD 23</td><td>Dystocia with swelling of the vulva, red material around the nose, and piloerection; developing fetus lodged in the vaginal canal, mild pelvic dilation of the kidneys, brown fluid in the uterus and vagina.</td></tr>
</table></td></tr>
</table>

	Euthanized in extremis; incomplete delivery	GD 22	Dystocia with salivation, piloerection, and unkempt appearance; black foreign material in stomach that is apparent fetal/placental tissue.

Doses are in mg/kg/day. No uterine or fetal information was provided for the dams with early mortality.

Clinical Signs and Body Weight

≥ 50 mg/kg/day: Dose-dependent increase in salivation in 3/25, 3/25, and 12/25 females at 50, 100 and 150 mg/kg/day, respectively, beginning as early as GD 12 which progressed into the lactation period (present in 12/25, 14/24, and 18/23 females and was accompanied by red discolored hair in the lower jaw in 2/25, 8/24, and 14/23 females at 50, 100, and 150 mg/kg/day, respectively).

Delivery Data

150 mg/kg/day: 8% decreases in total and liveborn pups/litter (outside of lab historical control range, but within the control range for other contract labs) relative to controls (see table below).

Dose (mg/kg/day)	0	50	100	150	HC mean [range]
No. Females on Study	25	25	25	12	300
No. Females Pregnant	25	24	24	24	300
Female Fertility Index	100	96	96	96	
No. Females Littered	25	24	23	22	300
Total Pups/Litter on Day 0 N (SD)	11.72 (1.621)	11.54 (2.206)	11.09 (2.214)	10.73 (2.334)	11.92 [11.1-12.7]
Liveborn Pups/Litter N (SD)	11.64 (1.705)	11.46 (2.146)	11.09 (2.214)	10.73 (2.334)	11.81 [10.9-12.7]
Live Pups/Litter Precull Day 4 N (SD)	11.4 (1.63)	11.5 (2.19)	11.0 (2.27)	10.5 (2.6)	11.64 [10.6-12.5]
Implantation Scars Counts (SD)	12.4 (1.73)	11.8 (2.19)	11.7 (1.54)	11.7 (1.86)	12.58 [11.7-13.2]

SD: standard deviation; HC: lab historical control

Necropsy Findings

≥ 50 mg/kg/day: Macroscopic changes included mild to moderate red discoloration of the mandibular (in 1/25, 4/24, and 1/23 females at 50, 100, and 150 mg/kg/day, respectively), mediastinal (in 4/24 and 1/24 females at 50 and 100 mg/kg/day, respectively), and renal (in 1/23 females at 150 mg/kg/day) lymph nodes. Moderate red foci and swollen/thickened liver was observed only at 50 mg/kg/day.

Concentrations in maternal plasma

Acalabrutinib
Maternal Tmax (hr): 0.5
Maternal T1/2 (hr): 3 to 4

Maternal Plasma TK on LD20

Dose (mg/kg/day)	Cmax (SD) (ng/mL)	AUC_{0-t} (SD) (hr*ng/mL)
50	651 (220)	1420 (301)
100	1730 (580)	4470 (1420)
150	3000 (841)	10300 (3940)

SD: standard deviation

F1 Generation

F1 mortality

≥ 100 mg/kg/day: 1/25 males at 100 mg/kg/day with red discoloration of the lung with mainstem bronchi and 1/25 males at 150 mg/kg/day with red discoloration of the thymus were found dead on Study Days 68 and 71, respectively. The cause of

	death is unknown (with no microscopic examination) but these macroscopic findings were also observed in the female dam found dead at 200 mg/kg/day in the pilot study and in one 50 mg/kg/day dam in this study.
F1 clinical observations	Unremarkable
F1 body weight	Unremarkable
F1 deveopmental landmarks	**150 mg/kg/day:** Static righting reflex occurred earlier (mean 2.1 days) compared to controls (mean 2.3 days). Air drop righting reflex was higher (16.4 days) compared to controls (16.2 days). These differences were statistically significant and outside of the historical control range, but of small magnitude and not considered adverse.
Auditory startle response, locomotor activity, FOB, etc	Unremarkable
Reproductive performance	Unremarkable
Necropsy Findings	**150 mg/kg/day:** 1/62 male pups on Day 28 had undeveloped renal papillae; 1/57 female pups had hepatodiaphragmatic nodule in the liver. **≥ 100 mg/kg/day:** Pups had absolute and relative liver weight decreases of -3 to -6%.
F2 Generation	Not tested

5.5.5. Other Toxicology Studies

Data:
No new information is provided in the current submission.

Applicant's Position:
Not applicable

Regulatory Authorities Assessment:
Regulatory authorities agree with the Applicant.

X
Pharmacology-Toxicology Reviewer

X
Pharmacology-Toxicology Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

Regulatory Authorities Assessment:
The proposed starting dose of acalabrutinib in the current supplement is 100 mg orally approximately every 12 hours with or without food in patients with CLL or SLL. The efficacy and safety of the proposed dose were supported by the results of Phase 3 Study ASCEND, which evaluated 100 mg acalabrutinib BID monotherapy vs. Investigator's choice (idelalisib + rituximab or bendamustine vs. rituximab) in patients with previously treated CLL (N=310). The applicant updated the population PK analysis for acalabrutinib and ACP-5862 (active metabolite) PK with the data from patients with CLL. The PK data in CLL were similar to the PK observed in the currently approved mantle cell lymphoma (MCL) population. The applicant also updated the labeling to recommend "avoid use" in patients with severe hepatic impairment based on applicant's submitted severe hepatic impairment trial results (Study ACE-HI-102).

From a clinical pharmacology perspective, this supplemental NDA is approvable.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:
Reference is made to original acalabrutinib NDA 210259 submitted on 13 June 2017 and approved on 31 October 2017. No new information concerning Pharmacology and Clinical Pharmacokinetics was generated in the ASCEND study; however, the previously approved data support a fixed 100 mg BID acalabrutinib dose for the treatment of patients with CLL.

Regulatory Authorities Assessment:
Regulatory authorities agree with Applicant's Position.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:
Reference is made to original acalabrutinib NDA 210259 submitted on 13 June 2017 and approved on 31 October 2017.

The Applicant's Position:
The acalabrutinib dose of 100 mg BID was identified as the recommended dose based on a review of all available safety, tolerability, pharmacokinetic, pharmacodynamic, and efficacy data in the Phase 1 component of Study ACE-CL-001. In addition, ensuring maximal BTK

occupancy over 24 hours may reduce development of resistance mechanisms and reduce the rate of tumor escape.

Regulatory Authorities Assessment:
Regulatory authorities agree with Applicant's Position.

6.2.2.2. Therapeutic Individualization

Data:

Specific Populations:

Patients with severe hepatic impairment:

Acalabrutinib was evaluated in subjects with severe hepatic impairment (HI) in study ACE-HI-102. This was a Phase 1, open-label, single-dose study to investigate the influence of severe hepatic impairment on the pharmacokinetics of acalabrutinib and its metabolite (ACP-5862). The primary objective of this study was to compare the plasma pharmacokinetics of acalabrutinib and its metabolite ACP-5862 in subjects with severe HI with that in matched-control subjects following a single-dose administration of 50 mg acalabrutinib. The concentration-time profiles of total acalabrutinib and ACP-5862 were well characterized and the PK parameters observed in normal hepatic function subjects were comparable with historical data (median T_{max} of 0.75 hour and $t_{1/2}$ ranging from 0.9 to 2.8 hours reported in the Calquence product label). Total (AUC) and peak (C_{max}) exposures to acalabrutinib were approximately 5-fold higher in subjects with severe HI than in subjects with normal hepatic function.

The secondary objective of this study was to evaluate the safety and tolerability of acalabrutinib in subjects with severe HI after a single-dose administration of 50 mg acalabrutinib.

There were no deaths, serious adverse events (SAEs), or subject discontinuations due to AEs in this study. There were no notable findings in the assessments for ECG, vital signs, clinical laboratory values, or physical examinations with respect to subject safety.

The Applicant's Position:
Total and peak exposure to total and unbound acalabrutinib increased approximately 5-fold and 3.6-fold, respectively, in subjects with severe HI when compared with healthy subjects. Higher bilirubin levels and prothrombin time values were associated with higher total acalabrutinib exposure parameters while higher albumin levels were associated with lower total acalabrutinib exposure parameters. The metabolism of acalabrutinib was affected by severe HI leading to increased systemic exposure and decreased systemic clearance. However, the total and peak exposures to total and unbound ACP-5862 were similar in subjects with severe HI and subjects with normal hepatic function. This is likely due to presystemic (intestinal-mediated) metabolism. No apparent trends were observed between Child-Pugh scores, albumin or bilirubin levels, prothrombin time and total ACP-5862 exposure pharmacokinetic (PK)

parameters. A single 50-mg oral dose of acalabrutinib appeared to be safe and well tolerated by this group of male and female subjects with severe HI; however it is not recommended to administer acalabrutinib in patients with severe hepatic impairment (Child Pugh class C).

Regulatory Authorities Assessment:
Regulatory authorities agree with Applicant's Position. Acalabrutinib and ACP-5862 PK results from Study ACE-HI-102 are provided below :

Table 3 Statistical Comparisons of Total Plasma Acalabrutinib PK Parameters – Severe HI vs. Normal Hepatic Function

	Geometric Mean (%CV)		GMR (90% CI) vs. Normal hepatic function	
	$AUC_{0-\infty}$ (ng·h/mL)	C_{MAX} (ng/mL)	$AUC_{0-\infty}$	C_{MAX}
Severe HI	1169 (54%) [n=8]	726 (56%) [n=8]	5.16 (3.29, 8.08)	4.92 (2.50, 9.66)
Normal hepatic function	227 (55%) [n=8]	148 (117%) [n=8]	N/A	N/A

Source: Reviewer's analysis based on data from Applicant's Study ACE-HI-102 CSR

Table 4 Statistical Comparisons of Unbound Plasma Acalabrutinib PK Parameters – Severe HI vs. Normal Hepatic Function

	Geometric Mean (%CV)		GMR (90% CI) vs. Normal hepatic function	
	AUC_{0-last} (ng·h/mL)	C_{MAX} (ng/mL)	$AUC_{0-\infty}$	C_{MAX}
Severe HI	12 (32%) [n=8]	4.4 (39%) [n=8]	3.56 (2.50, 5.05)	3.77 (2.55, 5.56)
Normal hepatic function	3.2 (45%) [n=7]	1.2 (48%) [n=7]	N/A	N/A

Source: Reviewer's analysis based on data from Applicant's Study ACE-HI-102 CSR

Table 5 Statistical Comparisons of Total Plasma ACP-5862 PK Parameters – Severe HI vs. Normal Hepatic Function

	Geometric Mean (%CV)		GMR (90% CI) vs. Normal hepatic function	
	$AUC_{0-\infty}$ (ng·h/mL)	C_{MAX} (ng/mL)	$AUC_{0-\infty}$	C_{MAX}
Severe HI	782 (22%) [n=6]	169 (30%) [n=8]	0.96 (0.73, 1.26)	1.01 (0.63, 1.62)
Normal hepatic function	817 (37%) [n=8]	167 (75%) [n=8]	N/A	N/A

Source: Reviewer's analysis based on data from Applicant's Study ACE-HI-102 CSR

Table 6 Statistical Comparisons of Unbound Plasma ACP-5862 PK Parameters – Severe HI vs. Normal Hepatic Function

	Geometric Mean (%CV)		GMR (90% CI) vs. Normal hepatic function	
	AUC_{0-last} (ng·h/mL)	C_{MAX} (ng/mL)	$AUC_{0-\infty}$	C_{MAX}
Severe HI	5.4 (27%) [n=7]	1.5 (44%) [n=7]	0.96 (0.60, 1.54)	0.88 (0.51, 1.51)
Normal hepatic function	5.6 (68%) [n=7]	1.7 (75%) [n=7]	N/A	N/A

Source: Reviewer's analysis based on data from Applicant's Study ACE-HI-102 CSR

The labeling has been updated to reflect "avoid use" in patients with severe hepatic impairment and descriptive PK results are provided in Section 12.

Note that Study ACE-HI-102 fulfills the following PMR issued at the time of original NDA accelerated approval:

- PMR 3291-3: Conduct a clinical PK trial to determine an appropriate safe dose of acalabrutinib in patients with severe hepatic impairment. This trial should be designed and conducted in accordance with the FDA Guidance for Industry entitled "PK in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

6.2.2.3. Outstanding Issues

Data:

PMR 3291-3 Study ACE-HI-102, a phase 1, open-Label, single-dose Study to investigate the influence of severe hepatic impairment on the pharmacokinetics of acalabrutinib and its metabolite (ACP-5862) has completed enrollment according to projected enrollment rates. This trial was designed and conducted in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labelling."

The Applicant's Position:
PM3921-3, Final CSR for Study ACE-HI-102 is submitted in this sNDA. Patients with severe hepatic impairment are not recommended for treatment with acalabrutinib.

Regulatory Authorities Assessment:
There are no outstanding clinical pharmacology-related issues in the current submission. Study ACE-HI-102 CSR fulfills PMR 3291-3, as noted in Section 6.2.2.2 Therapeutic Individualization of this Assessment Aid.

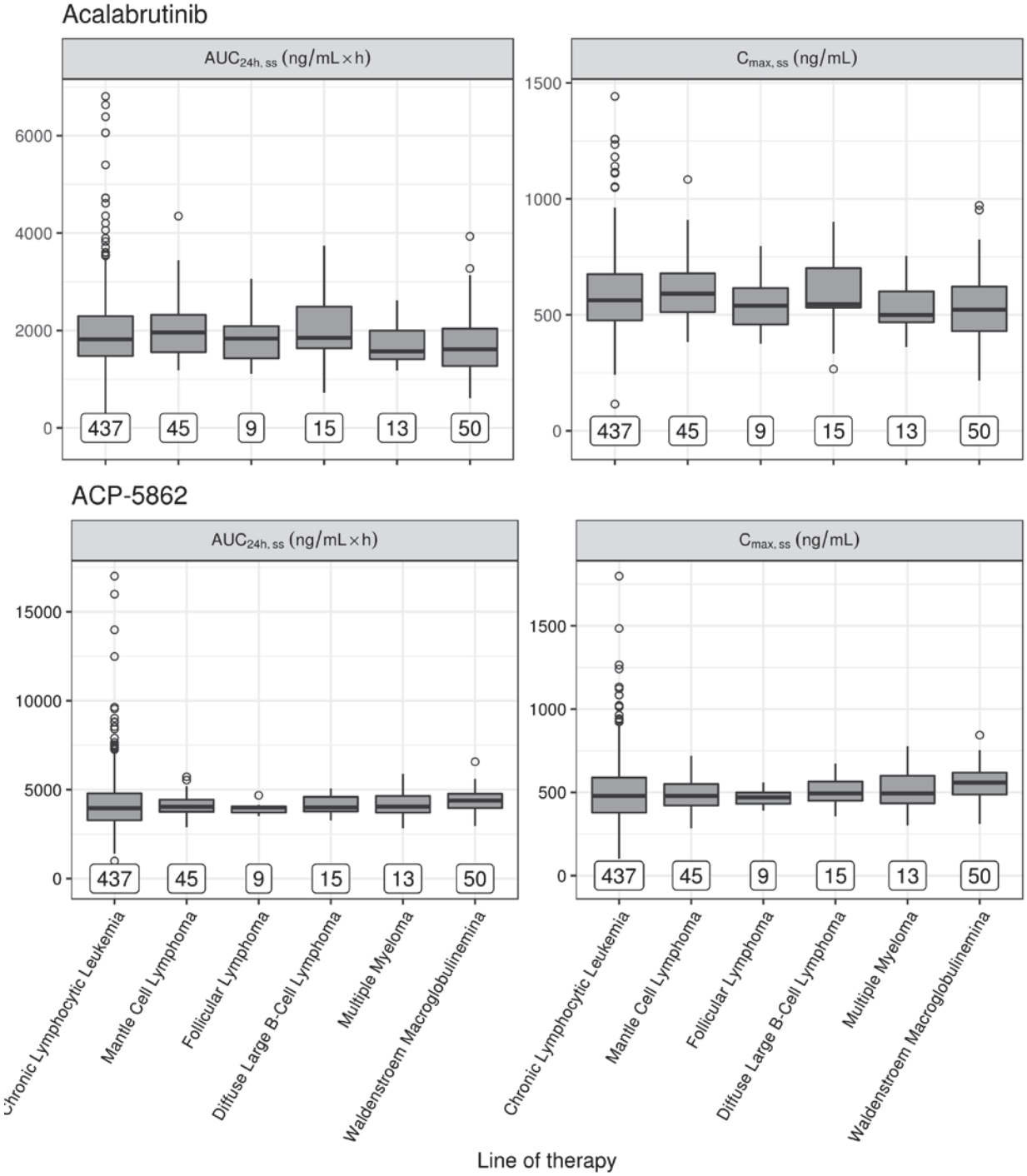
6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:
Reference is made to original acalabrutinib NDA 210259 submitted on 13 June 2017 and approved on 31 October 2017.

A comparison of acalabrutinib and ACP-5862 exposures across various B-cell malignancies, including CLL and MCL, is shown in Figure 1. Overall, the exposures are similar between CLL and MCL indicating similarity of PK across the 2 indications.

Figure 1 Comparison of Steady State Acalabrutinib and ACP-5862 Exposures Across Various B-cell Malignancies, Including CLL and MCL

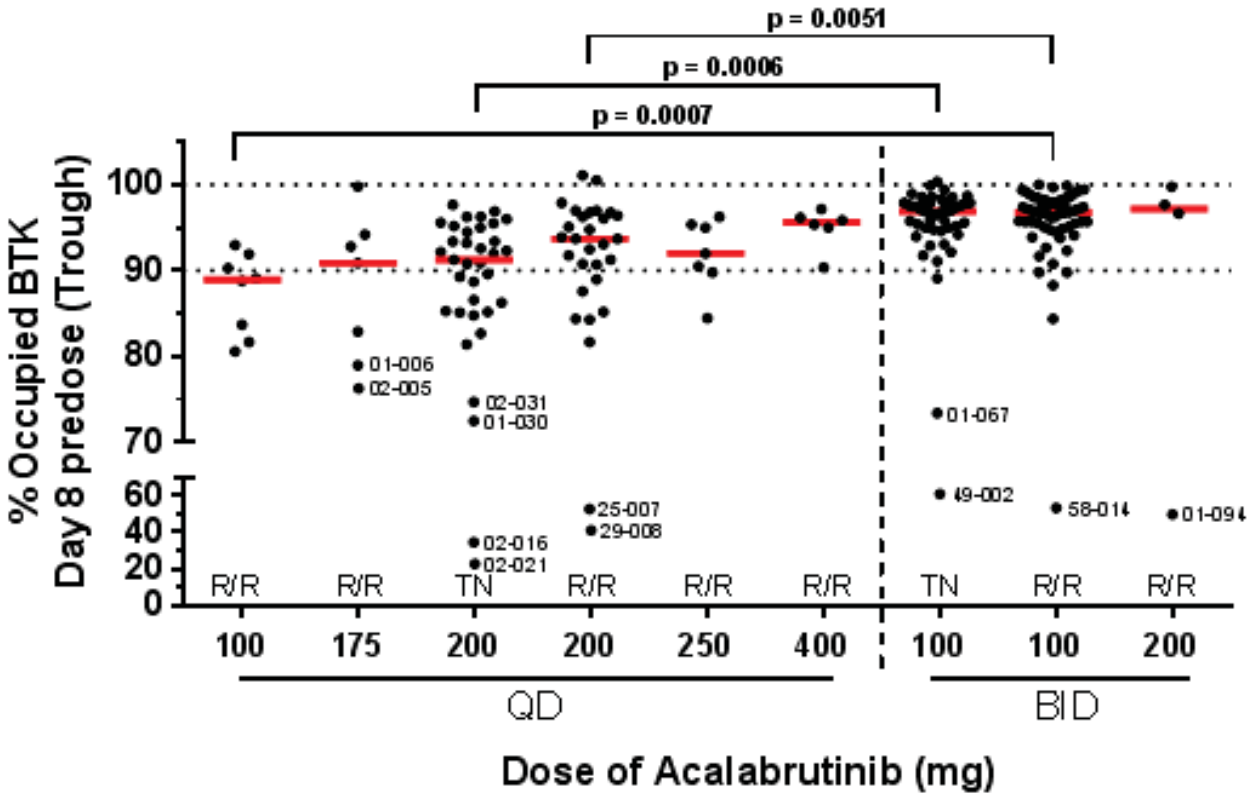


Notes: Boxplot of acalabrutinib exposures (top) and ACP-5862 exposures (bottom) versus indication. The black line within the box shows the median and the box's upper and lower edges show the IQR. Whiskers extend to the highest value that is within 1.5*IQR. Data outside whiskers are shown as circles.

Source: Module 5.3.5.3 from Population Pharmacokinetics Report (D8220C00009), Appendix 7, Figure 9.

Acalabrutinib 100 mg BID dose provided maximal BTK occupancy with least interpatient variability at trough for subjects with R/R and treatment-naive (TN) CLL (Study ACE-CL-001); 95% of subjects maintained >90% BTK occupancy at the trough timepoint (i.e., 12 hour post-dose; (Figure 2).

Figure 2 BTK Occupancy (%) in Subjects with R/R and Treatment-Naive (TN) CLL at Trough



Percent BTK occupancy at trough on Day 8

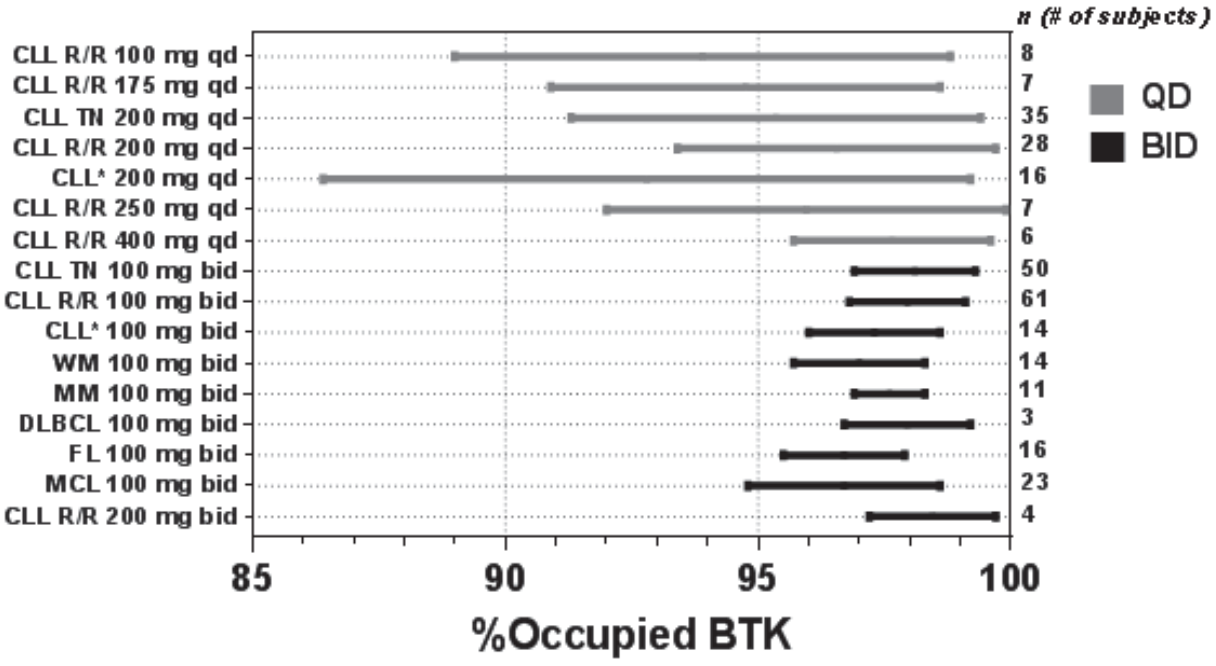
	100 mg QD R/R	175 mg QD R/R	200 mg QD TN	200 mg QD R/R	250 mg QD R/R	400 mg QD R/R	100 mg BID TN	100 mg BID R/R	200 mg BID R/R
Median	89.0	90.9	91.3	93.7	92.0	95.7	96.9	96.8	97.2
Mean	87.4	88.0	86.6	89.8	91.9	95.0	95.3	95.3	86.0
SD	4.7	8.7	15.7	12.9	4.1	2.4	6.3	6.2	24.2
CV%	5.4	9.9	18.1	14.4	4.5	2.5	6.6	6.5	28.1

	Percent BTK occupancy at trough on Day 8								
	100 mg QD R/R	175 mg QD R/R	200 mg QD TN	200 mg QD R/R	250 mg QD R/R	400 mg QD R/R	100 mg BID TN	100 mg BID R/R	200 mg BID R/R
n	8	7	35	29	7	6	51	62	4

BID=twice daily; BTK=Bruton tyrosine kinase; CLL=chronic lymphocytic leukemia; CV=coefficient of variation; n=number of subjects; QD=once daily; R/R=relapsed/refractory; SD=standard deviation; TN=treatment naïve. Horizontal lines depict median values; (unpaired, parametric, 2 tailed t-test used for statistical testing); values in red are p-values <0.05.
Source: Module 2.7.2 Summary of Clinical Pharmacology Studies, Section 3.4.2, Figure 36.

Additionally, the BTK occupancy with the 100-mg BID dose was consistently high (≥95%) across multiple B-cell malignancies, including CLL and MCL (Figure 3). Overall, the results support acalabrutinib dose of 100mg BID appropriate for use in CLL indications.

Figure 3 Median BTK Occupancy Range Over the Daily Dosing Interval at Steady-State across All Studies Investigating Acalabrutinib in Subjects with B-cell Malignancies



BID=twice daily; CLL=chronic lymphocytic leukemia; DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; MCL=mantle cell lymphoma; MM=multiple myeloma; QD=once daily; R/R=relapsed/refractory; TN=treatment naive; WM=Waldenström Macroglobulinemia.
Notes: Grey lines represent QD dosing; black lines BID dosing.
The y-axis shows the B-cell malignancy and acalabrutinib dose for each study cohort. Percent of occupied BTK is displayed on the x-axis; lines represent the range of BTK occupancy from trough level to peak level (4 hours

postdose) for each cohort, with the left cap representing the median occupancy at trough and right cap representing the median occupancy at peak.
Source: Module 2.7.2 Summary of Clinical Pharmacology Studies, Section 3.4.2, Figure 38.

The reports for population PK (D8220C00009), exposure versus efficacy (D8220C00010), and exposure versus safety (D8220C00011) analyses, including supporting programs and datasets, will be included in the submission package.

The key modeling changes, compared to previous submission for MCL indication, are described below in Table 7:

Table 7 Key Changes in Modeling Between Current (CLL) and Previous (MCL) Filing

Modeling Change	CLL	MCL
Population PK	• Plasma concentrations of acalabrutinib and ACP-5862, and relevant covariate data from 13 clinical trials, including data from 182 healthy subjects and 569 subjects with B-cell malignancies, were analyzed • A simultaneous population model characterizing the PK of acalabrutinib and ACP-5862 was developed • To adequately characterize the absorption profile, a mixture model on relative bioavailability (F1) with the mixture defined for each dosing occasion, and between occasion variability on duration of zero-order input (D1) was implemented • Covariates in the final model included health group (healthy versus patient), acid reducing agents (proton pump inhibitors), ECOG (eastern cooperative oncology group) status and body weight	• Plasma concentrations of acalabrutinib and relevant covariate data from 12 clinical trials were analyzed, including data from 285 healthy subjects and 292 subjects with B-cell malignancies • Only acalabrutinib PK was characterized • Acalabrutinib absorption was characterized using lag time and D1 • Covariates in the final model included health group (healthy versus patient), dose, eGFR, acid reducing agents, sex, race, hepatic impairment and body weight
Exposure-Efficacy Analyses	• Data from a total of 274 subjects with previously untreated CLL in Study ACE-CL-007 were included • Acalabrutinib and ACP-5862 steady state AUC was used as the exposure metric. To account for contribution of the major active metabolite, ACP-5862, to overall activity acalabrutinib and ACP-5862 molar exposures were adjusted with respective BTK potency and protein binding, and expressed as 'total active AUC' (exposure metric for the total active moiety),	• Data from Study ACE-LY-004 in patients with MCL (n=45) were included • Acalabrutinib steady state AUC and C_{max} used as exposure metric

Modeling Change	CLL	MCL
Exposure-Safety Analyses	• Pooled data from 8 clinical studies, involving a total of 567 subjects with B-cell malignancies were included • Acalabrutinib, ACP-5862, and total active steady state AUC used as exposure metric	• Pooled data from 6 clinical studies including a total of 292 subjects with B-cell malignancies were included • Acalabrutinib steady state AUC and C_{max} used as exposure metric

The Applicant's Position:
The clinical pharmacology and PK data submitted in the original NDA supports a fixed 100 mg BID acalabrutinib dose for the treatment of adult patients with CLL. Results from additional bioanalytical and PopPK data remain consistent with the data provided in the original NDA.

Regulatory Authorities Assessment:
Regulatory authorities agree with Applicant's Position. The Applicant's updated PopPK analysis (Population Pharmacokinetics Report D8220C00009) resulted in different PK parameter estimates as compared to the numbers reported in the original NDA. The PK parameters of acalabrutinib and its active metabolite (ACP-5862) in Section 12.3 Pharmacokinetics of USPI were further updated based on post-hoc PK estimates from the updated PopPK analysis. Refer to 19.4 OCP Appendices (Technical documents supporting OCP recommendations) for details.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:
Yes. The evidence of effectiveness of acalabrutinib was demonstrated in the original NDA 210259 approved on 31 October 2017.

The Applicant's Position:
The results from ASCEND are consistent with previously observed efficacy results.

Regulatory Authorities Assessment:
Regulatory authorities agree with Applicant's Position. Refer to Section 8 Statistical and Clinical Evaluation of this Assessment Aid for detailed efficacy results from Study ASCEND.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:
Yes. The safety profile of the proposed dosing regimen is appropriate. Reference is made to original acalabrutinib NDA 210259 submitted on 13 June 2017 and approved on 31 October 2017. Dose selection was based on results of the phase 2 dose-finding study (ACE-CL-001), which evaluated acalabrutinib dosing regimens of 100 to 400 mg QD and 100 to 200 mg BID in patients with CLL. High response rates were observed across all doses; however, based on BTK occupancy, 100 mg BID resulted in maximal BTK occupancy with the least inter-

patient variability at steady-state trough.

The Applicant's Position:
The dosing regimen remains suitable for the proposed patient population in CLL.

Regulatory Authorities Assessment:
Regulatory authorities agree with Applicant's Position. The Applicant's proposed acalabrutinib doing regimen of 100 mg BID in patients with CLL/SLL was additionally supported by the comparable acalabrutinib exposure as in patients with MCL and generally flat exposure-response relationships for both efficacy endpoints (progression-free survival [PFS], best overall response [BOR] and lesion size), and safety measurements (any Grade ≥3 TEAEs, any Grade ≥2 TEAEs of clinically special interest, including anemia, cardiac event, hypertension, infection, neutropenia, and thrombocytopenia) at acalabrutinib 100 mg BID monotherapy or in combination with obinutuzumab in patients with CLL. Refer to Section 8 Statistical and Clinical Evaluation of this Assessment Aid for detailed safety results from Study ASCEND.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Data:

Age, Race, and Body Weight

Age (42 to 90 years), sex, race (Caucasian, African American), and body weight did not have clinically meaningful effects on the PK of acalabrutinib and its active metabolite, ACP-5862, based on population PK analysis.

Renal Impairment

Acalabrutinib undergoes minimal renal elimination. Based on population PK analysis, no clinically relevant PK difference was observed in 543 patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥ 30 mL/min/1.73m^2, as estimated by modification of diet in renal disease (MDRD) equation. Acalabrutinib PK has not been evaluated in patients with severe renal impairment (eGFR < 29 mL/min/1.73m^2, MDRD) or renal impairment requiring dialysis.

Hepatic Impairment

Acalabrutinib is metabolized in the liver. In hepatic impairment studies, compared to subjects with normal liver function (n=6), acalabrutinib exposure (AUC) was increased by 1.9-fold, 1.5-fold, and 5.3-fold in subjects with mild (n=6) (Child-Pugh A), moderate (n=6) (Child-Pugh B) and severe (n=8) (Child-Pugh C) hepatic impairment, respectively. Based on a population PK analysis, no clinically relevant PK difference was observed in subjects with mild (n=79) or moderate (n=6) hepatic impairment (total bilirubin between 1.5 to 3 times the upper limit of normal [ULN] and any AST) relative to subjects with normal (n=651) hepatic function (total bilirubin and AST within ULN).

The Applicant's Position:
There are no dose modifications recommended for patients with mild or moderate hepatic impairment (Child-Pugh class A or Child-Pugh class B); however it is not recommended to administer acalabrutinib in patients with severe hepatic impairment (Child Pugh class C).

Regulatory Authorities Assessment:
Regulatory authorities agree with Applicant's Position. The labeling has been updated to reflect "avoid use" in patients with severe hepatic impairment. The FDA recommends no dose adjustments for patients with mild or moderate hepatic impairement (NCI or Child-Pugh class). The Applicant's updated population PK model supports no need for dose adjustment based on patients' age (32 to 90 years), sex, weight (40 to 149 kg), race (Caucasian, African American), mild to moderate renal impairment (eGFR ≥ 30 mL/min/1.73m^2, as estimated by MDRD), and mild to moderate hepatic impairment (total bilirubin less and equal to upper limit of normal [ULN] and AST greater than ULN, or total bilirubin greater than ULN and any AST) relative to patients with normal hepatic function (total bilirubin and AST within ULN), which is consistent with the original labeling recommendation.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:
No new drug-drug interaction or food effect was observed with acalabrutinib. Acalabrutinib can be taken with or without food as stated in the original NDA 210259.

The Applicant's Position:
No new information regarding food-drug or drug-drug interactions have been identified in this sNDA submission. The currently labelled food-drug or drug-drug interactions remain applicable.

Regulatory Authorities Assessment:
The applicant submitted various in vitro metabolism and transporter DDI reports to support the following labeling updates:

- Acalabrutinib
  - **Metabolism:** not an inhibitor of UGT1A1 or UGT2B7
  - **Transporter:** substrate of BCRP, not an inhibitor of MATE2-K or MATE1
- ACP-5862
  - **Metabolism:** not an inhibitor of UGT1A1 or UGT2B7
  - **Transporter:** substrate of P-gp and BCRP, not a substrate of OATP1B1 or OATP1B3, not an inhibitor of P-gp, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE2-K, BCRP, and may be a MATE1 inhibitor (clinical relevance not likely since only 0.5% of ACP-5862 is excreted renally)

Regulatory authorities agree with the labeling updates based on the submitted in vitro metabolism and transporter DDI reports.

X
Clinical Pharmacology Reviewer

X
Clinical PharmacologyTeam Leader

X
Pharmacometrics Reviewer

X
Pharmacometrics Team Leader

7 Sources of Clinical Data

The Applicant's Position:

Data are submitted for a total of 11 clinical studies. Five of these studies evaluated acalabrutinib in patients with CLL, 5 studies evaluated acalabrutinib in patients with other hematologic malignancies, and 1 study evaluated acalabrutinib in volunteers with severe hepatic impairment. Details of the studies that support efficacy and safety for the pivotal study ASCEND are provided in Table 8 below.

7.1. Table of Clinical Studies

The Applicant's Description:

Table 8 Listing of Clinical Trials Relevant to this NDA (Module 5.2)

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
ASCEND (ACE-CL-309)	NCT 02970318	Phase 3, randomized, OL	Arm A: Acalabrutinib 100 mg BID, starting on Cycle 1 Day 1 Administered orally in 28-day cycles until disease progression or unacceptable drug-related toxicity Arm B: Idelalisib 150 mg orally BID until disease progression or unacceptable toxicity + rituximab 375 mg/m^2 IV (Day 1 of Cycle 1), 500 mg/m^2 every 2 wks for 4 doses and then every 4 wks for 3 doses for a total of 8 infusions. or Bendamustine 70mg/m^2 IV, Day 1 and 2 of each cycle for up to 6 cycles. + rituximab 375 mg/m^2 IV (Day 1 of Cycle 1) and 500 mg/m^2 (Day 1 of Cycle 2-6).	PFS, response, safety	Until PD or unacceptable toxicity	310	R/R CLL	102 centers in 25 countries
Studies to Support Safety								
15-H-0016	NCT 02337829	Phase 2 OL, randomized	Acalabrutinib 200 mg QD or 100 mg BID Administered orally in 28-day cycles until disease progression or unacceptable drug-related toxicity	Response, safety, PD	Until PD or unacceptable toxicity	48	CLL/SLL	1 center in 1 country

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
ACE-CL-001	NCT 02029443	Phase 1 (escalation): OL, sequential group, dose escalation Phase 2 (expansion): OL	Phase 1: Acalabrutinib 100 to 400 mg QD; 100 or 200 mg BID Phase 2: Acalabrutinib 200 mg QD or 100 mg BID Administered orally in 28-day cycles until disease progression or unacceptable drug-related toxicity	MTD, response, safety, PK, PD	Until PD or unacceptable toxicity	306	CLL/SLL, RS, PLL	12 centers in 3 countries
ACE-CL-003	NCT 02296918	Phase 1, OL	Cohort 1 and 2: Acalabrutinib 100 mg BID orally + obinutuzumab IV 100 mg (Day 1 of Cycle 2), 900 mg (Day 2 of Cycle 2), and 1000mg (Day 8 and 15 of Cycle 2, Day 1 of Cycles 3-7). For subjects treated at dose level -1, obinutuzumab IV 100 mg (Day 1 of Cycle 2), 650 mg (Day 2 of Cycle 2), and 750mg (Day 8 and 15 of Cycle 2, Day 1 of Cycles 3-7) Cohort 3: Acalabrutinib 100 mg BID orally + rituximab 375 mg/m^2 IV (Day 1, 8, 15, 22 of Cycle 2 and Day 1 of Cycles 3-7) + venetoclax orally 400mg/day following a weekly dose ramp-up (Cycle 3), 400mg/day until end of Cycle 15 Cohort 4: Acalabrutinib 100 mg BID orally + rituximab 375 mg/m^2 IV (Day 1, 2, 8, 15 of Cycle 2 and Day 1 of Cycles 3-7) + venetoclax orally 400 mg/day following a weekly dose ramp-up	Response, safety, PK, PD	Until PD or unacceptable toxicity	70	CLL/SLL/PLL	1 center in 1 country

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
			(Cycle 3), 400mg/day until end of Cycle 15 Treatment administered in 28-day cycles until disease progression or unacceptable drug related toxicity					
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacology studies)								
ACE-HI-102	NCT 03968848	Phase I, OL, single dose	Single, oral, 50-mg dose of acalabrutinib	PK (intrinsic factor), safety	7-27 days	16	Severe hepatic impairment	3 centers in 1 country

OL, open-label

The Applicant's Position:

The primary study supporting the evaluation of efficacy in this sNDA is ASCEND (ACE-CL-309), which compared acalabrutinib 100 mg BID to idelalisib+rituximab (IR) or bendamustine+ rituximab (BR). A detailed description of the results is provided in the sections below.

Regulatory Authorities Assessment:

ASCEND is the primary study supporting both efficacy and safety, with a cut-off date of 15 Jan 2019. Cut-off dates for supportive studies are provided in Section 8.2.2. However, the Applicant's table of clinical studies is missing two key supportive safety studies, which are summarized in Table 9: ELEVATE-TN (ACE-CL-007), the pivotal randomized trial in treatment-naïve CLL and the basis for NDA210259 S-007, and ACE-LY-004, the pivotal single-arm trial in relapsed or refractory MCL.

Table 9 Additional Clinical Trials Relevant to this NDA

Trial Identity	Design	Regimen	Study Endpoints	No. of patients enrolled	No. of Sites
Controlled trials supporting safety					
ELEVATE-TN (ACE-CL-007) NCT02475681	Phase 3, randomized, open-label trial in previously untreated CLL	Arm A, Obinutuzumab + chlorambucil for 6 cycles. Arm B, Acalabrutinib + Obinutuzumab: Acalabrutinib 100 mg Q12H until disease progression or unacceptable toxicity, with up to 6 cycles of obinutuzumab. Arm C, Acalabrutinib monotherapy: 100 mg Q12H until disease progression or unacceptable toxicity.	PFS, response, safety	535: Arm A : 177 Arm B: 179 Arm C: 179	142 sites, 18 countries
Other trials supporting safety					
ACE-LY-004 NCT02213926	Phase 2, single-arm trial in MCL after 1-5 prior therapies	Acalabrutinib monotherapy 100 mg Q12H until disease progression or unacceptable toxicity.	ORR	124	40 sites, 9 countries

Source: FDA

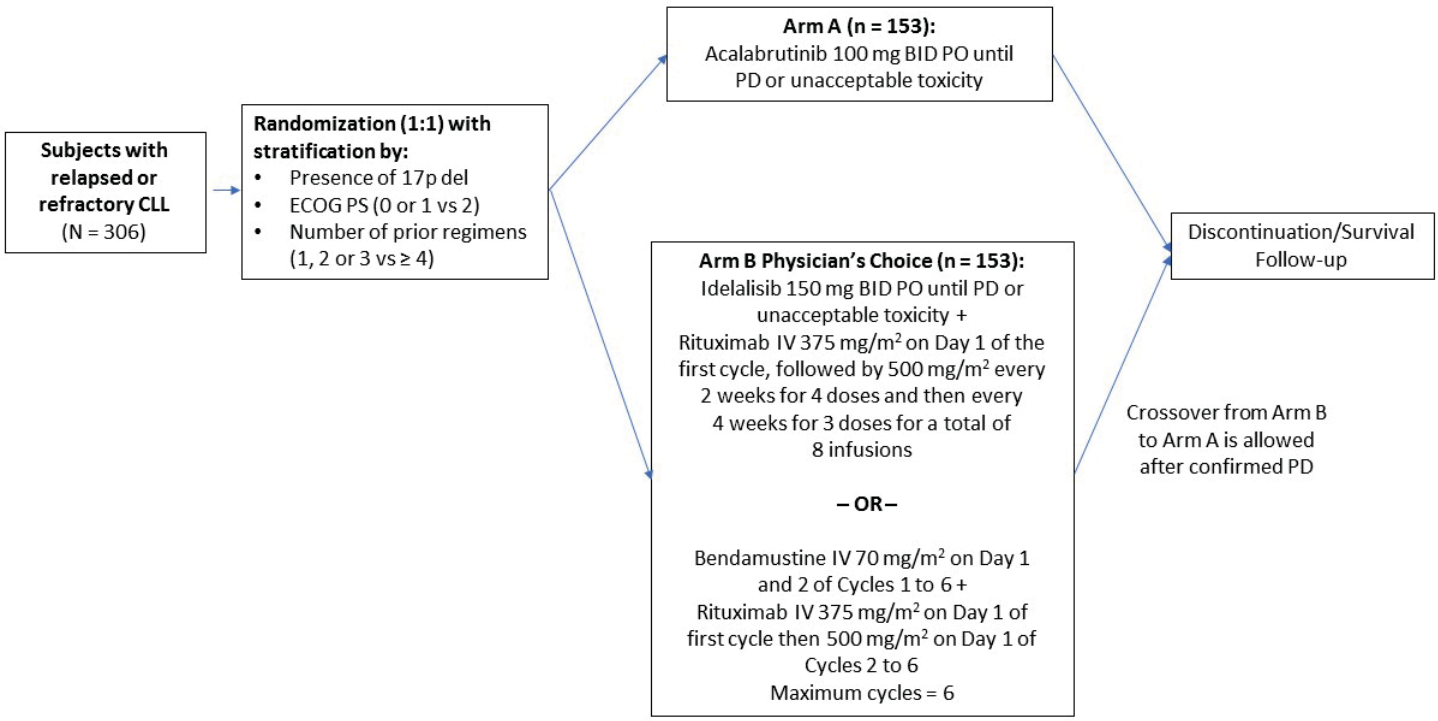
8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. ASCEND (ACE-CL-309)

The Applicant's Description:

Figure 4 Trial Design of ASCEND (ACE-CL-309)



BID=twice per day; CLL=chronic lymphocytic leukemia; ECOG PS=Eastern Cooperative Oncology Group performance status; IV=intravenous; PD=progressive disease; PO=oral.
n=planned sample size per each treatment arm.
Source: ASCEND Clinical report, Figure 1.

ASCEND is an ongoing Phase 3, open-label, randomized, multicenter study designed to evaluate the efficacy and safety of acalabrutinib monotherapy versus IR or BR in subjects with R/R CLL.

Subjects were randomized in a 1:1 ratio into 2 arms: subjects randomized to Arm A received acalabrutinib monotherapy; subjects randomized to Arm B received investigator's choice of either IR or BR. Randomization was based on the following stratification factors: presence of 17p deletion, Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 versus 2), and number of prior therapies (1, 2 or 3 versus ≥4).

Each treatment cycle was 28 days (4 weeks). Subjects in Arm A received acalabrutinib orally starting Cycle 1 Day 1 until unacceptable drug-related toxicity or disease progression. Subjects in Arm B who received the IR regimen received idelalisib orally starting Cycle 1 Day 1 until disease progression or unacceptable toxicity, and rituximab on Day 1 of the first cycle, then every 2 weeks for 4 doses and then every 4 weeks for 3 doses for a total of 8 infusions. Subjects in Arm B who received the BR regimen received bendamustine as an IV infusion on Days 1 and 2 of each 28-day cycle, for a maximum of 6 cycles, and rituximab on Day 1 of Cycles 1 to 6.

After progression, subjects were followed for survival status, subsequent anticancer therapy, and additional malignancy occurrence approximately every 12 weeks until death, withdrawal by subject, loss to follow-up, or study closure.

Key Inclusion Criteria:

Key inclusion criteria as specified in ASCEND Protocol Amendment 5.0 (Global) are as follows:

- Men and women ≥18 years of age with an ECOG performance status of 0 to 2 and who had a documented CD20-positive CLL. Must have received ≥1 prior systemic therapy for CLL.
- Diagnosis of CLL that met published diagnostic criteria (Hallek et al. 2008): monoclonal B-cells (either kappa or lambda light chain restricted) that are clonally co-expressing ≥1 B-cell marker (CD19, CD20, or CD23) and CD5; prolymphocytes may comprise ≤55% of blood lymphocytes; and presence of $\geq 5x10^9$ B lymphocytes/L (5000/µL) in the peripheral blood (at any point since initial diagnosis).
- Active disease that met ≥1 of the following IWCLL 2008 criteria for requiring treatment: evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia (hemoglobin <10 g/dL) and/or thrombocytopenia (platelets <100,000/µL); massive (i.e., ≥6 cm below the left costal margin), progressive, or symptomatic splenomegaly; massive nodes (i.e., ≥10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy; progressive lymphocytosis with an increase of >50% over a 2-month period or a lymphocyte doubling time (LDT) of <6 months. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (e.g., infections) should be excluded; autoimmune anemia and/or thrombocytopenia that is poorly responsive to standard therapy; or constitutional symptoms documented in the subject's chart with supportive objective measures, as appropriate, defined as ≥1 of the following disease-related symptoms or signs: unintentional weight loss ≥10% within the previous 6 months before screening, significant fatigue (ECOG performance score 2; inability to work or perform usual activities), fevers higher than 100.5°F or 38.0°C for ≥2 weeks before screening without evidence of infection, or night sweats for >1 month before screening without evidence of infection.
- Met the following laboratory parameters:
    - ANC $\geq 0.75x10^9$/L (750 cells/µL), or $\geq 0.50x10^9$/L (500 cells/µL) in subjects with documented bone marrow involvement, and independent of growth factor support 7 days before assessment.

- Platelet count ≥50x10^9/L (50,000 cells/µL), or ≥30x10^9/L (30,000 cells/µL) in subjects with documented bone marrow involvement, and without transfusion support 7 days before assessment. Subjects with transfusion dependent thrombocytopenia are excluded. If an investigator has chosen BR as the Arm B treatment, platelets must be ≥75x10^9/L (75,000 cells/µL).
- Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.0xULN.
- Total bilirubin ≤1.5xULN.
- Estimated creatinine clearance of ≥30 mL/min, calculated using the formula of Cockcroft and Gault [(140 Age) • Mass (kg)/(72 • creatinine mg/dL); multiply by 0.85 if female].

Key Exclusion Criteria:

Key exclusion criteria as specified in ASCEND Protocol Amendment 5.0 (Global) are as follows:

- Known central nervous system (CNS) lymphoma or leukemia.
- Known prolymphocytic leukemia or history of or currently suspected Richter's syndrome.
- Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura.
- Prior exposure to a B-cell lymphoma (BCL)-2 inhibitor (e.g., venetoclax/ABT-199) or a B-cell receptor (BCR) inhibitor (e.g., BTK inhibitors or PI3K inhibitors). Received any chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days before first dose of study drug.
- History of prior malignancy except for the following:
  - Malignancy treated with curative intent and with no evidence of active disease present for more than 2 years before screening and felt to be at low risk for recurrence by treating physician.
  - Adequately treated lentigo maligna melanoma without current evidence of disease or adequately controlled nonmelanomatous skin cancer.
  - Adequately treated carcinoma in situ without current evidence of disease.
- Prothrombin time/International Normalized Ratio (INR) or activated partial thromboplastin time (aPTT) (in the absence of a Lupus anticoagulant) > 2.0 x ULN.
- History of confirmed progressive multifocal leukoencephalopathy (PML), HIV, active cytomegalovirus (CMV) infection (active viremia as evidenced by positive polymerase chain reaction [PCR] result for CMV DNA), active hepatitis B or C infection, malabsorption syndrome, significant cardiovascular disease
- Requires treatment with a strong CYP3A inhibitor/inducer, proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole), or corticosteroid use >20 mg daily prednisone equivalent within 1 week before first dose of study drug except as indicated for other medical conditions.

Regulatory Authorities Assessment:

Regulatory authorities agree with the Applicant's description of the ASCEND study design. The

intended dosage for acalabrutinib is more accurately described as 100 mg approximately every 12 hours, rather than twice daily or BID.

As described under Patient Disposition, 155 patients were randomized to each arm. In the investigator's choice arm, idelalisib+rituximab was the predominant regimen (76% of the control arm; 119 randomized patients), whereas few patients had BR planned (24% of the control arm; 36 randomized patients).

Study Endpoints

The Applicant's Description:

The primary efficacy endpoint of the study is PFS (defined as the time from randomization until disease progression or death from any cause) as assessed by the IRC per IWCLL 2008 criteria.

Secondary efficacy endpoints include the following:

- INV-assessed PFS per IWCLL 2008 criteria.
- INV-assessed ORR (defined as the proportion of patients who achieve a best response of complete remission [CR], complete remission with incomplete bone marrow recovery [CRi], nodular partial remission [nPR], or partial remission [PR]) per IWCLL 2008 criteria.
- IRC-assessed ORR per IWCLL 2008 criteria.
- OS (defined as the time from randomization to the date of death due to any cause).
- PROs as measured by change in scores from baseline to each assessment in the FACIT-Fatigue.
- INV- and IRC-assessed DOR (defined as the time from the first documentation of objective response to the earlier time of disease progression [assessed by the IRC per IWCLL 2008 criteria] or death from any cause).
- TTNT (defined as the time from randomization to institution of non protocol-specified treatment for CLL. For crossover patients, TTNT should be defined as time from initial treatment of acalabrutinib to institution of nonprotocol-specified treatment for CLL).

Statistical Analysis Plan and Amendments

The Applicant's Description:

The statistical analysis plan was discussed with FDA and finalized before the conduct of the pre-specified interim analysis of the ASCEND study, at which time the the Applicant was unblinded to treatment randomization assignment at the aggregate level.

The primary efficacy analysis was based on assessment from an Independent Review Committee (IRC). The IRC reviewed radiologic evaluations assessed by independent central radiologists. Assessment of response and progression was conducted in accordance with the IWCLL 2008 criteria for CLL (Hallek et al. 2008), with the modification that treatment-related lymphocytosis in the absence of other signs or symptoms of disease progression was not considered progressive disease (PD) (Cheson et al. 2012). The investigator evaluated sites of

disease by radiologic imaging (primary), physical examination or other procedures as necessary, review of hematology and serum chemistry results, and disease-related symptoms. The same methods of assessment used to assess disease at baseline were to be used throughout the study. Confirmation of CR required bone marrow analysis and radiologic tumor assessment. A central laboratory performed all hematology testing for the primary endpoint analysis. Baseline tumor assessments were performed at screening, and response evaluations were done every 12 weeks (±14 days) through Cycle 25, and then every 24 weeks (±14 days) thereafter.

Analysis Populations

The ITT population was defined as all randomized subjects, to be analyzed according to the arm to which they were randomly assigned, following "intent-to-treat" principle.

All efficacy analyses except OS were performed for the ITT population during the main study period. OS was analyzed based on the ITT population during the whole study period—that is, main study period + crossover period. In addition, the ITT population was used to summarize disposition, demographics, and baseline disease characteristics.

Power and Sample Size

The study was expected to enroll approximately 306 subjects with a 1:1 randomization ratio between Arm A and B. With an event-driven design, the final analysis of PFS was planned when a total of 119 IRC-assessed PFS events had been observed. The interim analysis of PFS was to be conducted when approximately two-thirds of the IRC-assessed PFS events for the final analysis (i.e., 79 events) had been observed. Under the model assumption of a median PFS of 31 months for subjects in Arm A versus 17 months for subjects in Arm B, the study was sized to achieve approximately 90% power to detect a hazard ratio (HR) (Arm A/Arm B) of 0.55 for PFS, which translates into 82% relative and a 14-month absolute increase in median PFS time at the 1-sided significance level of 0.025. Given the study assumptions, the minimum detectable treatment difference of PFS at the final analysis corresponds to a HR of approximately 0.69.

Analysis Methods

All efficacy analyses were performed at the 2-sided significance level.

The following 3 randomization stratification factors (collected via interactive voice/web response system [IXRS]) were used for the stratified analyses: presence of 17p deletion (yes versus no), ECOG status (2 versus ≤1), and number of prior therapies (1–3 versus ≥4). For the primary efficacy analysis of IRC-assessed PFS, if there was at least one stratum that had fewer than 2 events (where a stratum was defined as stratification factor 1 * stratification factor 2 * stratification factor 3), stratification factors were to be collapsed until all strata had at minimum 2 events for the primary endpoint. The stratification factors were to be collapsed in the following order:

1. ECOG performance status (2 versus ≤1)
2. Presence of 17p deletion (yes versus no)

Based on the data as of data cutoff date (15 January 2019), ECOG status was collapsed according to the pre-specified rule. Thus, only the number of prior therapies (1-3 versus ≥4) and presence of 17p deletion were used as stratification factors in the stratified analysis. The same stratification factors were applied for all stratified analyses.

The primary efficacy analysis was to compare PFS as assessed by IRC between Arms A and B in the ITT population using a stratified log-rank test adjusting for randomization stratification factors. The estimate of the HR (Arm B/Arm A) and the corresponding 95% CI was computed using a Cox proportional hazards model stratified by randomization stratification factors. Kaplan-Meier (KM) curve was used to estimate the distribution of PFS. PFS rate based on KM point estimate and the corresponding 95% CI were calculated at selected timepoints for each treatment arm. Sensitivity analyses in support of the primary analysis of PFS included unstratified analysis, analysis including PFS without censoring for subsequent anticancer therapy, analysis including PFS events after 2 or more consecutively missed visits, and the exclusion of subjects with important protocol deviations from the analysis. Selected subgroup analyses were also performed.

Sensitivity Analyses

The following sensitivity analyses were planned for IRC-assessed PFS in support of the primary analysis: unstratified analysis, PFS analyzed as the time from date of randomization to the date of first IRC-assessed disease progression or death due to any cause, whichever comes first, regardless of the use of subsequent anticancer therapy, IRC-assessed PD or death after 2 or more consecutively missed visits included as a PFS event, and excluding subjects with important protocol deviations from the analysis.

Subgroup Analysis

Subgroup analyses were performed using potential prognostic variables at screening or baseline listed below to investigate the consistency and robustness of the primary analysis: presence of 17p deletion (yes versus no); ECOG status (0, 1 versus 2); number of prior therapies (1-3 versus ≥4); age group (<65 versus ≥65); age group (<75 versus ≥75); sex (male versus female) ; race (white versus non-white); geographic region (North America versus Australia, New Zealand versus Western Europe versus Central and Eastern Europe versus Asia); Rai stage at screening (Stage 0-II versus III-IV); bulky disease (<5 cm versus ≥5 cm); β2-microglobulin at baseline (≤3.5 mg/L versus >3.5 mg/L); presence of 11q deletion (yes versus no); TP53 mutation (yes versus no); 17p deletion and TP53 mutation (yes versus no); 17p deletion or TP53 mutation (yes versus no); immunoglobulin heavy-chain variable (IGHV) (mutated versus unmutated); 17p deletion, TP53 mutation, or 11q deletion (yes versus no); and 17p deletion, TP53 mutation, 11q deletion, or unmutated IGHV (yes versus no).

The subgroup analyses for the stratification factors (presence of 17p deletion, ECOG performance status, and number of prior therapies) were based on the values entered into the IXRS; all other factors were based on values recorded on the eCRF.

The HR (Arm A versus Arm B) with the corresponding 2-sided 95% CI was calculated based on an unstratified Cox regression model for each subgroup. The HRs and the corresponding 2-sided 95% CIs were displayed for all subgroups graphically in a forest plot.

ORR was summarized by number and percentage of subjects, and the corresponding 95% CI was calculated based on normal approximation (using Wilson's score). ORR was analyzed using the Cochran-Mantel-Haenszel (CMH) test adjusting for randomization stratification factors. The concordance between investigator-assessed and IRC-assessed best overall response was summarized by treatment arm. OS, investigator-assessed PFS, IRC- and investigator-assessed DOR, and TTNT were analyzed in the same fashion as that for primary efficacy endpoint described above. A sensitivity analysis for OS was conducted in which Arm B subjects who crossed over to receive acalabrutinib were censored at the day prior to first dose of acalabrutinib.

For the PROs, time to first improvement (TTFI) for the FACIT-Fatigue scale was defined as the duration of time from the date of randomization to the date of the first improvement in PRO scores of at least 1 threshold unit. The primary analysis for the FACIT-Fatigue scale was the change from baseline at Week 48 (corresponding to Cycle 13). Kaplan-Meier curves were used to estimate the distribution of TTFI. The 50th percentile of Kaplan-Meier estimates were used to estimate the median duration of TTFI. A two-sided 95% CI is provided for these estimates. Median TTFI was compared using stratified log rank test adjusting for randomization stratification factors. An unstratified log rank test was also conducted as a sensitivity analysis.

Multiplicity Adjustments

To control the overall Type I error at 0.05 level, the Lan-DeMets alpha-spending function based on the O'Brien-Fleming boundary was used to split α into α1 and α2 for the interim and final analyses, respectively. The nominal α1 and α2 levels were determined based on the actual information fraction at the time of the interim analysis. If the primary endpoint achieved statistical significance, tests of key secondary endpoints of IRC-assessed ORR and OS were to be performed in a sequential hierarchical manner based on a closed testing procedure specified below:

1. IRC-assessed ORR
2. OS

If the primary endpoint of IRC-assessed PFS achieved statistical significance at the interim analysis, the IRC-assessed ORR was to be tested at an α level of 0.05, given that almost all responses would have been observed at that time (thus the interim and final analyses of IRC-assessed ORR would be the same).

If the IRC-assessed ORR achieved statistical significance, the OS was to be tested at the same α level spent for the primary endpoint of IRC-assessed PFS at interim and final analyses, respectively.

Table 10 SAP Amendments Summary

Version/Date	Summary of Major Changes and Rationale
Version 1.0, 23 March 2018	Original SAP
Version 2.0, 23 January 2019	1. Added a table for planned PFS analyses, the efficacy stopping boundary, and the estimated timing of these analyses – Section 2.4 2. Clarified the hierarchical testing procedure for the key secondary endpoints – Section 2.6 3. Removed crossover population – Section 3.3 4. Clarified the definition of treatment-emergent period and treatment emergent adverse events – Section 4.1.6, Section 8.1.1 5. Added the rule for collapsing stratification factors – Section 7 6. Clarified the censoring rule for primary analysis for IRC-assessed PFS – Section 7.1.1 7. Updated the planned sensitivity and subgroup analyses for primary efficacy endpoint – Section 7.1.3, Section 7.1.4 8. Updated the censoring rule for the primary and sensitivityanalysis for overall survival – Section 7.2
Version 3.0, 6 March 2019	1. Updated the censoring rule for primary analysis andsensitivity analysis for IRC-assessed PFS – Section 7.1.1, Section 7.1.3 2. Added the operational definition of the last adequate IRC assessment – Section 7.1.1

Regulatory Authorities Assessment:

Regulatory authorities agree with the Applicant's proposed sample size and power calculation based on the IRC-assessed PFS, the analysis population, and statistical analysis methods for the efficacy endpoints. The proposed approach using the Lan and DeMets alpha-spending function with O'Brien-Fleming boundaries is appropriate for calculating the efficacy stopping boundaries at interim and final analysis for IRC-assessed PFS. The table below describes in detail the timing and efficacy stopping boundary at each of the planned analyses.

Table 11 Summary of Planned PFS Analyses

Analysis	NO. of IRC-assessed PFS events	Information Fraction	Efficacy Stopping Boundary	Estimated Timing
Interim	79	66%	$P < 0.012$ or observed HR < 0.57	19 Months
Final	119	100%	$P < 0.046$ or observed HR < 0.69	27 Months

FDA also agrees with applicant's proposed hierarchical testing procedure to adjust for multiplicity of testing secondary endpoints in the order of:

1. IRC-assessed ORR

2. OS

However, the Applicant did not provide sufficient information on OS (e.g. number of OS events, desired power, assumed true difference in OS between the treatment arms, number of planned analyses, timing of these analyses, etc.). Further, the Applicant proposed to use the same efficacy stopping boundary of the IRC-assessed PFS for the OS analysis at the interim and final. Although it is acceptable, this method is not often practiced because the information fraction of PFS and OS is different at the analysis time. An efficacy stopping boundary based on the actual information fraction of OS events at interim would be recommended. Lastly, even though the SAP stated that a statistically significant interim finding for IRC-assessed PFS would be followed by an IRC-assessed ORR analysis using alpha of 0.05, the key secondary endpoints, including IRC-assessed ORR should have followed a closed-testing procedure, i.e. the same alpha level that was allocated for the IRC-assessed PFS interim analysis to control the overall type I error rate(e.g., H. M. James Hung et al, 2007).

Protocol Amendments

The Applicant's Description:
There were 6 global protocol amendments to the ASCEND study. Table 12 below summarizes relevant changes to the protocol. These changes have not significantly impacted the trial integrity or interpretation of the results.

Table 12 Protocol Amendments

Number (date of internal approval)	Reasons for Amendment
Amendment 1.0 (Global) (04 August 2016) Amendment made before the start of subject recruitment	• To allow continued access to study drug for subjects who are experiencing clinical benefit at the end of the study. • Revised exclusion criterion to clarify that subjects with controlled, asymptomatic atrial fibrillation during screening were allowed to enroll on study. • Text was added based on updated guidance from the ZYDELIG SmPC and RITUXAN prescribing information.
Amendment 2.0 (Global) (03 October 2016)	• Additional hematology assessments were added to align with updated guidance on monitoring requirements in subjects treated with idelalisib. • Text was revised to clarify requirements for PJP prophylaxis and CMV monitoring based on updated guidance from the ZYDELIG SmPC. • Added required reporting of SAEs considered related to study drug(s) or study procedures after the end of the *protocol*-defined AE reporting period.

Number (date of internal approval)	Reasons for Amendment
Amendment 2.1 (Global) (13 October 2016)	• Text was revised to clarify that subjects will be followed for both disease progression and death. • Clarified that CMV testing was to be performed only in subjects assigned to idelalisib treatment (later revised again via Protocol Amendment 5.0). • Text was revised to follow updated guidance from the ZYDELIG SmPC and US PI, including monitoring subjects for signs of infection and interrupting idelalisib if infection is suspected.
Amendment 3.0 (Global) (11 May 2017)	• Changes were made to align text with the updated Acalabrutinib Investigator Brochure (v 6.0). • Update was made to indicate the change in grading criteria from IWCLL to CTCAE. • Exclusion criteria were modified to exclude only subjects with active viremia (positive PCR result for CMV DNA). • Hematological AEs were to be graded using CTCAE instead of IWCLL criteria for the purpose of assessing severity in AE reporting. • Response criteria were updated per Cheson et al. 2012
Amendment 4.0 (Global) (29 June 2017)	• Monthly HBV testing was extended to align with the study visit schedule
Amendment 5.0 (Global) (17 November 2017)	• IRC verification of PD was no longer required for subjects to be eligible for crossover. • Changed test parameters to align with new measures implemented to manage infection risks. Required CMV testing prior to and periodically during the study. • Text revised based on new risks of opportunistic infections associated with bendamustine.

Regulatory Authorities Assessment:
Regulatory authorities agree with the Applicant's description of protocol amendments.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant's Description:

ASCEND was conducted in compliance with ICH Good Clinical Practice Regulations and ethical principles from the Declaration of Helsinki. The original protocol and protocol amendments were approved by an independent IRB/Ethics Committee associated with each study center. Signed Informed consent was obtained from all participants prior to enrolment in the study.

The Applicant's Position:
ASCEND was conducted in compliance with Good Clinical Practice Regulations.

Regulatory Authorities Assessment:
Full compliance with Good Clinical Practice Regulations cannot be confirmed. Regulatory

authorities agree that a statement indicating compliance with GCP was provided in the application.

Financial Disclosure

The Applicant's Description:

Financial disclosure information was collected from all investigators participating in the pivotal ASCEND study. Additional details are provided in Section 0 of this AA.

The Applicant's Position:

None of the disclosures submitted revealed a potential conflict of interest.

Regulatory Authorities Assessment:

Regulatory authorities agree that none of the disclosures submitted revealed a potential conflict of interest; however, financial disclosure information was missing for 8 subinvestigators.

Patient Disposition

The Applicant's Description:

A total of 310 subjects were enrolled and randomized in the study and 307 subjects were treated; 3 subjects (1 in the acalabrutinib arm and 2 in the IR/BR arm) withdrew consent before receiving any study treatment. As of the data cutoff date (15 January 2019), 30 (19.4%) subjects in the acalabrutinib arm and 111 (71.6%) subjects in the IR/BR arm had discontinued randomized study treatment. The primary reason for discontinuation of acalabrutinib was AEs (17 [11.0%] subjects). In the IR/BR arm, the primary reason for discontinuing idelalisib was AEs (58 [37.4%] subjects), and the primary reason for discontinuing bendamustine and rituximab was completed treatment (30 [19.4%] subjects and 123 [79.4%] subjects, respectively) (Table 13).

Table 13 Subject Disposition (ITT Population)

	No. (%) of Subjects			
	Arm A	Arm B		
	Acalabrutinib (N=155)	IR/BR Total (N=155)	IR (N=119)	BR (N=36)
Subjects randomized (Intent-to-Treat Population)	155 (100.0%)	155 (100.0%)	119 (100.0%)	36 (100.0%)
Treated with investigational product (Safety Population)	154 (99.4%)	153 (98.7%)	118 (99.2%)	35 (97.2%)
Randomized but not treated[a]	1 (0.6%)	2 (1.3%)	1 (0.8%)	1 (2.8%)
Acalabrutinib				
Subjects on study drug	124 (80.0%)	0	0	0
Subjects who discontinued study drug	30 (19.4%)	0	0	0
Primary reason for study drug discontinuation				
Adverse event	17 (11.0%)	0	0	0
Death	1 (0.6%)	0	0	0

	No. (%) of Subjects			
	Arm A	Arm B		
	Acalabrutinib (N=155)	IR/BR Total (N=155)	IR (N=119)	BR (N=36)
Investigator discretion	1 (0.6%)	0	0	0
Progressive disease	10 (6.5%)	0	0	0
Other[b]	1 (0.6%)	0	0	0
Idelalisib				
Subjects on study drug	0	42 (27.1%)	42 (35.3%)	0
Subjects who discontinued study drug	0	76 (49.0%)	76 (63.9%)	0
Primary reason for study drug discontinuation				
Adverse event	0	58 (37.4%)	58 (48.7%)	0
Investigator discretion	0	2 (1.3%)	2 (1.7%)	0
Progressive disease	0	11 (7.1%)	11 (9.2%)	0
Withdrawal of consent	0	1 (0.6%)	1 (0.8%)	0
Other[c]	0	4 (2.6%)	4 (3.4%)	0
Bendamustine				
Subjects on study drug	0	0	0	0
Subjects who discontinued study drug	0	35 (22.6%)	0	35 (97.2%)
Primary reason for study drug discontinuation				
Adverse event	0	4 (2.6%)	0	4 (11.1%)
Completed treatment	0	30 (19.4%)	0	30 (83.3%)
Progressive disease	0	1 (0.6%)	0	1 (2.8%)
Rituximab				
Subjects on study drug	0	0	0	0
Subjects who discontinued study drug	0	153 (98.7%)	118 (99.2%)	35 (97.2%)
Primary reason for study drug discontinuation				
Adverse event	0	20 (12.9%)	14 (11.8%)	6 (16.7%)
Completed treatment	0	123 (79.4%)	95 (79.8%)	28 (77.8%)
Investigator discretion	0	3 (1.9%)	3 (2.5%)	0
Progressive disease	0	2 (1.3%)	1 (0.8%)	1 (2.8%)
Withdrawal of consent	0	1 (0.6%)	1 (0.8%)	0
Other[c]	0	4 (2.6%)	4 (3.4%)	0
Subjects who discontinued all study treatment[d]	30 (19.4%)	111 (71.6%)	76 (63.9%)	35 (97.2%)
Subjects who exited study[e]	18 (11.6%)	28 (18.1%)	21 (17.6%)	7 (19.4%)
Primary reason for study exit				
Death	15 (9.7%)	18 (11.6%)	13 (10.9%)	5 (13.9%)
Withdrawal of consent	3 (1.9%)	10 (6.5%)	8 (6.7%)	2 (5.6%)
Time on study (months)[e]				
Mean (SD)	15.81 (3.54)	15.05 (4.45)	15.11 (4.34)	14.84 (4.84)
Median	16.10	15.74	16.07	15.49
Min, Max	0.53, 22.41	0.03, 22.05	0.03, 22.05	0.53, 20.80

[a] 3 subjects (1 in the acalabrutinib arm and 2 in the IR/BR arm) withdrew consent before receiving any study treatment.

[b] Acalabrutinib was discontinued for 1 subject at the subject's request (ASCEND clinical report, Listing 16.2.1.1).

[c] One subject discontinued idelalisib due to the subject's worsening clinical condition, and discontinued rituximab due to the protocol-specified requirement of discontinuation in the event of toxicity lasting >28 days. One subject discontinued idelalisib because treatment was interrupted for >28 days due to AE.

One subject discontinued idelalisib due to subject's decision. One subject discontinued idelalisib because idelalisib was withheld for >30 days. One subject discontinued rituximab due to missing the Cycle 2 Day 15 dose. One subject discontinued rituximab for an unknown reason (listed as "patient die" with a date of death approximately 8 months after the last rituximab dose). One subject discontinued rituximab due to missing the Cycle 2 Day 15 dose (ASCEND clinical report, Listing 16.2.1.1).

[d] Discontinued all study treatment per randomization assignment. Arm B subjects who crossed over are summarized separately.

[e] Study exit and time on study based on the whole study period - that is, main study period + crossover period.

BR=bendamustine/rituximab; IR=idelalisib/rituximab; Max=maximum; Min=minimum; SD=standard deviation.
Source: ASCEND clinical report, Table 14.1.1.3.

The Applicant's Position:

With a median follow-up of 16.10 months in the acalabrutinib arm and 15.74 months in the IR/BR arm, 264 (85.2%) subjects in both arms were still on study and 46 (14.8%) subjects had exited the study. The primary reason for study exit was death (15 [9.7%] subjects in the acalabrutinib arm and 18 [11.6%] subjects in the IR/BR arm). Thirty-five subjects in the IR/BR (29 subjects previously on IR and 6 subjects previously on BR) crossed over to acalabrutinib monotherapy. Six of these crossover subjects discontinued acalabrutinib treatment as of the data cutoff date, including 3 subjects who discontinued due to an AE, 2 subjects who discontinued treatment due to progressive disease (PD), and 1 subject who discontinued for another reason.

Regulatory Authorities Assessment:

Regulatory authorities agree in general with the Applicant's description of patient disposition. Apart from treatment discontinuation due to AEs, full details of patient disposition were not confirmed. FDA disagrees with the text regarding number of patients who discontinued treatment due to AEs. As described in Table 13 and Section 8.2.4, in the IR arm, AEs led to treatment discontinuation in approximately half of patients, rather than 37%.

Protocol Violations/Deviations

The Applicant's Description:

Important protocol deviation categories were "deviation from inclusion/exclusion criteria," "received prohibited concomitant medication," "initial informed consent not obtained properly," "subject not managed according to protocol," and "study medication." No subjects had deviations from inclusion/exclusion criteria or received prohibited concomitant medication.

Twenty-three (7.4%) subjects had at least 1 important protocol deviation. Three subjects (all in the acalabrutinib arm) had deviations involving the informed consent process, all of which were failure to verbally inform the subjects about a safety memo before re-consenting with an updated ICF version. Two subjects had protocol deviations involving study medication dosing, 1 subject in the acalabrutinib arm with low study medication compliance during some cycles, and 1 subject in the IR/BR arm (on BR) who received a higher than protocol-specified dose of bendamustine during Cycle 1. Eighteen subjects (5 in the acalabrutinib arm and 13 in the IR/BR arm) had deviations classified as "subject not managed according to study protocol," which

included missed safety or efficacy assessments, toxicity management, and withdrawal criteria (Table 14).

Table 14 Important Protocol Deviations (ITT Population)

	No. (%) of Subjects	
	Arm A Acalabrutinib (N=155)	Arm B IR or BR (N=155)
Subjects with any important protocol deviations	9 (5.8%)	14 (9.0%)
Initial Informed Consent not obtained properly	3 (1.9%)	0
Subject not managed according to protocol	5 (3.2%)	13 (8.4%)
Study medication	1 (0.6%)	1 (0.6%)

BR=bendamustine/rituximab; IR=idelalisib/rituximab; ITT=intent-to-treat.
Subjects with more than one deviation will be summarized once at each deviation.
Source: ASCEND clinical report, Table 14.1.14.

The Applicant's Position:

A sensitivity analysis conducted on PFS excluding subjects with important protocol deviations did not demonstrate a significant impact on the overall interpretation of efficacy results for this study and the subjects with the important protocol deviations were retained in the analysis population.

Regulatory Authorities Assessment:

There is a numerically higher incidence of reported important protocol deviations in the control arm compared to the treatment arm (9.0% vs. 5.8%, respectively). The difference in number of protocol deviations between the two treatment arms is evaluated in the sensitivity analysis. It is unlikely that this difference affects the overall interpretation of efficacy.

Table of Demographic Characteristics

The Applicant's Description:

The median age for all subjects was 67 years (range: 32-90). About two-thirds (62.9%) of subjects were ≥65 years old, and 21.0% of subjects were ≥75 years old. About two-thirds (67.1%) of subjects were male, 92.3% were white, and 89.0% were not Hispanic or Latino. Most subjects were enrolled in Central and Eastern Europe (63.9%) or Western Europe (21.0%) (Table 15).

Table 15 Demographics and Baseline Characteristics (ITT Population)

	No. (%) of Subjects		
	Arm A Acalabrutinib (N=155)	**Arm B IR or BR (N=155)**	**Total (N=310)**
Age (years)			
Mean (SD)	66.9 (9.9)	66.7 (9.6)	66.8 (9.7)
Median	68	67	67
Min, Max	32, 89	34, 90	32, 90
<65	58 (37.4%)	57 (36.8%)	115 (37.1%)
≥65	97 (62.6%)	98 (63.2%)	195 (62.9%)
<75	121 (78.1%)	124 (80.0%)	245 (79.0%)
≥75	34 (21.9%)	31 (20.0%)	65 (21.0%)
Sex			
Male	108 (69.7%)	100 (64.5%)	208 (67.1%)
Female	47 (30.3%)	55 (35.5%)	102 (32.9%)
Race			
Asian	7 (4.5%)	7 (4.5%)	14 (4.5%)
Native Hawaiian or other Pacific Islander	0	1 (0.6%)	1 (0.3%)
White	145 (93.5%)	141 (91.0%)	286 (92.3%)
Not Reported	3 (1.9%)	6 (3.9%)	9 (2.9%)
Ethnicity			
Hispanic or Latino	2 (1.3%)	6 (3.9%)	8 (2.6%)
Not Hispanic or Latino	147 (94.8%)	129 (83.2%)	276 (89.0%)
Not reported	6 (3.9%)	20 (12.9%)	26 (8.4%)
Region			
North America	8 (5.2%)	9 (5.8%)	17 (5.5%)
Australia, New Zealand	9 (5.8%)	7 (4.5%)	16 (5.2%)
Western Europe	32 (20.6%)	33 (21.3%)	65 (21.0%)
Central and Eastern Europe	99 (63.9%)	99 (63.9%)	198 (63.9%)
Asia	7 (4.5%)	7 (4.5%)	14 (4.5%)

BR=bendamustine/rituximab; ECOG=Eastern Cooperative Oncology Group; IR=idelalisib/rituximab; ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation.
Source: ASCEND clinical report, Table 14.1.2.1.

The Applicant's Position:
There were no noteworthy differences in demographics between the 2 treatment arms.

Regulatory Authorities Assessment:
Regulatory authorities agree with the Applicant's description. The demographic characteristics of the treatment arms appear to be balanced.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The Applicant's Description:
The median time from initial CLL diagnosis to randomization in the study was 79.0 months (range: 3.1-314.4). Most subjects (87.1%) had a baseline ECOG performance status of ≤1.

Almost half of subjects (48.7%) had tumor bulk ≥5 cm. Baseline Rai intermediate risk (stage I or II) was reported in 56.1% of subjects and high risk (stage III or IV) was reported in 41.6% of subjects. 17p deletion, 11q deletion, unmutated IGHV, and TP53 mutation were seen in 15.8%, 26.8%, 78.4%, and 23.5% of subjects, respectively, and 87.7% of subjects had at least 1 of these chromosomal characteristics. Approximately 80% of subjects had B2-microglobulin >3.5 mg/L. Constitutional symptoms were reported at baseline for 60.6% of subjects, including weight loss, fever, night sweats, and fatigue. Just over half of subjects (53.2%) had cytopenia at baseline, including low platelets (36.8%), low hemoglobin (30.6%), and low ANC (7.4%) (Table 16).

Table 16 Baseline Disease Characteristics (ITT Population)

	No. (%) of Subjects		
	Arm A Acalabrutinib (N=155)	**Arm B IR or BR (N=155)**	**Total (N=310)**
ECOG performance status			
0	58 (37.4%)	55 (35.5%)	113 (36.5%)
1	78 (50.3%)	79 (51.0%)	157 (50.6%)
2	19 (12.3%)	21 (13.5%)	40 (12.9%)
Time from diagnosis to randomization (months)			
Mean (SD)	88.48 (54.52)	87.09 (51.57)	87.78 (52.99)
Median	85.3	79.0	79.0
Min, Max	3.1, 314.4	5.0, 254.2	3.1, 314.4
Bulky disease			
<5 cm	79 (51.0%)	80 (51.6%)	159 (51.3%)
≥5cm	76 (49.0%)	75 (48.4%)	151 (48.7%)
Rai stage			
0	2 (1.3%)	4 (2.6%)	6 (1.9%)
I	39 (25.2%)	32 (20.6%)	71 (22.9%)
II	49 (31.6%)	54 (34.8%)	103 (33.2%)
III	21 (13.5%)	18 (11.6%)	39 (12.6%)
IV	44 (28.4%)	46 (29.7%)	90 (29.0%)
Binet stage			
A	24 (15.5%)	25 (16.1%)	49 (15.8%)
B	67 (43.2%)	61 (39.4%)	128 (41.3%)
C	54 (34.8%)	53 (34.2%)	107 (34.5%)
Missing	10 (6.5%)	16 (10.3%)	26 (8.4%)
IGHV			
Mutated	33 (21.3%)	26 (16.8%)	59 (19.0%)
Unmutated	118 (76.1%)	125 (80.6%)	243 (78.4%)
Undetermined	3 (1.9%)	2 (1.3%)	5 (1.6%)
Cytopenia			
ANC ≤1.5x10^9/L	14 (9.0%)	9 (5.8%)	23 (7.4%)
Hemoglobin ≤11 g/dL	49 (31.6%)	46 (29.7%)	95 (30.6%)
Platelets ≤100x10^9/L	57 (36.8%)	57 (36.8%)	114 (36.8%)
All of the above	4 (2.6%)	4 (2.6%)	8 (2.6%)
Any of the above	85 (54.8%)	80 (51.6%)	165 (53.2%)
Constitutional symptoms			

	No. (%) of Subjects		
	Arm A Acalabrutinib (N=155)	Arm B IR or BR (N=155)	Total (N=310)
Any constitutional symptom	91 (58.7%)	97 (62.6%)	188 (60.6%)
Weight loss	8 (5.2%)	15 (9.7%)	23 (7.4%)
Fever	8 (5.2%)	8 (5.2%)	16 (5.2%)
Night sweats	81 (52.3%)	84 (54.2%)	165 (53.2%)
Fatigue	20 (12.9%)	25 (16.1%)	45 (14.5%)
17p deletion - Yes	28 (18.1%)	21 (13.5%)	49 (15.8%)
11q deletion - Yes	39 (25.2%)	44 (28.4%)	83 (26.8%)
TP53 mutation - Yes	39 (25.2%)	34 (21.9%)	73 (23.5%)
17p deletion and TP53 mutation - Yes	22 (14.2%)	13 (8.4%)	35 (11.3%)
17p deletion, TP53 mutation or 11q deletion - Yes	79 (51.0%)	78 (50.3%)	157 (50.6%)
17p deletion, TP53 mutation, 11q deletion, or unmutated IGHV - Yes	135 (87.1%)	137 (88.4%)	272 (87.7%)

ANC=absolute neutrophil count; BR=bendamustine/rituximab; ECOG=Eastern Cooperative Oncology Group; IGHV=immunoglobulin heavy-chain variable; IR=idelalisib/rituximab; ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation.
Source: ASCEND clinical report, Table 14.1.2.1, Table 14.1.2.2.

Subjects in this study had a median of 2 prior therapies (range: 1-10), with a median time of 24.1 months (range: 1.0-158.9) since the most recent therapy (Table 17). Thirty-four (11.0%) subjects had ≥4 prior therapies for CLL. The most common prior anti-CLL therapies included alkylators other than bendamustine (85.2%), anti-CD20 monoclonal antibodies (80.3%), and purine analogues (68.7%).

Table 17 Prior CLL Therapy (ITT Population)

	No. (%) of Subjects		
	Arm A Acalabrutinib (N=155)	Arm B IR or BR (N=155)	Total (N=310)
Time since last prior CLL therapy to first dose (months)			
n	154	153	307
Mean (SD)	31.52 (27.96)	29.65 (27.15)	30.59 (27.53)
Median	26.4	22.7	24.1
Min, Max	1.0, 158.9	1.1, 156.2	1.0, 158.9
Number of prior therapies			
1	82 (52.9%)	67 (43.2%)	149 (48.1%)
2	40 (25.8%)	46 (29.7%)	86 (27.7%)
3	17 (11.0%)	24 (15.5%)	41 (13.2%)
≥4	16 (10.3%)	18 (11.6%)	34 (11.0%)
Median	1	2	2
Min, Max	1, 8	1, 10	1, 10
Type of prior therapy			
Purine Analogues	109 (70.3%)	104 (67.1%)	213 (68.7%)
Alkylators other than bendamustine	133 (85.8%)	131 (84.5%)	264 (85.2%)
Bendamustine	47 (30.3%)	48 (31.0%)	95 (30.6%)

	No. (%) of Subjects		
	Arm A Acalabrutinib (N=155)	Arm B IR or BR (N=155)	Total (N=310)
Anti-CD20 monoclonal antibodies	130 (83.9%)	119 (76.8%)	249 (80.3%)
Stem cell transplant	1 (0.6%)	1 (0.6%)	2 (0.6%)
Other[a]	9 (5.8%)	6 (3.9%)	15 (4.8%)

BR=bendamustine/rituximab; CLL=chronic lymphocytic leukemia; IR=idelalisib/rituximab; ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation.

[a] 6 subjects received an anti-CD52 antibody, 3 subjects received an anti-CD19 antibody, 2 subjects received an immunomodulatory agent, 1 subject received an anti-PDL1 antibody, 1 subject received anti-CD23 antibody, 1 subject received hydroxycarbamide, and 1 subject received an autologous dendritic cell vaccine.

Source: ASCEND clinical report, Table 14.1.3.3.

The Applicant's Position:

There were no noteworthy differences in baseline disease characteristics or prior CLL therapies between the 2 treatment arms.

Regulatory Authorities Assessment:

FDA disagrees with the Applicant's interpretation of no noteworthy differences in baseline characteristics. The acalabrutinib arm in general tended to be less heavily pretreated, with 53% having only 1 prior therapy, versus 43% in the control arm. The randomization stratification factor, 1-3 vs. 4 or more prior therapies, was not sufficient to balance the treatment arms, which had a median number of prior therapies of 1 and 2 in the acalabrutinib and control arms, respectively. However, FDA evaluated this difference in a PFS sensitivity analysis, the results of which were consistent with the primary PFS analysis. Regulatory authorities agree that, apart from number of prior therapies, the treatment arms were relatively well balanced with respect to baseline patient and treatment characteristics.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Description:

Treatment Compliance

Arm A: Acalabrutinib

All but 1 subject in Arm A received acalabrutinib. The median duration of acalabrutinib treatment was 15.7 months (range: 1.1-22.4) with 85.7% of subjects receiving ≥1 year of therapy. Median relative acalabrutinib dose intensity was 99.5%.

Arm B: Idelalisib/Rituximab and Bendamustine/Rituximab

The median duration of idelalisib treatment was 11.5 months (range: 0.1-21.1) for subjects who received IR, with a median relative dose intensity of 91.2%. The median duration of bendamustine treatment was 5.6 months (range: 1.0-7.1) for subjects who received BR, with a median relative dose intensity of 96.4%. The median duration of rituximab was 5.5 months

(range: 0.9-8.5) for subjects treated with IR and 5.5 months (range: 0.9-7.1) for subjects treated with BR, with a median relative dose intensity of 98.2% and 97.9% in the IR and BR groups, respectively.

Regulatory Authorities Assessment:
Regulatory authorities agree with the Applicant's position. However, the exposure data warrant emphasis, as they are critical to interpretation of the efficacy results. The difference in duration of exposure to randomized treatment is substantial, with the median treatment duration being 2-fold longer to acalabrutinib than to the investigator's choice regimens combined.

On FDA analysis, in the acalabrutinib arm, the median treatment duration was 15.7 months, with 94% of patients treated for ≥ 6 months and 86% of patients treated for ≥ 1 year. In contrast, in the investigator's choice arm, the median treatment duration was 8.4 months, with 59% of patients treated for ≥ 6 months and 37% treated for ≥ 1 year. Thus, the superior PFS results with acalabrutinib than investigator's choice reflects, to some extent, the effect of more treatment versus less.

The Applicant's Description:

Concomitant Medications
The most common therapeutic classes of concomitant medications taken by subjects in the acalabrutinib and IR/BR arms, respectively, were antibacterials for systemic use (64.5% and 85.2%), analgesics (38.7% and 91.6%), antigout preparations (56.8% and 58.7%), antihistamines for systemic use (16.8% and 89.0%), antivirals for systemic use (41.3% and 62.6%), corticosteroids for systemic use (17.4% and 87.7%), agents acting on the renin-angiotensin system (34.8% and 38.1%), antithrombotic agents (32.3% and 39.4%), drugs for acid related disorders (25.8% and 44.5%), beta blocking agents (29.0% and 27.1%), mineral supplements (16.8% and 28.4%), and blood substitutes and perfusion solutions (15.5% and 29.0%). Concomitant medications that were used in ≥20% of subjects overall and used notably more frequently by subjects on acalabrutinib versus IR/BR included lipid-modifying agents (24.5% and 16.1%, respectively), while those used less frequently by subjects on acalabrutinib versus IR/BR, respectively, included analgesics (38.7% versus 91.6%), antihistamines for systemic use (16.8% versus 89.0%), antivirals for systemic use (41.3% versus 62.6%), corticosteroids for systemic use (17.4% versus 87.7%), drugs for acid related disorders (25.8% versus 44.5%), mineral supplements (16.8% versus 28.4%), blood substitutes and perfusion solutions (15.5% versus 29.0%), and antidiarrheals and intestinal anti-inflammatory/anti-infective agents (9.7% versus 33.5%).

The Applicant's Position:
Overall, the concomitant treatments administered were representative of those commonly prescribed for patients of the target population and were not considered to have impacted the study results.

Regulatory Authorities Assessment:
Regulatory authorities agree with the Applicant's position.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The Applicant's Description:

Primary Endpoint: PFS as Assessed by IRC

The primary test to compare PFS between treatment arms was the two-sided log-rank test, stratified by randomization stratification factors. With a median follow-up of 16.10 months in the acalabrutinib arm and 15.74 months in the IR/BR arm, the median estimated PFS for acalabrutinib was not reached; the median estimated PFS for IR/BR was 16.5 months (95% CI: 14.0, 17.1). Acalabrutinib monotherapy demonstrated a statistically significant improvement in IRC-assessed PFS compared with IR/BR, with a 69% reduction in risk of disease progression or death (HR=0.31 [95% CI: 0.20, 0.49]; p<0.0001) (Table 18, Figure 5).

The KM estimate of the proportion of subjects without a PFS event at 12 months was 87.8% (95% CI: 81.3, 92.1) for acalabrutinib and 68.0% (95% CI: 59.4, 75.1) for IR/BR. The KM estimate of the proportion of subjects without a PFS event at 18 months was 79.0% (95% CI: 69.7, 85.8) for acalabrutinib and 38.6% (95% CI: 27.3, 49.8) for IR/BR (Table 18, Figure 5).

A KM plot for PFS by IRC assessment with 95% Hall-Wellner Bands is provided in Figure 6 for the ITT population.

Table 18 Analysis of Progression-Free Survival by IRC Assessment (ITT Population) – Primary Endpoint

	Acalabrutinib (N=155)	IR or BR (N=155)
Subject Status		
Events,[a] n (%)	27 (17.4%)	68 (43.9%)
Death	8 (5.2%)	9 (5.8%)
Disease progression	19 (12.3%)	59 (38.1%)
Censored,[b] n (%)	128 (82.6%)	87 (56.1%)
Randomization	2 (1.3%)	4 (2.6%)
Last adequate assessment before data cutoff	123 (79.4%)	82 (52.9%)
Last adequate assessment before subsequent anticancer therapy	3 (1.9%)	1 (0.6%)
Progression-free survival (months)		
Median (95% CI)	NE (NE, NE)	16.5 (14.0, 17.1)
Min, Max	0.0+, 22.4+	0.0+, 20.0+
Stratified analysis (versus Arm B)		
Hazard ratio (95% CI)[c]	0.31 (0.20, 0.49)	
p-value[d]	<0.0001	
Unstratified analysis (versus Arm B)		
Hazard ratio (95% CI)[e]	0.30 (0.19, 0.48)	
p-value[f]	<0.0001	

	Acalabrutinib (N=155)	**IR or BR (N=155)**
KM estimates of PFS by timepoint (%)		
6 Months PFS Rate (95% CI)	96.1 (91.5, 98.2)	93.9 (88.6, 96.8)
9 Months PFS Rate (95% CI)	92.7 (87.3, 95.9)	82.4 (75.0, 87.7)
12 Months PFS Rate (95% CI)	87.8 (81.3, 92.1)	68.0 (59.4, 75.1)
15 Months PFS Rate (95% CI)	82.6 (75.0, 88.1)	54.9 (45.4, 63.5)
18 Months PFS Rate (95% CI)	79.0 (69.7, 85.8)	38.6 (27.3, 49.8)

BR=bendamustine/rituximab; CI=confidence interval; IR=idelalisib/rituximab; IRC=Independent Review Committee; ITT=intent-to-treat; IXRS=interactive voice/web response system; KM=Kaplan-Meier; Max=maximum; Min=minimum; NE=not estimable; PFS=progression-free survival.

[a] Based on the earliest contributing assessment.

[b] Based on the latest contributing assessment.

[c] Based on stratified Cox proportional hazards model, stratified by randomization stratification factors as recorded in IXRS

[d] Based on stratified log-rank test, stratified by randomization stratification factors as recorded in IXRS

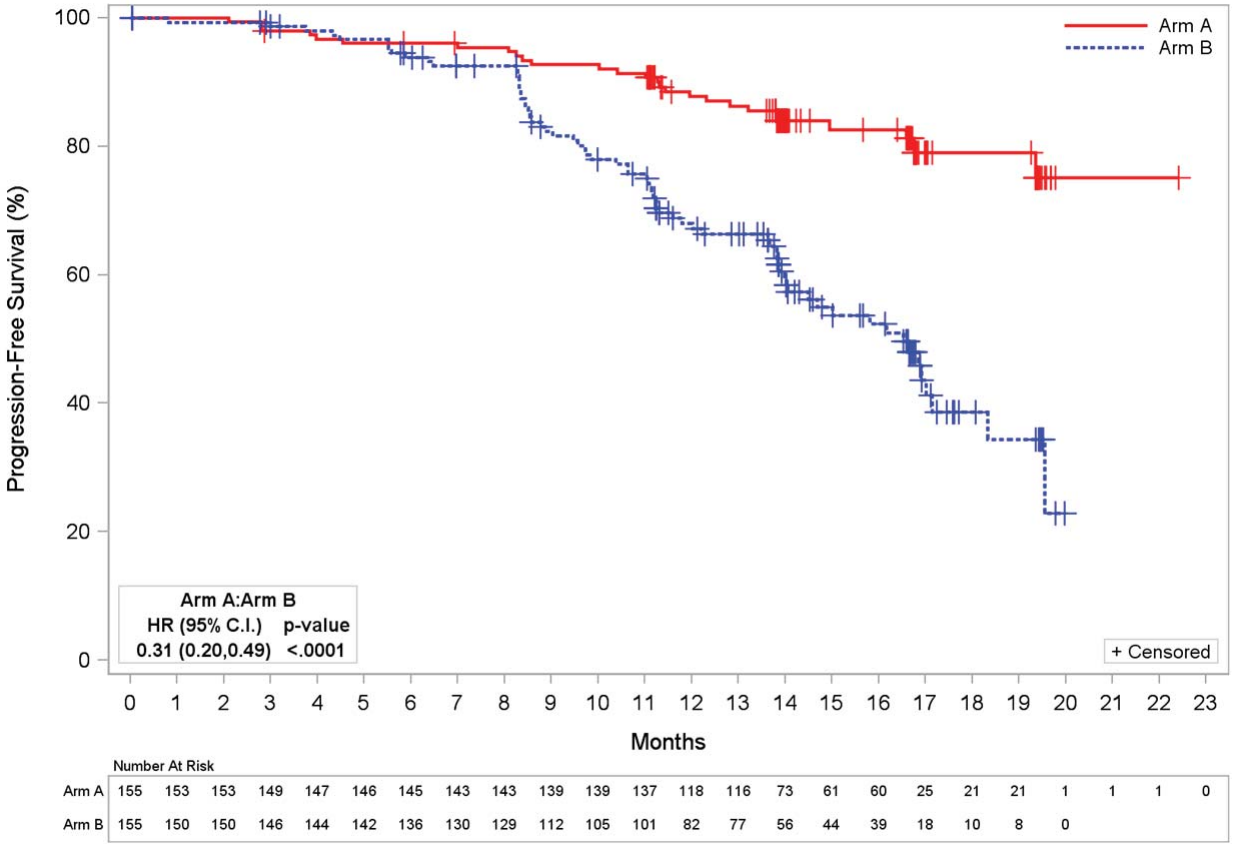
[e] Based on unstratified Cox proportional hazards model.

[f] Based on unstratified log-rank test.

Time to event (or time to censor for censored subjects) is calculated as date of disease progression or death (censoring date for censored subjects) - randomization date + 1. Months are derived as days/30.4375.

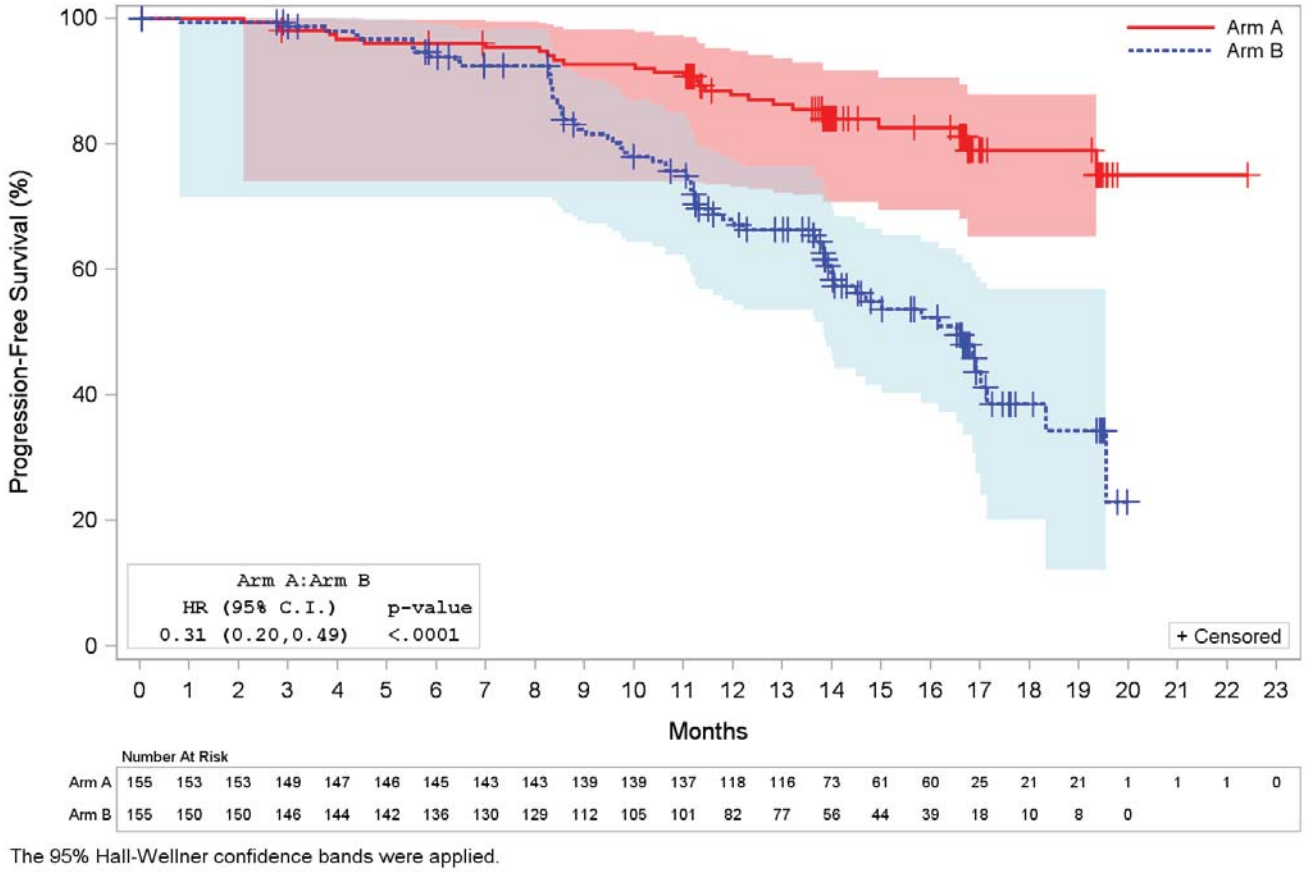
Source: ASCEND clinical report, Table 14.2.1.

Figure 5 **Kaplan-Meier Plot for Progression-Free Survival by IRC Assessment (ITT Population) – Primary Endpoint**



CI=confidence interval; HR=hazard ratio.
Source: ASCEND clinical report, Figure 14.2.1.8.

Figure 6 **Kaplan-Meier Plot for Progression-Free Survival by IRC Assessment with 95% Hall-Wellner Bands (ITT Population)**



The 95% Hall-Wellner-confidence bands were applied.
Arm A = acala, Arm B = IR/BR
Source: Ad-hoc figure from ASCEND per FDA Request.

Examination of Subgroups

Acalabrutinib demonstrated improved PFS compared with IR/BR was notable in the following subgroups associated with poor prognosis (Table 19).

Table 19 **Subgroup Analysis of Progression-Free Survival by IRC Assessment (ITT Population) – Primary Endpoint**

	Responders/Subjects		
	Arm A Acalabrutinib (N=155)	**Arm B IR or BR (N=155)**	**Hazard Ratio (95% CI)**
	Number of Events/Subjects	Number of Events/Subjects	
Overall			
Primary analysis	27/155	68/155	0.30 (0.19, 0.48)
Presence of 17p deletion			

	Responders/Subjects		
	Arm A Acalabrutinib (N=155)	**Arm B IR or BR (N=155)**	**Hazard Ratio (95% CI)**
Yes	4/28	12/26	0.21 (0.07, 0.68)
No	23/127	56/129	0.33 (0.21, 0.54)
ECOG at randomization			
0, 1	24/137	60/135	0.30 (0.18, 0.48)
2	3/18	8/20	0.36 (0.10, 1.37)
Age group			
<65	7/58	27/57	0.20 (0.09, 0.46)
≥65	20/97	41/98	0.40 (0.23, 0.68)
<75	19/121	55/124	0.26 (0.15, 0.44)
≥75	8/34	13/31	0.54 (0.22, 1.30)
Sex			
Male	22/108	45/100	0.34 (0.20, 0.57)
Female	5/47	23/55	0.21 (0.08, 0.57)
Race			
White	24/145	63/141	0.28 (0.18, 0.45)
Non-white	3/10	5/14	0.61 (0.14, 2.56)
Region			
Asia	2/7	3/7	0.44 (0.07, 2.64)
Australia and New Zealand	2/9	2/7	0.50 (0.07, 3.61)
Central and Eastern Europe	18/99	45/99	0.31 (0.18, 0.54)
North America	0/8	4/9	NE (NE, NE)
Western Europe	5/32	14/33	0.32 (0.12, 0.89)
Rai stage at screening			
Stage 0-II	16/90	35/90	0.36 (0.20, 0.66)
Stage III-IV	11/65	33/64	0.24 (0.12, 0.47)
Bulky disease			
<5 cm	14/79	28/80	0.36 (0.19, 0.69)
≥5 cm	13/76	40/75	0.26 (0.14, 0.49)
B2-microglobin at baseline			
≤3.5 mg/L	4/32	9/25	0.25 (0.07, 0.82)
>3.5 mg/L	23/120	59/126	0.33 (0.20, 0.53)
IgHV			
Mutated	5/33	10/26	0.32 (0.11, 0.94)
Unmutated	22/118	56/125	0.32 (0.19, 0.52)
Presence of 11q deletion - Yes	6/39	20/44	0.28 (0.11, 0.70)
TP53 mutation - Yes	8/39	20/34	0.24 (0.11, 0.56)
17p deletion or TP53 mutation - Yes	8/45	23/42	0.21 (0.09, 0.48)
17p deletion and TP53 mutation - Yes	4/22	7/13	0.20 (0.06, 0.69)
17p deletion, TP53 mutation, 11q deletion, or unmutated IgHV - Yes	23/135	63/137	0.27 (0.17, 0.44)
17p deletion, TP53 mutation, or 11q deletion - Yes	14/79	39/78	0.27 (0.15, 0.49)
Complex karyotype - Yes	12/50	24/46	0.32 (0.16, 0.63)

ECOG PS=Eastern Cooperative Oncology Group performance status; IgHV=immunoglobulin heavy-chain variable; IRC=Independent Review Committee; ITT=intent-to-treat.

[a] Per Interactive voice/web response system (IXRS) record.
Source: ASCEND clinical report, Figure 14.2.1.11.

Sensitivity Analyses

The key sensitivity analysis of PFS without censoring for subsequent anticancer therapy was consistent with the primary analysis and showed similar improvement in PFS for acalabrutinib compared with IR/BR (HR=0.33 [95% CI: 0.22, 0.52]; p<0.0001). All other sensitivity analyses were also consistent with the primary analysis, with HR ranging from 0.29-0.31, which was statistically significant for all analyses (p<0.0001) (Table 20,Figure 7).

Per the Agency's request, sensivity analysis was performed on IRC-assessed PFS using weighted log-rank test, stratified by number of prior therapy (1 3 vs. 4+) and del 17p status as recorded in IXRS, to compare between acalabrutinib and IR/BR. The results remain consistent with the primary analysis result and confirm the robustness of the primary analysis (Table 21).

Table 20 Sensitivity Analyses of Progression-Free Survival by IRC Assessment (ITT Population) – Primary Endpoint

	Arm A Acalabrutinib (N=155)	Arm B IR or BR (N=155)
Sensitivity analysis 1: include PFS without censoring for subsequent anticancer therapy		
Events, n (%)[a]	30 (19.4%)	70 (45.2%)
Death	10 (6.5%)	10 (6.5%)
Disease Progression	20 (12.9%)	60 (38.7%)
Censored, n (%)[b]	125 (80.6%)	85 (54.8%)
Progression-free survival (months)		
Median (95% CI)	NE (NE, NE)	16.5 (14.0, 17.1)
Min, Max	0.0+, 22.4+	0.0+, 20.0+
Stratified analysis (versus Arm B)		
Hazard ratio (95% CI)[c]	0.33 (0.22, 0.52)	
p-value[d]	<0.0001	
Sensitivity analysis 2: include PFS events after ≥2 consecutively missed visits		
Events, n (%)[a]	27 (17.4%)	68 (43.9%)
Death	8 (5.2%)	9 (5.8%)
Disease Progression	19 (12.3%)	59 (38.1%)
Censored, n (%)[b]	128 (82.6%)	87 (56.1%)
Progression-free survival (months)		
Median (95% CI)	NE (NE, NE)	16.5 (14.0, 17.1)
Min, Max	0.0+, 22.4+	0.0+, 20.0+
Stratified analysis (versus Arm B)		
Hazard ratio (95% CI)[c]	0.31 (0.20, 0.49)	
p-value[d]	<0.0001	
Sensitivity analysis 3: exclude subjects with important protocol deviation		
Events, n (%)[a]	24/146 (16.4%)	61/141 (43.3%)
Death	7/146 (4.8%)	8/141 (5.7%)

	Arm A Acalabrutinib (N=155)	Arm B IR or BR (N=155)
Disease Progression	17/146 (11.6%)	53/141 (37.6%)
Censored, n (%)[b]	122/146 (83.6%)	80/141 (56.7%)
Progression-free survival (months)		
Median (95% CI)	NE (NE, NE)	16.5 (14.0, 18.3)
Min, Max	0.0+, 22.4+	0.0+, 20.0+
Stratified analysis (versus Arm B)		
Hazard ratio (95% CI)[c]	0.29 (0.18, 0.47)	
p-value[d]	<0.0001	
Sensitivity analysis 4: use eCRF-recorded stratification factors		
Events, n (%)[a]	27 (17.4%)	68 (43.9%)
Death	8 (5.2%)	9 (5.8%)
Disease Progression	19 (12.3%)	59 (38.1%)
Censored, n (%)[b]	128 (82.6%)	87 (56.1%)
Progression-free survival (months)		
Median (95% CI)	NE (NE, NE)	16.5 (14.0, 17.1)
Min, Max	0.0+, 22.4+	0.0+, 20.0+
Stratified analysis (versus Arm B)		
Hazard ratio (95% CI)[e]	0.30 (0.19, 0.47)	
p-value[f]	<0.0001	

BR=bendamustine/rituximab; CI=confidence interval; eCRF=electronic case report form; IR=idelalisib/rituximab; IRC=Independent Review Committee; ITT=intent-to-treat; IXRS=interactive voice/web response system; KM=Kaplan-Meier; Max=maximum; Min=minimum; NE=not estimable; PFS=progression-free survival; SD=standard deviation.

[a] Based on the earliest contributing assessment.

[b] Based on the latest contributing assessment.

[c] Based on stratified Cox proportional hazards model, stratified by randomization stratification factors as recorded in IXRS

[d] Based on stratified log-rank test, stratified by randomization stratification factors as recorded in IXRS

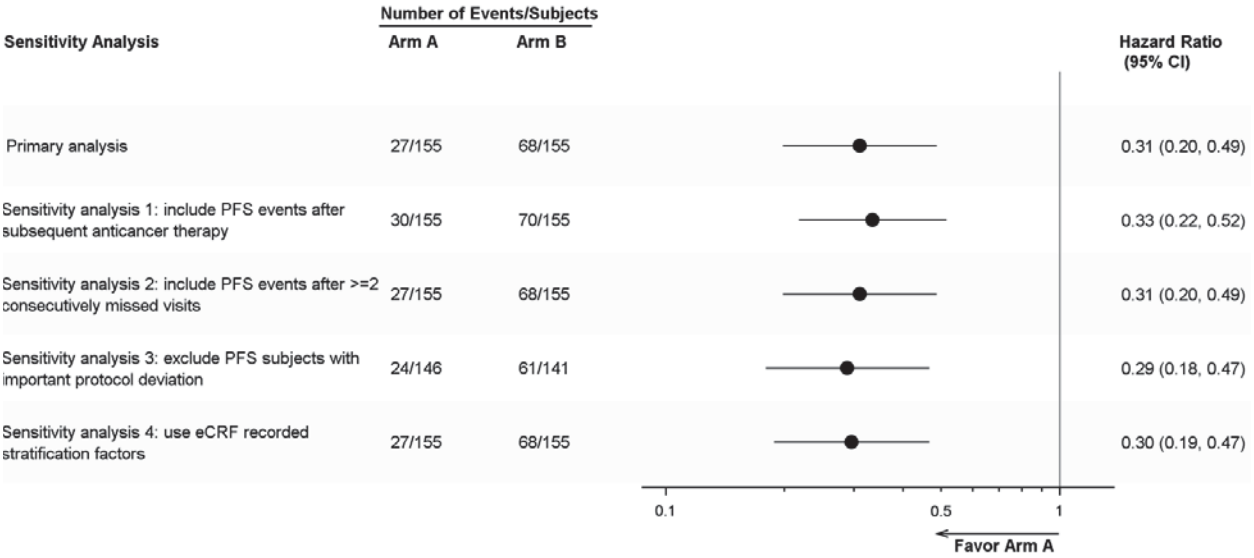
[e] Based on stratified Cox proportional hazards model, stratified by randomization stratification factors as recorded in eCRF.

[f] Based on stratified log-rank test, stratified by randomization stratification factors as recorded in eCRF.

Time to event (or time to censor for censored subjects) is calculated as date of disease progression or death (censoring date for censored subjects) - randomization date + 1. Months are derived as days/30.4375.

Source: ASCEND clinical report, Table 14.2.1.1, Table 14.2.1.2, Table 14.2.1.3, Table 14.2.1.4

Figure 7 **Forest Plot for Sensitivity Analysis of Progression-Free Survival by IRC Assessment (ITT Population) – Primary Endpoint**



eCRF=electronic case report form; IRC=Independent Review Committee; ITT=intent-to-treat; PFS=progression-free survival.
Source: ASCEND clinical report, Figure 14.2.1.10.

Table 21 **Progression Free Survival (PFS) by IRC Assessment by Weighted Log-Rank Test (Harrington-Fleming) (ITT Population) – Primary Endpoint**

	Arm A (Acala) (N=155)	Arm B (IR/BR) (N=155)
Subject Status		
Events - n(%)[a]	27 17.4%)	68 (43.9%)
Death	8 (5.2%)	9 5.8%)
Disease Progression	19 (12.3%)	59 (38.1%)
Censored - n(%)[b]	128 (82.6%)	87 (56.1%)
Randomization	2 (1.3%)	4 (2.6%)
Last adequate assessment before data cutoff	123 (79.4%)	82 (52.9%)
Last adequate assessment before subsequent anticancer therapy	3 (1.9%)	1 (0.6%)
Progression Free Survival (months)		
Q1 (95% CI)	NE (14.9, NE)	11.0 (9.0, 12.0)
Median (95% CI)	NE (NE, NE)	16.5 (14.0, 17.1)
Q3 (95% CI)	NE (NE, NE)	19.5 (18.3, NE)
Min, Max	0.0+, 22.4+	0.0+, 20.0+
Fleming(0,0)		
Stratified Analysis (vs. Arm B)		
Chi-Square	28.9836	
DF	1	
p-value[c]	<.0001	
Unstratified Analysis (vs. Arm B)		
Chi-Square	30.4839	
DF	1	
p-value[d]	<.0001	
Fleming(0,1)		

	Arm A (Acala) (N=155)	Arm B (IR/BR) (N=155)
Stratified Analysis (vs. Arm B)		
Chi-Square	25.5574	
DF	1	
p-value[c]	<.0001	
Unstratified Analysis (vs. Arm B)		
Chi-Square	29.1077	
DF	1	
p-value[d]	<.0001	
Fleming(0,2)		
Stratified Analysis (vs. Arm B)		
Chi-Square	17.9665	
DF	1	
p-value[c]	<.0001	
Unstratified Analysis (vs. Arm B)		
Chi-Square	21.0309	
DF	1	
p-value[d]	<.0001	
Fleming(0,3)		
Stratified Analysis (vs. Arm B)		
Chi-Square	12.5637	
DF	1	
p-value[c]	0.0004	
Unstratified Analysis (vs. Arm B)		
Chi-Square	15.5991	
DF	1	
p-value[d]	<.0001	
Fleming(0,4)		
Stratified Analysis (vs. Arm B)		
Chi-Square	8.8829	
DF	1	
p-value[c]	0.0029	
Unstratified Analysis (vs. Arm B)		
Chi-Square	11.9749	
DF	1	
p-value[d]	0.0005	
Fleming(0,5)		
Stratified Analysis (vs. Arm B)		
Chi-Square	6.4222	
DF	1	
p-value[c]	0.0113	
Unstratified Analysis (vs. Arm B)		
Chi-Square	9.4659	
DF	1	
p-value[d]	0.0021	
K-M Estimates of PFS by Timepoint		
6 Months PFS Rate (95% CI)	96.1 (91.5, 98.2)	93.9 (88.6, 96.8)
9 Months PFS Rate (95% CI)	92.7 (87.3, 95.9)	82.4 (75.0, 87.7)
12 Months PFS Rate (95% CI)	87.8 (81.3, 92.1)	68.0 (59.4, 75.1)
15 Months PFS Rate (95% CI)	82.6 (75.0, 88.1)	54.9 (45.4, 63.5)
18 Months PFS Rate (95% CI)	79.0 (69.7, 85.8)	38.6 (27.3, 49.8)

BR=bendamustine/rituximab; CI=confidence interval; IR=idelalisib/rituximab; IRC=Independent Review Committee; ITT=intent-to-treat; IXRS=interactive voice/web response system; KM=Kaplan-Meier; Max=maximum; Min=minimum; NE=not estimable; PFS=progression-free survival.

[a] Based on the earliest contributing assessment.
[b] Based on the latest contributing assessment.
[c] Based on stratified weighted log-rank test (Harrington-Fleming), stratified by number of prior therapy (1-3 vs. 4+) and del 17p status as recorded in IXRS.
[d] Based on unstratified weighted log-rank test (Harrington-Fleming).

Time to event (or time to censor for censored subjects) is calculated as date of disease progression or death (censoring date for censored subjects) - randomization date + 1. Months are derived as days/30.4375. NE: not estimable.
Source: Ad-hoc table from ASCEND per FDA Request.

The Applicant's Position:

Acalabrutinib monotherapy demonstrated a statistically significant improvement in IRC-assessed PFS compared with IR/BR. The PFS benefit of acalabrutinib compared with IR/BR was consistent across all prespecified subgroups, including age, race, sex, geographic region, presence of chromosomal abnormalities, number of prior therapies, and baseline disease status, with HR ranging from 0.20 to 0.84. The key sensitivity analysis of PFS without censoring for subsequent anticancer therapy was consistent with the primary analysis and showed similar improvement in PFS for acalabrutinib compared with IR/BR.

Regulatory Authorities Assessment:

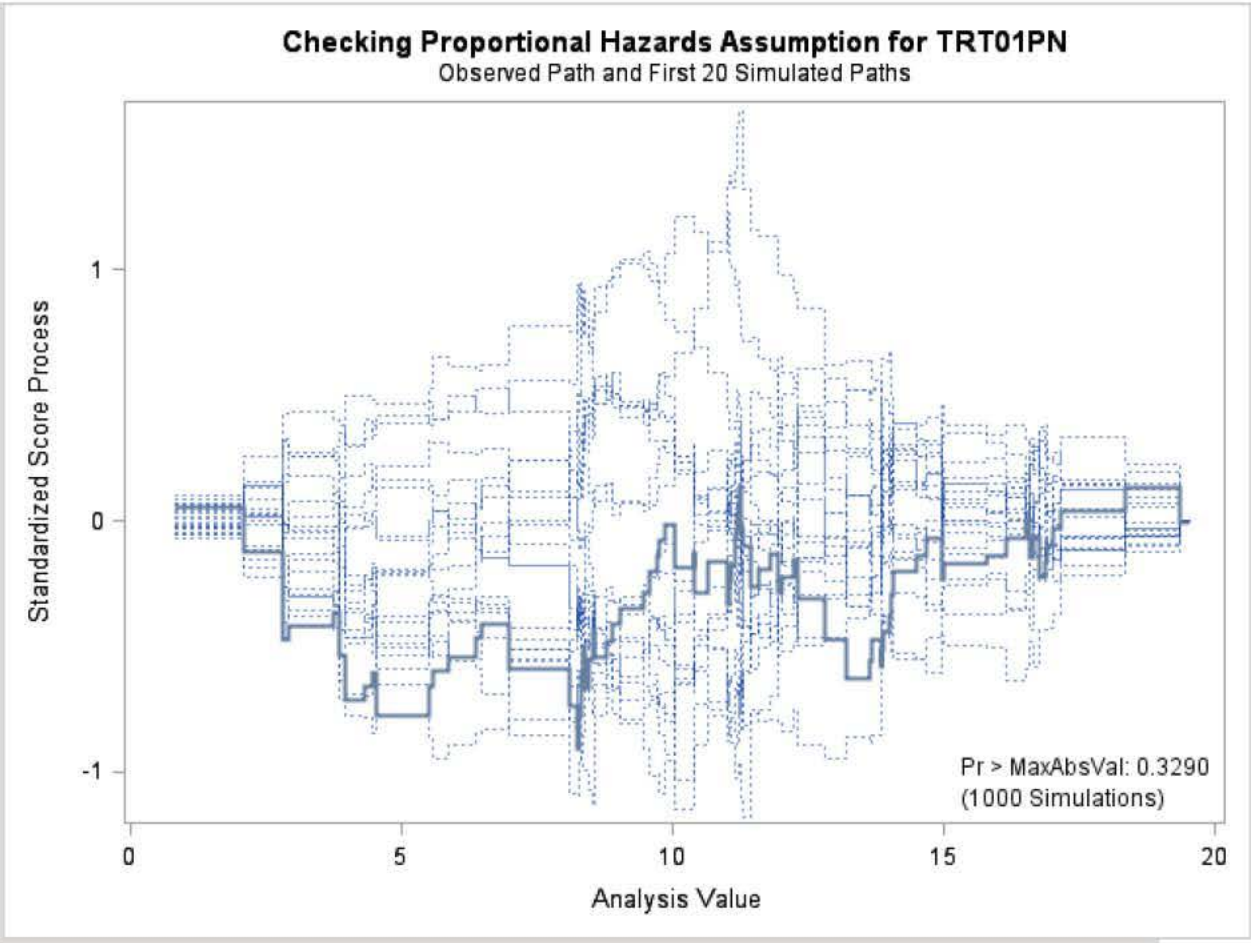
The efficacy assessment was conducted at the pre-specified interim analysis. During the review, FDA had concerns with the validity of the proportional hazard (PH) assumption because the Kaplan-Meier curves of IRC-assessed PFS for both acalabrutinib and IR/BR arms seemed to overlap up to month 9 (Figure 5). If PH assumption was not met, both log-rank test and Cox regression model could produce biased results. The following tests were performed to assess the PH assumption:

- Adding the interaction term, log of survival time by treatment, to the Cox regression model. This interaction term had a non-statistically significant P value of 0.1357.

- Kolmogorov-type supremum test. This test yielded a non-statistically significant P value of 0.3290

- Standardized score process plot (Figure 8).

Figure 8 Standard Score Process Plot



Since the observed score process (solid blue line) did not appear different from the simulated score processes (dotted blue lines) and the two tests for PH yielded non-significant P values, the PH assumption was met.

Regulatory authorities agree that acalabrutinib monotherapy demonstrated a statistically significant improvement in IRC-assessed PFS compared with IR/BR. Further, Regulatory authorities agree that the benefit of IRC-assessed PFS in acalabrutinib monotherapy was robust from the results of the sensitivity analyses presented.

FDA does not agree that the KM Estimates of PFS by different timepoints should be presented in Table 14, 17. These estimates can be misleading because they only present estimates at one single time point and cannot represent the overall effect of the treatment.

FDA does not agree with applicant's statement that the PFS benefit of acalabrutinib compared with IR/BR was consistent across all prespecified subgroups. Subgroups analyses are exploratory and conclusion of PFS benefit in these subgroups based on estimated HR is not

appropriate. After review, FDA concludes that no outlier subgroups were identified.

FDA does not agree that p-values should be included in Table 16 and 17. These sensitivity analyses are considered exploratory and are not adjusted for multiplicity. All p-values presented in Table 16 and 17 are nominal and could be misleading.

FDA conducted additional sensitivity analysis for the number of prior lines of therapy 1 vs 1+ in addition to 1-3 vs 4+ to examine the observed difference at baseline. The result from this analysis is consistent with the result from the primary PFS analysis, hence, the observed imbalance in number of prior lines of therapy at baseline does not affect the PFS benefit of acalabrutinib.

Data Quality and Integrity

The Applicant's Description: Not applicable

The Applicant's Position:
No issues were identified with the data quality or integrity from ASCEND which could affect the efficacy results.

Regulatory Authorities Assessment:
Regulatory authorities agree with the Applicant's position.

Efficacy Results- Secondary and Other Relevant Endpoints

The Applicant's Description:

PFS by Investigator Assessment
Investigator-assessed PFS was consistent with the primary analysis. Acalabrutinib demonstrated a statistically significant improvement in investigator-assessed PFS compared with IR/BRs (HR=0.28 [95% CI: 0.18, 0.45]; p<0.0001). With a median follow-up of 16.10 months in the acalabrutinib arm and 15.74 months in the IR/BR arm, the median estimated PFS for acalabrutinib was not reached; the median estimated PFS for IR/BR was 16.2 months (95% CI: 14.0, not reached) (Table 22, Figure 9).

The KM estimate of the proportion of subjects without a PFS event at 12 months was 88.7% (95% CI: 82.4, 92.8) for acalabrutinib and 67.4% (95% CI: 59.1, 74.4) for IR/BR. The KM estimate of the proportion of subjects without a PFS event at 18 months was 82.8% (95% CI: 74.6, 88.5) for acalabrutinib and 43.9% (95% CI: 33.4, 53.8) for IR/BR (Table 22, Figure 9).

Table 22 Analysis of Progression-Free Survival by Investigator Assessment (ITT Population: Censoring at Subsequent Anticancer Therapy)

	Arm A Acalabrutinib (N=155)	Arm B IR or BR (N=155)
Subject Status		
Events,[a] n (%)	24 (15.5%)	68 (43.9%)
Death	7 (4.5%)	10 (6.5%)
Disease progression	17 (11.0%)	58 (37.4%)
Censored,[b] n (%)	131 (84.5%)	87 (56.1%)
Randomization	0	3 (1.9%)
Last adequate assessment before data cutoff	129 (83.2%)	83 (53.5%)
Last adequate assessment before subsequent anticancer therapy	2 (1.3%)	1 (0.6%)
Progression-free survival (months)		
Median (95% CI)	NE (NE, NE)	16.2 (14.0, NE)
Min, Max	0.5+, 22.4+	0.0+, 20.0+
Stratified analysis (versus Arm B)		
Hazard ratio (95% CI)[c]	0.28 (0.18, 0.45)	
p-value[d]	<0.0001	
Unstratified analysis (versus Arm B)		
Hazard ratio (95% CI)[e]	0.28 (0.18, 0.45)	
p-value[f]	<0.0001	
KM estimates of PFS by timepoint (%)		
6 Months PFS Rate (95% CI)	94.1 (89.0, 96.9)	92.7 (87.2, 95.9)
9 Months PFS Rate (95% CI)	92.1 (86.5, 95.4)	83.1 (76.0, 88.3)
12 Months PFS Rate (95% CI)	88.7 (82.4, 92.8)	67.4 (59.1, 74.4)
15 Months PFS Rate (95% CI)	84.5 (77.2, 89.6)	53.5 (44.3, 61.8)
18 Months PFS Rate (95% CI)	82.8 (74.6, 88.5)	43.9 (33.4, 53.8)

BR=bendamustine/rituximab; CI=confidence interval; IR=idelalisib/rituximab; ITT=intent-to-treat; IXRS=interactive voice/web response system; KM=Kaplan-Meier; Max=maximum; Min=minimum; NE=not estimable; PFS=progression-free survival.

[a] Based on the earliest contributing assessment.

[b] Based on the latest contributing assessment.

[c] Based on stratified Cox proportional hazards model, stratified by randomization stratification factors as recorded in IXRS

[d] Based on stratified log-rank test, stratified by randomization stratification factors as recorded in IXRS

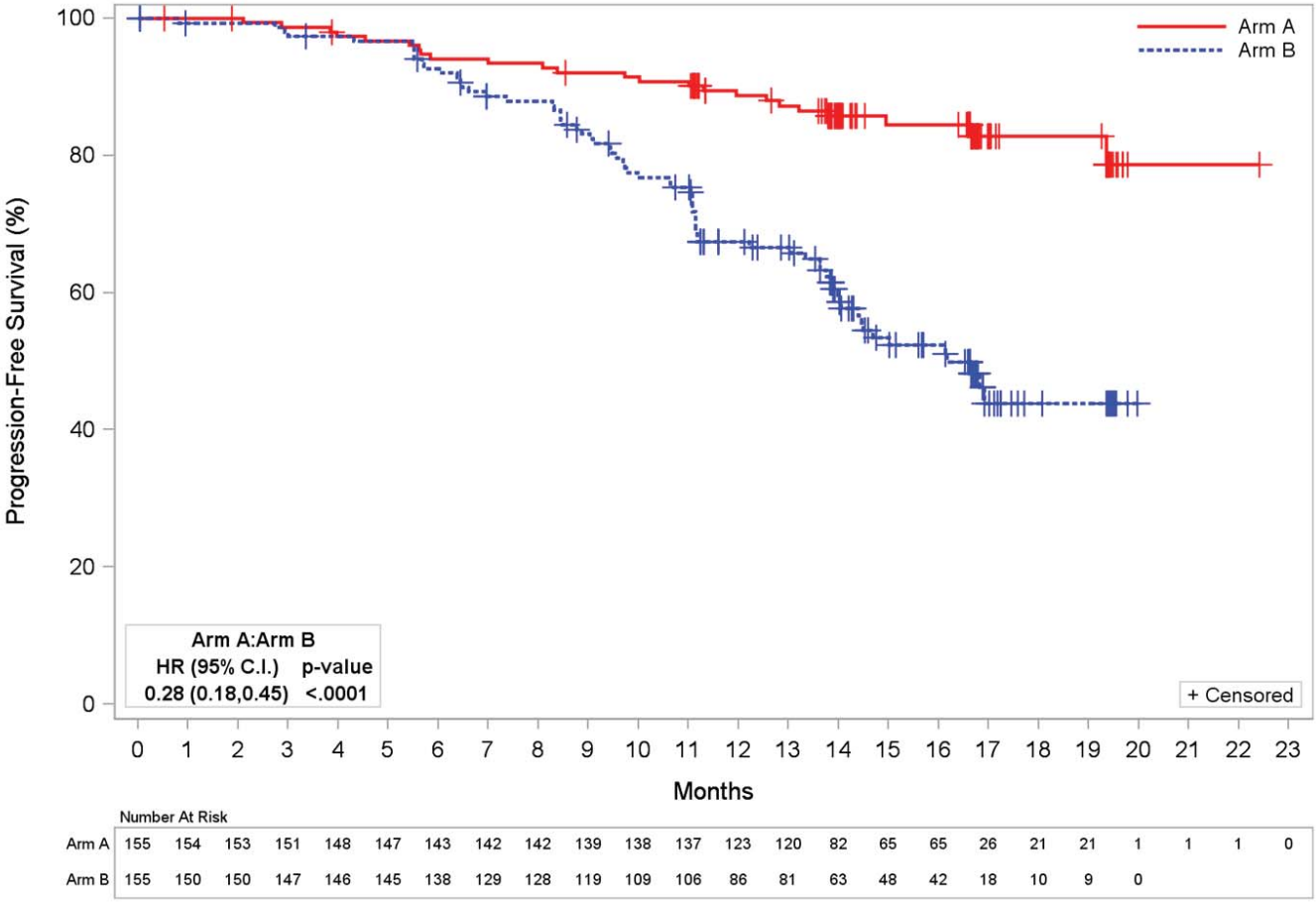
[e] Based on unstratified Cox proportional hazards model.

[f] Based on unstratified log-rank test.

Time to event (or time to censor for censored subjects) is calculated as date of disease progression or death (censoring date for censored subjects) - randomization date + 1. Months are derived as days/30.4375.

Source: ASCEND clinical report, Table 14.2.1.5.

Figure 9 Kaplan-Meier Plot for Progression-Free Survival by Investigator Assessment: Censoring at Subsequent Anticancer Therapy (ITT Population)



CI=confidence interval; HR=hazard ratio.
Source: ASCEND clinical report, Figure 14.2.1.12.

Concordance Between IRC-Assessed and Investigator-Assessed PD

The overall concordance rates between the IRC-assessed and investigator-assessed PD for acalabrutinib and IR/BR were 93.5% and 81.3%, respectively (Table 23).

Table 23 Concordance between IRC- and Investigator-Assessed PD (ITT Population)

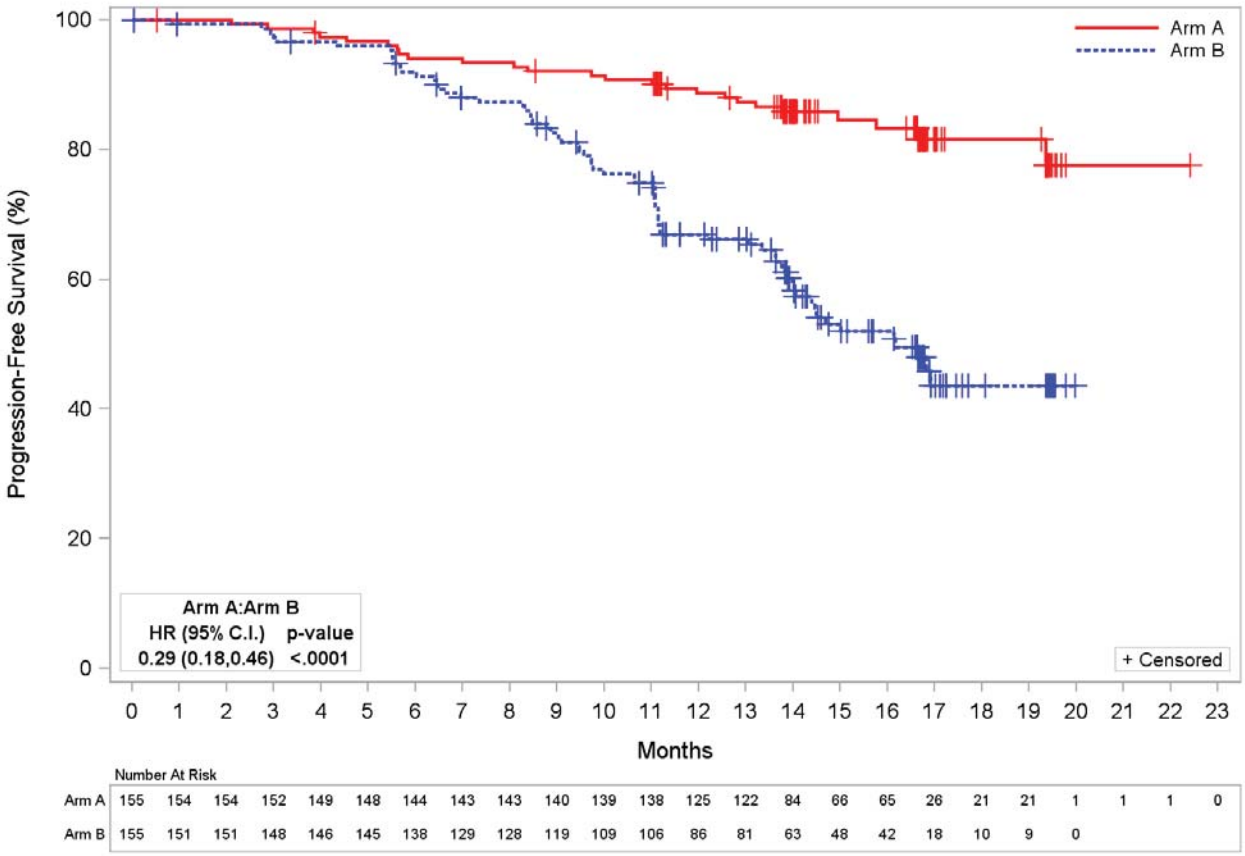
	PD by Investigator		
PD by IRC	**Yes**	**No**	**Total**
Arm A: Acalabrutinib (N=155)			
Yes	13 (8.4%)	6 (3.9%)	19 (12.3%)
No	4 (2.6%)	132 (85.2%)	136 (87.7%)
Total	17 (11.0%)	138 (89.0%)	155 (100%)
Overall concordance rate	93.5%		
Arm B: IR/BR (N=155)			
Yes	44 (28.4%)	15 (9.7%)	59 (38.1%)
No	14 (9.0%)	82 (52.9%)	96 (61.9%)
Total	58 (37.4%)	97 (62.6%)	155 (100%)
Overall concordance rate	81.3%		

BR=bendamustine/rituximab; IR=idelalisib/rituximab; IRC=Independent Review Committee; ITT=intent-to-treat; PD=progressive disease.
Source: ASCEND clinical report, Table 14.2.1.7.

Sensitivity Analyses

A sensitivity analysis of PFS by investigator assessment including PFS without censoring for subsequent anticancer therapy was consistent with the primary analysis (HR=0.29 [95% CI: 0.18, 0.46]; p<0.0001) (Figure 10).

Figure 10 Kaplan-Meier Plot for Sensitivity Analysis of Progression-Free Survival by Investigator Assessment Including PFS Events After Subsequent Anticancer Therapy (ITT Population)



Source: ASCEND clinical report, Figure 14.2.1.13.

Investigator-Assessed and IRC-assessed ORR

Per IRC assessment, the ORR for acalabrutinib and IR/BR was 81.3% (95% CI: 74.4, 86.6) and 75.5% (95% CI: 68.1, 81.6), respectively (p=0.2248). PR was achieved in 126 (81.3%) subjects in the acalabrutinib group 115 (74.2%) subjects in the IR/BR group. No acalabrutinib subjects and 2 IR/BR subjects achieved a CR. The ORR including PRL for acalabrutinib and IR/BR subjects, respectively, was 88.4% (95% CI: 82.4, 92.5) and 77.4% (95% CI: 70.2, 83.3), with a statistically significant difference between arms of 11.0% (95% CI: 2.7, 19.3; p=0.0110) (Table 24).

Per investigator assessment, the ORR for acalabrutinib and IR/BR was 79.4% (95% CI: 72.3, 85.0) and 83.2% (95% CI: 76.6, 88.3), respectively (p=0.3453). PR was achieved in 116 (74.8%) acalabrutinib subjects and 123 (79.4%) IR/BR subjects. Two acalabrutinib subjects and 5 IR/BR subjects achieved a CR. The ORR including PRL for acalabrutinib and IR/BR was 92.9% (95% CI: 87.7, 96.0) and 87.1% (95% CI: (80.9, 91.5), respectively (p=0.0849) (Table 24).

Table 24 Best Overall Response by IRC and Investigator Assessment (ITT Population)

	IRC Assessment		Investigator Assessment	
	Arm A Acalabrutinib (N=155)	Arm B IR or BR (N=155)	Arm A Acalabrutinib (N=155)	Arm B IR or BR (N=155)
Best Overall Response, n (%)				
CR	0	2 (1.3%)	2 (1.3%)	5 (3.2%)
CRi	0	0	1 (0.6%)	1 (0.6%)
nPR	0	0	4 (2.6%)	0
PR	126 (81.3%)	115 (74.2%)	116 (74.8%)	123 (79.4%)
PRL	11 (7.1%)	3 (1.9%)	21 (13.5%)	6 (3.9%)
SD	9 (5.8%)	12 (7.7%)	7 (4.5%)	11 (7.1%)
PD	2 (1.3%)	1 (0.6%)	1 (0.6%)	3 (1.9%)
UNK or missing	7 (4.5%)	22 (14.2%)	3 (1.9%)	6 (3.9%)
ORR (CR+CRi+nPR+PR), n (%)	126 (81.3%)	117 (75.5%)	123 (79.4%)	129 (83.2%)
95% CI[a]	(74.4%, 86.6%)	(68.1%, 81.6%)	(72.3%, 85.0%)	(76.6%, 88.3%)
ORR difference (versus Arm B)	5.8%		-3.9%	
95% CI[a]	(-3.3%, 14.9%)		(-12.5%, 4.8%)	
p-value[b]	0.2248		0.3453	
ORR+PRL (CR+CRi+nPR+PR+PRL), n (%)	137 (88.4%)	120 (77.4%)	144 (92.9%)	135 (87.1%)
95% CI[a]	(82.4%, 92.5%)	(70.2%, 83.3%)	(87.7%, 96.0%)	(80.9%, 91.5%)
ORR+PRL difference (versus Arm B)	11.0%		5.8%	
95% CI[a]	(2.7%, 19.3%)		(-0.8%, 12.5%)	
p-value[b]	0.0110		0.0849	

BR=bendamustine/rituximab; CI=confidence interval; CR=complete response; CRi=complete response with incomplete blood count recovery; IR=idelalisib/rituximab; IRC=Independent Review Committee; ITT=intent-to-treat; IXRS=interactive voice/web response system; nPR=nodular partial response; ORR=overall response rate; PR=partial response; PRL=partial response with lymphocytosis; SD=stable disease; UNK=unknown.

[a] 95% CI based on Normal approximation (with use of Wilson's score).

[b] Based on Cochran-Mantel-Haenzel test with adjustment for randomization stratification factors as recorded in IXRS.

Source: ASCEND clinical report, Table 14.2.2, Table 14.2.2.1.

Subgroup Analysis of ORR by IRC Assessment

In general, IRC-assessed ORR was consistent across most prespecified subgroups (Table 25).

Table 25 Overall Response Rate by IRC Assessment by for Selected Subgroups (ITT Population)

	Arm A Acalabrutinib		Arm B IR or BR	
	Responders/ Subjects	ORR (%) (95% CI)	Responders/ Subjects	ORR (%) (95% CI)
Overall	126/155	81.3 (74.2, 87.1)	117/155	75.5 (67.9, 82.0)
Presence of 17p deletion				
Yes	25/28	89.3 (71.8, 97.7)	19/26	73.1 (52.2, 88.4)
No	101/127	79.5 (71.5, 86.2)	98/129	76.0 (67.7, 83.1)
ECOG PS at randomization				

	Arm A Acalabrutinib		Arm B IR or BR	
	Responders/ Subjects	ORR (%) (95% CI)	Responders/ Subjects	ORR (%) (95% CI)
0, 1	114/137	83.2 (75.9, 89.0)	102/135	75.6 (67.4, 82.5)
2	12/18	66.7 (41.0, 86.7)	15/20	75.0 (50.9, 91.3)
Number of prior therapies				
1-3	116/139	83.5 (76.2, 89.2)	105/138	76.1 (68.1, 82.9)
≥4	10/16	62.5 (35.4, 84.8)	12/17	70.6 (44.0, 89.7)
Age group				
<65	49/58	84.5 (72.6, 92.7)	40/57	70.2 (56.6, 81.6)
≥65	77/97	79.4 (70.0, 86.9)	77/98	78.6 (69.1, 86.2)
<75	100/121	82.6 (74.7, 88.9)	95/124	76.6 (68.2, 83.7)
≥75	26/34	76.5 (58.8, 89.3)	22/31	71.0 (52.0, 85.8)
Sex				
Male	87/108	80.6 (71.8, 87.5)	75/100	75.0 (65.3, 83.1)
Female	39/47	83.0 (69.2, 92.4)	42/55	76.4 (63.0, 86.8)
Race				
White	119/145	82.1 (74.8, 87.9)	106/141	75.2 (67.2, 82.1)
Non-white	7/10	70.0 (34.8, 93.3)	11/14	78.6 (49.2, 95.3)
Rai stage at screening				
Stage 0-II	72/90	80.0 (70.2, 87.7)	70/90	77.8 (67.8, 85.9)
Stage III-IV	54/65	83.1 (71.7, 91.2)	46/64	71.9 (59.2,82.4)
Bulky disease				
<5 cm	62/79	78.5 (67.8, 86.9)	59/80	73.8 (62.7, 83.0)
≥5 cm	64/76	84.2 (74.0, 91.6)	58/75	77.3 (66.2, 86.2)
B2-microglobulin at baseline				
≤3.5 mg/L	22/32	68.8 (50.0, 83.9)	19/25	76.0 (54.9, 90.6)
>3.5 mg/L	101/120	84.2 (76.4, 90.2)	96/126	76.2 (67.8, 83.3)
IGHV				
Mutated	25/33	75.8 (57.7, 88.9)	21/26	80.8 (60.6, 93.4)
Unmutated	98/118	83.1 (75.0, 89.3)	94/125	75.2 (66.7, 82.5)
Presence of 11q deletion - Yes	29/39	74.4 (57.9, 87.0)	32/44	72.7 (57.2, 85.0)
TP53 mutation - Yes	34/39	87.2 (72.6, 95.7)	24/34	70.6 (52.5, 84.9)
17p deletion, TP53 mutation, 11q deletion, or unmutated IGHV - Yes	112/135	83.0 (75.5, 88.9)	104/137	75.9 (67.9, 82.8)
Complex karyotype - Yes	40/50	80.0 (66.3, 90.0)	31/46	67.4 (52.0, 80.5)

BR=bendamustine/rituximab; CI=confidence interval; del=deletion; IR=idelalisib/rituximab; ITT=intent-to-treat; IXRS=interactive voice/web response system; ECOG PS=Eastern Cooperative Oncology Group performance status; IGHV=immunoglobulin heavy-chain variable; IRC=Independent Review Committee; ITT=intent-to-treat.
Source: ASCEND clinical report, Figure 14.2.2.3.

Richter's Transformation

Four subjects in the acalabrutinib arm and 5 subjects in the IR/BR arm (4 treated with IR, 1 treated with BR) had Richter's transformation during the study.

FDA reviewer comment: *This represents cases of reported Richter's transformation. Whether transformation occurred in each case is not established due to lack of biopsy confirmation.*

The Applicant's Description:

Concordance Between IRC-Assessed and Investigator-Assessed Best Overall Response
The overall concordance rates between the IRC-assessed and investigator-assessed ORR for acalabrutinib and IR/BR were 86.5% and 80.0%, respectively (Table 26).

Table 26 Concordance between IRC- and Investigator-Assessed Best Overall Response (ITT Population)

	Responder by Investigator			
Responder by IRC	**Yes**	**No**	**Unknown/missing**	**Total**
Arm A: Acalabrutinib (N=155)				
Yes	117 (75.5%)	9 (5.8%)	0	126 (81.3%)
No	5 (3.2%)	17 (11.0%)	0	22 (14.2%)
Unknown/missing[a]	1 (0.6%)	3 (1.9%)	3 (1.9%)	7 (4.5%)
Total	123 (79.4%)	29 (18.7%)	3 (1.9%)	155 (100%)
Overall concordance rate	86.5%			
Arm B: IR/BR (N=155)				
Yes	112 (72.3%)	5 (3.2%)	0	117 (75.5%)
No	4 (2.6%)	12 (7.7%)	0	16 (10.3%)
Unknown/missing[a]	13 (8.4%)	3 (1.9%)	6 (3.9%)	22 (14.2%)
Total	129 (83.2%)	20 (12.9%)	6 (3.9%)	155 (100%)
Overall concordance rate	80.0%			

CR=complete response; CRi=complete response with incomplete blood count recovery; IRC=Independent Review Committee; ITT=intent-to-treat; nPR=nodular partial response; PR=partial response.

[a] 'UNK' category includes 6 subjects without any postbaseline IRC response assessment, and 20 subjects with IRC global assessment as 'Not Applicable' whereas their IRC timepoint assessments included 'PR' at either a single timepoint or at non-consecutive timepoints. Missing=subjects without any postbaseline investigator assessment.

Responder=CR+CRi+nPR+PR.
Source: ASCEND clinical report, Table 14.2.2.2.

Overall Survival

With a median follow-up of 16.10 months in the acalabrutinib arm and 15.74 months in the IR/BR arm, 15 (9.7%) subjects in the acalabrutinib arm and 18 (11.6%) subjects in the IR/BR arm had died. The median OS was not reached in either treatment arm, with a HR of 0.84 (95% CI: 0.42, 1.66; p=0.6089) (Table 27).

The KM estimate of OS at 12 months for acalabrutinib and IR/BR was 94.1% (95% CL: 89.0, 96.9) and 90.6% (95% CI: 84.6, 94.3), respectively. The KM estimate of OS at 18 months for acalabrutinib and IR/BR was 89.7% (95% CI: 83.4, 93.7) and 88.1% (95% CI: 81.4, 92.5), respectively (Table 27).

The median OS was not reached in either treatment arm, with a HR of 0.84 (95% CI: 0.42, 1.66; p=0.6089) (Figure 11).

Sensitivity analysis of OS censoring at crossover is consistent with the primary OS analysis.

Table 27 Overall Survival (ITT Population)

	Arm A Acalabrutinib (N=155)	Arm B IR or BR (N=155)
Subject Status		
Events, n (%)[a]	15 (9.7%)	18 (11.6%)
Death	15 (9.7%)	18 (11.6%)
Censored, n (%)[b]	140 (90.3%)	137 (88.4%)
Alive	140 (90.3%)	137 (88.4%)
Overall survival (months)		
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.5+, 22.4+	0.0+, 22.0+
Stratified Analysis (versus Arm B)		
Hazard Ratio (95% CI)[c]	0.84 (0.42, 1.66)	
p-value[d]	0.6089	
KM estimates of OS by timepoint (%)		
6 Months OS Rate (95% CI)	98.1 (94.1, 99.4)	96.7 (92.3, 98.6)
9 Months OS Rate (95% CI)	96.1 (91.5, 98.2)	93.3 (87.9, 96.3)
12 Months OS Rate (95% CI)	94.1 (89.0, 96.9)	90.6 (84.6, 94.3)
15 Months OS Rate (95% CI)	90.8 (85.0, 94.5)	89.2 (82.9, 93.2)
18 Months OS Rate (95% CI)	89.7 (83.4, 93.7)	88.1 (81.4, 92.5)
21 Months OS Rate (95% CI)	89.7 (83.4, 93.7)	85.5 (76.4, 91.3)

BR=bendamustine/rituximab; CI=confidence interval; IR=idelalisib/rituximab; IRC=Independent Review Committee; ITT=intent-to-treat; IXRS=interactive voice/web response system; KM=Kaplan-Meier; Max=maximum; Min=minimum; NE=not estimable; OS=overall survival.

[a] Death of any cause.

[b] Based on the latest contributing assessment.

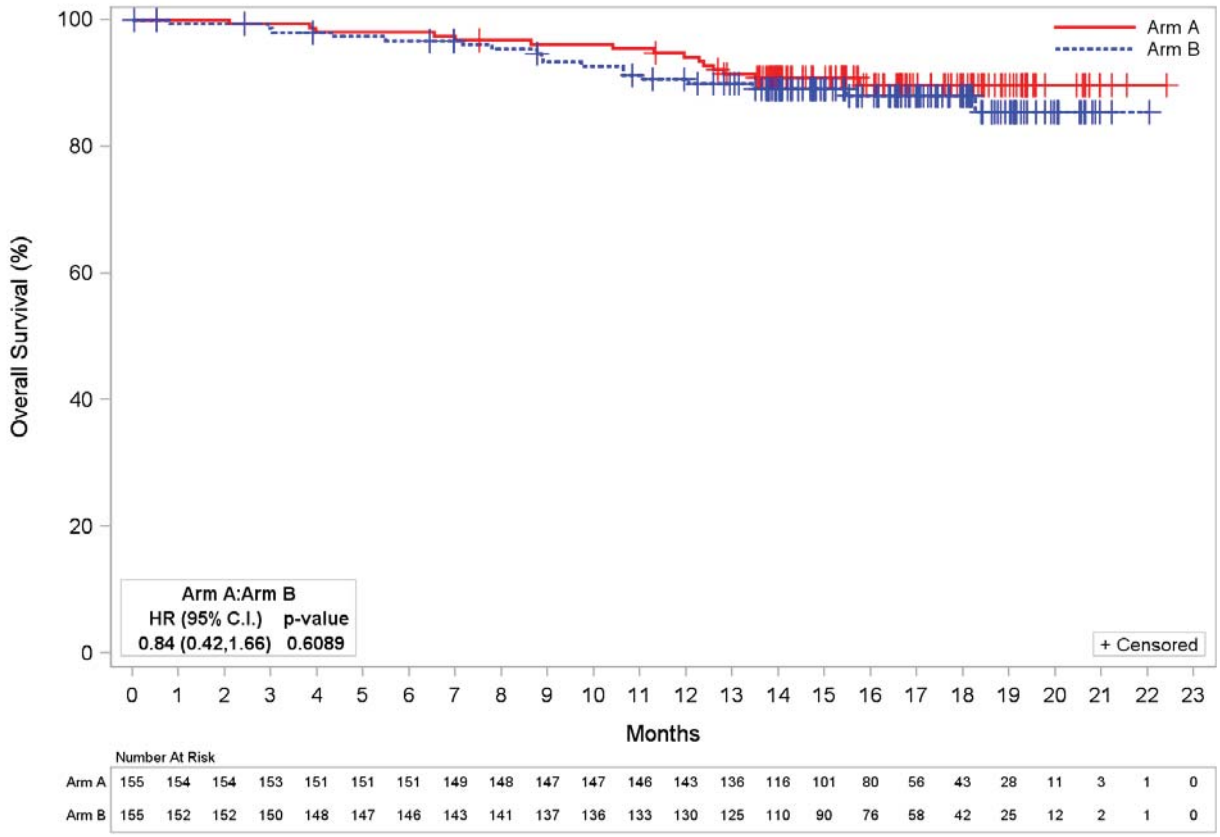
[c] Based on stratified Cox proportional hazards model, stratified by randomization stratification factors as recorded in IXRS.

[d] Based on stratified log-rank test, stratified by randomization stratification factors as recorded in IXRS.

Time to event (or time to censor for censored subjects) is calculated as date of death (censoring date for censored subjects) - randomization date + 1. Months are derived as days/30.4375.

Source: ASCEND clinical report, Table 14.2.3.

Figure 11 Kaplan-Meier Plot for Overall Survival (ITT Population)



Source: ASCEND clinical report, Figure 14.2.3.2.

Investigator- and IRC-Assessed Duration of Response

Acalabrutinib demonstrated a clinically relevant improvement in IRC-assessed DOR (HR=0.33 [95% CI: 0.19, 0.59]) and investigator-assessed DOR (HR=0.20 [95% CI: 0.10, 0.42]) compared with IR/BR. The median DOR was not reached based on IRC assessment (range: 0.0+ to 19.6+ months for acalabrutinib and 2.1+ to 16.8+ months for IR/BR) or investigator assessment (range: 0.0+ to 19.6+ months for acalabrutinib and 0.0+ to 16.8+ months for IR/BR). Based on IRC assessment, disease progression in the acalabrutinib and IR/BR arms occurred in 9.5% and 35.9% of subjects, respectively, and based on investigator assessment, disease progression in the acalabrutinib and IR/BR arms occurred in 5.7% and 34.1% of subjects, respectively (Table 28).

The KM estimate of the proportion of responders without a PFS event at 12 months for acalabrutinib and IR/BR was 85.0 (95% CI: 76.1, 90.8) and 59.5% (95% CI: 48.2, 69.1), respectively, based on IRC assessment, and 90.0% (95% CI: 81.3, 94.8) and 57.2% (95% CI: 46.6, 66.5), respectively, based on investigator assessment (Table 28).

Table 28 Duration of Response by IRC and Investigator Assessment (ITT Population)

	IRC Assessment		Investigator Assessment	
	Arm A Acalabrutinib (N=126)	Arm B IR or BR (N=117)	Arm A Acalabrutinib (N=123)	Arm B IR or BR (N=129)
Subject Status				
Events, n (%)[a]	16 (12.7%)	46 (39.3%)	9 (7.3%)	50 (38.8%)
Death	4 (3.2%)	4 (3.4%)	2 (1.6%)	6 (4.7%)
Disease progression	12 (9.5%)	42 (35.9%)	7 (5.7%)	44 (34.1%)
Censored, n (%)[b]	110 (87.3%)	71 (60.7%)	114 (92.7%)	79 (61.2%)
Last adequate assessment before data cutoff	110 (87.3%)	70 (59.8%)	114 (92.7%)	78 (60.5%)
Last adequate assessment before subsequent anticancer therapy	0	1 (0.9%)	0	1 (0.8%)
Duration of response (months)				
Median (95% CI)	NE (NE, NE)	13.6 (11.9, NE)	NE (NE, NE)	13.9 (11.3, NE)
Min, Max	0.0+, 19.6+	2.1+, 16.8+	0.0+, 19.6+	0.0+, 16.8+
Stratified analysis (versus Arm B)				
Hazard ratio (95% CI)[c]	0.33 (0.19, 0.59)		0.20 (0.10, 0.42)	
p-value[d]	<0.0001		<0.0001	
KM estimates of DOR by timepoint (%)				
6 months DOR rate (95% CI)	94.8 (88.7, 97.6)	87.6 (79.7, 92.6)	95.4 (89.2, 98.0)	82.1 (74.1, 87.8)
9 months DOR rate (95% CI)	87.8 (79.9, 92.8)	71.0 (60.9, 78.9)	93.3 (86.4, 96.8)	71.3 (62.1, 78.6)
12 months DOR rate (95% CI)	85.0 (76.1, 90.8)	59.5 (48.2, 69.1)	90.0 (81.3, 94.8)	57.2 (46.6, 66.5)
15 months DOR rate (95% CI)	81.8 (70.1, 89.2)	41.4 (28.2, 54.1)	90.0 (81.3, 94.8)	47.8 (36.0, 58.6)

BR=bendamustine/rituximab; CI=confidence interval; DOR=duration of response; IR=idelalisib/rituximab; IRC=Independent Review Committee; ITT=intent-to-treat; IXRS=interactive voice/web response system; KM=Kaplan-Meier; Max=maximum; Min=minimum; NE=not estimable.

[a] Based on the earliest contributing assessment.

[b] Based on the latest contributing assessment.

[c] Based on stratified Cox proportional hazards model, stratified by randomization stratification factors as recorded in IXRS.

[d] Based on stratified log-rank test, stratified by randomization stratification factors as recorded in IXRS.

Source: ASCEND clinical report, Table 14.2.4, Table 14.2.4.1.

Time to Next Treatment

Acalabrutinib significantly prolonged TTNT compared with IR/BR (HR=0.35 [95% CI: 0.21, 0.58]); p<0.0001). The median TTNT was not reached for acalabrutinib (range: 0.5+ to 22.4+ months) or for IR/BR (range: 0.0+ to 22.0+ months) (Table 29).

The KM estimate of the proportion of subjects without starting next anticancer treatment for acalabrutinib and IR/BR was 88.9% (95% CI: 82.8, 93.0) and 79.7% (95% CI: 72.3, 85.4), respectively, at 12 months, and 84.9% (95% CI: 77.9, 89.8) and 60.0% (95% CI: 50.1, 68.5), respectively, at 18 months (Table 29).

Table 29 Time to Next Treatment (ITT Population)

	Arm A Acalabrutinib (N=155)	Arm B IR or BR (N=155)
Subject Status		
Events, n (%)[a]	22 (14.2%)	53 (34.2%)
Death	9 (5.8%)	10 (6.5%)
Start of crossover therapy	0	35 (22.6%)
Start of subsequent anticancer therapy	13 (8.4%)	8 (5.2%)
Censored, n (%)[b]	133 (85.8%)	102 (65.8%)
Alive and no crossover/subsequent anticancer therapy	133 (85.8%)	102 (65.8%)
Time to next treatment (months)		
Median (95% CI)	NE (NE, NE)	NE (18.4, NE)
Min, Max	0.5+, 22.4+	0.0+, 22.0+
Stratified analysis (vs. Arm B)		
Hazard ratio (95% CI)[c]	0.35 (0.21, 0.58)	
p-value[d]	<0.0001	
KM estimates of TTNT by timepoint (%)		
6 Months TTNT Rate (95% CI)	96.1 (91.5, 98.2)	94.7 (89.7, 97.3)
9 Months TTNT Rate (95% CI)	93.5 (88.3, 96.4)	88.6 (82.4, 92.8)
12 Months TTNT Rate (95% CI)	88.9 (82.8, 93.0)	79.7 (72.3, 85.4)
15 Months TTNT Rate (95% CI)	87.6 (81.2, 91.9)	67.8 (59.2, 75.0)
18 Months TTNT Rate (95% CI)	84.9 (77.9, 89.8)	60.0 (50.1, 68.5)
21 Months TTNT Rate (95% CI)	84.9 (77.9, 89.8)	54.7 (43.0, 64.9)

BR=bendamustine/rituximab; CI=confidence interval; IR=idelalisib/rituximab; IRC=Independent Review Committee; ITT=intent-to-treat; IXRS=interactive voice/web response system; KM=Kaplan-Meier; Max=maximum; Min=minimum; NE=not estimable; TTNT=time to next treatment.

[a] Based on the earliest contributing assessment.

[b] Based on the latest contributing assessment.

[c] Based on stratified Cox proportional hazards model, stratified by randomization stratification factors as recorded in IXRS.

[d] Based on stratified log-rank test, stratified by randomization stratification factors as recorded in IXRS.

Time to event (or time to censor for censored subjects) is calculated as date of institution of nonprotocol-specified treatment (censoring date for censored subjects) - randomization date + 1. Months are derived as days/30.4375.

Source: ASCEND clinical report, Table 14.2.5.

Subsequent Anticancer Therapy

The most common subsequent anticancer therapies used by subjects in the acalabrutinib arm were anti-CD20 monoclonal antibodies (7 [4.5%] subjects), alkylators other than bendamustine (5 [3.2%] subjects), and venetoclax (5 [3.2%] subjects). The most common subsequent anticancer therapies used by subjects in the IR/BR arm were alkylators other than bendamustine and anti-CD20 monoclonal antibodies (11 [3.5%] subjects each), and venetoclax (7 [2.3%] subjects) (Table 30).

Table 30 Subsequent Anticancer Therapy for CLL (ITT Population)

	Arm A Acalabrutinib (N=155)	Arm B IR or BR (N=155)	Total (N=310)
Time from first dose to subsequent anticancer therapy (months)			
n	13	11	24
Mean (SD)	9.36 (4.33)	10.30 (5.13)	9.79 (4.63)
Median	10.2	11.1	10.3
Min, Max	2.0, 15.2	1.3, 18.6	1.3, 18.6
Number of subsequent anticancer therapies			
1	11 (7.1%)	8 (5.2%)	19 (6.1%)
2	2 (1.3%)	2 (1.3%)	4 (1.3%)
3	0	1 (0.6%)	1 (0.3%)
≥4	0	0	0
Median	1	1	1
Min, Max	1, 2	1, 3	1, 3
Type of subsequent anticancer therapy			
Purine analogues	0	0	0
Alkylators other than bendamustine	5 (3.2%)	6 (3.9%)	11 (3.5%)
Bendamustine	2 (1.3%)	1 (0.6%)	3 (1.0%)
Anti-CD20 monoclonal antibodies	7 (4.5%)	4 (2.6%)	11 (3.5%)
Ibrutinib	2 (1.3%)	4 (2.6%)	6 (1.9%)
Venetoclax	5 (3.2%)	2 (1.3%)	7 (2.3%)
Other[a]	1 (0.6%)	2 (1.3%)	3 (1.0%)

BR=bendamustine/rituximab; CLL=chronic lymphocytic leukemia; IR=idelalisib/rituximab; ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation.

[a] One subject received azacitidine and cytarabine + idarubicin, 1 subject received cytarabine + methotrexate, and 1 subject received dexamethasone monotherapy.

Three subjects received subsequent therapy for non-CLL malignancies of myelodysplastic syndrome/acute myeloid leukaemia (1 subject received azacitidine and cytarabine + idarubicin) and lung cancer (1 subject received cisplatin + vinorelbine and 1 subject received carboplatin + etoposide).

Based on the whole study period, that is, main study period + crossover study period.

Source: ASCEND clinical report, Table 14.1.3.4.

PROs by FACIT-Fatigue

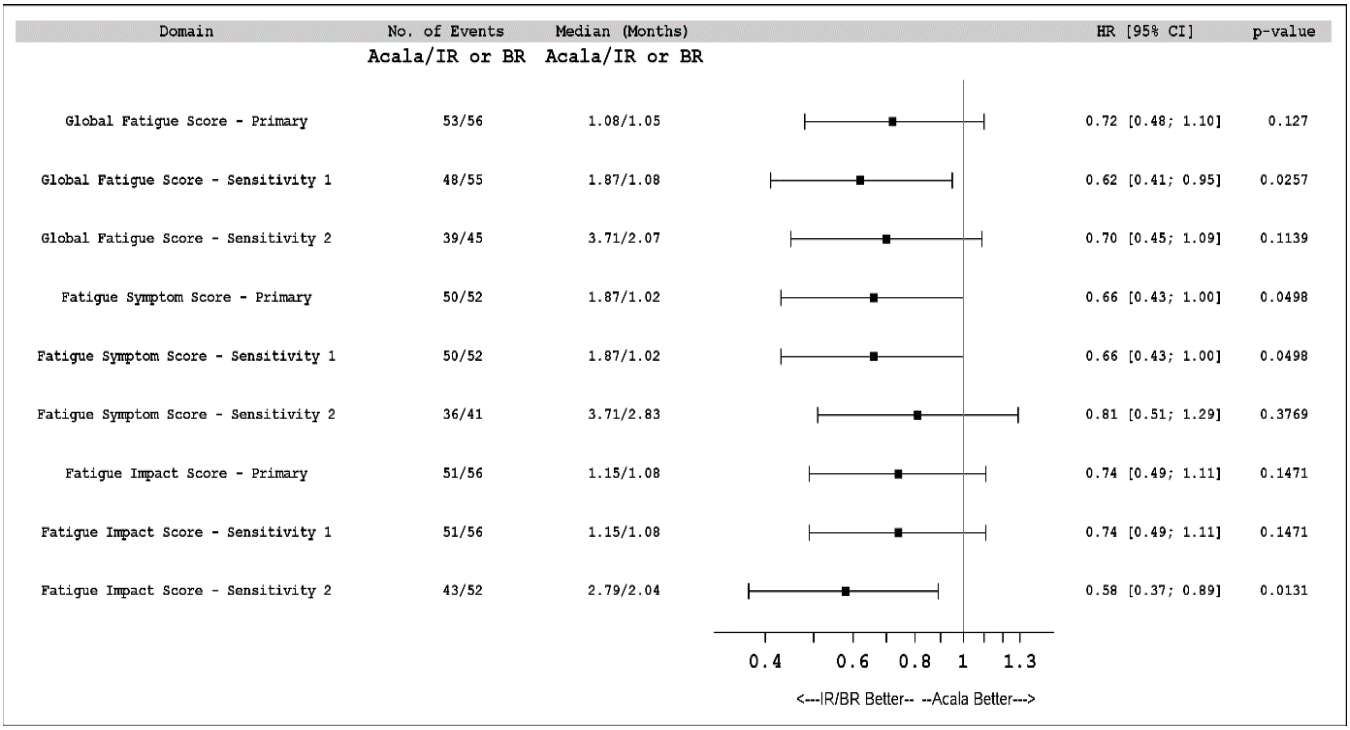
Time to Event Analysis – SF Population

All subjects in the Severe Fatigue (SF) population completed the FACIT-Fatigue at baseline as the FACIT-Fatigue score was used to assess the SF population threshold. The SF population was defined as all randomized subjects with a baseline FACIT-Fatigue score ≤34. At Week 48, 40 subjects in the acalabrutinib arm and 31 subjects in the IR/BR arm completed FACIT-Fatigue questionnaires meeting the minimum requirements for scoring (unadjusted completion rate=70.2% and 50.8%, respectively; adjusted completion rate=80.0% and 77.5%, respectively) in the SF population.

Overall, time to first improvement was slightly longer among the acalabrutinib arm. Median (95% CI) time to improvement in Global Fatigue Score (GFS) was 1.08 (1.02-1.22) for

acalabrutinib and 1.05 (0.99-1.12) months for IR/BR subjects with use of primary thresholds to define improvement. No significant differences were observed in time to first improvement when applying the primary thresholds. Among the sensitivity thresholds, time to first improvement was significantly shorter for the IR/BR arm for GFS (sensitivity analysis 1, p=0.0257) and FIS (sensitivity analysis 2, p=0.0131). However, differences between time to first improvement were small: 1.87 versus 1.08 months (sensitivity analysis 1 GFS) and 2.79 versus 2.04 months (sensitivity analysis 2 FIS) (Figure 12).

Figure 12 Time to First Improvement in FACIT-Fatigue Scores (SF Population)

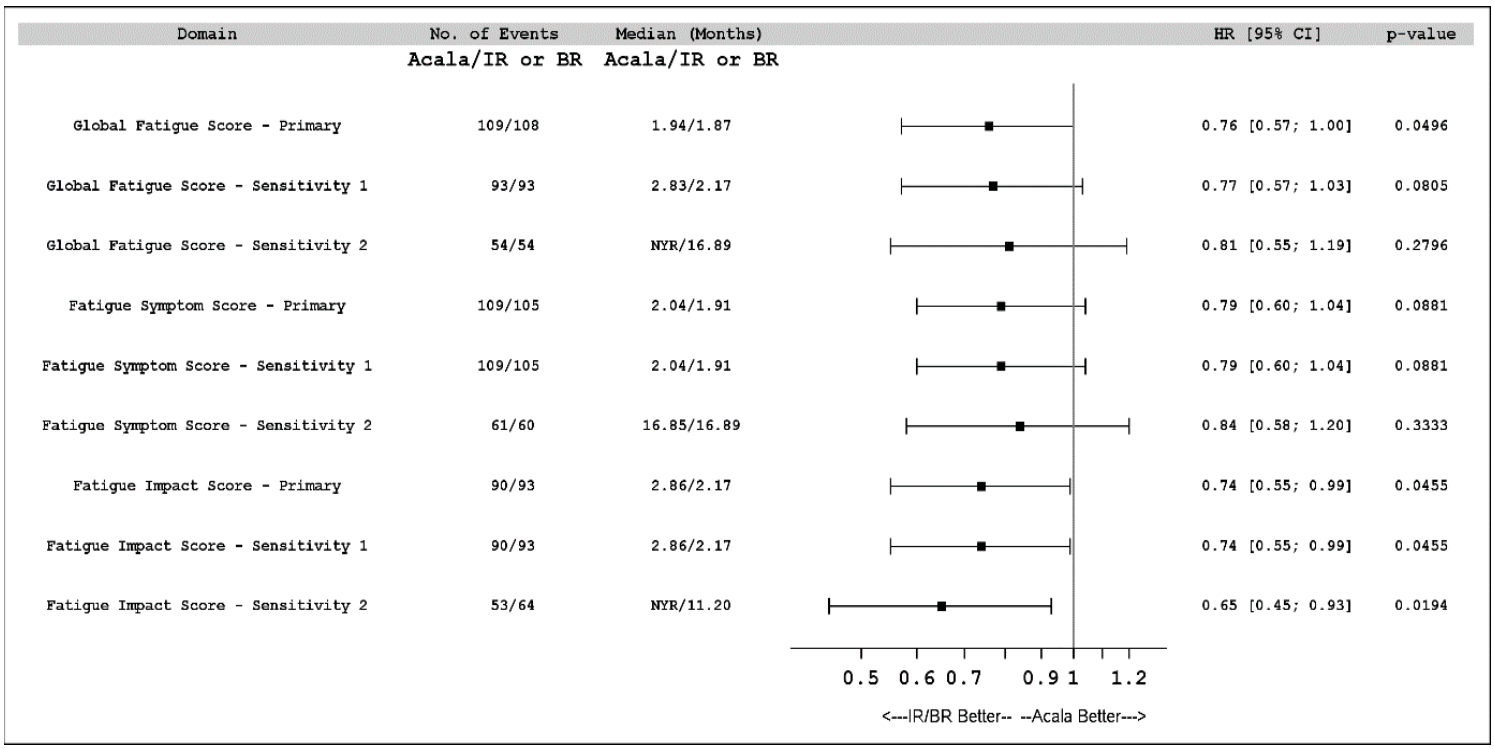


Time to Event Analysis – ITT Population

At Week 48, 117 subjects in the acalabrutinib arm and 77 subjects in the IR/BR arm completed FACIT-Fatigue questionnaires meeting the minimum requirements for scoring (unadjusted completion rate=75.5.2% and 49.7%, respectively; adjusted completion rate=83.6% and 70.6.5% respectively) in the ITT population (all randomized subjects).

Overall, time to first improvement was slightly longer among the acalabrutinib arm. Median (95%CI) time to improvement in the GFS was 1.94 (1.15-2.83) months for acalabrutinib and 1.87 (1.12-2.07) months for IR/BR with use of primary thresholds to define improvement. Time to first improvements was nominally significantly shorter for the IR/BR arm for GFS with use of the primary threshold (p=0.0496) and for FIS with use of primary and SA1 thresholds (p=0.0455), all favoring the IR/BR arm. However, differences between time to first improvement were small: 1.94 versus 1.87 months (PA GFS) and 2.86 versus 2.17 (PA and SA1 FIS) (Figure 13).

Figure 13 Time to First Improvement in FACIT-Fatigue Scores (ITT Population)



Source: ASCEND PRO report Table 11.1.2; Figure 11.1.2.

The Applicant's Position:

Analysis on the secondary endpoint of investigator-assessed PFS was consistent with primary analysis (HR=0.28 [95% CI: 0.18, 0.45]; p<0.0001). The clinical benefit with acalabrutinib was further demonstrated by a clinically relevant improvement in DOR for acalabrutinib compared with IR/BR, both by IRC assessment (HR=0.33) and investigator assessment (HR=0.20) and statistically significant prolongation of TTNT for acalabrutinib compared with IR/BR (HR=0.35; p<0.0001). ORR (CR+CRi+nPR+PR) for acalabrutinib and IR/BR was similar based on IRC assessment (81.3% and 75.5%, respectively) and investigator assessment (79.4% and 83.2%, respectively). ORR+PRL for acalabrutinib and IR/BR was 88.4% and 77.4%, respectively, based in IRC assessment, and 92.9% and 87.1%, respectively, based on investigator assessment.

Regulatory Authorities Assessment:

FDA does not agree with the Applicant's description on the secondary and relevant endpoints described in this section. Since IRC-assessed PFS crossed the efficacy boundary at the interim analysis, the results from IRC-assessed ORR analysis can be used to determine whether there is a statistically significant difference between acalabrutinib arm and IR/BR arm. This difference was 5.8% (95%CI: -3.3%, 14.9%) and not statistically significant (P-value=0.2248). Since IRC-assessed ORR did not cross the efficacy boundary, no further hypothesis testing should be conducted and the result from OS analysis is considered exploratory and should only be

described descriptively. The median OS was not reached in either treatment arm due to the early timing of analysis.

All other endpoints (i.e., investigator-assessed PFS, investigator-assessed ORR, IRC- and investigator-assessed duration of response, time to next treatment, PROs by FACIT-Fatigue) that the Applicant specified in this section were not adjusted for multiplicity. Hence, the results from these analyses should be considered exploratory only. Any inferential conclusion of benefit of acalabrutinib over IR/BR based on these results was not appropriate.

FDA does not agree that the KM Estimates of PFS by different timepoints should be presented in Table 18 and 23. These estimates are misleading because they only present estimates at one single time point and do not represent the overall effect of the treatment.

FDA does not agree with the interpretation of the duration of response analysis based on the ITT population. Caution should be used in interpreting the duration of response comparison because the analysis is conditional on subjects having had a response. The conditional set patients considered in the analysis no longer has the same baseline characteristics as the originally randomized set of patients. The treatment effect therefore could be confounded with an unknown variable.

Dose/Dose Response

The Applicant's Description:

See Section 6.2.1.

The Applicant's Position:

Dose response was evaluated using population pharmacokinetic and exposure-response analyses. (Section 6.2.1).

Regulatory Authorities Assessment:

Refer to the clinical pharmacology assessment.

Durability of Response

The Applicant's Description:

See above described Efficacy Results – Primary Endpoint (Including Sensitivity Analyses) and Efficacy Results – Secondary and other relevant endpoints.

The Applicant's Position:

Durability of response for 100mg tablets BID daily regimen in ASCEND was demonstrated by superior PFS versus the control group as well as duration of response and is discussed above under Efficacy Results – Primary Endpoint (Including Sensitivity Analyses) and Efficacy Results – Secondary and other relevant endpoints.

Regulatory Authorities Assessment:
FDA does not agree with the Applicant's claim that durability of response in ASCEND was demonstrated by DOR, because DOR is considered exploratory. Any claim of benefit of acalabrutinib based on DOR is not appropriate.

Persistence of Effect

The Applicant's Description:
See above described Efficacy Results- Secondary and other relevant endpoints.

The Applicant's Position:
Persistence of effect over time after treatment with acalabrutinib in ASCEND was demonstrated by a trend for prolonged OS (Efficacy Results –Secondary and other relevant endpoints). Acalabrutinib demonstrated a clinically relevant improvement in DOR compared with IR/BR, both by IRC assessment (HR=0.33 [95% CI: 0.19, 0.59]) and investigator assessment (HR=0.20 [95% CI: 0.10, 0.42]).

Regulatory Authorities Assessment:
FDA does not agree with Applicant's claim that persistence of effect after treatment was demonstrated by a trend for prolonged OS. At the time of analysis, the median OS was not reached in either acalabrutinib arm or IR/BR arm. It is not appropriate to make a claim based on immature data. In addition, the results from IRC-assessed and investigator-assessed DOR are considered exploratory, any inferential conclusion based on these results are not appropriate.

Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

The Applicant's Description:
Statistical results for exploratory endpoints were considered descriptive. Exploratory analyses were performed using the ITT population as defined in ASCEND CSR unless otherwise specified.

The Applicant's Position:
There was a trend toward an improvement in (absence of) constitutional symptoms during treatment in both treatment arms for any constitutional symptoms as well as for individual constitutional symptoms (Table 31).

Table 31 Disease-Related Symptoms (Constitutional Symptoms) (ITT Population)

	Arm A Acalabrutinib (N=155)	Arm B IR or BR (N=155)
Any Constitutional Symptom		
Present at Baseline	91	97
Absent at Cycle 2 Day 1	62 (68.1%)	56 (57.7%)
Absent at Cycle 3 Day 1	73 (80.2%)	64 (66.0%)

	Arm A Acalabrutinib (N=155)	Arm B IR or BR (N=155)
Absent at Cycle 4 Day 1	75 (82.4%)	72 (74.2%)
Absent at Cycle 5 Day 1	77 (84.6%)	73 (75.3%)
Absent at Cycle 6 Day 1	81 (89.0%)	79 (81.4%)
Absent at Cycle 7 Day 1	81 (89.0%)	61 (62.9%)
Absent at Cycle 10 Day 1	81 (89.0%)	47 (48.5%)
Absent at Cycle 13 Day 1	79 (86.8%)	39 (40.2%)
Absent at Cycle 16 Day 1	67 (73.6%)	26 (26.8%)
Absent at Cycle 19 Day 1	36 (39.6%)	14 (14.4%)
Absent at Cycle 22 Day 1	7 (7.7%)	2 (2.1%)
Absent at Cycle 25 Day 1	0	0
Absent at Posttreatment Disease Follow-Up 01	1 (1.1%)	18 (18.6%)
Absent at Posttreatment Disease Follow-Up 02	1 (1.1%)	20 (20.6%)
Absent at Posttreatment Disease Follow-Up 03	1 (1.1%)	17 (17.5%)
Absent at Posttreatment Disease Follow-Up 04	1 (1.1%)	14 (14.4%)
Absent at Posttreatment Disease Follow-Up 05	0	7 (7.2%)
Absent at Posttreatment Disease Follow-Up 06	0	3 (3.1%)
Absent at Posttreatment Disease Follow-Up 07	0	1 (1.0%)

BR=bendamustine/rituximab; IR=idelalisib/rituximab; ITT=intent-to-treat.
Source: ASCEND clinical report, Table 14.2.6.

Sustained hematologic improvement in subjects with cytopenia at baseline was similar in the acalabrutinib and IR/BR treatment arms (Table 32).

Table 32 Sustained Hematologic Improvement (ITT Population; Subjects with Cytopenia[s] Present at Baseline)

	Arm A Acalabrutinib (N=155)	Arm B IR or BR (N=155)
Present at baseline		
Neutropenia (absolute neutrophil count)	15 (9.7%)	11 (7.1%)
Anemia (hemoglobin)	50 (32.3%)	46 (29.7%)
Thrombocytopenia (platelet count)	58 (37.4%)	58 (37.4%)
Sustained hematologic improvement		
Absolute neutrophil count	10 / 15 (66.7%)	7 / 11 (63.6%)
Hemoglobin	40 / 50 (80.0%)	40 / 46 (87.0%)
Platelet count	45 / 58 (77.6%)	45 / 58 (77.6%)

BR=bendamustine/rituximab; IR=idelalisib/rituximab; ITT=intent-to-treat.
Sustained hematologic improvement was defined as hematologic improvement that persisted continuously ≥56 days (8 weeks) without blood transfusion or growth factors.
Source: ASCEND clinical report, Table 14.2.7.

Medical resource utilization was lower for acalabrutinib compared with IR/BR for the following parameters: number of hospitalizations per person-year, (1.8 versus 2.2), number of emergency department visits per person-year (1.4 versus 2.0), number of plasma, whole blood, and packed RBC transfusions per person-year (2.7 versus 3.9), and number of use of hematopoietic growth

factors per person-year (1.3 versus 2.8). The number of platelet transfusions per person-year was higher in the acalabrutinib arm compared with the IR/BR arm (3.7 versus 1.4, respectively) (Table 33).

Table 33 Medical Resource Utilization (ITT Population)

	Arm A Acalabrutinib (N=155)	Arm B IR or BR (N=155)
Number of hospitalizations (per person-year)	1.8	2.2
Planned hospitalizations (per person-year)	2.0	2.2
Unplanned hospitalizations (per person-year)	1.1	1.3
Number of emergency department visits (per person-year)	1.4	2.0
Number of plasma, whole blood, and packed RBC transfusions (per person-year)	2.7	3.9
Number of platelet transfusions (per person-year)	3.7	1.4
Number of use of hematopoietic growth factors (per person-year)	1.3	2.8

BR=bendamustine/rituximab; IR=idelalisib/rituximab; ITT=intent-to-treat.
Source: ASCEND clinical report, Table 14.2.8.

See PROs by FACIT-Fatigue under Secondary Efficacy and other relevant endpoints for effect on PRO endpoints.

Regulatory Authorities Assessment:
FDA does not agree with the Applicant's interpretation of these PRO endpoints. The point estimate comparisons on these parameters were not based on statistical evidence. Hence, any conclusion that implies one treatment yields better result than the other would be misleading.

Additional Analyses Conducted on the Individual Trial

The Applicant's Description:

No other analyses were conducted for the ASCEND trial.

The Applicant's Position: Not applicable

Regulatory Authorities Assessment:
The Applicant provided additional data for the endpoint of time to first response per IRC, in response to an October 16, 2019 information request. According to the submitted information, the median time to first response in recipients of acalabrutinib was 3.5 months (range: 0.03+, 19.8+).

8.1.3. Integrated Review of Effectiveness

Regulatory Authorities Assessment:

The efficacy of acalabrutinib in relapsed or refractory CLL is based on PFS per IRC in ASCEND, a multicenter, randomized, open-label phase 3 trial comparing acalabrutinib monotherapy (100 mg approximately every 12 hours until disease progression or unacceptable toxicity) to investigator's choice (IC) of idelalisib+rituximab (idelalisib 150 mg approximately every 12 hours until disease progression or unacceptable toxicity, with up to 8 rituximab infusions) or BR for 6 cycles. The trial enrolled patients with relapsed or refractory CLL after at least 1 prior systemic therapy, and notably excluded patients with transformed disease, prolymphocytic leukemia, or previous treatment with venetoclax, a BTK inhibitor, or a PI3K inhibitor. Of 310 patients total, 155 were assigned to acalabrutinib monotherapy, 119 to idelalisib+rituximab, and 36 to BR. The median age overall was 67 years (range: 32 to 90 years), 78% of patients had an unmutated IGHV, 28% had 17p deletion or TP53 mutation, and 42% had Rai stage III or IV disease. Baseline characteristics of the treatment arms were balanced with the exception of number of prior therapies; the acalabrutinib arm had a median of 1 prior therapy, versus 2 in the IC arm.

ASCEND successfully provided substantial evidence of efficacy, based on a statistically significant and clinically meaningful improvement in the primary endpoint of IRC-assessed PFS. On prespecified interim analysis, with a median follow-up of 16.1 months, the HR for IRC-assessed PFS (acalabrutinib/IC) was 0.31 (95% CI: 0.20, 0.49), with a p-value of <0.0001 (stratified log-rank test). Results of sensitivity analyses were consistent with the primary endpoint, and there were no outlier subgroups identified. However, there was no statistically significant difference in the key secondary endpoint of IRC-assessed ORR, nor any difference in the depth of response. In the acalabrutinib arm, the ORR was 81% (95% CI: 74, 87), with no CR or CRi, whereas in the control arm, the ORR was 75% (95% CI: 68, 82), with 1% CR and no CRi. At the time of analysis, median OS had not been reached in either arm.

The superior PFS in the acalabrutinib arm, without improvement in response rate, is likely attributable, at least in part, to the substantially longer duration of exposure to acalabrutinib than to the IC regimens. The median duration of exposure was 2-fold longer to acalabrutinib (median 15.7 months) than to IC (median 8.4 months). Interestingly, the PFS curves begin to separate at approximately 8 months, the median duration of exposure to IC. The longer duration of exposure to acalabrutinib reflects the more tolerable safety profile than idelalisib, coupled with the fixed duration of BR.

The results of ASCEND, in isolation, support regular approval of acalabrutinib for the treatment of adult patients with relapsed or refractory CLL after at least 1 prior therapy. Coupled with the results of the ELEVATE-TN trial in patients with previously untreated CLL, the totality of data supports regular approval of acalabrutinib for the treatment of adult patients with CLL.

Per FDA and TGA assessment, it justifiable to extend the indication to SLL, because SLL represents the same disease process as CLL. Thus, their recommended indication for

acalabrutinib is for the treatment of adult patients with CLL or SLL. (b) (4)

The recommended indications for approval of acalabrutinib in Canada are in combination with obinutuzumab or as monotherapy for the treatment of patients with previously untreated CLL, and as monotherapy for the treatment of patients with CLL who have received at least one prior therapy.

8.1.4. Assessment of Efficacy Across Trials

The Applicant's Description:

ELEVATE-TN Study (ACE-CL-007)
ELEVATE-TN is an ongoing Phase 3 open-label, randomized study in subjects with documented CD20–positive CLL who had not received any prior systemic treatment for CLL. The primary objective was to evaluate the efficacy of obinutuzumab+chlorambucil (Arm A) compared with acalabrutinib+obinutuzumab (Arm B) based on IRC assessment of PFS per IWCLL (Hallek et al. 2008) with incorporation of the clarification for treatment-related lymphocytosis (Cheson et al. 2012) in subjects with previously untreated CLL. The key secondary objective was to evaluate to evaluate the efficacy of obinutuzumab+chlorambucil (Arm A) compared with acalabrutinib monotherapy (Arm C) in terms of IRC-assessed PFS per IWCLL 2008 in subjects with untreated CLL.

The ITT population included 179 subjects in the acalabrutinib+obinutuzumab arm, 179 subjects in the acalabrutinib monotherapy arm, and 177 subjects in the obinutuzumab+chlorambucil arm.

The median duration of exposure to acalabrutinib in the acalabrutinib+obinutuzumab arm was 27.7 months (range: 0.7–40.3 months) and was 27.7 months (range 0.3–40.2 months) in the acalabrutinib monotherapy arm. The median duration of exposure to obinutuzumab was 5.5 months (range: 0.9–7.1 months) for the acalabrutinib+ obinutuzumab arm and 5.6 months (range: 0.9–7.4 months) for the obinutuzumab+chlorambucil arm. The median duration of chlorambucil exposure was 5.5 months (range: 0.5–7.2 months).

Primary Endpoint

The Applicant's Description:

Based on the stratified analysis, acalabrutinib+obinutuzumab demonstrated a statistically significant improvement in IRC-assessed PFS compared with obinutuzumab+chlorambucil, with a 90% reduction in risk of disease progression or death ($p<0.0001$) (Table 34).

Table 34 ELEVATE-TN: Analysis of Progression-Free Survival by IRC Assessment (ITT Population) – Primary Endpoint

	No. (%) of Subjects	
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm A Obinutuzumab+ Chlorambucil (N=177)**
Subject Status		
Events	14 (7.8)	93 (52.5)
Death	5 (2.8)	11 (6.2)
Progressive Disease	9 (5.0)	82 (46.3)
Censored	165 (92.2)	84 (47.5)
No Event Before Data Cutoff	154 (86.0)	64 (36.2)
No Postbaseline Assessment	1 (0.6)	11 (6.2)
No Event Before Taking Subsequent Anti-Cancer Therapy	3 (1.7)	3 (1.7)
Death or Progressive Disease After 2 or More Consecutive Missed Visits	2 (1.1)	1 (0.6)
No Event Before Study Exit	5 (2.8)	5 (2.8)
Progression Free Survival (Months)		
Q1 (95% CI)	NE (NE, NE)	14.4 (13.9, 16.6)
Median (95% CI)	NE (NE, NE)	22.6 (20.2, 27.6)
Q3 (95% CI)	NE (NE, NE)	NE (33.1, NE)
Min, Max	0.0+, 39.4+	0.0+, 39.6+
Stratified Analysis[a]		
Hazard Ratio (95% CI)[b]	0.10 (0.06, 0.17)	–
p-value[c]	<0.0001	–
Unstratified Analysis		
Hazard Ratio (95% CI)[b]	0.10 (0.06, 0.18)	–
p-value[c]	<0.0001	–
KM Estimates of PFS[d] by Timepoint		
6 Months (95% CI)	98.9 (95.5, 99.7)	97.0 (92.9, 98.7)
12 Months (95% CI)	95.9 (91.7, 98.0)	84.6 (78.0, 89.3)
18 Months (95% CI)	94.8 (90.2, 97.2)	65.6 (57.7, 72.4)
24 Months (95% CI)	92.7 (87.4, 95.8)	46.7 (38.5, 54.6)
30 Months (95% CI)	89.6 (82.0, 94.1)	34.2 (25.3, 43.2)
36 Months (95% CI)	89.6 (82.0, 94.1)	31.3 (21.8, 41.3)

CI=confidence interval; IRC=Independent Review Committee; ITT=intent-to-treat; KM=Kaplan-Meier; Max=maximum; Min=minimum; NE=not estimable; PFS=progression-free survival; Q1=quartile 1; Q3=quartile 3.

[a] Stratified by 17p deletion status (yes vs. no).

[b] Estimated based on stratified or unstratified Cox Proportional Hazards model for Hazard Ratio (95% CI), respectively.

[c] Estimated based on stratified or unstratified log-rank test for p-value, respectively.

[d] KM estimate of the proportion of subjects who were progression free at the timepoint.

Note: Time to event (or time to censor for censored subjects) was calculated as date of disease progression or death (censoring date for censored subjects) – randomization date + 1. Months were derived as days / 30.4375.
Note: "+" indicates a value from a censored subject.
Source: ELEVATE-TN clinical report, Table 14.2.1.

Based on the stratified analysis, acalabrutinib monotherapy demonstrated a statistically significant improvement in IRC-assessed PFS compared with obinutuzumab+ chlorambucil, with an 80% reduction in risk of disease progression or death (p<0.0001) (Table 35).

Table 35 ELEVATE-TN: Analysis of Progression-Free Survival by IRC Assessment (ITT Population) – Key Secondary Endpoint

	No. (%) of Subjects	
	Arm C Acalabrutinib Monotherapy (N=179)	**Arm A Obinutuzumab+ Chlorambucil (N=177)**
Subject Status		
Events	26 (14.5)	93 (52.5)
Death	6 (3.4)	11 (6.2)
Progressive Disease	20 (11.2)	82 (46.3%)
Censored	153 (85.5)	84 (47.5)
No Event Before Data Cutoff	139 (77.7)	64 (36.2)
No Postbaseline Assessment	5 (2.8)	11 (6.2)
No Event Before Taking Subsequent Anti-Cancer Therapy	2 (1.1)	3 (1.7)
Death or Progressive Disease After 2 or More Consecutive Missed Visits	3 (1.7)	1 (0.6)
No Event Before Study Exit	4 (2.2)	5 (2.8)
Progression Free Survival (Months)		
Q1 (95% CI)	34.2 (28.2, NE)	14.4 (13.9, 16.6)
Median (95% CI)	NE (34.2, NE)	22.6 (20.2, 27.6)
Q3 (95% CI)	NE (NE, NE)	NE (33.1, NE)
Min, Max	0.0+, 39.5+	0.0+, 39.6+
Stratified Analysis[a]		
Hazard Ratio (95% CI)[b]	0.20 (0.13, 0.30)	–
p-value[c]	<0.0001	–
Unstratified Analysis		
Hazard Ratio (95% CI)[b]	0.20 (0.13, 0.31)	–
p-value[c]	<0.0001	–
KM Estimates of PFS[d] by Timepoint		
6 Months (95% CI)	95.9 (91.6, 98.0)	97.0 (92.9, 98.7)
12 Months (95% CI)	92.9 (87.8, 95.9)	84.6 (78.0, 89.3)
18 Months (95% CI)	90.5 (84.9, 94.1)	65.6 (57.7, 72.4)
24 Months (95% CI)	87.3 (80.9, 91.7)	46.7 (38.5, 54.6)
30 Months (95% CI)	81.9 (73.3, 88.0)	34.2 (25.3, 43.2)
36 Months (95% CI)	63.9 (29.4, 84.9)	31.3 (21.8, 41.3)

CI=confidence interval; IRC=Independent Review Committee; ITT=intent-to-treat; KM=Kaplan-Meier; Max=maximum; Min=minimum; NE=not estimable; PFS=progression-free survival; Q1=quartile 1; Q3=quartile 3.

[a] Stratified by 17p deletion status (yes vs. no).

[b] Estimated based on stratified or unstratified Cox Proportional Hazards model for Hazard Ratio (95% CI), respectively.

[c] Estimated based on stratified or unstratified log-rank test for p-value, respectively.

[d] KM estimate of the proportion of subjects who were progression free at the timepoint.

Note: Time to event (or time to censor for censored subjects) was calculated as date of disease progression or death (censoring date for censored subjects) – randomization date + 1. Months were derived as days / 30.4375.
Note: "+" indicates a value from a censored subject.
Source: ELEVATE-TN clinical report, Table 14.2.1.

The Applicant's Position:
ELEVATE-TN demonstrated statistically significant and clinically meaningful improvements in progression-free survival. ELEVATE-TN was supported by and consistent with the efficacy results of the supporting studies.

Regulatory Authorities Assessment:
Refer to FDA's assessment of the primary endpoint in the Assessment AID for ELEVATE-TN (NDA 210259 S-007).

Secondary and Other Endpoints

The Applicant's Description:
Secondary efficacy endpoints in the Phase 3 pivotal study ELEVATE-TN included the following:

IRC-assessed ORR: ORR was defined as the proportion of subjects who achieved a best response of complete response (CR), CRi, nPR, or PR at or before initiation of subsequent anticancer therapy. ORR including PRL was defined as the proportion of subjects who achieved a best response of complete response (CR), CRi, nPR, PR or PRL at or before initiation of subsequent anticancer therapy. Best overall assessment was summarized by number and percentage of subjects for each response category. ORR was summarized by number and percentage of subjects, and its corresponding 95% CI was calculated based on normal approximation (with use of Wilson's score). ORR was analyzed using the Cochran-Mantel-Haenszel test, with adjustment for randomization stratification factors.

Time to Next Treatment (TTNT): TTNT was defined as the time from randomization to start date of nonprotocol specified subsequent anticancer therapy for CLL or death due to any cause, whichever came first. Subjects who did not have the above specified events prior to the data cutoff date were censored at the date of last visit. TTNT was analyzed in the same fashion as that for the primary efficacy analysis

Overall Survival (OS): OS was defined as the time from the date of randomization to death due to any cause. Subjects who were not known to have died prior to the analysis data cutoff date were right-censored as described in the respective SAP for each study.

IRC-assessed ORR

The IRC-assessed ORR difference between acalabrutinib+obinutuzumab and obinutuzumab+ chlorambucil was statistically significant (p<0.0001). Similar results were observed for IRC-assessed ORR including PRL (Table 36).

Table 36 ELEVATE-TN: Best Overall Response by IRC Assessment (ITT Population)

	No. (%) of Subjects		
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab+ Chlorambucil (N=177)**
Best Overall Response			
CR	23 (12.8)	1 (0.6)	8 (4.5)
CRi	1 (0.6)	0	0
nPR	1 (0.6)	2 (1.1)	3 (1.7)
PR	143 (79.9)	150 (83.8)	128 (72.3)
PRL	0	2 (1.1)	0
Stable Disease	4 (2.2)	8 (4.5)	15 (8.5)
Non-PD	1 (0.6)	0	2 (1.1)
NED	0	0	1 (0.6)
Progressive Disease	0	3 (1.7)	0
UNK[a]	6 (3.4)	12 (6.7)	12 (6.8)
Not Evaluable[b]	0	1 (0.6)	8 (4.5)
ORR (CR+CRi+nPR+PR)	168 (93.9)	153 (85.5)	139 (78.5)
95% CI[c]	(89.3, 96.5)	(79.6, 89.9)	(71.9, 83.9)
ORR Difference (vs. obinutuzumab+chlorambucil)	15.3	6.9	–
95% CI[c]	(8.3, 22.3)	(-1.0, 14.9)	–
p-value[d]	<0.0001	0.0763	–
ORR+PRL (CR+CRi+nPR+PR+PRL)	168 (93.9)	155 (86.6)	139 (78.5)
95% CI[c]	(89.3, 96.5)	(80.8, 90.8)	(71.9, 83.9)
ORR+PRL Difference (vs. obinutuzumab+chlorambucil)	15.3	8.1	–
95% CI[c]	(8.3, 22.3)	(0.2, 15.9)	–
p-value[d]	<0.0001	0.0376	–

CI=confidence interval; CR=complete response; CRi=CR with incomplete blood count recovery; IRC=Independent Review Committee; ITT=intent-to-treat; NED=no evaluable disease; Non-PD=not meeting criteria for progressive disease and not UNK; nPR=nodular partial response; ORR=overall response rate; PR=partial response; PRL=partial response with lymphocytosis; UNK=unknown.

[a] "UNK" category included 17 subjects with IRC global assessment as "Not Applicable" whereas their IRC timepoint assessments included "PR" at either a single timepoint or at nonconsecutive timepoints.

[b] These 9 subjects with no evaluable disease were those 9 subjects who were randomized to study drug but did not receive study drug (ELEVATE-TN clinical report, Section 10.1).

[c] 95% confidence interval based on Normal approximation (with use of Wilson's score).

[d] Based on Cochran-Mantel-Haenzel test with adjustment for 17p deletion status (yes vs no).

Note: CR, Cri, nPR, and PR were based on IRC global assessment; other response categories are derived from IRC assessment at each timepoint.

Source: ELEVATE-TN clinical report, Table 14.2.2.

Time to Next Treatment (TTNT)

As of the data cutoff date, the TTNT was significantly prolonged compared with obinutuzumab+ chlorambucil for both acalabrutinib+obinutuzumab (p<0.0001) and acalabrutinib monotherapy (p<0.0001) (Table 37).

Table 37 ELEVATE-TN: Time to Next Treatment (ITT Population)

	No. (%) of Subjects		
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab+ Chlorambucil (N=177)**
Subject Status			
Events	13 (7.3)	21 (11.7)	70 (39.5)
Death	8 (4.5)	10 (5.6)	15 (8.5)
Crossover Treatment	0	0	45 (25.4)
Subsequent Anticancer Therapy	5 (2.8)	11 (6.1)	10 (5.6)
Censored	166 (92.7)	158 (88.3)	107 (60.5)
No event before data cutoff	166 (92.7)	158 (88.3)	107 (60.5)
Time to Next Treatment (months)			
Q1 (95% CI)	NE (NE, NE)	NE (NE, NE)	19.9 (17.2, 21.5)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (28.9, NE)
Q3 (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Min, Max	1.3, 40.3+	0.1+, 40.1+	0.0+, 39.6+
Stratified Analysis[a]			
Hazard Ratio (95% CI)[b]	0.14 (0.08, 0.26)	0.24 (0.15, 0.40)	–
p-value[c]	<0.0001	<0.0001	–
KM Estimates of TTNT[d] by Timepoint			
6 Months (95% CI)	97.8 (94.2, 99.2)	96.6 (92.6, 98.5)	95.3 (90.9, 97.6)
12 Months (95% CI)	94.9 (90.5, 97.3)	94.3 (89.7, 96.9)	92.9 (87.9, 95.9)
18 Months (95% CI)	93.2 (88.4, 96.1)	92.6 (87.5, 95.6)	78.5 (71.5, 84.0)
24 Months (95% CI)	93.2 (88.4, 96.1)	90.2 (84.7, 93.8)	67.0 (59.2, 73.6)
30 Months (95% CI)	93.2 (88.4, 96.1)	87.9 (81.8, 92.1)	55.5 (46.5, 63.5)
36 Months (95% CI)	90.0 (80.0, 95.2)	86.3 (79.2, 91.1)	50.2 (40.3, 59.3)

CI=confidence interval; ITT=intent-to-treat; KM=Kaplan-Meier; Max=maximum; Min=minimum; NE=not estimable; Q1=quartile 1; Q3=quartile 3; TTNT=time to next treatment.

[a] Stratified by 17p deletion status (yes vs. no).

[b] Estimated based on stratified Cox Proportional Hazards model for Hazard Ratio (95% CI).

[c] Estimated based on stratified log-rank test for p-value.

[d] Kaplan-Meier estimates of proportion of subjects who have not received next treatment at timepoint.

Note: Time to event (or time to censor for censored subjects) was calculated as date of death (censoring date for censored subjects) – randomization date + 1; Months were derived as days / 30.4375.

Source: ELEVATE-TN clinical report, Table 14.2.3.

Overall Survival (OS)

Overall survival is summarized in Table 38.

Table 38 ELEVATE-TN: Overall Survival (ITT Population)

	No. (%) of Subjects		
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab+ Chlorambucil (N=177)**
Subject Status			
Events[a]	9 (5.0)	11 (6.1)	17 (9.6)
Death	9 (5.0)	11 (6.1)	17 (9.6)
Censored[b]	170 (95.0)	168 (93.9)	160 (90.4)
Alive	170 (95.0)	168 (93.9)	160 (90.4)
Overall Survival (months)			
Q1 (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Q3 (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Min, Max	1.7, 40.4+	0.1+, 40.8+	0.0+, 40.7+
Stratified Analysis[c]			
Hazard Ratio (95% CI)[d]	0.47 (0.21, 1.06)	0.60 (0.28, 1.27)	–
p-value[e]	0.0577	0.1556	–
KM Estimates of OS[f] by Timepoint			
6 Months (95% CI)	98.3 (94.9, 99.5)	98.9 (95.5, 99.7)	97.1 (93.2, 98.8)
12 Months (95% CI)	96.1 (91.9, 98.1)	98.3 (94.8, 99.4)	96.5 (92.4, 98.4)
18 Months (95% CI)	94.9 (90.5, 97.3)	97.1 (93.2, 98.8)	94.7 (90.1, 97.2)
24 Months (95% CI)	94.9 (90.5, 97.3)	94.7 (90.2, 97.2)	91.7 (86.3, 95.0)
30 Months (95% CI)	94.9 (90.5, 97.3)	93.5 (88.6, 96.3)	89.9 (83.9, 93.7)
36 Months (95% CI)	94.9 (90.5, 97.3)	93.5 (88.6, 96.3)	88.1 (80.7, 92.8)

CI=confidence interval; ITT=intent-to-treat; KM=Kaplan-Meier; Max=maximum; Min=minimum; NE=not estimable; OS=overall survival; Q1=quartile 1; Q3=quartile 3.

[a] Included all deaths on study, including deaths after crossover for obinutuzumab+chlorambucil subjects who crossed over.

[b] Based on subject's last known date of alive on study.

[c] Stratified by 17p deletion status (yes vs. no).

[d] Estimated based on stratified Cox Proportional Hazards model for Hazard Ratio (95% CI).

[e] Estimated based on stratified log-rank test for p-value.

[f] KM estimate of proportion subjects who were alive at the timepoint.

Note: Time to event (or time to censor for censored subjects) was calculated as date of death (censoring date for censored subjects) – randomization date + 1; Months are derived as days / 30.4375.

Note: "+" indicates a value from a censored subject.

Source: ELEVATE-TN clinical report, Table 14.2.4.

The Applicant's Position:

Results from the secondary efficacy endpoints from ELEVATE-TN were consistent with the results from ASCEND.

Regulatory Authorities Assessment:
Since the difference of IRC-assessed ORR was not statistically significant between acalabrutinib monotherapy and Obinutuzumab+chlorambucil through the pre-specified hierarchical testing procedure, the superior benefit of acalabrutinib was only demonstrated in the combinational therapy with obinutuzumab in this endpoint. This is consistent with the finding from ASCEND study since the acalabrutinib also failed to show significant benefit over the control arm as monotherapy in ORR. The median OS was not reached in any of the treatment arms, which is also consistent with the finding from the ASCEND study. No inferential comparison should be concluded from the results of TTNT analysis because it was an exploratory endpoint and the analysis was not adjusted for multiplicity.

Subpopulations

The Applicant's Description:
In ELEVATE-TN, the PFS benefit of both acalabrutinib+obinutuzumab and acalabrutinib monotherapy compared with obinutuzumab+chlorambucil was consistent across all prespecified subgroups, including age, race, sex, geographic region, presence of chromosomal abnormalities, and baseline disease status, with HR ranging from 0.02–0.22 for acalabrutinib+ obinutuzumab and from 0.07–0.76 for acalabrutinib monotherapy (Table 39).

Table 39 ELEVATE-TN: Subgroup Analysis of Progression-Free Survival by IRC Assessment (ITT Population) – Primary Endpoint

	Responders/Subjects		
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	Arm A Obinutuzumab+ Chlorambucil (N=177)	Hazard Ratio (95% CI)
Overall			
Primary analysis	14/179	93/177	0.10 (0.06, 0.17)
Presence of 17p deletion[a]			
Yes	3/21	11/117	0.13 (0.04, 0.46)
No	11/158	82/160	0.09 (0.05, 0.17)
ECOG at randomization[a]			
0, 1	12/169	86/168	0.09 (0.05, 0.17)
2	2/10	7/9	0.16 (0.03, 0.79)
Geographic region[a]			
North America and Western Europe	6/104	50/103	0.08 (0.03, 0.18)
Other	8/75	43/74	0.13 (0.06, 0.27)
Region			
North America	5/64	30/61	0.10 (0.04, 0.26)
South America	0/5	4/7	NE (NE, NE)
Western Europe	3/49	25/52	0.09 (0.03, 0.30)
Central and Eastern Europe	5/48	23/40	0.12 (0.04, 0.31)
Australia and New Zealand	1/13	11/17	0.09 (0.01, 0.73)
Age group			

	Responders/Subjects		
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm A Obinutuzumab+ Chlorambucil (N=177)**	**Hazard Ratio (95% CI)**
<65	1/35	16/24	0.02 (0.00, 0.17)
≥65	13/144	77/153	0.13 (0.07, 0.23)
<75	8/126	66/125	0.08 (0.04, 0.16)
≥75	6/53	27/52	0.17 (0.07, 0.42)
Sex			
Male	8/111	58/106	0.09 (0.04, 0.18)
Female	6/68	35/71	0.12 (0.05, 0.29)
Race			
White	14/164	88/165	0.11 (0.06, 0.19)
Non-white	0/15	5/12	NE (NE, NE)
Rai stage at screening			
Stage 0-II	3/93	54/99	0.04 (0.01, 0.12)
Stage III-IV	11/86	39/78	0.18 (0.09, 0.35)
Bulky disease			
<5 cm	10/131	53/116	0.12 (0.06, 0.24)
≥5 cm	4/46	39/55	0.07 (0.02, 0.19)
B2-microglobin at baseline			
≤3.5 mg/L	2/44	14/42	0.11 (0.03, 0.49)
>3.5 mg/L	12/132	78/132	0.10 (0.05, 0.18)
IgHV			
Mutated	3/74	14/59	0.15 (0.04, 0.52)
Unmutated	11/103	78/116	0.08 (0.04, 0.16)
Presence of 11q deletion - Yes	4/31	26/33	0.09 (0.03, 0.26)
TP53 mutation - Yes	2/21	14/21	0.04 (0.01, 0.22)
17p deletion or TP53 mutation - Yes	3/25	16/25	0.10 (0.03. 0.34)
17p deletion and TP53 mutation - Yes	2/13	9/12	0.02 (0.00, 0.24)
17p deletion, TP53 mutation, 11q deletion, or unmutated IgHV - Yes	11/117	83/129	0.08 (0.04, 0.15)
17p deletion, TP53 mutation, or 11q deletion - Yes	7/53	41/55	0.10 (0.04, 0.22)
Complex karyotype - Yes	3/29	20/32	0.09 (0.03, 0.29)

ECOG=Eastern Cooperative Oncology Group; ITT=intent-to-treat; NE=not estimable.

[a] Per Interactive voice/web response system (IXRS) record.

Source: ELEVATE-TN clinical report, Figure 14.2.1.9.1.

PFS improvement with acalabrutinib monotherapy compared with obinutuzumab+chlorambucil was notable in the following subgroups associated with poor prognosis: 17p deletion, 11q deletion, TP53 mutation, unmutated IGHV, Rai stage III-IV, B2-microglobin >3.5 mg/L at baseline, and bulky disease ≥5 cm (Table 40).

Table 40 ELEVATE-TN: Subgroup Analysis of Progression-Free Survival by IRC Assessment (ITT Population) – Key Secondary Endpoint

	Responders/Subjects		
	Arm C Acalabrutinib Monotherapy (N=179)	Arm A Obinutuzumab+ Chlorambucil (N=177)	Hazard Ratio (95% CI)
Overall			
Primary analysis	26/179	93/177	0.20 (0.13, 0.30)
Presence of 17p deletion[a]			
Yes	4/19	11/117	0.20 (0.06, 0.64)
No	22/160	82/160	0.20 (0.12, 0.31)
ECOG at randomization[a]			
0, 1	21/167	86/168	0.18 (0.11, 0.28)
2	5/12	7/9	0.48 (0.15, 1.52)
Geographic region[a]			
North America and Western Europe	21/105	50/103	0.30 (0.18, 0.51)
Other	5/74	43/74	0.08 (0.03, 0.21)
Region			
North America	14/70	30/61	0.30 (0.16, 0.56)
South America	0/8	4/7	NE (NE, NE)
Western Europe	8/42	25/52	0.29 (0.13, 0.65)
Central and Eastern Europe	3/46	23/40	0.07 (0.02, 0.24)
Australia and New Zealand	1/13	11/17	0.10 (0.01, 0.79)
Age group			
<65	5/28	16/24	0.19 (0.07, 0.52)
≥65	21/151	77/153	0.20 (0.12, 0.32)
<75	16/129	66/125	0.15 (0.09, 0.27)
≥75	10/50	27/52	0.35 (0.17, 0.72)
Sex			
Male	19/111	58/106	0.23 (0.14, 0.39)
Female	7/68	35/71	0.14 (0.06, 0.32)
Race			
White	24/170	88/165	0.18 (0.12, 0.29)
Non-white	2/9	5/12	0.62 (0.12, 3.19)
Rai stage at screening			
Stage 0-II	7/92	54/99	0.10 (0.04, 0.21)
Stage III-IV	19/87	39/78	0.34 (0.19, 0.59)
Bulky disease			
<5 cm	15/107	53/116	0.23 (0.13, 0.40)
≥5 cm	10/68	39/55	0.14 (0.07, 0.27)
B2-microglobin at baseline			
≤3.5 mg/L	4/38	14/42	0.26 (0.09, 0.79)
>3.5 mg/L	22/140	78/132	0.18 (0.11, 0.30)
IgHV			
Mutated	10/58	14/59	0.69 (0.31, 1.56)
Unmutated	16/119	78/116	0.11 (0.07, 0.19)
Presence of 11q deletion - Yes	3/31	26/33	0.07 (0.02, 0.22)

	Responders/Subjects		
	Arm C Acalabrutinib Monotherapy (N=179)	**Arm A Obinutuzumab+ Chlorambucil (N=177)**	**Hazard Ratio (95% CI)**
TP53 mutation - Yes	5/19	14/21	0.15 (0.05, 0.46)
17p deletion or TP53 mutation - Yes	6/23	16/25	0.23 (0.09, 0.61)
17p deletion and TP53 mutation - Yes	2/12	9/12	0.03 (0.00, 0.28)
17p deletion, TP53 mutation, 11q deletion, or unmutated IgHV - Yes	18/129	83/129	0.13 (0.08, 0.21)
17p deletion, TP53 mutation, or 11q deletion - Yes	8/52	41/55	0.11 (0.05, 0.24)
Complex karyotype - Yes	3/31	20/32	0.10 (0.03, 0.33)

ECOG=Eastern Cooperative Oncology Group; del=deletion; IgHV=immunoglobulin heavy-chain variable; IRC=Independent Review Committee; ITT=intent-to-treat; NE=not estimable.

[a] Per Interactive voice/web response system (IXRS) record.

Source: ELEVATE-TN clinical report, Figure 14.2.1.9.2.

IRC-assessed ORR was also consistent across most prespecified subgroups (Table 41).

Table 41 ELEVATE-TN: Overall Response Rate by IRC Assessment by for Selected Subgroups (ITT Population)

	No. (%) of Subjects					
	Arm B Acalabrutinib+ Obinutuzumab (N=179)		Arm C Acalabrutinib Monotherapy (N=179)		Arm A Obinutuzumab+ Chlorambucil (N=177)	
	Responders/ Subjects	ORR (%) (95% CI)	Responders/ Subjects	ORR (%) (95% CI)	Responders/ Subjects	ORR (%) (95% CI)
Overall	168/179	93.9 (89.3, 96.5)	153/179	85.5 (79.6, 89.9)	139/177	78.5 (71.9, 83.9)
Presence of 17p deletion[a]						
Yes	18/21	85.7 (65.4, 95.0)	14/19	73.7 (51.2, 88.2)	9/17	52.9 (31.0, 73.8)
No	150/158	94.9 (90.3, 97.4)	139/160	86.9 (80.8, 91.3)	130/160	81.3 (74.5, 86.5)
ECOG PS at randomization						
0, 1	160/169	94.7 (90.2, 97.2)	145/167	86.8 (80.9, 91.1)	134/168	79.8 (73.1, 85.1)
2	8/10	80.0 (49.0, 94.3)	8/12	66.7 (39.1, 86.2)	5/9	55.6 (26.7, 81.1)
Age group						
<65	35/35	100 (90.1, 100)	23/28	82.1 (64.4, 92.1)	17/24	70.8 (50.8, 85.1)
≥65	133/144	92.4 (86.8, 95.7)	130/151	86.1 (79.7, 90.7)	122/153	79.7 (72.2, 85.3)
<75	123/126	97.6 (93.2, 99.2)	114/129	88.4 (81.7, 92.8)	95/125	76.0 (67.8, 82.6)
≥75	45/53	84.9 (72.9, 92.1)	39/50	78.0 (64.8, 87.2)	44/52	84.6 (72.5, 92.0)
Sex						
Male	107/111	96.4 (91.1, 98.6)	94/111	84.7 (76.8, 90.2)	85/106	80.2 (71.6, 86.7)
Female	61/68	89.7 (80.2, 94.9)	59/68	86.8 (76.7, 92.9)	54/71	76.1 (65.0, 84.5)
Race						
White	153/164	93.3 (88.4, 96.2)	146/170	85.9 (79.9, 90.3)	130/165	78.8 (71.9, 84.3)
Non-white	15/15	100 (79.6, 100)	7/9	77.8 (45.3, 93.7)	9/12	75.0 (46.8, 91.1)
Rai stage at screening						
Stage 0-II	92/93	98.9 (94.2, 99.8)	85/92	92.4 (85.1, 96.3)	82/99	82.8 (74.2, 89.0)
Stage III-IV	76/86	88.4 (79.9, 93.6)	68/87	78.2 (68.4, 85.5)	57/78	73.1 (62.3, 81.7)
Bulky disease						
<5 cm	123/131	93.9 (88.4, 96.9)	95/107	88.8 (81.4, 93.5)	92/116	79.3 (71.1, 85.7)
≥5 cm	43/46	93.5 (82.5, 97.8)	57/68	83.8 (73.3, 90.7)	43/55	78.2 (65.5, 87.1)
B2-microglobin at baseline						
≤3.5 mg/L	43/44	97.7 (88.2, 99.6)	31/38	81.6 (66.6, 90.8)	27/42	64.3 (49.2, 77.0)
>3.5 mg/L	124/132	93.9 (88.5, 96.9)	121/140	86.4 (79.8, 91.1)	109/132	82.6 (75.2, 88.1)

	No. (%) of Subjects					
	Arm B Acalabrutinib+ Obinutuzumab (N=179)		Arm C Acalabrutinib Monotherapy (N=179)		Arm A Obinutuzumab+ Chlorambucil (N=177)	
	Responders/ Subjects	ORR (%) (95% CI)	Responders/ Subjects	ORR (%) (95% CI)	Responders/ Subjects	ORR (%) (95% CI)
IgHV						
Mutated	68/74	91.9 (83.4, 96.2)	44/58	75.9 (63.5, 85.0)	48/59	81.4 (69.6, 89.3)
Unmutated	98/103	95.1 (89.1, 97.9)	107/119	89.9 (83.2, 94.1)	89/116	76.7 (68.3, 83.5)
Complex karyotype - Yes	27/29	93.1 (78.0, 98.1)	26/31	83.9 (67.4, 92.9)	20/32	62.5 (45,3, 77.1)
Presence of 11q deletion - Yes	31/31	100 (89.0, 100)	27/31	87.1 (71.1, 94.9)	27/33	81.8 (65.6, 91.4)
TP53 mutation - Yes	18/21	85.7 (65.4, 95.0)	16/19	84.2 (62.4, 94.5)	10/21	47.6 (28.3, 67.6)
17p deletion, TP53 mutation, 11q deletion, or unmutated IgHV - Yes	110/117	94.0 (88.2, 97.1)	114/129	88.4 (81.7, 92.8)	97/129	75.2 (67.1, 81.8)

ECOG PS=Eastern Cooperative Oncology Group performance status; IgHV=immunoglobulin heavy-chain variable; IRC=Independent Review Committee; ITT=intent-to-treat.

[a] Per Interactive voice/web response system (IXRS) record.

Source: ELEVATE-TN clinical report, Figure 14.2.2.1.

The Applicant's Position:
Results of the subgroup analyses from ELEVATE-TN were consistent with the results from ASCEND.

Regulatory Authorities Assessment:
There were no outlier subgroups for IRC-assessed PFS were identified in ELEVATE-TN study.

8.1.5. Integrated Assessment of Effectiveness

The Applicant's Description: Not applicable

The Applicant's Position:
The varying study designs and differences in primary endpoint in this pivotal ASCEND study (IRC-assessed PFS) compared to the supporting studies does not allow for an integrated efficacy assessment.

Regulatory Authorities Assessment:
The Applicant's position is acceptable.

8.2. Review of Safety

The Applicant's Description:
Details are provided in the sections below.

The Applicant's Position:
The safety review of acalabrutinib 100 mg BID for this sNDA is primarily based on results from the ASCEND and ELEVATE-TN studies, with supporting data provided from the eight additional CLL and other hematologic malignancies studies. The integrated safety analyses demonstrated the safety profile for acalabrutinib 100 mg BID is consistent with that observed in the studies presented in the original NDA. No new safety concerns were observed with the acalabrutinib 100mg BID dose in the CLL studies.

Regulatory Authorities Assessment:
The ASCEND study, rather than ASCEND and ELEVATE-TN, is the primary basis of this safety review for this sNDA. Regulatory authorities agree that no new safety concerns arose with acalabrutinib 100 mg approximately Q12H in patients with previously treated or untreated CLL, compared to the overall safety profile described previously in patients with relapsed or refractory mantle cell lymphoma (MCL). The overall safety profile in previously treated CLL was similar to that in treatment-naïve CLL, with one exception: a signal for increased risk of second primary malignancies (SPMs) identified with acalabrutinib in the relapsed or refractory setting.

The integrated safety analyses presented by the Applicant include patients with Waldenström

macroglobulinemia (WM), multiple myeloma, follicular lymphoma, and diffuse large B-cell lymphoma who received various dose-schedules of acalabrutinib. Patients with the latter three histologies had limited exposure to acalabrutinib. It is preferable that the denominator for the USPI Warnings and precautions consist of patients with sufficient exposure to acalabrutinib 100 mg approximately Q12H as monotherapy or in combination with obinutuzumab. Refer to Section 8.2.2 (Table 45) for a description of the revised safety population.

8.2.1. Safety Review Approach

The Applicant's Position:

The safety population for ASCEND is defined as all subjects who received any amount of study drug (N=154 for acalabrutinib monotherapy and N=153 for IR or BR [IR, N=118; BR, N=35]. These safety results are presented in the sections below.

The clinical review of safety for this sNDA is based on the following:

- Clinical study report for studies ELEVATE-TN, ASCEND, ACE-CL-001, 15-H-0016, ACE-CL-003, ACE-LY-002, ACE-LY-003, ACE-LY-004, ACE-MY-001, and ACE-WM-001
- Statistical analysis plan for the Integrated Summary of Safety
- Integrated datasets from the studies listed in Table 35 in Section 8.2.2 below.
- Case report forms and safety narratives
- Summary of Clinical Safety
- Proposed labeling for Calquence

Regulatory Authorities Assessment:

Regulatory authorities agree with the Applicant's position. The safety population for ASCEND is the primary safety population. FDA conducted the primary safety analyses using the study-specific, rather than integrated, data analysis datasets, supplemented by the CSR and safety narratives. FDA also performed an integrated safety analysis focusing on selected events of clinical interest (ECIs), using a subset of the integrated datasets described above. However, as previously noted, FDA tailored the integrated safety analysis to patients with CLL or SLL, MCL, and WM who received acalabrutinib 100 mg approximately Q12H as monotherapy or in combination with obinutuzumab (N = 1029). This safety population is defined in Section 8.2.2 (Table 45).

FDA's safety analysis considers all-causality treatment-emergent AEs (TEAEs) in recipients of any study drug. TEAEs were defined as AEs that are new or worsened from baseline grade or are unknown to have worsened from baseline. Laboratory grading is based on CTCAE rather than Hallek 2008 criteria. The primary safety window (on-treatment period) for ASCEND is approximately 30 days after last study drug, with censoring for subsequent anticancer therapy. For increased sensitivity, FDA used a combination of individual MedDRA preferred terms (PTs) and custom groupings of PTs as defined in the Appendix (Table 72), which the Applicant agreed to adopt in the Assessment Aid and labeling for reporting the results of ASCEND. Refer also to

Section 8.2.3.

8.2.2. Review of the Safety Database

The Applicant's Description:
The clinical safety data supporting the proposed indication of acalabrutinib for adult subjects with CLL is based on acalabrutinib-treated subjects from 10 open-label Phase 1, 2, and 3 clinical studies of acalabrutinib in hematologic malignancies (Table 42).

The safety review was conducted using the integrated datasets from clinical studies ELEVATE-TN, ASCEND, ACE-CL-001, 15-H-0016, ACE-CL-003, ACE-LY-002, ACE-LY-003, ACE-LY-004, ACE-MY-001, and ACE-WM-001. A data pool including patients with previously untreated CLL, R/R CLL, activated B-cell diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, multiple myeloma, and Waldenström macroglobulinemia was used to develop the safety profile of acalabrutinib 100 mg BID in patients with hematologic malignancies. Additionally, data pools consisting of patients receiving acalabrutinib monotherapy from the pivotal CLL studies, CLL patients receiving acalabrutinib monotherapy, or CLL patients receiving acalabrutinib in combination with obinutuzumab were analyzed. Furthermore, a data pool consisting of CLL patients receiving acalabrutinib monotherapy or acalabrutinib in combination with obinutuzumab was analyzed. The safety review will focus on data from CLL patients from the individual pivotal studies, as well as the pooled population of all CLL patients receiving acalabrutinib monotherapy.

Table 42 provides the total number of subjects and brief study details for all studies that contributed safety data to the submission.

Table 43 provides a summary of treatment exposure for all studies that contributed safety data to the submission.

Table 42 Total Subjects From Clinical Studies That Contributed Safety Data to This Submission

	Total N[a]	Pivotal Studies		CLL Supportive Studies			Hematologic Malignancies Supportive Studies				
		ACE-CL-007	ACE-CL-309	ACE-CL-001	15-H-0016	ACE-CL-003	ACE-LY-002	ACE-LY-003[b]	ACE-LY-004	ACE-MY-001[b]	ACE-WM-001
Phase		3	3	1/2	2	1/2	1b	2	2	1b	2
Status		Ongoing	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing
Data cutoff date		08Feb2019	15Jan2019	04Jan2019	07Dec2018	01Nov2018	30Oct2017	01Jan2019	12Feb2018	30Apr2018	01Nov2018
Indication		CLL	CLL	CLL/SLL /RS/PLL	CLL/SLL	CLL/SLL	ABC/DLBCL	FL	MCL	MM	WM
Acalabrutinib Monotherapy Pivotal Population	**333**	179	154	NA	NA	NA	NA	NA	NA	NA	NA
Acalabrutinib Monotherapy CLL Population	**762[c]**	224	190	301	48	NA	NA	NA	NA	NA	NA
Combination CLL Population	**223**	178	NA	NA	NA	45	NA	NA	NA	NA	NA
Total Acalabrutinib CLL Population	**985[c]**	402	190	301	48	45	NA	NA	NA	NA	NA
Acalabrutinib Monotherapy Hematologic Malignancies Population	**1040[c]**	224	190	301	48	NA	21	14	124	13	106
Treatment Arm											
Acalabrutinib Monotherapy		179	154	301	48	NA	21	14	124	13	106
Acalabrutinib + Obinutuzumab		178	NA	NA	NA	45	NA	NA	NA	NA	NA
Crossover from Control Arm to Acalabrutinib		45	36								

ABC DLBCL=activated B-cell diffuse large B-cell lymphoma; CLL=chronic lymphocytic leukemia; FL=follicular lymphoma; MCL=mantle cell lymphoma; MM=multiple myeloma; NA=not applicable: PLL=prolymphocytic leukemia; RS=Richter's syndrome; SLL=small lymphocytic leukemia; WM=Waldenström macroglobulinemia.

[a] The total number is based on the actual number of subjects treated with acalabrutinib.

[b] Other combination groups are not included in the analysis.

[c] Subjects who crossed over from control arm to acalabrutinib monotherapy are included in this pooled population.

Source: Module 2.7.4, Table 1.

Overall Exposure

The Applicant's Description:

In the pivotal study ASCEND, for subjects in the acalabrutinib monotherapy arm, 24.7% of subjects completed at least 24 months of acalabrutinib treatment, with a median duration of exposure of 15.7 months (range: 1.1 to 22.4 months). Treatment exposure for

the safety pools is summarized in Table 43.

Table 43 Summary of Treatment Exposure From Clinical Studies That Contributed Safety Data to This Submission

	Mono Pivotals (N=333)	Mono CLL (N=762)	Combo CLL (N=223)	Total CLL (N=985)	Mono HemMalig (N=1040)
Duration of Exposure (months)[a]					
n	333	760	223	983	1038
Mean (SD)	21.0 (9.48)	24.9 (15.35)	28.5 (9.33)	25.8 (14.29)	23.6 (15.20)
Median	19.3	24.9	29.8	27.1	24.6
Min, Max	0.3, 40.2	0.0, 58.5	0.7, 44.9	0.0, 58.5	0.0, 58.5
Patient Year	581.9	1579.3	530.1	2109.4	2037.7
<= 6 months	24 (7.2%)	107 (14.0%)	10 (4.5%)	117 (11.9%)	188 (18.1%)
> 6 to <= 12 months	23 (6.9%)	68 (8.9%)	11 (4.9%)	79 (8.0%)	96 (9.2%)
> 12 to <= 24 months	141 (42.3%)	191 (25.1%)	14 (6.3%)	205 (20.8%)	226 (21.7%)
> 24 to <= 36 months	132 (39.6%)	177 (23.2%)	150 (67.3%)	327 (33.2%)	273 (26.3%)
> 36 months	13 (3.9%)	217 (28.5%)	38 (17.0%)	255 (25.9%)	255 (24.5%)

Source: ISS Table 4.1.

The Applicant's Position:
Acalabrutinib was well tolerated and showed an acceptable safety profile that is consistent with the other acalabrutinib clinical trials.

Regulatory Authorities Assessment:
Regulatory authorities agree that acalabrutinib carries an acceptable safety profile in patients with CLL that is consistent with the safety profile previously described in MCL. However, it is a generalization to state that acalabrutinib was well tolerated. The Applicant makes this statement throughout the NDA review.

The next sections expand on exposure and the definition of the integrated safety population.

A. *Exposure in the Primary Safety Population*

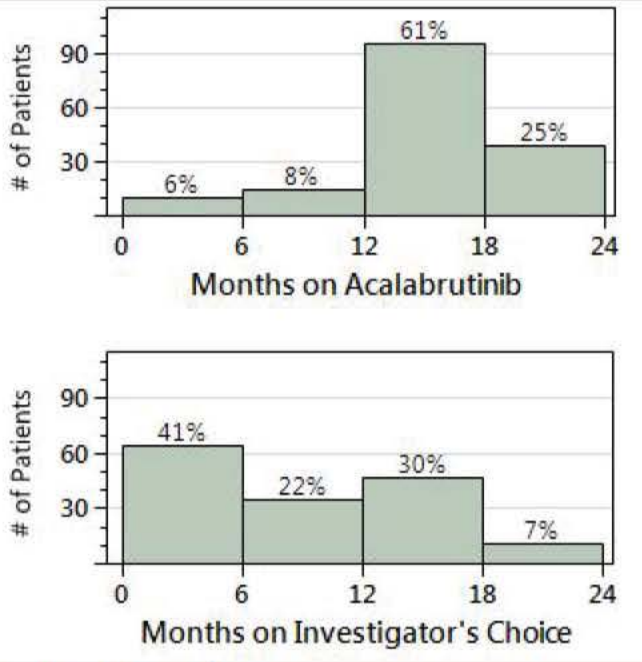
An evaluation of exposure was not presented for the primary safety population. There are marked differences in duration of exposure to randomized treatment in ASCEND, which is important for the assessment of both safety and efficacy (Table 44 and Figure 14). The median treatment duration was 1.9 times longer to acalabrutinib (15.7 months) than to IC (median 8.4 months). In the IC group, 41% of treated patients received < 6 months of treatment, with 37% receiving at least 12 months. In contrast, only 6% of the acalabrutinib group received < 6 months of treatment, with 86% receiving at least 12 months.

Table 44 Exposure in Primary Safety Population (ASCEND)

Exposure	Treatment received		
	Acalabrutinib (N = 154)	**Investigator's choice (N =153)** [a, b]	**Idelalisib component of IR (N = 118)**
Treatment duration, months			
Median	15.7	8.4	11.5
Range	1.1, 22.4	0.1, 21.1	0.1, 21.1
Q1, Q3	13.8, 18.0	5.6, 14.0	5.6, 14.9
Patients on treatment by month, n			
< 6 mo	**9 (6%)**	**63 (41%)**	--
≥ 6 mo	145 (94%)	90 (59%)	
≥ 12 mo	**132 (86%)**	**56 (37%)**	
≥ 18 mo	38 (25%)	10 (7%)	
Mean relative dose intensity	97%	91% [c]	91%
Crossover to acalabrutinib, n	--	35 (23%)	29 (25%)

Source: FDA analysis
[a] 118 pts (78%) received IR, remainder BR.
[b] For BR, 29/35 pts (83%) received 6 cycles of bendamustine.
[c] Excluding rituximab

Figure 14 Exposure Distribution in the Primary Safety Population (ASCEND)



Source: FDA analysis

B. *Refinement of the Integrated Safety Population*

For the integrated safety analysis presented in the FDA assessments and in the USPI Warnings and Precautions, FDA revised the denominator to

- exclude patients with acalabrutinib dosing other than 100 mg Q12H,
- add recipients of combination therapy (acalabrutinib + obinutuzumab), and
- exclude patients with MM, DLBCL, and FL because of their limited exposure duration (median exposure 1 month, 2 months, and 6 months, respectively).

Table 45 summarizes this integrated safety population of 1029 patients, consisting of the majority of the total acalabrutinib CLL population (N = 805), patients with MCL (N = 124), and patients with WM (N = 100). In this revised safety population (median age, 68), the median duration of exposure to acalabrutinib was 26.1 months (Q1, Q3: 13.8, 34.6), with 902 patients (88%) treated for ≥ 6 months, 808 (79%) for ≥ 1 year, 590 (57%) for ≥ 2 years, and 198 (19%) for ≥ 3 years.

Table 45 Revised Integrated Safety Population for FDA Analysis (N = 1029)

	Total treated (from 1029)	Randomized Studies		CLL Supportive Studies			Other HM Supportive Studies	
		ACE-CL-007 (ELEVATE)	ACE-CL-309 (ASCEND)	ACE-CL-001	15-H-0016	ACE-CL-003	ACE-LY-004	ACE-WM-001
Phase		3	3	1/2	2	1/2	2	2
Data cutoff date		8Feb2019	15Jan2019	4Jan2019	7Dec2018	1Nov2018	12Feb2018	1Nov2018
Disease		CLL	CLL	CLL/SLL[b]	CLL/SLL	CLL/SLL	MCL	WM
Acala monotherapy, excluding crossover	**740**	179	154	159	24	NA	124	100
Acala monotherapy, after crossover from control arm	**80**	45	35	–	–	–	–	–
Acala + obinutuzumab	**209**	178	NA	NA	NA	31	NA	NA
Summary [a]								
Total CLL population	**805**							
Monotherapy	596							
With obinutuzumab	209							
Other HM (all monotherapy)	**224**							

[a] Acalabrutinib dose is 100 mg approximately Q12H for all patients.
[b] Excludes transformed CLL (RS, PLL) because of different acalabrutinib dosing.

Relevant Characteristics of the Safety Population

The Applicant's Description:

Demographic and baseline characteristics were generally similar across the 5 analysis populations. Among Mono HemMalig subjects, the mean age was 66.6 years (median: 67.0 years), with a range of 32 to 90 years. Most subjects were white (88.8%) and male (67.7%). Mean calculated BMI was 27.2 kg/m2, and most subjects (93.0%) had a baseline ECOG status of 0 or 1. Subjects reported a median of 1 prior systemic treatment regimen (Table 46).

Table 46 Demographic and Baseline Characteristics

	Mono Pivotals (N=333)	Mono CLL (N=762)	Combo CLL (N=223)	Total CLL (N=985)	Mono HemMalig (N=1040)
Age (years)					
Mean (SD)	68.5 (8.82)	66.4 (9.36)	68.6 (8.97)	66.9 (9.31)	66.6 (9.86)
Median	69.0	67.0	69.0	68.0	67.0
Min, Max	32, 89	32, 89	41, 88	32, 89	32, 90
<65, n (%)	85 (25.5)	288 (37.8)	61 (27.4)	349 (35.4)	388 (37.3)
≥65 and <75, n (%)	164 (49.2)	318 (41.7)	104 (46.6)	422 (42.8)	424 (40.8)
≥75, n (%)	84 (25.2)	156 (20.5)	58 (26.0)	214 (21.7)	228 (21.9)
Sex, n (%)					
Male	217 (65.2)	508 (66.7)	143 (64.1)	651 (66.1)	704 (67.7)
Female	116 (34.8)	254 (33.3)	80 (35.9)	334 (33.9)	336 (32.3)
Race, n (%)					

	Mono Pivotals (N=333)	Mono CLL (N=762)	Combo CLL (N=223)	Total CLL (N=985)	Mono HemMalig (N=1040)
American Indian or Alaska Native	0	1 (0.1)	0	1 (0.1)	1 (0.1)
Asian	7 (2.1)	14 (1.8)	3 (1.3)	17 (1.7)	16 (1.5)
Black or African American	4 (1.2)	26 (3.4)	5 (2.2)	31 (3.1)	34 (3.3)
Native Hawaiian or Other Pacific Islander	0	1 (0.1)	0	1 (0.1)	1 (0.1)
White	314 (94.3)	698 (91.6)	208 (93.3)	906 (92.0)	923 (88.8)
Other	0	11 (1.4)	0	11 (1.1)	15 (1.4)
Missing/NA	8 (2.4)	11 (1.4)	7 (3.1)	18 (1.8)	50 (4.8)
Ethnicity, n (%)					
Hispanic	12 (3.6)	21 (2.8)	3 (1.3)	24 (2.4)	29 (2.8)
Non-Hispanic	303 (91.0)	715 (93.8)	212 (95.1)	927 (94.1)	943 (90.7)
Missing/NA	18 (5.4)	26 (3.4)	8 (3.6)	34 (3.5)	68 (6.5)
Geographic region, n (%)					
North America	78 (23.4)	400 (52.5)	109 (48.9)	509 (51.7)	508 (48.8)
South America	7 (2.1)	8 (1.0)	5 (2.2)	13 (1.3)	8 (0.8)
Western Europe	75 (22.5)	140 (18.4)	48 (21.5)	188 (19.1)	286 (27.5)
Central and Eastern Europe	144 (43.2)	177 (23.2)	48 (21.5)	225 (22.8)	199 (19.1)
Australia and New Zealand	22 (6.6)	28 (3.7)	13 (5.8)	41 (4.2)	30 (2.9)
Asia	7 (2.1)	9 (1.2)	0	9 (0.9)	9 (0.9)
Weight (kg)					
n	333	760	223	983	1037
Mean (SD)	79.7 (18.29)	80.2 (17.82)	80.5 (18.24)	80.3 (17.91)	79.6 (17.50)
Median	78.2	79.4	79.0	79.3	78.5
Min, Max	41, 149	39, 155	47, 142	39, 155	39, 155
Body Mass Index (kg/m^2)					
n	328	746	219	965	1014
Mean (SD)	27.7 (5.20)	27.4 (5.11)	27.9 (5.44)	27.5 (5.19)	27.2 (5.05)
Median	27.1	26.7	27.0	26.7	26.5
Min, Max	17.6, 48.5	15.6, 48.5	18.1, 50.5	15.6, 50.5	15.6, 48.5
ECOG Status, n (%)					
0	148 (44.4)	292 (38.3)	104 (46.6)	396 (40.2)	437 (42.0)
1	152 (45.6)	415 (54.5)	110 (49.3)	525 (53.3)	530 (51.0)
2	33 (9.9)	54 (7.1)	9 (4.0)	63 (6.4)	71 (6.8)
3	0	1 (0.1)	0	1 (0.1)	2 (0.2)
Number of prior anticancer therapies					
N	333	762	223	985	1026
Mean (SD)	0.88 (1.30)	1.36 (1.94)	0.27 (1.03)	1.11 (1.83)	1.62 (1.93)
Median	0.00	1.00	0.00	0.00	1.00
Min, Max	0, 8	0, 13	0, 9	0, 13	0, 13

CLL=chronic lymphocytic leukemia; ECOG=Eastern Cooperative Oncology Group; Max=maximum; Min=minimum; NA=not available; SD=standard deviation
Summarized for safety population by actual treatment arm.
Body mass index was calculated as weight (kg)/height in m^2
Source: Module 5.3.5.3, ISS Table 2, and ISS Table 3.

The Applicant's Position:
There were no noteworthy differences in demographics between the studies.

Regulatory Authorities Assessment:
Regulatory authorities agree with the Applicant's assessment. Demographics in the primary safety population are virtually identical to those of the ITT efficacy population, described in Section 8.1.2. There were no noteworthy differences in demographics between the ASCEND treatment arms.

Adequacy of the Safety Database

The Applicant's Description:
The size of the database for the pivotal ASCEND safety pool is adequate to provide an estimate of adverse reactions that may be associated with acalabrutinib use in the CLL population. The database from the total pooled population (N=1040) includes patients with other hematologic malignancies (CLL, NHL, WM) and provides supportive safety. Demographic and baseline characteristics of subjects treated with acalabrutinib 100 mg BID were generally representative of the CLL population. Treated subjects varied with regards to age, sex, race, and ethnicity. The duration of treatment in the Total CLL Population is adequate to provide assessment of adverse reactions.

The Applicant's Position:
The safety database of acalabrutinib is considered to be adequate to assess the safety of the 100 mg BID dose.

Regulatory Authorities Assessment:
Regulatory authorities agree with the Applicant's assessment.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Description: Not applicable

The Applicant's Position:
No issues were identified regarding data integrity or submission quality that had an effect on the clinical safety review. The submission included adequate narratives for events of clinical interest as agreed with FDA. No safety update is required.

Regulatory Authorities Assessment:
Regulatory authorities agree with the Applicant's position.

Categorization of Adverse Events

The Applicant's Description:

AEs and serious adverse (SAEs) were coded using the MedDRA reporting system, version 21.1. AEs were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03. AEs were summarized by treatment arm as treated. Treatment-emergent adverse events (TEAEs) were defined as any event with an onset date on or after the first dose date of study drug or any ongoing event that worsened in severity after the first dose date of study drug, and prior to 30 days after the date of the last dose of study drug or the first date starting new anticancer therapy. All AEs and SAEs discussed in this AA are treatment-emergent unless otherwise specified.

Selected AEs for additional analyses (events of clinical interest [ECIs]) have been identified based on nonclinical findings, emerging data from clinical studies relating to acalabrutinib, and pharmacological effects of an approved BTK inhibitor. The AEs selected for dedicated analysis were evaluated using Standardized MedDRA Queries, where available, by SOC, or by sponsor-defined baskets of MedDRA Adverse Event Grouped Terms. The following ECIs were summarized: cardiac events (including subsets of atrial fibrillation and ventricular tachyarrhythmias), cytopenias (anemia, leukopenia [including subsets of neutropenia and other leukopenia], thrombocytopenia), hemorrhage (including subset of major hemorrhage), hepatotoxicity, hypertension, infections, interstitial lung disease/pneumonitis, second primary malignancies (including subset of second primary malignancies excluding non-melanoma skin), and tumor lysis syndrome.

The Applicant's Position:
Adverse events were collected as specified in the ASCEND protocol.

Regulatory Authorities Assessment:
As described in Section 8.2.1, for increased sensitivity, FDA used a combination of individual MedDRA PTs and custom groupings of PTs as defined in the Appendix (Table 72), which the Applicant agreed to adopt in the Assessment Aid and labeling for reporting results of ASCEND. In addition to AEs that are new or worsened from baseline grade, FDA also considered AEs that are unknown to have worsened from baseline as treatment-emergent.

Routine Clinical Tests

The Applicant's Description:

The ASCEND protocol prespecified the various clinical laboratory evaluations to be performed before study entry, throughout the study, and at the follow-up evaluation. Hematology tests included a complete blood count (CBC) with differential including, but not limited to white blood cell count, hemoglobin, hematocrit, platelet count, ANC, and ALC. Chemistry tests included albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate/ phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid.

The Applicant's Position:
Laboratory assessments were carried out as specified in the ASCEND protocol.

Regulatory Authorities Assessment:
Regulatory authorities agree with the Applicant's position.

8.2.4. Safety Results

8.2.4.1 Deaths

The Applicant's Description:
Fifteen (9.7%) subjects who received acalabrutinib and 18 (11.8%) subjects who received IR or BR died as of the data cutoff date, including 3 subjects in the IR group who died after crossover to acalabrutinib treatment. The most common primary cause of death in all treatment groups was an AE, reported in 5.2%, 7.6%, and 11.4% of subjects in the acalabrutinib, IR, and BR groups, respectively. Narratives for all subjects who received acalabrutinib and died are provided. Summary of deaths is provided in Table 47.

Table 47 Summary of Deaths (Safety Population)

	No. (%) of Subjects		
	Arm A	Arm B	
	Acalabrutinib (N=154)	IR (N=118)	BR N=35)
Deaths[a], n (%)	15 (9.7%)	13 (11.0%)	5 (14.3%)
Primary cause of death			
Adverse event	8[b] (5.2%)	9[c] (7.6%)	4 (11.4%)
Richter's transformation	1 (0.6%)	3 (2.5%)	1 (2.9%)
Disease progression	5 (3.2%)	0	0
Unknown	1 (0.6%)	1 (0.8%)	0
Within 30 days after last dose of study drug			
Deaths, n (%)	7 (4.5%)	3 (2.5%)	1 (2.9%)
Primary cause of death			
Adverse event	5 (3.2%)	3 (2.5%)	1 (2.9%)
Disease progression	1 (0.6%)	0	0
Richter's transformation	1 (0.6%)	0	0
More than 30 days after last dose of study drug			
Deaths, n (%)	8 (5.2%)	10 (8.5%)	4 (11.4%)
Primary cause of death			
Adverse event	3 (1.9%)	6 (5.1%)	3 (8.6%)
Richter's transformation	0	3 (2.5%)	1 (2.9%)
Disease progression	4 (2.6%)	0	0
Unknown	1 (0.6%)	1 (0.8%)	0

BR=bendamustine/rituximab; IR=idelalisib/rituximab.

[a] All deaths in the whole study period are included, that is, main study period + crossover period.

[b] Does not include the following 2 subjects, one of which had Grade 5 cerebral ischaemia during the main study period, and the other who had Grade 5 pneumonia during the crossover period, which became fatal on 20 January 2019 (after the data cutoff date).

[c] Includes one subject captured in the IR/BR arm who had Grade 5 Sepsis during the crossover period.

Source: ASCEND clinical report, Table 14.3.3.1.

Grade 5 (fatal) TEAEs occurred in 6 (3.9%) subjects who received acalabrutinib, 5 (4.2%) subjects who received IR, and 2 (5.7%) subjects who received BR. There were no acalabrutinib-related Grade 5 TEAEs (Table 48).

Table 48 Treatment Emergent Adverse Events Resulting in Death (Safety Population)

System Organ Class /Preferred Term	No. (%) of Subjects		
	Arm A	Arm B	
	Acalabrutinib (N=154)	IR (N=118)	BR (N=35)
Number of subjects with fatal adverse events - n(%)	**6(3.9%)**	**5(4.2%)**	**2(5.7%)**
Cardiac disorders	**0**	**3(2.5%)**	**1(2.9%)**
Cardiac failure acute	0	0	1(2.9%)
Cardiac failure chronic	0	1(0.8%)	0
Cardiopulmonary failure	0	1(0.8%)	0
Myocardial infarction	0	1(0.8%)	0
Infections and infestations	**1(0.6%)**	**1(0.8%)**	**0**
Sepsis	1(0.6%)	0	0
Pneumonia pseudomonal	0	1(0.8%)	0
Metabolism and nutrition disorders	**1(0.6%)**	**0**	**0**
Cachexia	1(0.6%)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3(1.9%)**	**0**	**1(2.9%)**
Brain neoplasm	1(0.6%)	0	0
Lung neoplasm malignant	1(0.6%)	0	0
Neuroendocrine carcinoma	1(0.6%)	0	0
Gastric neoplasm	0	0	1(2.9%)
Nervous system disorders	**1(0.6%)**	**0**	**0**
Cerebral ischaemia	1(0.6%)	0	0
Respiratory, thoracic and mediastinal disorders	**0**	**1(0.8%)**	**0**
Interstitial lung disease	0	1(0.8%)	0

MedDRA version: 21.1
A subject with multiple severity grades for a given TEAE was counted only once under the maximum severity.
Source: Ad-hoc analysis of ASCEND datasets.

The Applicant's Position:

Acalabrutinib was well tolerated and showed an acceptable safety profile that is consistent with the other acalabrutinib clinical trials.

Regulatory Authorities Assessment:

FDA disagrees with the Applicant's assessment of attribution of fatal AEs. All fatal AEs were at least possibly attributable to acalabrutinib, including deaths from SPMs.

Table 49 summarizes all reported deaths according to treatment group and cause, per FDA adjudication. In this analysis, fatal AEs represent all-cause events that occurred in the absence of next anticancer therapy or PD. FDA classified deaths occurring in the setting of untreated PD (not directly attributable to PD but occurring in its context) as PD deaths. In recipients of acalabrutinib, fatal AEs within 30 days of last dose were reported in 2.6% of patients in the randomized cohort and 2.9% of patients after crossover, with the leading causes in all acalabrutinib recipients combined being SPM and infection.

Table 49 On-Treatment Deaths in ASCEND (FDA Analysis)

Treatment Group	# Deaths ≤ 30 Days After Last Dose
Acalabrutinib – Randomized (N = 154)	
After next anticancer therapy or PD	3
AE	**4 (2.6%)** [a]
SPM	2
Infection	1
Cachexia	1
Acalabrutinib – Cross-over (N = 35)	
After next anticancer therapy or PD	2
AE (infection)	**1 (2.9%)**
IR (N = 118)	
After next anticancer therapy or PD	0
AE [b]	**3 (2.5%)**
Cardiac or cardiopulmonary	2
Infection	0
Interstitial lung disease	1
Unknown	0
BR (N = 34)	
After next anticancer therapy or PD	0
AE (cardiac failure) [b]	**1 (2.9%)**

Source: FDA analysis

[a] Additionally, 1 patient died from SPM >30 days after last dose, in the context of untreated CLL progression.

[b] Narratives were not provided for the control arm.

8.2.4.2 Serious Adverse Events

The Applicant's Description:

SAEs occurred in 28.6%, 55.9%, and 25.7% of subjects who received acalabrutinib, IR, and BR, respectively, and most SAEs were Grade ≥3 (Table 50). Among subjects treated with acalabrutinib, the most common SAE was pneumonia (8 [5.2%] subjects).

Table 50 Serious Treatment-Emergent Adverse Events Reported in ≥2% of Subjects in the Acalabrutinib Arm (Safety Population)

System Organ Class /Preferred Term	No. (%) of Subjects					
	Arm A		Arm B			
	Acalabrutinib (N=154)		IR (N=118)		BR (N=35)	
	Any	Grades ≥3	Any	Grades ≥3	Any	Grades ≥3
Subjects with at least one Serious TEAE	**44(28.6%)**	**41(26.6%)**	**66(55.9%)**	**60(50.8%)**	**9(25.7%)**	**9(25.7%)**
Cardiac disorders	**6(3.9%)**	**4(2.6%)**	**4(3.4%)**	**4(3.4%)**	**3(8.6%)**	**3(8.6%)**
Gastrointestinal disorders	**4(2.6%)**	**4(2.6%)**	**23(19.5%)**	**21(17.8%)**	**0**	**0**
Infections and infestations	**20(13.0%)**	**19(12.3%)**	**27(22.9%)**	**23(19.5%)**	**4(11.4%)**	**4(11.4%)**
Pneumonia	8(5.2%)	8(5.2%)	10(8.5%)	9(7.6%)	1(2.9%)	1(2.9%)

System Organ Class /Preferred Term	No. (%) of Subjects					
	Arm A		Arm B			
	Acalabrutinib (N=154)		IR (N=118)		BR (N=35)	
	Any	Grades ≥3	Any	Grades ≥3	Any	Grades ≥3
Injury, poisoning and procedural complications	**5(3.2%)**	**4(2.6%)**	**3(2.5%)**	**3(2.5%)**	**0**	**0**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**9(5.8%)**	**7(4.5%)**	**0**	**0**	**1(2.9%)**	**1(2.9%)**
Respiratory, thoracic and mediastinal disorders	**7(4.5%)**	**7(4.5%)**	**8(6.8%)**	**7(5.9%)**	**0**	**0**

MedDRA version: 21.1
A subject with multiple severity grades for a given TEAE was counted only once under the maximum severity.
Source: Ad-hoc analysis of ASCEND datasets.

The Applicant's Position:

Compared with IR, acalabrutinib was associated with a lower incidence of SAEs (28.6% versus 55.9%).

Regulatory Authorities Assessment:

Regulatory authorities agree with the overall incidence of SAEs but not the leading causes. On FDA analysis (Table 51), the incidence of at least one SAE was 29%, 56%, and 26% in recipients of acalabrutinib, IR, and BR, respectively. By system organ class, infection was the leading cause of SAEs in recipients of acalabrutinib (incidence 13%), followed by neoplasms (6%, compared to none in the IR group).

By grouped PTs, upper respiratory tract infection was the leading cause of SAEs in all treatment groups, occurring in 29% of acalabrutinib recipients, whereas lower respiratory tract infection SAEs (including pneumonia) occurred in 6% of acalabrutinib recipients.

Table 51 SAEs in Acalabrutinib Arm by SOC and Preferred Term in ASCEND (FDA Analysis)

Event	Acalabrutinib (N = 154)	IR (N = 118)	BR (N = 35)
Any grade ≥ 4 AE, n (%)	28 (18%)	47 (40%)	9 (26%)
Any SAE, n (%)	44 (29%)	66 (56%)	9 (26%)
SAEs in ≥ 2% of acalabrutinib arm by SOC, %			
Infections and infestations	13	23	11
Neoplasms	6	0	2.9
Respiratory, thoracic, mediastinal	4.5	6.8	0
Cardiac disorders	3.9	3.4	8.6
Injury, poisoning, procedural	3.2	2.5	0
Gastrointestinal	2.6	19	0
SAEs in ≥ 5% of acalabrutinib arm by grouped PT, %			
Respiratory tract infection (any)	29	56	26
Upper	29	26	17
Lower, including pneumonia [a]	6	15	6
Unspecified	1.9	0.8	9
SPM	6	0	2.9

Source: FDA analysis
Includes all-cause events reported up to 30 days after last dose, prior to any cross-over.
Bolded categories are involved ≥ 5% more with acalabrutinib than IR.
[a] Patients with pneumonia SAEs: 6%, 14%, and 2.8%, respectively

8.2.4.3 Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Description:

TEAEs that led to discontinuation of study treatment occurred in 16 (10.4%), 62 (52.5%), and 6 (17.1%) subjects in the acalabrutinib, IR, and BR treatment groups, respectively). In the acalabrutinib arm, 14 of the 16 subjects with TEAEs that led to discontinuation of acalabrutinib had Grade ≥3 events. Six of these TEAEs were reported as related to acalabrutinib, including Grade 4 brain neoplasm malignant (SAE), and Grade 3 events of cardiac failure congestive, bladder transitional cell carcinoma, cytopenia, increased alanine aminotransferase, and hepatitis B.

The Applicant's Position:

Compared with IR, acalabrutinib was associated with a lower incidence of TEAEs that led to treatment discontinuation (10.4% versus 52.5%).

Regulatory Authorities Assessment:

Regulatory authorities agree with the Applicant's position. However, the incidence of treatment discontinuation in the IR group differs slightly in this description and the CSR (Table 52).

8.2.4.4 Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Description:

Acalabrutinib had a lower percentage of subjects with TEAEs compared with IR for TEAEs that led to dose reduction (3.9% versus 12.7%), TEAEs that led to dose withholding (33.8% versus 64.4%), and TEAEs that led to study drug discontinuation (10.4% versus 52.5%). The percentage of subjects was similar in the acalabrutinib and BR treatment groups, respectively, for TEAEs that led to dose withholding (33.8% and 20.0%), and TEAEs that led to study drug discontinuation (10.4% and 17.1%). TEAEs that led to dose reduction were reported less frequently in the acalabrutinib group than in the BR group (3.9% versus 14.3%, respectively).

The Applicant's Position:

Fewer dose interruptions or reductions due to adverse events occurred for subjects treated with acalabrutinib than those treated with IR or BR.

Regulatory Authorities Assessment:

Regulatory authorities agree with the Applicant's position and verified that in the acalabrutinib arm, AEs led to dose interruption in 34% of patients, dose reduction in 3.9%, and permanent discontinuation in 10%. Table 52 summarizes actions due to AEs as reported in the CSR. The acalabrutinib arm had a lower incidence of dose reduction, interruption, and discontinuation than idelalisib. For idelalisib, discontinuations from AEs were mainly due to immune-mediated AEs.

Table 52 Treatment Modifications Due to AEs in ASCEND

Action due to AE	Acalabrutinib	Idelalisib +/- R	Benda +/- R
Dose reduction	6 (3.9%)	15 (13%)	5 (14%)
Dose interruption	52 (34%)	86 (73%)	8 (23%)
Discontinuation	16 (10%)	59 (50%)	4 (11%)

Source: CSR Table 34

Table 53 summarizes reasons for treatment modifications in the acalabrutinib arm based on FDA adjudication. For acalabrutinib, causes of dose reduction were heterogeneous. SPMs followed by infection were the leading AEs resulting in acalabrutinib discontinuation, whereas respiratory tract infections (upper or lower) followed by neutropenia were the leading causes of acalabrutinib dose interruption.

Table 53 Causes of AE-Related Modifications of Acalabrutinib (ASCEND)

Acalabrutinib Actions due to AE (from N of 154)	# of Patients
Dose reduction (n = 6; 3.9%)	
Diarrhea, musculoskeletal pain, skin hemorrhage	1
Diarrhea	1
Bleeding	1
ITP	1
Neutropenia	1
Infection	1
Dose interruption of any duration (n = 52; 34%)	
Reasons in ≥ 10% of affected patients:	
Respiratory tract infection	15/52 (29%)
Neutropenia	11 (21%)
Diarrhea or gastroenteritis	5 (10%)
Discontinuation (n = 16; 10%)	
SPM	**6/16 (38%)**
Nonmelanoma skin cancer	1
Brain neoplasm [a]	2
Lung cancer	1
Bladder cancer	1
Prostate cancer	1
Infection	**3/16 (19%)**
Peritonitis	1
Respiratory tract infection	1
Hepatitis B	1
Cytopenias	2
Cardiac or vascular	2
Pain	2

Source: FDA analysis
[a] One specified as malignant; other unspecified but fatal

8.2.4.5 Significant Adverse Events

The Applicant's Description:

Most subjects who received acalabrutinib, IR, or BR had ECIs (82.5%, 95.8%, and 74.3%, respectively). ECI categories reported in ≥10% of subjects who received acalabrutinib included infections (56.5%), hemorrhage (26.0%), leukopenia (21.4%; all events were neutropenia), anemia (14.9%), thrombocytopenia (14.3%), cardiac events (13.0%), and second primary malignancies (11.7%). ECI categories reported in ≥10% of subjects who received IR included infections (65.3%), leukopenia (53.4%; including 50.8% with neutropenia), hepatotoxicity (28.0%), and thrombocytopenia (16.9%). ECI categories reported in ≥10% of subjects who received BR included infections (48.6%), leukopenia (37.1%; all events were neutropenia), thrombocytopenia (17.1%), and anaemia (11.4%) (Table 54).

Table 54 Summary of Treatment-Emergent Events by ECI Category and FDA Grouped Preferred Terms (Safety Population)

	No. (%) of Subjects					
	Arm A		Arm B			
	Acalabrutinib (N=154)		IR (N=118)		BR (N=35)	
FDA Grouped PT	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Cardiac events	**20 (13.0%)**	**5 (3.2%)**	**9 (7.6%)**	**4 (3.4%)**	**3 (8.6%)**	**3 (8.6%)**
Atrial fibrillation or flutter[1]	8 (5.2%)	2 (1.3%)	4 (3.4%)	1 (0.8%)	1 (2.9%)	1 (2.9%)
Ventricular arrhythmias[1]	0	0	0	0	0	0
Cardiac arrhythmias[1]	12 (7.8%)	3 (1.9%)	5 (4.2%)	1 (0.8%)	1 (2.9%)	1 (2.9%)
Myocardial ischemia or infarction[1]	1 (0.6%)	1 (0.6%)	2 (1.7%)	2 (1.7%)	1 (2.9%)	1 (2.9%)
Supraventricular tachycardia[1]	10 (6.5%)	2 (1.3%)	5 (4.2%)	1 (0.8%)	1 (2.9%)	1 (2.9%)
Anemia[1]	**24 (15.6%)**	**18 (11.7%)**	**10 (8.5%)**	**8 (6.8%)**	**6 (17.1%)**	**5 (14.3%)**
Leukopenia	**33 (21.4%)**	**27 (17.5%)**	**63 (53.4%)**	**58 (49.2%)**	**13 (37.1%)**	**12 (34.3%)**
Neutropenia[1]	32 (20.8%)	26 (16.9%)	63 (53.4%)	58 (49.2%)	13 (37.1%)	12 (34.3%)
Febrile neutropenia[1]	1 (0.6%)	1 (0.6%)	3 (2.5%)	3 (2.5%)	1 (2.9%)	1 (2.9%)
Other Leukopenia	0	0	3 (2.5%)	3 (2.5%)	1 (2.9%)	0
Thrombocytopenia[1]	**22 (14.3%)**	**7 (4.5%)**	**20 (16.9%)**	**9 (7.6%)**	**6 (17.1%)**	**1 (2.9%)**
Hemorrhage or hematoma[1]	**24 (15.6%)**	**2 (1.3%)**	**6 (5.1%)**	**2 (1.7%)**	**2 (5.7%)**	**1 (2.9%)**
Major hemorrhage	3 (1.9%)	3 (1.9%)	3 (2.5%)	3 (2.5%)	1 (2.9%)	1 (2.9%)
Gastrointestinal hemorrhage[1]	3 (1.9%)	2 (1.3%)	2 (1.7%)	1 (0.8%)	0	0
Hemorrhage intracranial[1]	0	0	0	0	0	0
Hepatotoxicity	**7 (4.5%)**	**3 (1.9%)**	**33 (28.0%)**	**26 (22.0%)**	**3 (8.6%)**	**2 (5.7%)**
Hepatitis[1]	3 (1.9%)	1 (0.6%)	11 (9.3%)	7 (5.9%)	1 (2.9%)	0
Hyperbilirubinemia[1]	0	0	1 (0.8%)	0	0	0
Hypertension[1]	**5 (3.2%)**	**3 (1.9%)**	**5 (4.2%)**	**1 (0.8%)**	**0**	**0**
Infections	**87 (56.5%)**	**23 (14.9%)**	**77 (65.3%)**	**33 (28.0%)**	**17 (48.6%)**	**4 (11.4%)**
Cytomegalovirus infection[1]	0	0	8 (6.8%)	2 (1.7%)	0	0
Gastroenteritis[1]	2 (1.3%)	1 (0.6%)	4 (3.4%)	1 (0.8%)	2 (5.7%)	1 (2.9%)
Herpesvirus infection[1]	0	0	0	0	0	0
Lower respiratory tract infection[1]	20 (13.0%)	1 (0.6%)	11 (9.3%)	3 (2.5%)	3 (8.6%)	1 (2.9%)
Pneumonia[1]	19 (12.3%)	9 (5.8%)	22 (18.6%)	16 (13.6%)	2 (5.7%)	1 (2.9%)
Respiratory tract infection[1]	0	0	1 (0.8%)	0	0	0
Sepsis[1]	1 (0.6%)	1 (0.6%)	3 (2.5%)	3 (2.5%)	0	0
Upper respiratory tract infection[1]	44 (28.6%)	3 (1.9%)	31 (26.3%)	4 (3.4%)	6 (17.1%)	1 (2.9%)
Urinary tract infection[1]	7 (4.5%)	3 (1.9%)	7 (5.9%)	2 (1.7%)	0	0
Interstitial lung disease/Pneumonitis	**3 (1.9%)**	**2 (1.3%)**	**8 (6.8%)**	**4 (3.4%)**	**0**	**0**
Pneumonitis[1]	2 (1.3%)	2 (1.3%)	6 (5.1%)	4 (3.4%)	0	0
Second primary malignancies	**18 (11.7%)**	**6 (3.9%)**	**3 (2.5%)**	**0**	**1 (2.9%)**	**1 (2.9%)**
Second primary malignancies excluding non-melanoma skin	10 (6.5%)	5 (3.2%)	3 (2.5%)	0	1 (2.9%)	1 (2.9%)
Nonmelanoma skin cancer[1]	10 (6.5%)	1 (0.6%)	1 (0.8%)	0	0	0
Tumor lysis syndrome	**1 (0.6%)**	**1 (0.6%)**	**1 (0.8%)**	**1 (0.8%)**	**0**	**0**

[1] FDA grouped preferred terms

MedDRA version: 21.1

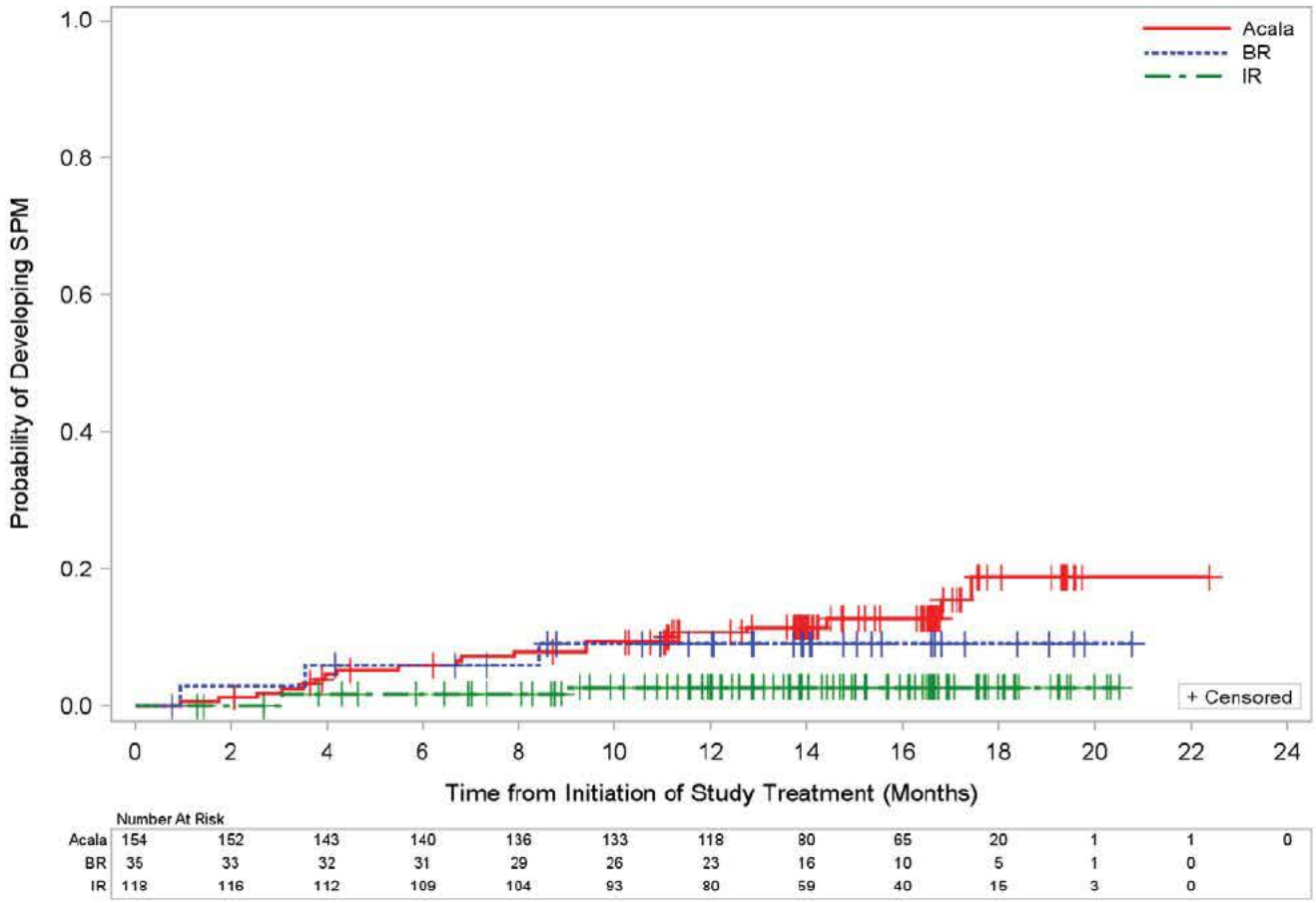
A subject with multiple severity grades for a given TEAE was counted only once under the maximum severity.

Source: Ad-hoc analysis of ASCEND datasets.

Treatment-emergent second primary malignancies occurred in 18 (11.7%), 3 (2.5%), and 1 (2.9%) subjects in the acalabrutinib, IR, and BR treatment groups, respectively. Grade ≥3 events occurred in 6 (3.9%) subjects treated with acalabrutinib and 1 (2.9%) subject treated with BR. Narratives for acalabrutinib-treated subjects with second primary malignancies, excluding non-melanoma skin, are provided in the application. Figure 15 below provides estimated cumulative

incidences based on a time-to-first event analysis.

Figure 15 **Time to Onset of Second Primary Malignancy Events – Failure Plot (Safety Population)**



Source: Ad-hoc analysis of ASCEND datasets per FDA request

The Applicant's Position:

Acalabrutinib was well tolerated and showed an acceptable safety profile that is consistent with the other acalabrutinib clinical trials.

Regulatory Authorities Assessment:

Regulatory authorities agree that the incidences of atrial fibrillation and major hemorrhage in ASCEND are consistent with other acalabrutinib trials, but disagrees with the Applicant's assessment of the several ECIs, including SPMs, cytopenias, and opportunistic infections.

A. *Second Primary Malignancies*

The incidence of SPMs in recipients of acalabrutinib, compared to the control arms, is substantially higher in ASCEND (Figure 15). In contrast, in patients with previously untreated

CLL, there was no signal of excess SPMs with acalabrutinib or acalabrutinib + obinutuzumab compared to chlorambucil + obinutuzumab (source: FDA review of NDA 210259 S-007).

In ASCEND, with an estimated median follow up (reverse Kaplan-Meier method) of 14.6 months overall (15.2 months for acalabrutinib, 14.0 months for IC), the estimated 1-year cumulative incidence of SPM was 10.8% (95% CI: 6.7, 17.0) in acalabrutinib recipients, and 4.2% (95% CI: 1.9, 9.1) after IC, translating into a HR of 3.23 (95% CI: 1.38, 8.85)(source: FDA analysis). Notably, however, these are not exposure-adjusted incidences. Table 55 summarizes the types of SPM after acalabrutinib, which were similarly distributed between nonmelanoma skin cancer and other solid tumors. The most common SPM was nonmelanoma skin cancer, reported in 12 patients (8%).

Among 1209 recipients of acalabrutinib with or without obinutuzumab (defined in Table 45), the Applicant reported SPMs in 12%, most frequently from skin cancer, reported in 6% of patients (source: labeling negotiations).

Table 55 Types of SPM in the Acalabrutinib Arm of ASCEND

Acalabrutinib arm (N = 154): Type of SPM or first SPM, with censoring for next anticancer therapy [a]	From 20 affected patients
Nonmelanoma skin cancer	**11 (7.1%)**
Other	**9 (5.8%)**
Brain neoplasm	2
Pancreatic neoplasm	1
Lung cancer	1
Melanoma [b]	1
Metastatic SCC	1
Neuroendocrine carcinoma	1
Bladder cancer	1
Prostate cancer	1

Source: FDA analysis.
[a] For patients with more than one SPM, the first is listed.
[b] Followed by nonmelanoma skin cancer

B. *Cytopenias and Other Lab-Related AEs*

Cytopenias:

Hematologic events, including neutropenia, anemia, and thrombocytopenia, are underreported in the AE dataset used to generate Table 54 compared to the laboratory dataset. The incidence of grade 1-2 hematologic AEs is substantially underreported, whereas the incidence of grade 3-4 hematologic AEs more closely mirrors the dedicated laboratory analysis. Refer to Section 8.2.4.7 on "Laboratory Findings" for a TE laboratory analysis of ASCEND using the dedicated laboratory dataset. The Appendix (Table 74) also

demonstrates the underreporting of hematologic events using the AE dataset alone, and the increased incidences when AE and laboratory data are integrated.

On FDA analysis of the expanded safety population (N = 1209), grade 3 or 4 treatment-emergent cytopenias, based on lab shift analysis, included neutropenia (23%), anemia (8%), and thrombocytopenia (7%), with grade 4 neutropenia developing in 12% (Table 56).

Table 56 TE Hematologic Abnormalities (≥ 20%) in FDA's Expanded Safety Population

Laboratory abnormality	From N of 1029:		
	Any grade, %	Grade 3 or 4, %	Grade 4, %
Neutropenia	44	23	11.8
Anemia	43	8	0
Thrombocytopenia	34	7	3.0
Leukopenia	29	5	0.6
Lymphopenia	24	7	1.2
Lymphocytosis	22	15	0
Leukocytosis	21	21	0

Source: FDA analysis based on ISS lab dataset

Tumor lysis syndrome: The TLS incidence is potentially underreported, because reporting was based on the PT rather than laboratory and chart review.

Hepatotoxicity: The Applicant reported no cases of Hy's law in ASCEND.

C. ***Infection***

Serious and opportunistic infections are insufficiently characterized in the Applicant's description.

Herpesvirus infection: In ASCEND, the incidence of any-grade herpesvirus infection is not 0%, but rather 4.5%, 6%, and 9% in recipients of acalabrutinib, IR, and BR, respectively.

Other opportunistic or serious infections: Infections other than those in Table 54 are relevant to the acalabrutinib safety analysis. In the expanded safety population (N = 1209), FDA evaluated infections by combining AEs under the "Infections and Infestations" SOC with neutropenic fever AEs. Grade ≥ 3 infection or infection SAEs developed in 198 patients (19%), with respiratory tract infections as the leading cause. The majority of infections developed in the absence of reported Grade ≥ 3 neutropenia.

Grade ≥ 3 or serious respiratory tract infections developed in 111 patients (11%), with pneumonia as the leading cause (6% of all patients). Opportunistic infection of any grade, inclusive of sepsis, developed in 125 patients (12%). As summarized in Table 57, opportunistic infections included systemic fungal infections, hepatitis B reactivation, EBV reactivation, and a fatal case of PML.

Table 57 Opportunistic Infections in FDA's Expanded Safety Population (N = 1209)

Type of infection (any grade)	From N of 1209
Systemic fungal	**9**
Fungal pneumonia	5 [a]
Aspergillus infection, unspecified	2
Disseminated cryptococcosis	1
Candida sepsis	1 [b]
Viral	
Herpesvirus	63 (6%)
PML	1 [c]
JC virus UTI	1
CMV viremia	1
Hepatitis B or hepatitis B reactivation	3
EBV reactivation	3
Respiratory tract infection	
Parainfluenzae	5
Metapneumovirus	1
Respiratory syncytial virus	2
Other [d]	
Sepsis	27 (2.6%)
Febrile neutropenia	20 (1.9%)
Encephalitis	2
Stenotrophomonas infection	1

Source: FDA analysis

[a] Includes bronchopulmonary aspergillosis (2 cases), unspecified fungal pneumonia (2), PJP (1)

[b] Also included under "sepsis" category

[c] Grade 5; occurred after acala + obinutuzumab for previously untreated CLL

[d] Excludes PTs describing "atypical pneumonia"

FDA Reviewer Comments:

- *The clinical reviewer recommends that the acalabrutinib Warning and Precaution on "Infection" be renamed "Serious and Opportunistic Infections" to directly convey the main concern. With the integrated safety analysis, the signal for opportunistic infection has strengthened. However, because the majority of patients in the integrated safety population have CLL, it is unclear to what degree acalabrutinib versus the underlying malignancy contributes to this observed risk. In ASCEND, the incidence of infection-related AEs and SAEs was lower in recipients of acalabrutinib compared to IR, despite the longer duration of treatment with acalabrutinib.*
- *It is notable that most Grade ≥ 3 or serious infections appear to have occurred in the absence of severe neutropenia. To further characterize infection risk with acalabrutinib, FDA requested a dataset on Grade ≥ 3 or serious infections in ASCEND and ELEVATE-TN that included data on neutrophil counts, hypogammaglobinemia,*

and infection prophylaxis at the time of infection. However, the extent of missing laboratory data precluded an informative analysis (source: response to October 16, 2019 information request).

D. *Hemorrhage*

On FDA analysis, major bleeding defined as serious or Grade ≥ 3 bleeding, or any grade of CNS or retinal bleed, occurred in 3.4% of 1209 patients in the expanded safety population, with gastrointestinal bleeding as the leading site (Table 58). Excluding grade 2 nonserious retinal bleeding, this incidence was 3.2%. For incidences of any-grade bleeding, refer to Table 62.

Table 58 Sites of Major Bleeding in Expanded Safety Population

Site	N patients (35 total)	% (from N of 1209)
GI	9	0.7%
GU	5	0.4%
Mucosal [a]	5	0.4%
CNS	4	0.3%
Retinal	3	0.2%
Soft tissue	3	0.2%
Post procedural	2	0.2%
Respiratory tract	1	0.1%
Joint	1	0.1%
Tumor	1	0.1%
Unspecified	1	0.1%

Source: FDA analysis

[a] Epistaxis, blood blister, sublingual

E. *Atrial Fibrillation*

In the expanded safety population (N = 1209), Grade 3 atrial fibrillation or flutter occurred in 1.1% of patients, with all grades of atrial fibrillation or flutter reported in 4.1% of all patients (source: FDA analysis).

8.2.4.6 Treatment Emergent Adverse Events and Adverse Reactions

The Applicant's Description

Common TEAEs that occurred in ≥10% of acalabrutinib-treated subjects were headache (22.1%), neutropenia (19.5%), diarrhoea (18.2%), anaemia and cough (14.9% each), upper respiratory tract infection (14.3%), pyrexia (12.3%), thrombocytopenia (11.0%), and pneumonia and respiratory tract infection (10.4% each). Most TEAEs in the acalabrutinib arm were Grade 1 or 2 (Table 59).

Common TEAEs that occurred in ≥10% of IR-treated subjects were diarrhoea (46.6%), neutropenia (44.9%), pyrexia (18.6%), cough (15.3%), upper respiratory tract infection (14.4%),

thrombocytopenia (13.6%), and pneumonia (11.9%). Common TEAEs that occurred in ≥10% of BR-treated subjects were neutropenia (34.3%),), pyrexia (17.1%), diarrhoea and thrombocytopenia (14.3% each), and anaemia and upper respiratory tract infection (11.4% each) (Table 59).

Table 59 Treatment Emergent Adverse Events in ≥10% of Subjects in the Acalabrutinib Arm (Safety Population)

System Organ Class /Preferred Term	No. (%) of Subjects					
	Arm A		Arm B			
	Acalabrutinib (N=154)		IR (N=118)		BR (N=35)	
	Any	Grades ≥3	Any	Grades ≥3	Any	Grades ≥3
Number of Subjects with at least 1 TEAE	**144(93.5%)**	**76(49.4%)**	**117(99.2%)**	**106(89.8%)**	**28(80.0%)**	**17(48.6%)**
Blood and lymphatic system disorders	**59(38.3%)**	**40(26.0%)**	**67(56.8%)**	**58(49.2%)**	**15(42.9%)**	**14(40.0%)**
Neutropenia	30(19.5%)	24(15.6%)	53(44.9%)	47(39.8%)	12(34.3%)	11(31.4%)
Anaemia	23(14.9%)	18(11.7%)	10(8.5%)	8(6.8%)	4(11.4%)	3(8.6%)
Thrombocytopenia	17(11.0%)	6(3.9%)	16(13.6%)	9(7.6%)	5(14.3%)	1(2.9%)
Cardiac disorders	**20(13.0%)**	**5(3.2%)**	**9(7.6%)**	**4(3.4%)**	**3(8.6%)**	**3(8.6%)**
Gastrointestinal disorders	**62(40.3%)**	**5(3.2%)**	**80(67.8%)**	**33(28.0%)**	**14(40.0%)**	**2(5.7%)**
Diarrhoea	28(18.2%)	2(1.3%)	55(46.6%)	28(23.7%)	5(14.3%)	0
General disorders and administration site conditions	**44(28.6%)**	**5(3.2%)**	**44(37.3%)**	**10(8.5%)**	**17(48.6%)**	**3(8.6%)**
Pyrexia	19(12.3%)	1(0.6%)	22(18.6%)	8(6.8%)	6(17.1%)	1(2.9%)
Infections and infestations	**87(56.5%)**	**23(14.9%)**	**77(65.3%)**	**33(28.0%)**	**17(48.6%)**	**4(11.4%)**
Upper respiratory tract infection	22(14.3%)	3(1.9%)	17(14.4%)	4(3.4%)	4(11.4%)	1(2.9%)
Pneumonia	16(10.4%)	8(5.2%)	14(11.9%)	10(8.5%)	2(5.7%)	1(2.9%)
Respiratory tract infection	16(10.4%)	2(1.3%)	8(6.8%)	1(0.8%)	0	0
Injury, poisoning and procedural complications	**30(19.5%)**	**4(2.6%)**	**20(16.9%)**	**5(4.2%)**	**9(25.7%)**	**1(2.9%)**
Investigations	**24(15.6%)**	**7(4.5%)**	**44(37.3%)**	**26(22.0%)**	**8(22.9%)**	**3(8.6%)**
Metabolism and nutrition disorders	**29(18.8%)**	**5(3.2%)**	**33(28.0%)**	**6(5.1%)**	**3(8.6%)**	**0**
Musculoskeletal and connective tissue disorders	**44(28.6%)**	**5(3.2%)**	**27(22.9%)**	**3(2.5%)**	**3(8.6%)**	**0**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**26(16.9%)**	**8(5.2%)**	**6(5.1%)**	**0**	**2(5.7%)**	**2(5.7%)**
Nervous system disorders	**45(29.2%)**	**3(1.9%)**	**19(16.1%)**	**1(0.8%)**	**3(8.6%)**	**0**
Headache	34(22.1%)	1(0.6%)	7(5.9%)	0	0	0
Respiratory, thoracic and mediastinal disorders	**41(26.6%)**	**7(4.5%)**	**36(30.5%)**	**8(6.8%)**	**3(8.6%)**	**0**
Cough	23(14.9%)	0	18(15.3%)	1(0.8%)	2(5.7%)	0
Skin and subcutaneous tissue disorders	**42(27.3%)**	**4(2.6%)**	**36(30.5%)**	**8(6.8%)**	**5(14.3%)**	**1(2.9%)**
Vascular disorders	**23(14.9%)**	**6(3.9%)**	**15(12.7%)**	**4(3.4%)**	**8(22.9%)**	**0**

MedDRA version: 21.1
A subject with multiple severity grades for a given TEAE was counted only once under the maximum severity.
Source: Ad-hoc analysis of ASCEND datasets.

The number of subjects with adverse drug reactions is provided in Table 60 in decreasing incidence by system organ class and preferred term.

Table 60 Subject Incidence of Acerta-Defined Adverse Drug Reactions by FDA Grouped Preferred Terms (Safety Population)

	No. (%) of Subjects					
	Arm A		Arm B			
	Acalabrutinib (N=154)		IR (N=118)		BR (N=35)	
Grouped Term	All Grades	Grades ≥3	All Grades	Grades ≥3	All Grades	Grades ≥3
Abdominal pain [1]	**13 (8.4%)**	**0**	**11 (9.3%)**	**1 (0.8%)**	**1 (2.9%)**	**0**
Bruising [1]	**16 (10.4%)**	**0**	**3 (2.5%)**	**0**	**0**	**0**
Rash [1]	**14 (9.1%)**	**1 (0.6%)**	**25 (21.2%)**	**7 (5.9%)**	**4 (11.4%)**	**0**
Hemorrhage or hematoma [1]	**24 (15.6%)**	**2 (1.3%)**	**6 (5.1%)**	**2 (1.7%)**	**2 (5.7%)**	**1 (2.9%)**
Second Primary Malignancy [2]	**18 (11.7%)**	**6 (3.9%)**	**3 (2.5%)**	**0**	**1 (2.9%)**	**1 (2.9%)**
Second Primary Malignancy, excluding non-melanoma skin [2]	10 (6.5%)	5 (3.2%)	3 (2.5%)	0	1 (2.9%)	1 (2.9%)
Nonmelanoma skin cancer [1]	10 (6.5%)	1 (0.6%)	1 (0.8%)	0	0	
Infection [2]	**87 (56.5%)**	**23 (14.9%)**	**77 (65.3%)**	**33 (28.0%)**	**17 (48.6%)**	**4 (11.4%)**
Atrial fibrillation or flutter [1]	**8 (5.2%)**	**2 (1.3%)**	**4 (3.4%)**	**1 (0.8%)**	**1 (2.9%)**	**1 (2.9%)**
Cytopenias						
Anemia [1]	24 (15.6%)	18 (11.7%)	10 (8.5%)	8 (6.8%)	6 (17.1%)	5 (14.3%)
Leukopenia [2]	33 (21.4%)	27 (17.5%)	63 (53.4%)	58 (49.2%)	13 (37.1%)	12 (34.3%)
Neutropenia [1]	32 (20.8%)	26 (16.9%)	63 (53.4%)	58 (49.2%)	13 (37.1%)	12 (34.3%)
Other Leukopenia [2]	0	0	3 (2.5%)	3 (2.5%)	1 (2.9%)	0
Thrombocytopenia [1]	22 (14.3%)	7 (4.5%)	20 (16.9%)	9 (7.6%)	6 (17.1%)	1 (2.9%)
Musculoskeletal pain [1]	**23 (14.9%)**	**2 (1.3%)**	**18 (15.3%)**	**2 (1.7%)**	**1 (2.9%)**	**0**
Hypertension [1]	**5 (3.2%)**	**3 (1.9%)**	**5 (4.2%)**	**1 (0.8%)**	**0**	**0**
Diarrhea or colitis [1]	**28 (18.2%)**	**2 (1.3%)**	**58 (49.2%)**	**30 (25.4%)**	**5 (14.3%)**	**0**
Dizziness [1]	**10 (6.5%)**	**0**	**4 (3.4%)**	**0**	**2 (5.7%)**	**0**
Fatigue [1]	**23 (14.9%)**	**3 (1.9%)**	**15 (12.7%)**	**1 (0.8%)**	**11 (31.4%)**	**2 (5.7%)**
Headache [1]	**34 (22.1%)**	**1 (0.6%)**	**7 (5.9%)**	**0**	**0**	**0**
Nausea [1]	**11 (7.1%)**	**0**	**15 (12.7%)**	**1 (0.8%)**	**7 (20.0%)**	**0**

[1] FDA grouped terms
[2] As per Acerta ADR definition
MedDRA version: 21.1
Source: Ad-hoc analysis of ASCEND datasets.

The Applicant's Position:

Acalabrutinib was well tolerated and showed an acceptable safety profile that is consistent with the other acalabrutinib clinical trials.

Regulatory Authorities Assessment:

Regulatory authorities agree in general with the Applicant's position. Because of differences in grouping of PTs, FDA's characterization of common TEAEs (Table 61) differs slightly from the Applicant's. TEAEs by PT or grouped PT, in order of decreasing frequency, are described in the Appendix (Table 73). Table 61 presents selected TEAEs by SOC and PT. In Table 61, for increased sensitivity, TEAEs involving more than one SOC are listed under the main SOC, and incidences of hematologic AEs are derived by integrating the AE and laboratory datasets. AEs in ASCEND are first presented, followed by AEs in FDA's integrated safety population (N = 1029).

ASCEND

In patients with relapsed or refractory CLL in ASCEND, the most common TEAEs (incidence ≥

30%) with acalabrutinib were neutropenia, anemia, and thrombocytopenia. Other common TEAEs (incidence ≥ 15%) included upper and lower respiratory tract infections, lymphocytosis, headache, diarrhea, musculoskeletal pain, bleeding, and fatigue.

Table 61 All-Cause TEAEs (≥ 10%) with Acalabrutinib in ASCEND (FDA analysis)

SOC / PT or grouped PT	Acalabrutinib (N = 154), %		Idelalisib+R (N = 118), %		BR (N = 35), %	
	Any	G 3-5 [b]	Any	G 3-5	Any	G 3-5 [b]
Blood, lymphatic system [a]						
Neutropenia	48	23	79	53	80	40
Anemia	47	15	43	8	57	17
Thrombocytopenia	33	6	41	13	54	6
Lymphocytosis	26	19	23	18	2.9	2.9
Leukocytosis	25	25	10	10	0	0
Leukopenia	15	1.3	42	8	74	26
Infection						
Upper respiratory tract infection	29	1.9	26	3.4	17	2.9
Lower respiratory tract infection [c]	23	6	26	15 [d]	14	6
Pneumonia	12	6	19	14	6	2.9
Neurologic						
Headache	22	0.6	6	0	0	0
Gastrointestinal						
Diarrhea or colitis	18	1.3	47	24	14	0
Respiratory, mediastinal, thoracic						
Cough	18	0	17	0.8	6	0
Vascular						
Hemorrhage	15	1.3	7	2.5	9	3
General disorders, admin site						
Fatigue	15	1.9	13	0.8	31	6
Pyrexia	12	0.6	19	7	17	3
Musculoskeletal, connective tissue						
Musculoskeletal pain	15	1.3	15	1.7	2.9	0
Skin, subcutaneous						
Bruising	10	0	2.5	0	0	0

Source: FDA analysis. **Bolded** PTs occur ≥ 5% more with acalabrutinib than IR.

[a] Derived from AE and laboratory data.

[b] None listed were grade 5.

[c] Includes pneumonia

[d] Fatal in 1 case.

Minor variations between this table and the final PI are possible due to methodologic differences in the Applicant's and FDA's analysis.

FDA's Integrated Safety population

In the expanded safety population, consisting of 1209 recipients of acalabrutinib 100 mg approximately Q12H with or without obinutuzumab (Table 45), the overall safety profile of acalabrutinib was similar to that described in ASCEND and the registrational trial for MCL. In this integrated safety population, the most common AEs (≥ 30%) were anemia, neutropenia, upper respiratory tract infection, thrombocytopenia, headache, diarrhea, and musculoskeletal pain. Similarly, in the 511 patients with CLL who received acalabrutinib +/- obinutuzumab as randomized treatment in ASCEND and ELEVATE-TN combined, the most common AEs (≥ 30% any grade) were anemia, neutropenia, thrombocytopenia, leukocytosis, headache, upper respiratory tract infection, and diarrhea (source: FDA analysis).

Table 62 All-Cause TEAEs (≥ 15%) with Acalabrutinib in FDA's Expanded Safety Population

PT or Grouped PT	From N of 1029 recipients of acala 100 mg Q12H +/- obinutuzumab:	
	Any grade, %	Grade ≥ 3, %
HEMATOLOGIC [a]		
Anemia	47	11
Neutropenia	44	24
Thrombocytopenia	36	8
Leukopenia	29	5
Lymphopenia	24	7
Lymphocytosis	22	15
Leukocytosis	21	21
NON-HEMATOLOGIC		
Upper respiratory tract infection	38	1.9
Headache	37	1.1
Diarrhea	35	2.9
Musculoskeletal pain	34	1.7
Bruising	27	0
Fatigue	27	2.0
Rash	26	1.1
Cough	25	0.2
Lower respiratory tract infection [b]	22	7 [c]
Hemorrhage [d]	22	2.5 [d]
Nausea	21	0.9
Arthralgia	18	0.7
Dizziness	16	0.2
Edema	15	0.7
Abdominal pain	15	0.9

Source: FDA analysis

[a] Derived from AE and lab data. All-grade hematology AEs, without considering lab data, included neutropenia 18%, anemia 13%, thrombocytopenia 10%.

[b] Includes pneumonia (9% all grade, 4.6% grade ≥ 3).

PT or Grouped PT	From N of 1029 recipients of acala 100 mg Q12H +/- obinutuzumab:	
	Any grade, %	Grade ≥ 3, %

[c] Includes 5 fatal events, all from pneumonia.
[d] Includes 1 fatal event of CNS bleed. Grouping excludes purpura, bruising, and petechiae.

8.2.4.7 Laboratory Findings

The Applicant's Description:

Analysis of laboratory data from ASCEND showed that the frequency of the following hematologic abnormalities was lower in subjects treated with acalabrutinib compared with IR and BR, respectively: decreased ANC (46.8% versus 78.8% and 80.0%), decreased ALC (5.2% versus 15.3% and 71.4%), and decreased leukocytes (15.6% versus 42.4% and 74.3%) . Clinically important hematology abnormalities graded by Hallek 2008 criteria are presented in Table 63.

Table 63 Treatment-Emergent Neutrophil, Hemoglobin, Platelet Toxicities per Hallek 2008 Criteria (Safety Population)

	No. (%) of Subjects					
	Arm A		Arm B			
	Acalabrutinib (N=154)		IR (N=118)		BR (N=35)	
	All Grades[a]	Grade 3/4[a]	All Grades[a]	Grade 3/4[a]	All Grades[a]	Grade 3/4[a]
ANC, hemoglobin, or platelets						
Any (decrease)	112 (72.7%)	37 (24.0%)	104 (88.1%)	62 (52.5%)	33 (94.3%)	15 (42.9%)
ANC (decrease)	74 (48.1%)	32 (20.8%)	94 (79.7%)	59 (50.0%)	29 (82.9%)	14 (40.0%)
Hemoglobin (decrease)	55 (35.7%)	1 (0.6%)	24 (20.3%)	0	16 (45.7%)	1 (2.9%)
Platelets (decrease)	55 (35.7%)	7 (4.5%)	53 (44.9%)	12 (10.2%)	25 (71.4%)	3 (8.6%)

[a] Hallek et al. 2008.
The maximum toxicity grade experienced after the date of the first dose of study drug, and prior to the earlier of 37 days after the last dose of study drug or starting of new anticancer therapy (including acalabrutinib for subjects who crossed over), was considered for each subject.
ANC=absolute neutrophil count; BR=bendamustine/rituximab; IR=idelalisib/rituximab.
Source: ASCEND clinical report, Table 14.3.7.1.

By CTCAE, Grade 3 or 4 decreases were reported in 31.8%, 52.5%, and 45.7% of subjects in the 3 treatment groups, respectively. The frequency of the following hematologic abnormalities was notably lower in subjects treated with acalabrutinib compared with IR and BR, respectively: decreased ANC (46.8% versus 78.8% and 80.0%), decreased ALC (5.2% versus 15.3% and 71.4%), and decreased leukocytes (15.6% versus 42.4% and 74.3%) (Table 64).

Table 64 Treatment-Emergent Laboratory Abnormality in Hematology by CTCAE Toxicity Grade (Safety Population)

	No. (%) of Subjects					
	Arm A		Arm B			
	Acalabrutinib (N=154)		IR (N=118)		BR (N=35)	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
ANC, hemoglobin, or platelets						
Any (decrease)	114 (74.0%)	49 (31.8%)	106 (89.8%)	62 (52.5%)	34 (97.1%)	16 (45.7%)
ANC (decreased)	72 (46.8%)	34 (22.1%)	93 (78.8%)	60 (50.8%)	28 (80.0%)	14 (40.0%)
Hemoglobin (decreased)	71 (46.1%)	20 (13.0%)	49 (41.5%)	5 (4.2%)	19 (54.3%)	4 (11.4%)
Platelets (decreased)	39 (25.3%)	6 (3.9%)	42 (35.6%)	13 (11.0%)	18 (51.4%)	2 (5.7%)
ALC (increased)	40 (26.0%)	30 (19.5%)	26 (22.0%)	20 (16.9%)	1 (2.9%)	1 (2.9%)
ALC (decreased)	8 (5.2%)	2 (1.3%)	18 (15.3%)	6 (5.1%)	25 (71.4%)	12 (34.3%)
Leukocytes (increased)	38 (24.7%)	38 (24.7%)	12 (10.2%)	12 (10.2%)	0	0
Leukocytes (decreased)	24 (15.6%)	2 (1.3%)	50 (42.4%)	11 (9.3%)	26 (74.3%)	9 (25.7%)

ALC=absolute lymphocyte count; ANC=absolute neutrophil count; BR=bendamustine/rituximab; CTCAE=Common Terminology Criteria for Adverse Events; IR=idelalisib/rituximab.
Treatment-emergent laboratory abnormality is defined as the event when postbaseline laboratory value with grade worse than baseline grade was observed in specified direction. The maximum toxicity grade experienced after the date of the first dose of study drug, and prior to the earlier of 37 days after the last dose of study drug or starting of new anticancer therapy (including acalabrutinib for subjects who crossed over), was considered for each subject.
Source: ASCEND clinical report, Table 14.3.7.2.

The frequency of the following laboratory abnormalities was lower in subjects treated with acalabrutinib compared with IR and BR, respectively: increased ALT (14.9% versus 59.3% and 25.7%), decreased albumin (4.5% versus 9.3% and 5.7%), increased alkaline phosphatase (9.1% versus 27.1% and 22.9%), increased AST (13.0% versus 47.5% and 31.4%), and decreased calcium (4.5% versus 13.6% and 11.4%) (Table 65).

There were no acalabrutinib-treated subjects with elevations ≥3×ULN in ALT or AST concurrent with total bilirubin ≥2×ULN.

Table 65 Treatment-Emergent Laboratory Abnormality in Chemistry (Safety Population)

Lab Test (Direction of Change Relative to Baseline)	No. (%) of Subjects					
	Arm A		Arm B			
	Acalabrutinib (N=154)		IR (N=118)		BR (N=35)	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
ALT (increase)	23 (14.9%)	3 (1.9%)	70 (59.3%)	27 (22.9%)	9 (25.7%)	1 (2.9%)
Albumin (decrease)	7 (4.5%)	0	11 (9.3%)	0	2 (5.7%)	0
ALP (increase)	14 (9.1%)	0	32 (27.1%)	1 (0.8%)	8 (22.9%)	0
AST (increase)	20 (13.0%)	1 (0.6%)	56 (47.5%)	15 (12.7%)	11 (31.4%)	1 (2.9%)
Bilirubin (increase)	20 (13.0%)	2 (1.3%)	19 (16.1%)	2 (1.7%)	9 (25.7%)	4 (11.4%)
Calcium (increase)	3 (1.9%)	1 (0.6%)	8 (6.8%)	1 (0.8%)	3 (8.6%)	3 (8.6%)

Lab Test (Direction of Change Relative to Baseline)	No. (%) of Subjects					
	Arm A		Arm B			
	Acalabrutinib (N=154)		IR (N=118)		BR (N=35)	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Calcium (decrease)	7 (4.5%)	0	16 (13.6%)	3 (2.5%)	4 (11.4%)	0
Creatinine (increase)	118 (76.6%)	3 (1.9%)	89 (75.4%)	1 (0.8%)	26 (74.3%)	3 (8.6%)
Glucose (increase)	75 (48.7%)	6 (3.9%)	59 (50.0%)	7 (5.9%)	18 (51.4%)	0
Glucose (decrease)	16 (10.4%)	0	12 (10.2%)	0	0	0
Magnesium (increase)	43 (27.9%)	1 (0.6%)	41 (34.7%)	0	9 (25.7%)	0
Magnesium (decrease)	7 (4.5%)	1 (0.6%)	10 (8.5%)	2 (1.7%)	1 (2.9%)	0
Phosphate (decrease)	33 (21.4%)	1 (0.6%)	33 (28.0%)	8 (6.8%)	1 (2.9%)	0
Potassium (increase)	17 (11.0%)	2 (1.3%)	20 (16.9%)	2 (1.7%)	10 (28.6%)	1 (2.9%)
Potassium (decrease)	18 (11.7%)	0	18 (15.3%)	4 (3.4%)	4 (11.4%)	0
Sodium (increase)	43 (27.9%)	0	31 (26.3%)	0	8 (22.9%)	0
Sodium (decrease)	13 (8.4%)	5 (3.2%)	24 (20.3%)	5 (4.2%)	6 (17.1%)	2 (5.7%)
Urate (increase)	23 (14.9%)	23 (14.9%)	13 (11.0%)	13 (11.0%)	8 (22.9%)	8 (22.9%)

ALP= Alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BR=bendamustine/rituximab; CTCAE=Common Terminology Criteria for Adverse Events; IR=idelalisib/rituximab.
Treatment-emergent laboratory abnormality is defined as the event when post-baseline laboratory value with grade worse than baseline grade was observed in specified direction.
The maximum toxicity grade experienced after the date of the first dose of study drug, and prior to the earlier of 37 days after the last dose of study drug or starting of new anticancer therapy (including acalabrutinib for subjects who crossed over), was considered for each subject.
CTCAE version: 4.03.
Source: ASCEND clinical report, Table 14.3.7.3.

Lymphocytosis occurred for more subjects treated with acalabrutinib (70.8%) compared with IR (50.9%) and BR (2.9%) (Table 66).

Table 66 Summary of Lymphocytosis (Safety Population)

	Arm A	Arm B	
	Acalabrutinib (N=154)	IR (N=118)	BR N=35)
Subjects with baseline and postbaseline ALC	154	116	35
Subjects with lymphocytosis, n (%)	109 (70.8%)	59 (50.9%)	1 (2.9%)
95% CI[a]	(62.9%, 77.8%)	(41.4%, 60.3%)	(0.1%, 14.9%)
Peak ALC for subjects with lymphocytosis (10^9/L)			
n	109	59	1
Mean (SD)	149.3 (138.20)	93.6 (123.67)	27.6 (NE)
Median	113.4	50.0	27.6
Min, Max	6.3, 720.7	5.7, 775.9	27.6, 27.6
Time to lymphocytosis (weeks)[b]			
n	109	59	1
Mean (SD)	4.5 (4.45)	4.2 (10.53)	0.3 (NE)
Median	4.0	1.3	0.3
Min, Max	0.7, 34.9	0.3, 64.0	0.3, 0.3

	Arm A	Arm B	
	Acalabrutinib (N=154)	IR (N=118)	BR N=35)
Duration of lymphocytosis (weeks)[c]			
n	109	59	1
Resolved (event)	103 (94.5%)	58 (98.3%)	1 (100.0%)
Not resolved (censored)	6 (5.5%)	1 (1.7%)	0
Median (95% CI)	10.1 (5.3, 12.9)	3.1 (2.0, 4.0)	1.0 (NE, NE)
Min, Max	0.6, 81.1+	0.1+, 45.7	1.0, 1.0

ALC=absolute lymphocyte count; BR=bendamustine/rituximab; IR=idelalisib/rituximab; Max=maximum; Min=minimum; SD=standard deviation.

[a] Exact binomial confidence interval.

[b] Number of weeks from first dose date of study treatment to first postbaseline ALC that met the lymphocytosis criteria. Descriptive statistics are presented.

[c] Number of weeks from the first postbaseline ALC which met the lymphocytosis criteria to the earliest date of the following ALC that met the resolution of lymphocytosis criteria or date of censoring (date of last nonmissing ALC). The Kaplan-Meier method was used to estimate the median time.

'+' on Min or Max means subject was not recovered (censored) at the last ALC measurement. Data prior to the earlier of 37 days after the last dose of study drug or starting of new anticancer therapy (including acalabrutinib for subjects who crossed over), was considered for each subject. Lymphocytosis was defined as ALC increasing ≥50% from baseline and achieving level ≥$5x10^9$/L. Resolution of lymphocytosis occurred when ALC decreased to the baseline level or lower or achieving level of <$5x10^9$/L for subjects with lymphocytosis.
Source: ASCEND clinical report, Table 14.3.7.6.

The Applicant's Position:

Laboratory assessments were carried out as specified in the ASCEND Protocol. Acalabrutinib was well tolerated and showed an acceptable safety profile that is consistent with the other acalabrutinib clinical trials. Among subjects treated with acalabrutinib, there were no clinically significant mean changes in hematology or clinical laboratory values, serum immunoglobulin values, T/B/NK cell counts, or vital sign values over time. There was a trend toward worsening of baseline toxicity grade for some hematology parameters, including increased ALC, decreased ANC, decreased hemoglobin, decreased platelets, and increased leukocytes.

Regulatory Authorities Assessment:

FDA disagrees with the Applicant's assessment of laboratory trends. Cytopenias are a Warning and Precaution in the acalabrutinib USPI. In ASCEND, hematologic AEs were among the most common AEs reported in recipients of acalabrutinib, and had a higher incidence on dedicated lab-shift analysis (Table 67) compared to analysis of the AE dataset. Findings are similar in the expanded safety population; refer to Section 8.2.5.4.

Table 67 TE Laboratory Abnormalities (≥ 10%) with Acalabrutinib in ASCEND

	Acalabrutinib (N = 154), %			Idelalisib + Rituximab (N = 118), %			BR (N = 35), %		
	Any	G 3-4	G 4	Any	G 3-4	G 4	Any	G 3-4	G 4
Hematology [a]									
Neutropenia	47	22	7	79	51	25	80	37	23
Anemia	46	13	0	42	4.2	0	54	11	0
Lymphocytosis	26	19	0	22	17	0	2.9	2.9	0
Thrombocytopenia	25	3.9	2.6	36	11	0.8	51	6	2.9
Leukocytosis	25	25	0	10	10	0	0	0	0
Leukopenia	16	1.3	0.6	42	9	2.5	74	26	6
Chemistry									
Creatinine increase	77	1.9	1.3	75	0.8	0.8	74	9	9
Hyperglycemia	49	3.9	0	50	6	0.8	51	0	0
Hypermagnesemia	28	0.6	0	35	0	0	26	0	0
Hypernatremia	28	0	0	26	0	0	23	0	0
Hypophosphatemia	21	0.6	0	28	7	0	2.9	0	0
ALT increase	15	1.9	0	59	23	3.4	26	2.9	0
Hyperuricemia	15	15	4.5	11	11	3.4	23	23	2.9
AST increase	13	0.6	0	47	13	0.8	31	2.9	0
Bilirubin increase	13	1.3	0.6	16	1.7	1.7	26	11	9
Hypokalemia	12	0	0	15	3.4	0.8	11	0	0
Hyperkalemia	11	1.3	0	17	1.7	0.8	29	2.9	0
Hypoglycemia	10	0	0	10	0	0	0	0	0

Source: FDA analysis. **Bolded** terms occur ≥ 5% more with acalabrutinib than IR.
[a] Grading per CTCAE criteria.

8.2.4.8 Vital Signs

The Applicant's Description:

Body temperature, heart rate (beats/min), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and weight were collected for ASCEND. There were no notable differences between treatment arms in shifts in vital signs during the study.

The Applicant's Position:

There were no clinically important differences in mean systolic and diastolic blood pressure, heart rate, temperature, and body weight from baseline to last postbaseline values for either the acalabrutinib arm or the IR/BR arm, and no notable differences between treatment arms.

Regulatory Authorities Assessment:

FDA did not verify this analysis.

8.2.4.9 Electrocardiograms (ECGs)

The Applicant's Description:

ECGs were performed at screening only. No subjects met the exclusion criteria of QTcF >480 msec at baseline. One subject in the IR/BR arm had a clinically significant abnormal ECG at baseline.

Cardiac events were reported in more subjects who received acalabrutinib (20 [13.0%] subjects) compared with IR (9 [7.6%] subjects) or BR (3 [8.6%] subjects). Grade ≥3 cardiac events were reported with similar frequency in the 3 treatment groups (5 [3.2%], 4 [3.8%], and 3 [8.6%] subjects in the acalabrutinib, IR, and BR groups, respectively).

The Applicant's Position:
Overall, acalabrutinib showed an acceptable safety and tolerability profile which is consistent with the other acalabrutinib monotherapy clinical trials.

Regulatory Authorities Assessment:
Regulatory authorities agree.

8.2.4.10 QT

The Applicant's Description: Not Applicable

The Applicant's Position: Not Applicable

Regulatory Authorities Assessment:
There are no new data on QT in this supplement.

8.2.4.11 Immunogenicity

The Applicant's Description: Not Applicable

The Applicant's Position: Not applicable

Regulatory Authorities Assessment:
Regulatory authorities agree.

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Description: Not Applicable

The Applicant's Position:
No new potential safety issues were identified as a result of the safety review of acalabrutinib 100 mg BID.

Regulatory Authorities Assessment:
Refer to Section 8.2.4.5, "Significant Adverse Events" for an evaluation of ECIs and this position statement. Additional FDA analyses of selected ECIs, including SPMs, infections, bleeding, cytopenias, and atrial fibrillation, are presented in that section.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Description:
No safety related data were collected in the ASCEND PRO analyses.

The Applicant's Position: Not Applicable.

Regulatory Authorities Assessment:
Regulatory authorities agree.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Description:
Safety analyses were not conducted by demographic subgroups.

The Applicant's Position:
Acalabrutinib was well tolerated and showed an acceptable safety profile that is consistent with the other acalabrutinib clinical trials.

Regulatory Authorities Assessment:
FDA disagrees. Safety analyses were conducted by demographic subgroups. The summary of clinical safety (Section 5.1) presents such an analysis in 1040 patients with hematologic malignancies who received acalabrutinib monotherapy at various doses. For TEAEs reported in ≥ 10% of patients,

- Patients age ≥ 65 had a numerically higher incidence of at least one grade ≥ 3 AE (58%; 379/652) than patients age < 65 (47%; 184/388).
- The incidence of at least one grade ≥ 3 AE was similar among White patients (54%; 494/923) and Non-White patients (58%; 59/101), and according to gender.

To inform labeling, FDA explored safety by age group in the 929 of 1209 patients in the FDA integrated safety population who had CLL, SLL, or MCL. This population was selected in order to permit use of the same population for safety and efficacy reporting in PI Section 8.3. In this group, 68% were age ≥ 65 and 24% were age ≥ 75. Compared to patients age < 65, patients age ≥ 65 had numerically higher incidences of grade ≥ 3 AEs and SAEs (Table 68).

Table 68 Safety by Age Group

Age group (from N of 929)	Grade ≥ 3 AEs	SAEs
≥ 65 (N = 629) [a]	373/629 (59%)	245/629 (39%)
< 65 (N = 300)	135/300 (45%)	76/300 (25%)

Source: FDA analysis
[a] 222 were age ≥ 75.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Description:
No new information is provided in the current submission.

The Applicant's Position: Not applicable

Regulatory Authorities Assessment:
Regulatory authorities agree.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development
The Applicant's Description:
No new information is provided in the current submission.

The Applicant's Position: Not applicable

Regulatory Authorities Assessment:
Regulatory authorities agree. The current USPI for acalabrutinib includes a Warning and Precaution for SPM.

Human Reproduction and Pregnancy
The Applicant's Description:
No new information is provided in the current submission.

The Applicant's Position: Not applicable

Regulatory Authorities Assessment:
Although no new information about human reproduction or pregnancy was provided, there is new information on the potential for acalabrutinib to cause dystocia based on animal data, with a resultant change in the USPI. Refer to Section 5 (nonclinical pharmacology/toxicology).

Pediatrics and Assessment of Effects on Growth
The Applicant's Description:
No new information is provided in the current submission.

The Applicant's Position: Not applicable

Regulatory Authorities Assessment:
Regulatory authorities agree.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
The Applicant's Description:
There was no experience of overdose reported in the clinical studies of acalabrutinib.

Acalabrutinib is intended to be prescribed by specialists in hematology and oncology.

The Applicant's Position:
There is no evidence that acalabrutinib produces physical or psychological dependence in patients with hematological malignancies.

Regulatory Authorities Assessment:
Regulatory authorities agree.

Safety in Patients with Hepatic Impairment
Regulatory Authorities Assessment:
Refer to Section 6 (clinical pharmacology) for safety considerations in patients with hepatic impairment. The acalabrutinib USPI will be revised to indicate that acalabrutinib should be avoided in patients with severe hepatic impairment.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience
The Applicant's Description:
Calquence was first registered in the United States on 31 Oct 2017 at a dosage of 100 mg BID for the treatment of adult patients with MCL who have received at least one prior therapy. Calquence has since been approved in additional markets for the same indication and dosage cited above. The cumulative world-wide post-approval patient exposure since launch is estimated to be (b) (4) patient-years. Details are provided in the acalabrutinib PBRER dated 21 June 2019. Cumulative review of all the safety data from this post-marketing period has not identified any new safety concerns.

The Applicant's Position:
No new safety concerns were identified from post-marketing experience that impact the safety profile of acalabrutinib as presented in the acalabrutinib PBRER dated 21 June 2019. Acalabrutinib was well tolerated and showed an acceptable safety profile that is consistent with the other acalabrutinib clinical trials.

Regulatory Authorities Assessment:
Regulatory authorities agree with the Applicant's assessment.

Expectations on Safety in the Postmarket Setting
The Applicant's Description: Not applicable.

The Applicant's Position:
Safety information collected from the post-market setting is expected to be consistent with data collected in the clinical trials.

Regulatory Authorities Assessment:

Regulatory authorities agree with the Applicant's assessment.

8.2.11. Integrated Assessment of Safety

The Applicant's Description:
In the Mono CLL population, approximately 85.7%, 76.8%, 51.7%, and 28.5% of subjects completed more than 6, 12, 24, and 36 months of acalabrutinib treatment, respectively, with a median duration of exposure of 24.9 months (range: 0 to 58.5months). Total exposure was 1579.3 patient-years. In the Mono HemMalig population, 850 (81.7%), 754 (72.5%), 528 (50.8%), and 255(24.5%) of subjects completed more than 6, 12, 24, and 36 months of acalabrutinib treatment, respectively, with a median duration of exposure of 24.6 months (range: 0 to 58.5 months). Total exposure was 2037.7 patient-years.
Safety data from the Mono Pivotals population demonstrated a well-tolerated and manageable safety profile which is favorable relative to the comparator arms. The majority of TEAEs observed were low grade and non-serious. These benefits are supported by the results seen in the broader CLL Mono and CLL Combo populations, and further supported by the results seen in the Mono HemMalig population.

Acalabrutinib 100 mg BID is associated with the following risks based on the safety profile that was observed in the Mono HemMalig population (N=1040), and is consistent with observations seen in the pivotal Phase 3 studies and the CLL Mono population:

- Atrial fibrillation/flutter of any grade severity was reported in 4.4% of subjects in the Mono HemMalig population. Grade ≥3 events were reported in 1.3% of subjects.

- Anemia, neutropenia, and thrombocytopenia were reported in 13.8%, 15.7%, and 8.9% of subjects in the Mono HemMalig population, respectively; febrile neutropenia was reported in 1.9% of subjects. Grade ≥3 cytopenias based on laboratory measurements included anemia (10.1%), neutropenia (20.7%), and thrombocytopenia (6.9%). SAEs of anemia were reported in 19 (1.8%) subjects. Twenty (1.9%) subjects had a neutropenia SAE; of these, 16 subjects had SAEs of febrile neutropenia and 3 subjects had SAEs of neutropenic sepsis. Four (0.4%) subjects had an SAE in the ECI category of thrombocytopenia.

- Major hemorrhage events, defined as Grade ≥3, SAE, and/or any grade or seriousness of CNS hemorrhage, were reported in 3.6% of subjects. The most frequently reported sites of major hemorrhage in the Mono HemMalig population were the GI tract (GI hemorrhage, gastric hemorrhage, hematemesis, rectal hemorrhage, and upper GI hemorrhage; 8 subjects) and the CNS (intracranial hemorrhage, cerebral microhemorrhage, intracranial hematoma, subarachnoid hemorrhage, and traumatic intracranial hemorrhage; 6 subjects), followed by the nose (epistaxis; 4 subjects).

- Grade ≥3 TEAEs of infection occurred in 17.6% of subjects in the Mono HemMalig population, with pneumonia as the most frequently reported Grade ≥3 infection (4.9%). Fatal infections were reported in 20 (1.9%) subjects.

- Second primary malignancies were reported in 12.2% of subjects in the Mono HemMalig population; the most frequent were skin malignancies, including basal cell carcinoma (3.8%) and squamous cell carcinoma of the skin (2.9%). Second primary malignancies (excluding nonmelanoma skin neoplasms) were reported in 6.5% of subjects in the Mono HemMalig population.

- The most common adverse reactions reported were of Grade 1 or 2 severity. These included headache, diarrhea, nausea, constipation, vomiting, bleeding events (hematuria, epistaxis, bruising), rash, musculoskeletal pain, fatigue and asthenia, dizziness, and arthralgia. One subject developed drug-induced TLS meeting the Howard's criteria.

Safety data for the Combo CLL population (N=223) revealed a generally similar profile to the Mono HemMalig population. In addition to the higher rate of infusion related reactions with combination therapy (13.9% in the Combo CLL population versus 0.8% in the Mono HemMalig population), subjects in the Combo CLL population had a higher incidence of neutropenia, thrombocytopenia, and infection events compared with the Mono HemMalig population.

While there are risks associated with taking acalabrutinib, active monitoring and preventive measures assist in their mitigation. Mitigation measures are provided in the product labeling.

The Applicant's Position:
Acalabrutinib was well tolerated and showed an acceptable safety profile that is consistent with the other acalabrutinib clinical trials.

In patients with CLL, acalabrutinib offers a favorable benefit-risk profile, with high response rates which were durable, and an acceptable safety profile. The data support acalabrutinib 100 mg BID as an important treatment option for patients with this serious and life-threatening disease.

Regulatory Authorities Assessment:
Regulatory authorities agree that acalabrutinib 100 mg approximately every 12 hours carries an acceptable safety profile in the intended population. Stating that acalabrutinib was well tolerated is a generalization; however, AEs were manageable in the majority of patients.

SUMMARY AND CONCLUSIONS: Section 8

8.3. Statistical Issues

Regulatory Authorities Assessment:

Several non-critical statistical issues were identified during the review of ASCEND study.

For the key secondary endpoints, the Applicant did not provide sufficient information on OS (e.g. number of OS events, desired power, assumed true difference in OS between the treatment arms, number of planned analyses, timing of these analyses, etc.) Further, the Applicant proposed to use the same efficacy stopping boundary of the IRC-assessed PFS for the OS analysis at the interim and final. Although it is acceptable, this method is not often practiced because the information fraction of PFS and OS is different at the analysis time. An efficacy stopping boundary based on the actual information fraction of OS events at interim would be recommended. Lastly, even though the SAP stated that a statistically significant interim finding for IRC-assessed PFS would be followed by an IRC-assessed ORR analysis using alpha of 0.05, the key secondary endpoints, including IRC-assessed ORR should have followed a closed-testing procedure, i.e. the same alpha level that was allocated for the IRC-assessed PFS interim analysis to control the overall type I error rate (e.g., H. M. James Hung et al, 2007). The statistical test did not reject the null hypothesis of IRC-assessed ORR at the time of the interim analysis and further testing of OS stopped according to the pre-specified hierarchical order. Any future updates of the efficacy results (IRC-assessed PFS, IRC-assessed ORR, OS) to the USPI from the final analysis of the study should keep FWER within the pre-specified 2-sided 0.05.

For the analysis of the IRC-assessed PFS, FDA had concerns with the validity of the proportional hazard (PH) assumption because the Kaplan-Meier curves of IRC-assessed PFS for both acalabrutinib and IR/BR arms seemed to overlap up to month 9 (Figure 5). If PH assumption was not met, both log-rank test and Cox regression model could produce biased results. Several statistical tests were conducted to assess the validity of the PH and the results showed the assumption was indeed valid.

8.4. Conclusions and Recommendations

Regulatory Authorities Assessment: The results of ASCEND, in isolation, support regular approval of acalabrutinib for the treatment of adult patients with relapsed or refractory CLL after at least 1 prior therapy. It is justifiable to extend the indication to SLL, because SLL represents the same disease process as CLL. ASCEND demonstrated substantial evidence of efficacy based on PFS per IRC with acalabrutinib monotherapy, compared to investigator's choice. The safety profile of acalabrutinib was acceptable, and was consistent with the safety profile in an integrated analysis of over 1000 patients with hematologic malignancies treated with acalabrutinib at the intended dose-schedule with or with obinutuzumab. Coupled with the results of the ELEVATE-TN trial in patients with previously untreated CLL, the totality of data supports regular approval of acalabrutinib for the treatment of adult patients with CLL or SLL.

X	X
Statistical Reviewer	Statistical Team Leader
X	X
Clinical Reviewer	Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

Regulatory Authorities Assessment:

This application was not presented to external consultants because it did not raise significant efficacy or safety issues for the proposed indication.

10 Pediatrics

The Applicant's Position:
Not applicable.

Regulatory Authorities Assessment:
Acalabrutinib is exempt from the pediatric study requirements in 21 CFR 314.55. It received Orphan Drug Designation for CLL. Additionally, CLL occurs almost exclusively in adults.

11 Labeling Recommendations

Data:

Table 69 Summary of Significant Labeling Changes

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's Proposed Labeling**
1: Indications and Usage	A broad chronic lymphocytic leukemia (CLL/SLL) indication is proposed, in addition to the already labelled Mantle Cell Lymphoma (MCL) indication	The recommended new indication for Calquence, with regular approval, is for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).
2.1: Dosage and Administration-Recommended Dosage	Added language about CALQUENCE combination therapy with obinutuzumab and obinutuzumab PI is referred for dosing Dosage and Administration within the Highlights section remain the same as there is no change to CALQUENCE dosage, administration, and toxicity management recommendations	The frequency of Calquence dosing was changed throughout the PI from "twice daily" to "approximately every 12 hours" until disease progression or unacceptable toxicity. For the recommended dosage, acalabrutinib monotherapy is specified for MCL, CLL, or SLL, whereas acalabrutinib in combination with obinutuzumab is specified for previously untreated CLL or SLL.
2.2: Dose Modifications	Dose Modifications are separated into the following 4 sections: • Section 2.2 Dose Modifications for Adverse Reactions • Section 2.3 Dose Modifications for Use with CYP3A Inhibitors or Inducers • Section 2.4 Concomitant Use with Gastric Acid Reducing Agents • Section 2.5 Dose Modifications for Use in Hepatic Impairment (new section) Note: No changes to text within sections 2.2, 2.3 and 2.4. Sec 2.5 is a newly added section	A new section on "Recommended Dosage for Hepatic Impairment" states to avoid administration of Calquence in patients with severe hepatic impairment; dose modifications are not required for patients with mild or moderate hepatic impairment. The organization of this section was revised to reflect the order in which prescribers will need the information.
6.1: Adverse Reactions-Clinical Trials Experience	Most common adverse reactions reported in MCL and CLL are separated by indication Proposal to use cutoff of ≥ 20% to define	In addition to separating the most common ARs by indication, FDA added text at the start of Section 6.1 to describe the composition, exposure, and most common ARs

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's Proposed Labeling**
	common adverse reactions	in the expanded safety population that informs the Warnings and Precautions (N = 1029). The cutoff for "common" ARs varies by indication, but is not a substantive issue.
8.6: Use in Specific Populations- Hepatic Impairment	Added recommendations for severe hepatic impairment based on recent studies. Consistent with Sec 2.5 listed above	Regulatory authorities agree. However, this is not the only substantive change in Section 8. Refer to Table 70.
12.3 Pharmacokinetics	Updated text on acalabrutinib and ACP-5862 (its active metabolite) Population PK results. Absorption: Updated median time to peak plasma concentrations for ACP-5862 Distribution: Updated reversible binding to human plasma protein and in vitro mean blood-to-plasma ratio for ACP-5862 Elimination: Updated the median $t_{1/2}$ for ACP-5862 and mean apparent oral clearance (CL/F) for acalabrutinib and ACP-5862 Specific Populations: *Age, Race, and Body Weight*: added text for ACP-5862 *Renal Impairment:* Added data on mild or moderate renal impairment (eGFR ≥ 30 mL/min/1.73m^2) *Hepatic Impairment*: Added data on patients with mild, moderate, and severe hepatic impairment Drug Interaction Studies: *Metabolic Pathways:* Included additional metabolic pathways Drug Transporter Systems: Added text on ACP-5862 substrates and that ACP-5852 does not inhibit specific hepatic trasnporters. Added text on ACP-5862 and co-administration of MATE1 and BCRP substrates	Regulatory authorities agree.

The Applicant's Position:

Based on the findings and results from studies ASCEND and ELEVATE-TN, the Applicant is proposing the above mentioned significant changes in the CALQUENCE label.

Regulatory Authorities Assessment:
Other significant labeling changes are summarized in Table 70.

Table 70 FDA Summary of Other Significant Labeling Changes

Section	Applicant's Proposed Labeling	Recommended Labeling
5. Warnings and Precautions	• Based on (b) (4) patients treated with Calquence monotherapy (b) (4) includes patients with (b) (4) • (b) (4) specific mention of opportunistic infection in the "Infection" warning.	• Revise denominator to 1029 patients with CLL/SLL, MCL, or WM treated with acalabrutinib 100 mg ~Q12H with or without acalabrutinib. • Expand on serious, grade ≥ 3, and opportunistic infections, renaming the warning "Serious and Opportunistic Infections."
6. Adverse Reactions	• Limited grouping of PTs in AR reporting • No data on less common but clinically significant ARs • No data on treatment-emergent chemistry abnormalities	• Expand the use of grouped PTs and revise the groupings for more sensitive labeling. • List selected clinically significant ARs with incidence < 15% to complement the table on common ARs. • Add selected treatment-emergent chemistry abnormalities.
8.1 Use in Specific Populations - Pregnancy	• May cause fetal harm.	• May cause fetal harm and dystocia.
8.5 Use in Specific Populations - Geriatrics	• No significant differences in safety according to age ≥ 65 vs. less	• Numerically higher rates of grade ≥ 3 AEs and SAEs in patients age ≥ 65
14. Efficacy	• Includes PFS subgroup analyses and the number of deaths per arm.	• Remove exploratory subgroup analyses. • Remove details of OS data, which are immature.

Source: FDA analysis

Health Canada's Assessment:

(b) (4)

The recommended indications for approval in Canada are:

Calquence (acalabrutinib) is indicated:
- in combination with obinutuzumab or as monotherapy for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL)
- as monotherapy for the treatment of patients with CLL who have received at least one prior therapy.

12 Risk Evaluation and Mitigation Strategies (REMS)

Regulatory Authorities Assessment:

The clinical review team does not recommend a REMS. Based on the risk/benefit profile of acalabrutinib, safety issues can be adequately managed through appropriate labeling and routine post-marketing surveillance.

13 Postmarketing Requirements and Commitment

Regulatory Authorities Assessment:
No new postmarketing requirements or commitments are recommended.

14 Division Director (DHOT) (NME ONLY)

X

Pharmacology-Toxiclogy Supervisor

15 Division Director (OCP)

X

Clinical Pharmacology Division Director

16 Division Director (OB)

X

Statistics Division Director

17 Division Director (Clinical)

(This section relies in part on the reviews of Drs. Angelo de Claro, Yvette Kasamon and Nicholas Richardson.)

Background: AstraZeneca UK Limited submitted concomitantly NDA 210259 (S-006) and NDA 210259 (S-007) on August 5, 2019, August 24, 2019, and September 24, 2019 (for S-006) and August 5, 2019, August 24, 2019, and September 23, 2019 for (S-007) respectively requesting that acalabrutinib (Calquence) be approved for the following indication: Treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). This request relied on the results of the ASCEND (ACE-CL-309) trial (S-006) and the ELEVATE-TN (NCT02475681) trial (S-007). Acalabrutinib had already been given Accelerated Approval for the following indication: Mantle cell lymphoma who have received at least one prior therapy.
The ASCEND trial enrolled 310 patients with CLL which is relapsed or refractory after ≥1 prior therapy who were randomized between acalabrutinib vs "investigator's choice": idelalisib with rituximab (IR=119 patients) or bendamustine with rituximab (BR=36 patients). The primary endpoint was independent review committee (IRC) assessed progression free survival (PFS).

The ELEVATE-TN trial randomized 535 patients with previously untreated CLL which was previously untreated between acalabrutinib with obinutuzumab, vs acalabrutinib alone vs obinutuzumab with chlorambucil. The primary endpoint was PFS by IRC.

Efficacy Results for ASCEND Trial: At the prespecified time of 16.1 months, the hazard ratio (HR) for IRC-assessed PFS for acalabrutinib vs investigators' choice was 0.31 (95% CI: 0.20, 0.49) p <0.0001 (stratified log rank test). The median PFS was not reached in the acalabrutinib arm and was 16.5 months (95% CI: 14.0, 17.1) in the investigator choice arm.

Efficacy for the ELEVATE-TN Trial: The results showed a statistically significant increase in PFS per IRC for both acalabrutinib with obinutuzumab (HR=0.1 (95% CI: 0.06, 0.17) p<0.0001 and acalabrutinib alone (HR=0.2 (95% CI: 0.13, 0.30) p<0.0001 when compared to obinutuzumab with chlorambucil.

Safety Results for ASCEND TRIAL: On the acalabrutinib arm, on study deaths were 2.6% and serious adverse events were observed in 29% of the patients. AEs led to permanent discontinuation in the acalabrutinib arm in 10% of the patients. The most common AEs (≥30%) included cytopenias.

Safety Results for ELEVATE-TN TRIAL: The safety population included 178 patients treated with acalabrutinib and obinutuzumab, 179 patients treated with acalabrutinib monotherapy, and 169 treated with obinutuzumab with chlorambucil. All 3 arms were similar with respect to the incidence of death within 30 days after the last dose of treatment (≤2%), serious adverse events (range was 22%-39%) and discontinuations due to toxicity (9% to 15%).

Benefit Risk: For treatment of CLL previously untreated or relapsed refractory after ≥1 prior therapy, the benefit risk profile was favorable.

Recommended Regulatory Action: This Supervisory Associate Division Director (A. Deisseroth) agrees with the review divisions in their recommendation of approval of acalabrutinib for the therapy of CLL.

X

Clinical Division Director

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X _____

19 Appendices

19.1. References

The Applicant's References:

Burger JA, Tedeschi A, Barr PB, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. N Engl J Med 2015;373:2425-37.

Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med 2013;369:32-42.

Byrd JC, Stilgenbauer S, Flinn IW. Chronic lymphocytic leukemia. Am Soc Hematol Educ Program. 2004:163-183.

Cheson BD, Byrd JC, Rai KR, et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. J Clin Oncol 2012;30:2820-2.

Cheson BD, Wendtner CM, Pieper A, et al. Optimal use of bendamustine in chronic lymphocytic leukemia, non-Hodgkin lymphomas, and multiple myeloma: treatment recommendations from an international consensus panel. Clin Lymphoma Myeloma Leuk 2010;10:21-7.

Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26 (Suppl 5):v78-84.

Eichhorst BF, Busch R, Stilgenbauer S, et al. First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. Blood 2009 Oct 15;114(16):3382-3391.

Eichhorst et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol. 2016 Jul;17(7):928-942.

Fischer K, Cramer P, Busch R, et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter Phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 2011;29:3559-66.

Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med 2014;370:997-1007.

Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood 2018a;131:2745-60.

Hallek M, Shanafelt TD, Barbara Eichhorst B. Chronic lymphocytic leukaemia. Lancet 2018b;391:1524–37.

Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, Phase 3 trial. Lancet 2010;376:1164-74.

Hallek M, Cheson BD,Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008;111:5446-56. Erratum in: Blood 2008;112:5259.

Han T, Ezdinli EZ, Shimaoka K, Desai DV. Chlorambucil vs combined chlorambucil-corticosteroid therapy in chronic lymphocytic leukemia. Cancer 1973;31:502–08.

Hillmen P, Skotnicki AB, Robak T, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. J Clin Oncol 2007;25:5616-23.

H. M. James Hung , Sue-Jane Wang & Robert O'Neill (2007) Statistical Considerations for Testing Multiple Endpoints in Group Sequential or Adaptive Clinical Trials, Journal of Biopharmaceutical Statistics, 17:6, 1201-1210, DOI: 10.1080/10543400701645405

Knospe WH, Loeb V Jr. Biweekly chlorambucil treatment of lymphocytic lymphoma. Cancer Clin Trials 1980;3:329–36.

Mato AR, Roeker LE, Allan JN, et al. Outcomes of front-line ibrutinib treated CLL patients excluded from landmark clinical trial. Am J Hematol 2018a;93:1394-401.

Mato AR, Nabhan C, Thompson MC, et al. Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis. Haematologica 2018b;103:874-9.

National Comprehensive Cancer Network (NCCN). Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia. Version 4.2019. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed 24 April 2019.

Noone AM, Howlader N, Krapcho M, et al (eds). SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER web site, April 2018.

O'Brien S, Jones JA, Coutre SE, et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. Lancet Oncol 2016;17:1409–18.

Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. N Engl J Med 2016;374:311–22.

Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med 2018;378:1107-20.

Shanafelt TD, Wang V, Kay NE, et al. A randomized Phase III study of ibrutinib (PCI-32765)-based therapy vs. standard fludarabine, cyclophosphamide, and rituximab (FCR) chemoimmunotherapy in untreated younger patients with chronic lymphocytic leukemia (CLL): a trial of the ECOG-ACRIN Cancer Research Group (E1912). Blood 2018;132:LBA-4.

Shanafelt TD, Wang V, Kay NE, et al. Ibrutinib–Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia N Engl J Med 2019;381:432-43.

Sharman JP, Coutre SE, Furman RR, et al. Final results of a randomized, Phase III study of rituximab with or without idelalisib followed by open-label idelalisib in patients with relapsed chronic lymphocytic leukemia. J Clin Oncol 2019;37:1391-402.

Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. Lancet Oncol 2016;17:768–78.

UK CLL Forum. Ibrutinib for relapsed/refractory chronic lymphocytic leukemia: a UK and Ireland analysis of outcomes in 315 patients. Haematologica 2016;101:1563-72.

Wiestner A. The role of B-cell receptor inhibitors in the treatment of patients with chronic lymphocytic leukemia. Haematologica 2015 Dec;100(12):1495-507.

Woyach JA, Smucker K, Smith LL, et al. Prolonged lymphocytosis during ibrutinib therapy is associated with distinct molecular characteristics and does not indicate a suboptimal response to therapy. Blood 2014;123:1810-7.

Woyach JA, Ruppert AS, Rai KR, et al. Impact of Age on Outcomes Following Initial Therapy with Chemotherapy and Different Chemoimmunotherapy Regimens in Patients with Chronic Lymphocytic Leukemia (CLL): Results of Sequential CALGB Studies Chemoimmunotherapy Regimens in Patients with Chronic Lymphocytic Leukemia (CLL): Results of Sequential CALGB Studies. J Clin Oncol 2013 Feb 1;31(4):440-447.

The FDA's References:
None.

19.2. Financial Disclosure

The Applicant's Position:
All investigators participating in study ASCEND were assessed for equity interest, significant payments, proprietary interests and other compensation. None of the investigators out of 601 total investigators had financial interests to disclose. Statements of due diligence in cases where the applicant was unable to obtain a signed financial disclosure form from the investigator, are included in the FDA Form 3454 provided in this sNDA submission.

Regulatory Authorities Assessment:
Regulatory authorities agree with the Applicant's position.

Covered Clinical Study: ASCEND

Was a list of clinical investigators provided:	Yes ☒	No ☐
Total number of investigators identified: 601		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 8		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

19.3. Nonclinical Pharmacology/Toxicology

Data:
See Section 5 above.

The Applicant's Position:
See Section 5 above.

Regulatory Authorities Assessment:
Refer to Section 5.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

Regulatory Authorities Assessment:

The Applicant updated the population PK analysis using 10,588 acalabrutinib and 2396 ACP-5862 (active metabolite) plasma concentrations from 182 healthy subjects in 5 Phase 1 trials and 569 patients with B-cell malignancies in 8 Phase 1b/2/3 trials. A simultaneous population PK model characterizing the PK of acalabrutinib and ACP-5862 was developed. Acalabrutinib concentration-time profile was characterized by a 2-compartment structural model with sequential zero- and first-order absorption and linear elimination, while ACP-5862 concentration-time profile was characterized by a 2-compartment structural model with a first-order production from acalabrutinib and linear elimination. The final population PK model was able to describe the acalabrutinib and ACP-5862 concentration-time profiles in patients with B-cell Malignancies.

Covariate analysis identified 6 statistically significant covariates on the PK parameters of acalabrutinib and ACP-5862, including concomitant use of proton pump inhibitors (PPI) on acalabrutinib relative bioavailability (F1) and duration of zero-order absorption (D1), subject type (healthy subject or patients with B-cell malignancies) and Eastern Cooperative Oncology Group (ECOG) score on acalabrutinib apparent clearance (CL/F), and body weight on ACP-5862 apparent clearance (CLM/F) and apparent central volume distribution (VcM/F). However, none of these covariates were considered clinically meaningful, given the generally flat exposure-response relationships for both efficacy endpoints (PFS, BOR and lesion size), and safety measurements (any Grade ≥3 TEAEs, any Grade ≥2 TEAEs of clinically special interest, including anemia, cardiac event, hypertension, infection, neutropenia, and thrombocytopenia) at acalabrutinib 100 mg BID monotherapy in patients with CLL.

The derived post-hoc PK parameter estimates of acalabrutinib and ACP-5862 in overall patients with B-cell malignancies from the final population PK analysis (Table 71) were included in Section 12.3 of USPI, as there was no significant difference in acalabrutinib and ACP-5862 PK exposures among patients with different types of B-cell malignancies, including CLL, MCL, FL, DLBCL, MM, and WM.

Table 71 Derived Post-hoc PK Parameter Estimates of Acalabrutinib and ACP-5862 from the Final Population PK Analysis in Patients with B-cell Malignancies following Acalabrutinib 100 mg twice daily

	PK parameter	Geometric mean (CV%)	Mean ± standard deviation	Median [min, max]
Acalabrutinib (n = 568)	AUC_{24h} (ng·h/mL)	1843 (38%)	1972 ± 801	1816 [284, 6807]
	C_{max} (ng/mL)	563 (29%)	585 ± 165	558 [115, 1442]
	C_{min} (ng/mL)	3.5 (79%)	4.6 ± 4.6	3.4 [0.1, 44]
	CL/F (L/h)	71 (35%)	75 ± 28	72 [19, 399]
	V_{ss} (L)	101 (52%)	122 ± 138	84 [69, 1757]
	$T_{1/2}$ (hour)	1 (59%)	1.2 ± 1.5	0.9 [0.3, 28]
	T_{max} (hour)	0.9 (24%)	0.9 ± 0.2	0.9 [0.5, 1.9]
ACP-5862 (n = 292)	AUC_{24h} (ng·h/mL)	3947 (43%)	4314 ± 2045	3832 [989, 17005]
	C_{max} (ng/mL)	451 (52%)	504 ± 240	470 [52, 1799]
	C_{min} (ng/mL)	47 (62%)	57 ± 44	44 [12, 386]
	CL/F (L/h)	13 (42%)	14 ± 6	14 [2.8, 60]
	V_{ss} (L)	67 (32%)	73 ± 52	63 [45, 796]
	$T_{1/2}$ (hour)	3.5 (24%)	3.6 ± 1.1	3.4 [2.1, 11]
	T_{max} (hour)	1.6 (20%)	1.6 ± 0.3	1.6 [0.9, 2.7]

AUC_{24h}: steady-state area under the plasma drug concentration over time curve from 0 to 24 h.
C_{max}: steady-state maximum plasma concentration.
C_{min}: steady-state minimum plasma concentration.
V_{SS}: steady-state volume of distribution.
$T_{1/2}$: terminal elimination half-life.
T_{max}: time to peak plasma concentrations.

19.5. FDA Grouping of Preferred Terms for Safety Analysis

Regulatory Authorities Assessment: The following grouping of terms was adopted for the primary safety analyses for ASCEND and ELEVATE-TN (NDA 210259-S007), as well as the FDA integrated safety analysis (N = 1029) performed subsequently using ISS datasets. Underlined terms were added upon review of the ISS.

Table 72 FDA Grouping of Preferred Terms for Primary Safety Analysis

Note: Not all listed PTs appear in the NDA datasets.

FDA Grouped PT	Included in Grouping	Not Included
Abdominal pain	All PTs containing "abdominal pain", Abdominal discomfort, Abdominal tenderness, Epigastric discomfort	
Anemia	All PTs containing "anemia", RBC count decreased	
Atrial fibrillation or flutter	Atrial fibrillation, Atrial flutter, Cardiac flutter	
Bruising	All PTs containing "bruise," "contusion," or "ecchymosis"	Petechiae, Purpura
Cardiac arrhythmias	High-level group term, "Cardiac arrhythmias"	
Cardiac failure	All PTs containing "cardiac failure", Congestive cardiomyopathy, Cardiomyopathy, Left ventricular failure, Cor pulmonale, Cardiopulmonary failure Added with ISS: Cardiogenic shock, Ischemic cardiomyopathy	ISS: Cardiomegaly, Hypertrophic cardiomyopathy, Ejection fraction decreased
Chest pain	Chest discomfort, Chest pain, Angina pectoris	Noncardiac chest pain
Colitis	Colitis, Colitis microscopic, Colitis ulcerative, Colitis erosive, Enterocolitis, Enterocolitis hemorrhagic **Note:** For ASCEND and ISS, "Diarrhea or colitis" grouping used	Enteritis ISS: colitis ischemic, infectious colitis (e.g. C difficile)
Cough	All PTs containing "Cough"	
Cytomegalovirus infection	Cytomegalovirus infection, Cytomegalovirus viremia	
Diarrhea	Diarrhea, Diarrhea hemorrhagic, Defecation urgency **Note:** For ASCEND, "Diarrhea or colitis" grouping used	Post procedural diarrhea
Diarrhea or colitis (for ASCEND)	All terms under FDA's grouping of "Diarrhea" and "Colitis"	
Dizziness	All PTs containing "Dizziness" or "Vertigo"	
Dyspnea	All PTs containing "Dyspnea"	

FDA Grouped PT	Included in Grouping	Not Included
Edema	Edema, Generalized edema, Face edema, Swelling face, Edema peripheral, Fluid overload, Fluid retention, Pulmonary edema, Acute pulmonary edema, Pulmonary congestion	Edema blister, Localized sites of edema (e.g. Localized edema, Lip edema, Nasal edema, Periorbital edema, Eye swelling) With ISS: Angioedema, Gravitational edema, Soft tissue swelling
Fatigue	Asthenia, Fatigue, Lethargy, ECOG performance status worsened	
Febrile neutropenia	Febrile neutropenia, Febrile bone marrow aplasia, Neutropenic infection, Neutropenic sepsis* *** Note: Neutropenic sepsis is counted under both the "febrile neutropenia" and "sepsis" PTs**	
Gastroenteritis	Gastroenteritis and specific types (e.g. viral), Enteritis	Gastroenteritis radiation, Gastritis, Duodenitis
Gastrointestinal hemorrhage	All PTs containing "Gastrointestinal hemorrhage", Gastric hemorrhage, Gastric ulcer hemorrhage, Large intestinal ulcer hemorrhage, Hematochezia, Hematemesis, Intestinal hemorrhage, Intestinal hemorrhage, Melena, Hemorrhoidal hemorrhage, Rectal hemorrhage, Small intestinal hemorrhage	
Headache	All PTs containing "headache", Migraine With ISS: Head discomfort	
Hemorrhage	All PTs containing "hemorrhage", "hemorrhagic", or "hematoma", all PTs contained in FDA's "Gastrointestinal hemorrhage" grouping, Menorrhagia, Hemarthrosis, Hemoptysis, Hematuria, Epistaxis ISS: Blood urine present, Extravasation blood, Hematospermia, Hematotympanum, Scrotal Hematocoele	Petechiae, Purpura, FDA's grouping for "Bruising"
Hemorrhage intracranial	Includes but is not limited to: Hemorrhage intracranial, Subdural hematoma, Subdural hemorrhage, Cerebral hemorrhage, Hemorrhagic stroke, Subarachnoid hemorrhage	
Hepatitis	All PTs containing "hepatitis", Hepatocellular injury, Hepatotoxicity, Drug-induced liver injury, Liver injury	FDA's "Transaminase elevation" grouping, PTs containing "Hepatic failure", Hepatic encephalopathy
Herpesvirus infection	High-level group term, "Herpes viral infection"	

FDA Grouped PT	Included in Grouping	Not Included
Hyperbilirubinemia	Blood bilirubin increased, Hyperbilirubinemia, Jaundice	
Hypertension	Hypertension, Essential hypertension, Blood pressure increased, Blood pressure systolic increased. ISS: hypertensive crisis, Malignant hypertension	
Hypotension	Hypotension, Diastolic hypotension, Orthostatic hypotension, Blood pressure decreased	
Leukocytosis [a]	Leukocytosis, Hyperleukocytosis, White blood cell count increase	
Lower respiratory tract infection	All PTs containing "bronchitis" or "lower respiratory tract infection", Bronchiolitis, Tracheitis, Lung infection. ISS: Infective exacerbation of bronchiectasis	Bronchiectasis
Musculoskeletal pain	Back pain, Musculoskeletal chest pain, Noncardiac chest pain, Musculoskeletal pain, Musculoskeletal discomfort, Myofascial pain syndrome, Neck pain, Pain in extremity, Myalgia, Spinal pain, Bone pain	Arthralgia, Musculoskeletal stiffness
Myocardial ischemia or infarction	Acute myocardial infarction, Myocardial ischemia, Angina unstable, Troponin increased, Acute coronary syndrome, Myocardial infarction, Coronary artery stenosis or occlusion	Angina pectoris
Nausea	Nausea, Retching	Procedural nausea
Neutropenia	Neutropenia, Neutrophil count decreased, Granulocytopenia	Febrile neutropenia
Nonmelanoma skin cancer	Squamous cell carcinoma of skin, Basal cell carcinoma, Bowen's disease, Basosquamous carcinoma, Lip squamous cell carcinoma	ISS: Neuroendocrine carcinoma of the skin
Pneumonia	All PTs containing "pneumonia", including within another word (e.g. bronchopneumonia), Bronchopulmonary aspergillosis, Lung infiltration, Lung consolidation	Lung infection
Pneumonitis	Pneumonitis, Acute respiratory distress syndrome, Interstitial lung disease	
Rash	All PTs containing "rash", all PTs containing "dermatitis" except as noted, Drug eruption, Drug reaction with eosinophilia and systemic symptoms, Erythema, Erythema multiforme, Generalized erythema, Toxic skin eruption, Palmar erythema, Palmoplantar keratoderma, Palmar-plantar erythrodysesthesia syndrome, Skin reaction, Skin toxicity, Stevens-Johnson syndrome, Toxic epidermal necrolysis. ISS: acute febrile neutrophilic dermatosis	All PTs containing "Eczema", Actinic keratosis, Folliculitis, Urticaria, Lichen planus, Herpes dermatitis. ISS: Erythema nodosum, Erythema annulare, Dermatitis infected
Renal insufficiency	All PTs containing "renal failure" or "nephropathy", Acute kidney injury, Blood creatinine increase, Creatinine renal clearance decreased, Glomerular filtration rate decreased, Renal impairment, Hypercreatinemia, Chronic kidney disease. ISS: Renal injury	
Respiratory tract infection	Respiratory tract infection + specific types (e.g. respiratory tract infection viral, respiratory syncytial virus infection,	Upper respiratory tract infection, Lower

FDA Grouped PT	Included in Grouping	Not Included
	influenza, Haemophilus infection), Influenza like illness, Sinobronchitis [b]	respiratory tract infection [b]
Sepsis	All PTs containing "Bacteremia" or "Sepsis", including within another word (e.g. urosepsis) Septic shock *** Note: Neutropenic sepsis is counted under both the "febrile neutropenia" and "sepsis" PTs**	
Supraventricular tachycardia	High-level term, "Supraventricular arrhythmias"	
Thrombocytopenia	Thrombocytopenia, Platelet count decreased	Immune thrombocytopenic purpura
Thrombosis or thromboembolism	All PTs containing "thrombosis" except as noted, Peripheral embolism, Pulmonary embolism	Superficial thrombosis, Embolic cerebral infarction
Transaminase elevation	Alanine aminotransferase increased, Aspartate aminotransferase increased, Alanine aminotransferase, Aspartate aminotransferase, Transaminase increased, Hypertransaminasemia, Hepatic enzyme increased	PTs under FDA's "Hepatitis" grouping, PTs containing "hepatic failure", Hepatic function abnormal
Upper respiratory tract infection	All PTs containing "upper respiratory tract infection," "sinusitis," "laryngitis," "tonsillitis," or "pharyngitis," including within another word (e.g. nasopharyngitis), all PTs containing "rhinitis" except as noted, Rhinovirus infection, Human rhinovirus test positive	Rhinitis allergic ISS: Allergic sinusitis, Reflux laryngitis, Epiglossitis
Urinary tract infection	All PTs containing "cystitis" or "urinary tract infection", Pyelonephritis, Kidney infection	
Ventricular arrhythmia	High-level term, "Ventricular arrhythmias and cardiac arrest"	

Source: FDA analysis

[a] Grouping for other lab-related AEs is similar, e.g., hyperglycemia = hyperglycemia + blood glucose increased, lymphopenia = lymphopenia + lymphocyte count decreased

[b] This grouping defines respiratory tract infection (RTI) of unspecified localization. Where designated, FDA also evaluated all "RTI" including the "Upper RTI" and "Lower RTI" grouping.

19.6. Additional Safety Analyses Conducted by FDA

A. TEAEs in ASCEND

Table 73 TEAEs in ≥ 5% of Acalabrutinib Group in ASCEND by Decreasing Frequency

PT or Grouped PT [a]	Acalabrutinib (N = 154), %	
	Any Grade	Grade 3-5 [b]
Neutropenia	48	23
Anemia	47	15
Thrombocytopenia	33	6
Upper respiratory tract infection	29	1.9
Lymphocytosis	26	19
Leukocytosis	25	25
Lower respiratory tract infection [c]	23	6
Headache	22	0.6
Diarrhea	18	1.3
Cough	18	0
Hemorrhage	15	1.3
Leukopenia	15	1.3
Fatigue	15	1.9
Musculoskeletal pain	15	1.3
Respiratory tract infection, unspecified	15	1.9
Pyrexia	12	0.6
Bruising	10	0
Abdominal pain	8	0
Arthralgia	8	0.6
Rash	8	0.6
Nausea	8	0
Lymphopenia	5	1.3
Constipation	6	0
Dizziness	6	0
Edema	6	0
Nonmelanoma skin cancer	6	0.6
Renal insufficiency	6	0.6
Dyspnea	6	1.3
Insomnia	6	0.6
Atrial fibrillation or flutter	5	1.3

Source: FDA analysis

[a] All hematology AEs represent combined AE and lab data.

[b] None in the table were Grade 5.

[c] Includes pneumonia. Incidence of pneumonia was 12% (6% Grade ≥ 3).

B. Reporting of Hematology AEs

Using AEs alone substantially underestimates the incidence of all-grade heme AEs, underestimating grade 3-4 heme AEs to a lesser extent (Table 74).

Table 74 AE vs. Laboratory Data on Hematologic Abnormalities (ASCEND)

	Acala (N = 154)				IR (N = 118)				BR (N = 35)			
	Any grade		G 3-4		Any grade		G 3-4		Any grade		G 3-4	
	N	%	N	%	N	%	N	%	N	%	N	%
AE Data												
Neutropenia	32	21%	26	22%	63	53%	58	49%	13	37%	12	34%
Anemia	24	16%	18	15%	10	8%	8	7%	6	17%	5	14%
Thrombocytopenia	22	14%	7	6%	20	17%	9	7%	6	17%	1	2.9%
Lab Data												
Neutropenia	72	47%	34	22%	93	79%	60	51%	28	80%	14	40%
Anemia	71	46%	20	13%	49	42%	5	4.2%	19	54%	4	11%
Thrombocytopenia	39	25%	6	3.9%	42	36%	13	11%	18	51%	2	6%
Integrated AE and Lab Data												
Neutropenia	74	48%	35	23%	93	79%	62	53%	28	80%	14	40%
Anemia	73	47%	23	15%	51	43%	9	8%	20	57%	6	17%
Thrombocytopenia	51	33%	9	6%	48	41%	15	13%	19	54%	2	6%

Source: FDA analysis

NDA 210259/S-006
NDA 210259/S-007

CALQUENCE (acalabrutinib)
Assessment Aid Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Clinical Reviewer (S-007)	Nick Richardson, DO, MPH	OOD/DHM2	Sections: 1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13	**Select one:** ☑ Authored ☐ Approved
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NDA 210259/S-006
NDA 210259/S-007

CALQUENCE (acalabrutinib)
Assessment Aid Signatures

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NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the Regulatory Authorities.

Application Type	Supplemental NDA
Application Number(s)	NDA 210259/S-007
Priority or Standard	Priority
Submit Date(s)	August 5, August 24, and September 23, 2019
Received Date(s)	August 5, August 24, and September 23, 2019
PDUFA Goal Date	March 23, 2020
Division/Office	Division of Hematology Products/OHOP
Review Completion Date	November 20, 2019
Established Name	Acalabrutinib
Trade Name	CALQUENCE
Pharmacologic Class	Kinase inhibitor
Code name	ACP-196
US Applicant	AstraZeneca UK Limited
Formulation(s)	capsule
Dosing Regimen	100 mg orally approximately every 12 hours
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s)	Treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)

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Reviewers of Multi-Disciplinary Review and Evaluation

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Health Canada Review Team for Assessment Aid

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Therapeutic Goods Administration (Australia) Review Team for Assessment Aid

Clinical Reviewer (Senior Medical Advisor Haematology Clinical Evaluation Unit 6)	(b) (6)
Non-Clinical Reviewer	
Co-lead Risk Management Evaluation Unit	

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCEND	ACE-CL-309
AST	aspartate aminotransferase
BCL	B-cell lymphoma
BCR	B-cell receptor
BID	twice daily
BLA	biologics license application
BR	bendamustine+rituximab
BRF	Benefit Risk Framework
BTK	Bruton tyrosine kinase inhibitor
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CIRS-G	Cumulative Illness Rating Score-Geriatric
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CTCAE	Common Terminology Criteria for Adverse Events
DMC	data monitoring committee
DOR	duration of response
ECG	electrocardiogram
ECI	event of clinical interest
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
ELEVATE-TN	ACE-CL-007
ESMO	European Society for Medical Oncology

ETASU	elements to assure safe use
FCR	fludarabine, cyclophosphamide, and rituximab
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GLP	good laboratory practice
GRMP	good review management practice
HI	hepatic impairment
HR	hazard ratio
ICH	International Conference on Harmonization
IGHV	immunoglobulin heavy-chain variable
IND	Investigational New Drug
IR	idelalisib+rituximab
IRC	Independent Review Committee
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
IXRS	interactive voice/web response system
KM	Kaplan-Meier
LDT	lymphocyte doubling time
MCL	mantle cell lymphoma
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NCCN	National Comprehensive Cancer Network
NDA	new drug application
NE	not estimable
NME	new molecular entity
OCS	Office of Computational Science
OL	open-label
OPQ	Office of Pharmaceutical Quality
ORR	overall response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	progressive disease
PFS	progression-free survival
PI	prescribing information

PK	pharmacokinetics
PMC	postmarketing commitment
PML	progressive multifocal leukoencephalopathy
PMR	postmarketing requirement
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
R/R	relapsed/refractory
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SLL	small lymphocytic lymphoma
SOC	standard of care
TEAE	treatment emergent adverse event
TIFI	time to first improvement
TN	treatment-naïve
TTNT	time to next treatment

1 Executive Summary

1.1. Product Introduction

Calquence (acalabrutinib) is a small-molecule inhibitor of Bruton tyrosine kinase (BTK)

Calquence received initial US approval in 2017. The currently approved indication for Calquence is:

- For the treatment of adult patients with mantle cell lymphoma who have received at least one prior therapy.
  This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The efficacy results from a single, multicenter, randomized, open-label, 3-arm, actively controlled trial (ACE-CL-007/ELEVATE-TN, NCT02475681) in 535 patients with previously untreated chronic lymphocytic leukemia provides substantial evidence of effectiveness for the following recommended indication: Treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

The ELEVATE-TN trial demonstrated clinically meaningful and statistically significant improvement in the primary efficacy endpoint, progression-free survival (PFS) per independent review committee (IRC) for both, acalabrutinib plus obinutuzumab [hazard ratio 0.10 (95% CI 0.06, 0.17), P-value <0.0001] and acalabrutinib monotherapy [hazard ratio 0.20 (95% CI 0.13, 0.30), P-value <0.0001] compared to the comparator arm of obinutuzumab plus chlorambucil. In addition, the key secondary endpoint of overall response rate was demonstrated to statistically significantly improved in the acalabrutinib plus obinutuzumab arm compared to obinutuzumab plus chlorambucil (94% versus 79%, p -value <0.0001). Progression-free survival and overall response rate endpoints are standard efficacy endpoints for oncology clinical trials and have been used in other FDA approvals. The use of a single randomized trial to support approval is acceptable due to the disease setting, consistent demonstration of superiority across multiple efficacy endpoints, and robust efficacy results on statistical evaluation. Because SLL represents the same disease process as CLL, the FDA review team recommends to extend the efficacy and safety outcomes to patients with previously untreated CLL.

1.3. Benefit-Risk Assessment (BRA)

In 535 adult patients with previously untreated chronic lymphocytic leukemia (CLL), a multicenter, randomized, open-label, actively controlled, 3-arm trial (ACE-CL-007/ELEVATE-TN, NCT02475681) demonstrated superiority of both, acalabrutinib plus obinutuzumab and acalabrutinib monotherapy, compared to obinutuzumab plus chlorambucil. Clinically meaningful and statistically significant improvement in progression-free survival for acalabrutinib plus obinutuzumab [hazard ratio 0.10 (95% CI 0.06, 0.17), P-value <0.0001] and acalabrutinib monotherapy [hazard ratio 0.20 (95% CI 0.13, 0.30), P-value <0.0001], combined with improved overall response rate for acalabrutinib plus obinutuzumab (94% versus 79%, p -value <0.0001), compared to the comparator arm of obinutuzumab plus chlorambucil, provides substantial evidence of effectiveness for the recommended indication. The recommended dosing regimen for acalabrutinib, as monotherapy or in combination with obinutuzumab, is 100 mg orally taken approximately every 12 hours until disease progression or unacceptable toxicity. When given in combination with obinutuzumab, start obinutuzumab at Cycle 2 Day 1 at 100 mg, followed by 900 mg on Cycle 2 Day 2, followed by 1000 mg on Days 8 and 15 of Cycle 2 and on Day 1 of each subsequent 28-day cycle, for a total of 6 cycles.

In the ELEVATE-TN safety population (178 patients on acalabrutinib plus obinutuzumab, 179 patients on acalabrutinib monotherapy, and 169 patients on obinutuzumab plus chlorambucil), the safety profile of acalabrutinib was consistent with the known safety profile of acalabrutinib across multiple clinical trials. The ELEVATE-TN treatment arms had a similar incidence of fatal toxicities during treatment or within 30 days from the last dose of treatment (≤2% per arm, most often from infection), serious adverse events (22% to 39%), and discontinuations due to toxicity (9% to 15%). However, there were some notable differences between the acalabrutinib monotherapy arm compared to the acalabrutinib plus obinutuzumab and obinutuzumab plus chlorambucil arms that include a lower incidence of grade 3 or 4 adverse events (44% vs. 70% and 70%, respectively), grade 4 adverse events (10% vs. 28% and 15%, respectively), and dose reductions (4%% vs.8% and 27%). The difference in grade 3 or 4 adverse events for the acalabrutinib plus obinutuzumab and obinutuzumab plus chlorambucil arm compared to acalabrutinib monotherapy were primarily due to differences in rates of cytopenias, infections, and infusion-related reactions. For acalabrutinib, as monotherapy or in combination with obinutuzumab in patients with CLL, the most common adverse reactions (≥30% in any study) were anemia, neutropenia, thrombocytopenia, leukocytosis, headache, upper respiratory tract infection, and diarrhea.

Benefit-Risk: The ELEVATE-TN trial demonstrated clinically meaningful and statistically significant improvement in progression-free survival for both acalabrutinib treatment arms and for overall response rate in the acalabrutinib plus obinutuzumab arm. The safety profile of acalabrutinib is consistent with the known safety profile, therefore the benefit-risk assessment of acalabrutinib, as monotherapy or in combination with obinutuzumab, is favorable for the treatment of adult patients with chronic lymphocytic leukemia. The recommended FDA indication for acalabrutinib includes patients with small lymphocytic lymphoma because it is the same disease as chronic lymphocytic leukemia.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Chronic lymphocytic leukemia (CLL) represent approximately 30% of all adult leukemias and is an incurable malignancy, with relapse nearly universal.	CLL is a serious and life-threatening disease.
Current Treatment Options	• Treatment options for patients with untreated CLL include multiagent chemoimmunotherapy. However, the majority of patients will experience disease relapse. • A large percentage of patients with CLL cannot tolerate multiagent chemoimmunotherapy due to age and comorbidities.	There is a need for more effective and tolerable first-line regimens for patients with CLL.
Benefit	• The ELEVATE-TN trial demonstrated clinically meaningful and statistically significant improvement in progression-free survival for both, acalabrutinib plus obinutuzumab [hazard ratio 0.10 (95% CI 0.06, 0.17), P-value <0.0001] and acalabrutinib monotherapy [hazard ratio 0.20 (95% CI 0.13, 0.30), P-value <0.0001] compared to the comparator arm of obinutuzumab plus chlorambucil. Additionally, overall response rate was demonstrated to be statistically significantly improved in the acalabrutinib plus obinutuzumab arm compared to obinutuzumab plus chlorambucil (94% versus 79%, p -value <0.0001).	Substantial evidence of efficacy was demonstrated for acalabrutinib plus obinutuzumab and acalabrutinib monotherapy over obinutuzumab plus chlorambucil.
Risk and Risk Management	• In the ELEVATE-TN safety population (178 patients on acalabrutinib plus obinutuzumab, 179 patients on acalabrutinib monotherapy, and 169 patients on obinutuzumab plus chlorambucil), the treatment arms had a similar incidence of fatal toxicities during treatment or within 30 days from the last dose of treatment (≤2% per arm, most often from infection), serious adverse events (22% to 39%), and discontinuations due to toxicity (9% to 15%). • The acalabrutinib monotherapy arm compared to the acalabrutinib plus obinutuzumab and obinutuzumab plus chlorambucil arms had a lower incidence of grade 3 or 4 adverse events (44% vs. 70% and 70%,	The safety profile of acalabrutinib, as monotherapy or in combination with obinutuzumab, is acceptable in the intended population and the risk can be appropriately mitigated through labeling with CALQUENCE. To further mitigate the risks with CALQUENCE, the prescribing information was updated to include relevant data in patients with CLL for the Warnings and Precautions for Serious and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	respectively), grade 4 adverse events (10% vs. 28% and 15%, respectively), and dose reductions (4%% vs.8% and 27%), primarily due to differences in rates of cytopenias, infections, and infusion-related reactions. • For acalabrutinib, as monotherapy or in combination with obinutuzumab in patients with CLL, the most common adverse reactions (≥30% in any study) were anemia, neutropenia, thrombocytopenia, leukocytosis, headache, upper respiratory tract infection, and diarrhea.	Opportunistic Infections, Hemorrhage, Cytopenias, Second Primary Malignancies, and Atrial Fibrillation. Additional sections of the prescribing information were updated to appropriately convey the risk with CALQUENCE.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
	X Clinical outcome assessment (COA) data, such as	
	X Patient reported outcome (PRO)	**Section 8.1.2**
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	

	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that was not submitted in the application, but was considered in this review.	

X _____
Cross-Disciplinary Team Leader

X _____
Clinical Reviewer

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Chronic lymphocytic leukemia (CLL) is a malignancy of B cells that predominantly affects an elderly population. It is the most prevalent form of adult leukemia, with an age-adjusted incidence of 3.3–6.4 per 100,000 person-years and a median age at diagnosis of 70 years (Noone et al. 2018). The diagnosis of CLL is established using peripheral blood and immunophenotyping and requires a minimum of $5x10^9$ monoclonal B cells that co-express the surface antigens CD5, CD19, CD20, and CD23. While patients with early disease have not been shown to have a survival advantage with early treatment, most patients will eventually require therapy for their disease with the onset of symptoms or cytopenias. Treatment of CLL is therefore often deferred in asymptomatic patients with early-stage disease and initiated once there is evidence for progressive or symptomatic/active disease as defined by International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines (Hallek et al. 2008, Hallek et al. 2018a). Despite the relatively long-life expectancy for early stage disease, CLL remains an incurable disease.

In the frontline setting, the treatment approach is determined by several key factors which include prognostic molecular markers such as cytogenetic abnormalities and mutational status of the B-cell receptor (BCR) immunoglobulin heavy-chain variable (*IGHV*) genes, age, and comorbidities. In patients without high-risk cytogenetics—for example, 17p deletion or *TP53* mutation—chemoimmunotherapy remains a standard of care as frontline therapy (NCCN 2019; Eichhorst et al. 2015). While fludarabine-based chemoimmunotherapy is standard for treatment-naive younger/fitter patients with CLL, the therapy for older patients or patients with comorbidities is less well defined. Chlorambucil has now long been a standard frontline treatment for CLL for elderly patients and patients with comorbidities regardless of age (Han et al. 1973; Knospe and Loeb 1980; Eichhorst et al. 2009). Subsequently the addition of anti-CD20 monoclonal antibodies to chlorambucil was demonstrated to prolong survival in elderly patients with comorbidities.

Chemoimmunotherapy has less favorable outcomes in patients who have high risk cytogenetics such as deletions in the long arm of chromosome 11 (11q deletion) or in the short arm of chromosome 17 (17p deletion). These patients may prove to be refractory to therapy and/or experience short remission durations and rapid progression of disease (Hallek et al. 2010, Hillmen et al. 2007). The development of novel molecularly targeted agents, particularly the Bruton tyrosine kinase (BTK) inhibitor ibrutinib, the phosphoinositide-3 kinase (PI3K)δ inhibitor idelalisib, and the apoptosis regulator BCL-2 antagonist venetoclax, have transformed the treatment paradigm for patients with CLL, particularly for those with high-risk disease who have

inferior outcomes with chemotherapy-based regimens. These agents have demonstrated compelling efficacy in subjects with high-risk CLL, with generally favorable safety profiles and a typically low incidence of myelosuppression (Mato et al. 2018a; Mato et al. 2018b; Moreno et al. 2019; O'Brien et al. 2016; Roberts et al. 2016; Seymour et al. 2018; Sharman et al. 2019; Shanafelt et al. 2018; Stilgenbauer et al, 2016; UK CLL Forum 2016).

Although chemoimmunotherapy yields response and potentially long progression-free survival (PFS), CLL remains incurable with relapse inevitable and most patients requiring multiple lines of therapy. Therapeutic choice after relapse requires the evaluation of the intensity of the previous therapies, the duration of response to those therapies, and patient comorbidities.

Standard therapeutic options for relapsed or refractory (R/R) CLL include combination chemoimmunotherapy regimens with bendamustine+rituximab (BR) and idelalisib+rituximab (IR) (Eichhorst et al. 2015; NCCN 2019; Hallek et al. 2018b; Fischer et al. 2011; Cheson et al. 2010; Furman et al. 2014). National Comprehensive Cancer Network (NCCN) guidelines recommend chemoimmunotherapy, including BR, as third-line treatment for R/R CLL but do not recommend it for patients with 17p deletion. European Society for Medical Oncology (ESMO) guidelines also do not recommend BR for patients with 17p deletion or TP53 mutation. They do, however, recommend repeating first-line chemoimmunotherapy (including BR) if relapse or progression occurred at least 24-36 months after initial chemoimmunotherapy. Although a viable option in the elderly population, BR is associated with hematologic toxicity and infections.

Novel regiments with targeted agents such as ibrutinib, idelalisib, and venetoclax are listed as treatment options for R/R CLL irrespective of 17p deletion or TP53 mutation in the NCCN and ESMO guidelines. The development of targeted therapies against B cell markers/antigens or against components of the BCR signaling pathway such as ibrutinib and idelalisib have demonstrated efficacy in CLL with less toxicity compared to chemoimmunotherapy (Wiestner 2015).

The BTK inhibitor ibrutinib is approved in previously untreated and R/R CLL settings (ibrutinib US prescribing information and SmPC 2019) based on superior clinical outcomes compared with standard treatment approaches, but ibrutinib has a distinct toxicity profile that may lead to therapy discontinuation (Burger et al. 2015; Byrd et al. 2013; Woyach et al. 2014). Therapy with other agents targeting the BCR signaling pathway such as the PI3Kδ inhibitor idelalisib has demonstrated efficacy but is also associated with clinically important safety risks, including hepatotoxicity, severe diarrhea or colitis, pneumonitis, severe cutaneous reactions, and intestinal perforation (idelalisib US prescribing information and SmPC 2018). Given the safety profile of these BCR pathway inhibitors, an unmet need exists for therapeutic agents which are better tolerated, potentially improving the benefit risk ratio.

Acalabrutinib is being evaluated in the previously untreated CLL patient population as monotherapy and in combination with obinutuzumab in the ongoing Phase 3 pivotal Study

ELEVATE-TN (ACE-CL-007), entitled, "A Randomized, Multicenter, Open-Label, 3 Arm Phase 3 Study of Obinutuzumab in Combination with Chlorambucil, ACP 196 in Combination with Obinutuzumab, and ACP-196 Monotherapy in Subjects with Previously Untreated Chronic Lymphocytic Leukemia" (NCT02475681). The primary objective is to evaluate the efficacy of obinutuzumab in combination with chlorambucil (Arm A) compared with acalabrutinib in combination with obinutuzumab (Arm B) based on Independent Review Committee (IRC) assessment of PFS per International Workshop on Chronic Lymphocytic Leukemia criteria (IWCLL, Hallek 2008) with incorporation of the clarification for treatment-related lymphocytosis (Cheson 2012) in subjects with previously untreated CLL.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's position.

2.2. Analysis of Current Treatment OptionsTable 1: Summary of NCCN Preferred Regimens for Previously Untreated Chronic Lymphocytic Leukemia

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval[1]	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues[2]	Other Comments
FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]						
Small molecules						
Ibrutinib	For the treatment of patients with frontline CLL	2016/full	420 mg taken orally once daily	Randomized, multicenter, open study of ibrutinib vs. chlorambucil (N=269). Primary endpoint was IRC-assessed PFS. Ibrutinib vs: Chlorambucil: Median PFS NR vs. 18.9 months. HR: 0.16 (0.09, 0.28). ORR: 82.4% vs. 35.3% (p<0.0001)	Hemorrhage, infections, cytopenias, cardiac arrhythmias, hypertension, tumor lysis syndrome, embryo-fetal toxicity, second primary malignancies	
Combination therapy						
Venetoclax	In combination w/obinutuzumab for treatment of previously untreated CLL or SLL	2019/full	5 week ramp up to 400 mg (20 50, 100, 200 mg tablets once daily orally for 1 week each (weeks 1-4)	Randomized, multicenter, open-label, Phase 3 study comparing the efficacy and safety of Venetoclax in combination with obinutuzumab (N=216) versus obinutuzumab in combination with chlorambucil (N=216). VEN + G vs. GClb: Primary endpoint was IRC-assessed PFS. 67% reduction in risk of progression or death. HR 0.33: 95% CI:0.22, 0.51. ORR: 85% to 71% (p=0.0007)	Tumor lysis syndrome, neutropenia, infections, immunization, embryo-fetal toxicity	

CLL=chronic lymphocytic leukemia; HR=hazard ratio; IRC=Independent Review Committee; NR=not reached; PFS=progression-free survival; SLL=small lymphocytic lymphoma.

[1] Accelerated approval or full approval

[2] Important Safety and Tolerability Issues include "Warnings and Precautions" from the original approved label

The Applicant's Position:

CLL is a serious and life-threatening condition for which there is currently no known cure. There is a high unmet medical need for treatments which control the disease and, importantly, do not significantly add to the burden of morbidity and risk of mortality already experienced by patients with this incurable condition. ELEVATE-TN (ACE-CL-007), a study in previously untreated CLL subjects, demonstrated that acalabrutinib has a statistically significant and clinically meaningful difference in PFS compared to combination standard of care therapies. Acalabrutinib is well tolerated by the majority of subjects, with very few treatment discontinuations or dose reductions due to adverse events (AEs). These data suggest acalabrutinib provides substantial improvement over currently available therapies and an important treatment option for patients with CLL.

In addition, the safety and tolerability of acalabrutinib in ELEVATE-TN was consistent with the known safety profile of acalabrutinib. Acalabrutinib may provide a new tolerable and effective chemo-free treatment option to CLL patients.

Regulatory Authorities Assessment:

The regulatory authorities agree that ibrutinib and venetoclax plus obinutuzumab are relevant treatment options for patients with previously untreated CLL. However, the claim that the ELEVATE-TN trial demonstrated that acalabrutinib provides substantial improvement in PFS compared to combination standard of care therapies relates only to the comparator of obinutuzumab plus chlorambucil. The efficacy and safety of acalabrutinib, as monotherapy or in combination with obinutuzumab, relative to other available therapies, such as venetoclax plus obinutuzumab and ibrutinib, have not been evaluated.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
Acalabrutinib was first approved by the United States Food and Drug Administration (FDA) on 31 October 2017 under accelerated approval for New Drug Application (NDA) 210259 for the treatment of adult patients with MCL who have received at least one prior therapy at a dosage of 100 mg twice daily (BID).

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's position.

3.2. Summary of Presubmission/Submission Regulatory ActivityThe Applicant's Position:

A summary of key interactions with the FDA regarding acalabrutinib development and ELEVATE-TN (ACE-CL-007), the pivotal study for this sNDA, is provided in Table 2.

Table 2: Major regulatory milestones for acalabrutinib development in relation to ELEVATE-TN (ACE-CL-007)

Date	Milestone and Details
27 Dec 2013	IND 118717 for treatment of B-cell malignancies activated (ACE-CL-001)
13 May 2015	Orphan Drug Designation granted for acalabrutinib for treatment of CLL
13 Jun 2017	NDA 210259 submitted for acalabrutinib for adult patients with MCL who have received at least one prior therapy
31 July 2017	BTD granted for acalabrutinib for treatment of MCL
31 Oct 2017	Acalabrutinib NDA 210259 approved under accelerated approval for adult patients with MCL who have received at least one prior therapy
23 May 2018	Type C Meeting, Agency approved the statistical analysis plans for the ELEVATE-TN interim analysis, and agreed that ongoing/completed toxicology studies are sufficient to support and sNDA for CLL
01 Feb 2019	Type C Written Responses, Agency approved the proposed format and content of sNDA for ELEVATE-TN and advised additional analyses to compliment the proposed safety pooling strategy
11 Apr 2019	FDA agreement of Sponsor's amended safety pooling strategy
07 Jun 2019	TC meeting to discuss ELEVATE-TN and ASCEND topline data and timeline for sNDAs
19 Jun 2019	BTD request submitted for acalabrutinib for CLL indications
12 Aug 2019	BTD granted for acalabrutinib monotherapy for treatment of adult patients with CLL

IND Investigational New Drug application; NDA New Drug Application; sNDA Supplementary New Drug Application, BTD Breakthrough Therapy Designation; IA interim analysis; CLL chronic lymphocytic leukemia

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's position. This supplement, involving

acalabrutinib in the setting of patients with previously untreated CLL, was submitted concurrently with NDA210259 S-006, involving acalabrutinib in the setting of patients with relapsed or refractory CLL. For both supplements, the Applicant agreed to participate in:

- Project Orbis involving collaborative NDA review by FDA, the Australian Therapeutic Good Administration, and Health Canada
- The Real-Time Oncology Review (RTOR) pilot. After negotiation of submission timelines, two RTOR presubmissions were received on 05 August 2019 and 26 August 2019, with final components received 24 September 2019.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

FDA Office of Scientific Investigations was consulted to perform an audit of the Sponsor for the conduct of the ACE-CL-007/ELEVATE-TN trial. The inspection included review of organizational charts, vendor list, vendor oversight, transfer of obligations, investigator agreements, financial disclosures, monitoring plans, monitoring reports, monitor qualifications, safety reports, adverse events, protocol deviations, and standard operating procedures. The inspection found no significant deficiencies with monitoring of the trial. In general, the sponsor maintained adequate oversight of the clinical trial, and appeared to be in compliance with Good Clinical Practice.

4.2. Product Quality

There was no new product quality data submitted and no product quality-related changes for this supplemental NDA.

4.3. Clinical Microbiology

Not applicable

4.4. Devices and Companion Diagnostic Issues

Not applicable

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Regulatory Authorities Assessment:
The Applicant updated animal:human safety margins to reflect the clinical exposure at the recommended dose in CLL patients and added the finding of dystocia in rats to Section 8.1 of the label. The Applicant submitted the pilot and GLP pre- and postnatal development studies to support the labeling changes, which were reviewed by the FDA. In the pilot pre- and postnatal development study in rats, acalabrutinib was administered by oral gavage at doses of 0, 100, 200, or 300 mg/kg/day once daily from Gestational Day (GD) 6 through Lactation Day (LD) 12. In the GLP pre- and postnatal development study in rats, acalabrutinib was administered by oral gavage at doses of 0, 50, 100, or 150 mg/kg/day from GD 6 through LD 20, and then F1 generation pups were followed to assess the developmental milestones from weaning through mating. The following findings from these studies will be included in the label: dystocia (prolonged/ difficult labor with or without a normal developing fetus lodged in the vaginal canal), underdeveloped renal papilla in F_1 generation pups observed in both studies, and mortality in F1 generation pups observed in the GLP study.]

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:
Reference is made to original acalabrutinib NDA 210259 submitted on 13 June 2017 and approved on 31 October 2017. The nonclinical pharmacology/toxicology profile for acalabrutinib has not changed and results support the treatment of patients with CLL with the intended therapeutic dose regimen of 100 mg BID.

Regulatory Authorities Assessment:
FDA disagrees with the Applicant's position. In the newly submitted pilot and GLP pre- and postnatal development studies, there were mortalities at 300 mg/kg in the pilot study and at doses ≥ 100 mg/kg in the GLP study due to fetal dystocia. Additionally, at doses ≥ 200 mg/kg in the pilot study, there were dams found dead with the cause of death undetermined since microscopic examination was limited in these animals to the kidneys. At the time when the fertility and embryo-fetal development study was reviewed for the original application, the maternal mortality at 200 mg/kg due to fetal dystocia was at very low incidence and not considered test article-related. In light of multiple studies showing dose-dependent dystocia, this finding is included in current labeling under Use in Specific Populations and 8.1; and, in 8.3 and 17 to advise females of reproductive potential to use effective contraception and to avoid pregnancy during treatment with acalabrutinib and for 1 week after the final dose. Also to be included are underdeveloped renal papilla in F1 pups and mortality in two F1 males (on Days 68 and 71 with red discoloration of the lungs or thymus) at ≥ 150 and 100 mg/kg, respectively.]

5.3. Pharmacology

Primary pharmacology

No new pharmacology data was submitted or is in need of review in the current submission.

Secondary Pharmacology

Data:
No new information is provided in the current submission.

The Applicant's Position:
Not applicable

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant.

Safety Pharmacology

Data:
No new information is provided in the current submission.

The Applicant's Position:
Not applicable

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant.

5.4. ADME/PK

Data:
No new information is provided in the current submission.

The Applicant's Position:
Not applicable.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant.

5.5. Toxicology

5.5.1. General Toxicology

Data:
No new information is provided in the current submission.

The Applicant's Position:
Not applicable

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant.

General toxicology; additional studies
Data:
No new information is provided in the current submission.

The Applicant's Position:
Not applicable

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)
Data:
No new information is provided in the current submission.

The Applicant's Position:
Not applicable

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant.

In Vitro Assays in Mammalian Cells
Data:
No new information is provided in the current submission.

The Applicant's Position:
Not applicable

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant.

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)
Data:
No new information is provided in the current submission.

The Applicant's Position:
Not applicable.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant.

Other Genetic Toxicity Studies *(For API only; does not refer to impurities)*
Data:
No new information is provided in the current submission.

The Applicant's Position:
Not applicable.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant.

5.5.3. Carcinogenicity

Data:
No new information is provided in the current submission.

The Applicant's Position:
Not applicable

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Data:
See Section Prenatal and Postnatal development below.

The Applicant's Position:
See Section Prenatal and Postnatal development below.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant.

Embryo-Fetal Development

Data:
No new information is provided in the current submission.

The Applicant's Position:
Not applicable

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant.

Prenatal and Postnatal Development

Data:
The study reports for the following 2 reproductive and toxicology studies are included in the sNDA submission:

- 2219-109 - A Pilot Pre- and Postnatal Development Toxicity Study in Rats
- 2219-111 - A Study of Toxic effects on Pre- and Postnatal Development, Including Maternal Function in Rats

2219-109 / A Pilot Pre- and Postnatal Development Toxicity Study in Rats
Key Study Findings:

- No effects of ACP-196 were noted on survival of P females at 100 mg/kg/day.
- Based on these findings, a high-dose level of 150 mg/kg/day was considered appropriate for the definitive pre- and postnatal developmental toxicity study in rats.

2219-111 - A Study of Toxic effects on Pre- and Postnatal Development, Including Maternal Function in Rats
Key Study Findings:

- No-observed-adverse-effect level (NOAEL) for P females was considered to be 50 mg/kg/day, with a corresponding $AUC_{(0-t)}$ on LD 20 of 1420 hr*ng/mL, based on the low incidence of dystocia observed at dose levels ≥100 mg/kg/day.
- In the F1 animals, the NOAEL for survival, growth, and physical and functional development was considered 150 mg/kg/day.

The Applicant's Position:

The results of reproductive toxicity studies conducted to date with acalabrutinib did not identify specific risks to fertility and embryofetal development.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant that there are no new specific risks to fertility and embryofetal development. However, it is noted that the animal: safety margins are now down to 2-fold due to new clinical exposure data. Considering the variation in exposure in both animals and humans, the safety margins may be even less in some patients. Further, the pharmacologically active ACP-5862 metabolite levels in patients are 2 times higher than acalabrutinib; however, metabolite levels in maternal and fetal plasma in rats are much lower than acalabrutinib and were not measured in rabbits, suggesting that some of the developmental and reproductive toxicities may be underpredicted in animals. The submitted data also reveals a new pregnancy complication risk for dystocia and F1 generation toxicity and mortality that was not previously included in the label. See data below for more information.

Study title/ number: ACP-196: A PILOT PRE- AND POSTNATAL DEVELOPMENTAL TOXICITY STUDY IN RATS/ 2219-109

Key Study Findings

- Acalabrutinib (ACP-196)-related mortality due to dystocia was observed at 300 mg/kg. Dams were found dead at doses ≥ 200 mg/kg/day, with some of the same macroscopic and microscopic findings as the dam with dystocia. A definitive cause of death could not be determined for animals found dead since microscopic examination was limited to the kidneys.
- Fetal toxicity, including underdeveloped renal papilla was observed in the presence of maternal toxicity at 200 mg/kg/day.
- On GD17, ACP-5862 metabolite levels in maternal plasma were ~0.5x acalabrutinib levels. On GD 18, acalabrutinib fetal plasma levels were ~0.5x maternal plasma levels. ACP-5862 plasma fetal plasma levels were 2 to 4% of maternal levels.
- Despite high maternal plasma and milk concentrations during lactation, very little (less than 1% of maternal plasma concentrations) acalabrutinib was detected in pup plasma during the lactation phase. The metabolite ACP-5862 was detected in pup plasma at levels less than 5% of maternal plasma levels.

Conducting laboratory and location:	(b) (4)
GLP compliance:	No

Methods

Dose and frequency of dosing:	0, 100, 200, or 300 mg/kg/day from GD 6 through LD 12
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4)

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the Regulatory Authorities.

	(b) (4) (w:v) and (b) (4) (w:v) in NANOpure Diamond Ultrapure water
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	6/sex/group; only females were dosed
Satellite groups:	Toxicokinetics (TK): 8 females/group (acalabrutinib treatment groups); 4 females/group (controls) taken 0.5, 1, 3, 9, and 24 hours postdose on GD 6 and 17; 1-hour postdose on GD18 (fetal plasma levels were also determined); and 1 and 3 hours postdose on LD 12 (maternal milk and pup plasma levels were also measured 3 hours postdose on LD12).
Study design:	Pregnant females (F0 dams) were administered acalabrutinib once daily from GD 6 through LD 12; females were allowed to deliver the F1 litters and rear the F1 pups until LD12 to evaluate the effects on the F0 dams and F1 generation pups; standardization of litter size (culling) to 8 pups/litter (4/sex when possible), occurred on postnatal day (PND) 4.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

<table>
<tr><th>Generation</th><th>Major Findings</th></tr>
<tr><td>F0 Dams</td><td></td></tr>
<tr><td>Mortality</td><td>Dams with Early Mortalities:
<table>
<tr><th>Dose</th><th>Disposition</th><th>Day</th><th>Cause of Death, Macroscopic and Microscopic (kidneys only) Findings</th></tr>
<tr><td>200</td><td>Found dead</td><td>GD 24</td><td>Undetermined*; macroscopic findings of red (pelvis) or tan (medulla) discoloration in the kidneys, red discoloration of the lung with mainstem bronchi, red discoloration and edema of the thymus, yellow (color of test compound) fluid within the thoracic and abdominal cavities, and yellow and red discoloration and edema of the pancreas; microscopic findings of moderate degree of kidney tubular degeneration/necrosis.</td></tr>
<tr><td rowspan="2">300</td><td>Found dead, pregnant</td><td>GD 22</td><td>Undetermined*; macroscopic findings of red discoloration of the adrenal glands and red (pelvis) discoloration of the kidneys; microscopic findings of moderate kidney tubular degeneration/ necrosis.</td></tr>
<tr><td>Euthanized in extremis, incomplete delivery</td><td>GD 23</td><td>Dystocia with clinical signs of hunched posture and activity decreased; macroscopic findings of yellow discoloration of the kidneys, liver, and skin, enlarged and black discoloration of renal lymph node, black discoloration of ovaries; microscopic findings of moderate kidney tubular degeneration/necrosis.</td></tr>
</table></td></tr>
</table>

<table>
<tr><td></td><td>* a definitive cause of death could not be determined for animals found dead since microscopic examination was limited to the kidneys. Doses are in mg/kg/day.</td></tr>
<tr><td>Clinical Signs and Body Weight</td><td>300 mg/kg/day: Bent tail was observed on LD 10-12 in 1/6 females.
≥ 100 mg/kg/day: Salivation was observed on GD 17-22 at all doses in animals with and without early mortality (1/6, 3/6, and 3/6 dams at 100, 200, and 300 mg/kg/day, respectively) and during the lactation phase in 1 to 4 animals per acalabrutinib treatment group. Mean body weight changes were generally transient and/or did not demonstrate a dose response.</td></tr>
<tr><td>Necropsy Findings (macroscopic)</td><td>300 mg/kg/day: Mild enlargement of the mandibular lymph node in 1/6 females.
≥ 100 mg/kg/day: Minimal to moderate red discoloration of the mandibular lymph node in 5/6, 3/5, and 1/4 females at 100, 200, and 300 mg/kg/day, respectively, and mild to moderate red discoloration of the renal lymph node in 2/6, 2/5, and 0/4 (1/2 with early mortality) females at 100, 200, and 300 mg/kg/day, respectively. Per protocol, no microscopic examination was performed on tissues from animals that survived to the terminal necropsy.</td></tr>
<tr><td>Concentrations in maternal, fetal and pup plasma; and maternal milk</td><td><u>Acalabrutinib</u>
Maternal Tmax (hr): 0.5
Maternal T1/2 (hr): 2 (3 for ACP-5862)

<u>Maternal Plasma TK on GD17</u>
<table>
<tr><th>Dose (mg/kg/day)</th><th>Cmax (ng/mL)</th><th>AUC_{0-t} (hr*ng/mL)</th></tr>
<tr><td>100</td><td>2520</td><td>9260</td></tr>
<tr><td>200</td><td>7060</td><td>17900</td></tr>
<tr><td>300</td><td>10100</td><td>26300</td></tr>
</table>
On GD17, maternal ACP-5862 AUC values were 55, 57, and 46% of 100, 200, and 300 mg/kg/day acalabrutinib values; Cmax values were 61, 42, and 34%, respectively.

On GD 18, mean fetal plasma acalabrutinib concentrations were lower than in maternal plasma. The mean acalabrutinib fetal plasma levels were ~40 to 50% of maternal levels. Mean fetal ACP-5862 plasma concentrations were 2 to 4% of maternal plasma concentrations.

Concentrations of acalabrutinib and ACP-5862 were higher in maternal milk than plasma. Maximum pup concentrations of acalabrutinib and ACP-5862 were less than 1 and <5% of maternal plasma levels (see original multidisciplinary review).</td></tr>
<tr><td>F1 Generation</td><td></td></tr>
<tr><td>F1 mortality</td><td>There were no acalabrutinib-related mortalities other than the litter of the dam with dystocia.</td></tr>
<tr><td>F1 clinical observations</td><td>200 mg/kg/day: Eight pups were thin and cold to the touch from one dam (who lost 24 g of body weight and had reduced food consumption (this female also had clinical signs of salivation) over lactation days 0 to 10 at 200 mg/kg/day. The dam also had macroscopic findings of moderate tan kidney discoloration, and mild to moderate red discoloration of the mandibular and renal lymph nodes.</td></tr>
<tr><td>F1 body weight</td><td>Unremarkable</td></tr>
<tr><td>F1 Necropsy Findings</td><td>There were no test article-related microscopic findings in pups from dams that survived to scheduled necropsy.

Fetal Observations in Dams with Early Mortality:</td></tr>
</table>

Dose	Dam Disposition	Day	Fetal Macroscopic Findings
200	Found dead	GD 24	Dam delivered 13 pups that had macroscopic findings of underdeveloped renal papilla (generally bilateral).
300	Found dead, pregnant	GD 22	Dam died pregnant with no information available on her pups other than "normal developing implant".
	Euthanized in extremis, incomplete delivery	GD 23	Macroscopic observations were within normal limits for the 8 pups that survived birth.

Doses are in mg/kg/day.

Study title/ number: ACP-196: A STUDY OF TOXIC EFFECTS ON PRE- AND POSTNATAL DEVELOPMENT, INCLUDING MATERNAL FUNCTION IN RATS/ 2219-111

Key Study Findings

- No-observed-adverse-effect level (NOAEL) for acalabrutinib (ACP-196) in pregnant females and F1 animals was considered to be 50 mg/kg/day, with a corresponding AUC(0-t) on LD 20 of 1420 hr*ng/mL. The NOAEL is based on the low, but consistently observed across studies, incidence of dystocia observed in dams and underdeveloped renal papilla and mortality (with red discoloration of the lung or thymus) in F1 offspring at dose levels ≥ 100 mg/kg/day.
- There was variability (large standard deviation) in maternal plasma levels of acalabrutinib.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 50, 100, or 150 mg/kg/day from GD 6 through LD 20

Route of administration: Oral gavage

Formulation/Vehicle: (b) (4) (w:v) and (b) (4) (w:v) in NANOpure Diamond Ultrapure water

Species/Strain: Rat/Sprague-Dawley

Number/Sex/Group: 25/sex/group; only females were dosed

Satellite groups: None. Blood samples were collected from the first 6 females/group at 0.5, 1, 3, 9, and 24 hours postdose on LD20.

Study design: Pregnant females (F0 dams) were administered acalabrutinib once daily from GD 6 through

LD 20; females were allowed to deliver the F1 litters and rear the F1 pups to weaning on LD/PND 21 to evaluate the effects on the F0 dams and F1 generation pups through weaning; standardization of litter size (culling) to 8 pups/litter (4/sex when possible), occurred on PND 4; F1 pups evaluated on LD 2 for static righting reflex and pinna detachment, on LD 11 for cliff aversion, LD 13 for eye opening, LD 16 for air drop righting reflex, LD 21 for neuropharmacological evaluation outlined by Irwin, and PND 22 for auditory response. On PND 28 a maximum of 25 males and 25 females per group were selected to continue on the study for assessment of sexual maturation and behavioral or reproductive performance (PND 28 for vaginal opening, PND 35 for preputial separation, motor activity and Functional Observational Battery (FOB) Observations, and learning and memory assessments). These F1 animals were mated (at least 80 days old) and uterine parameters were evaluated with necropsy on GD 13.

Deviation from study protocol affecting interpretation of results: No

Observations and Results

<table>
<tr><th>Generation</th><th>Major Findings</th></tr>
<tr><td>F0 Dams</td><td></td></tr>
<tr><td>Mortality</td><td>Unscheduled mortalities:
<table>
<tr><th>Dose</th><th>Disposition</th><th>Day</th><th>Cause of Death, Macroscopic (Maternal) Findings</th></tr>
<tr><td>100</td><td>Euthanized pregnant in extremis</td><td>GD 22</td><td>Dystocia with swelling of the vulva and anogenital region, purple skin discoloration in anogenital region, piloerection; developing fetus lodged in the vaginal canal and mild pelvic dilation of the kidneys.</td></tr>
<tr><td>150</td><td>Euthanized pregnant in extremis</td><td>GD 23</td><td>Dystocia with swelling of the vulva, red material around the nose, and piloerection; developing fetus lodged in the vaginal canal, mild pelvic dilation of the kidneys, brown fluid in the uterus and vagina.</td></tr>
<tr><td></td><td>Euthanized in extremis; incomplete delivery</td><td>GD 22</td><td>Dystocia with salivation, piloerection, and unkempt appearance; black foreign material in stomach that is apparent fetal/placental tissue.</td></tr>
</table>
Doses are in mg/kg/day. No uterine or fetal information was provided for the dams with early mortality.</td></tr>
</table>

<table>
<tr><td>Clinical Signs and Body Weight</td><td>≥ 50 mg/kg/day: Dose-dependent increase in salivation in 3/25, 3/25, and 12/25 females at 50, 100 and 150 mg/kg/day, respectively, beginning as early as GD 12 which progressed into the lactation period (present in 12/25, 14/24, and 18/23 females and was accompanied by red discolored hair in the lower jaw in 2/25, 8/24, and 14/23 females at 50, 100, and 150 mg/kg/day, respectively).</td></tr>
<tr><td>Delivery Data</td><td>150 mg/kg/day: 8% decreases in total and liveborn pups/litter (outside of lab historical control range, but within the control range for other contract labs) relative to controls (see table below).

<table>
<tr><th>Dose (mg/kg/day)</th><th>0</th><th>50</th><th>100</th><th>150</th><th>HC mean [range]</th></tr>
<tr><td>No. Females on Study</td><td>25</td><td>25</td><td>25</td><td>12</td><td>300</td></tr>
<tr><td>No. Females Pregnant</td><td>25</td><td>24</td><td>24</td><td>24</td><td>300</td></tr>
<tr><td>Female Fertility Index</td><td>100</td><td>96</td><td>96</td><td>96</td><td></td></tr>
<tr><td>No. Females Littered</td><td>25</td><td>24</td><td>23</td><td>22</td><td>300</td></tr>
<tr><td>Total Pups/Litter on Day 0 N (SD)</td><td>11.72 (1.621)</td><td>11.54 (2.206)</td><td>11.09 (2.214)</td><td>10.73 (2.334)</td><td>11.92 [11.1-12.7]</td></tr>
<tr><td>Liveborn Pups/Litter N (SD)</td><td>11.64 (1.705)</td><td>11.46 (2.146)</td><td>11.09 (2.214)</td><td>10.73 (2.334)</td><td>11.81 [10.9-12.7]</td></tr>
<tr><td>Live Pups/Litter Precull Day 4 N (SD)</td><td>11.4 (1.63)</td><td>11.5 (2.19)</td><td>11.0 (2.27)</td><td>10.5 (2.6)</td><td>11.64 [10.6-12.5]</td></tr>
<tr><td>Implantation Scars Counts (SD)</td><td>12.4 (1.73)</td><td>11.8 (2.19)</td><td>11.7 (1.54)</td><td>11.7 (1.86)</td><td>12.58 [11.7-13.2]</td></tr>
</table>
SD: standard deviation; HC: lab historical control</td></tr>
<tr><td>Necropsy Findings</td><td>≥ 50 mg/kg/day: Macroscopic changes included mild to moderate red discoloration of the mandibular (in 1/25, 4/24, and 1/23 females at 50, 100, and 150 mg/kg/day, respectively), mediastinal, (in 4/24 and 1/24 females at 50 and 100 mg/kg/day, respectively), and renal (in 1/23 females at 150 mg/kg/day) lymph nodes. Moderate red foci and swollen/thickened liver was observed only at 50 mg/kg/day.</td></tr>
<tr><td>Concentrations in maternal plasma</td><td><u>Acalabrutinib</u>
Maternal Tmax (hr): 0.5
Maternal T1/2 (hr): 3 to 4

<u>Maternal Plasma TK on LD20</u>
<table>
<tr><th>Dose (mg/kg/day)</th><th>Cmax (SD) (ng/mL)</th><th>AUC_{0-t} (SD) (hr*ng/mL)</th></tr>
<tr><td>50</td><td>651 (220)</td><td>1420 (301)</td></tr>
<tr><td>100</td><td>1730 (580)</td><td>4470 (1420)</td></tr>
<tr><td>150</td><td>3000 (841)</td><td>10300 (3940)</td></tr>
</table>
SD: standard deviation</td></tr>
<tr><td>F1 Generation</td><td></td></tr>
<tr><td>F1 mortality</td><td>≥ 100 mg/kg/day: 1/25 males at 100 mg/kg/day with red discoloration of the lung with mainstem bronchi and 1/25 males at 150 mg/kg/day with red discoloration of the thymus were found dead on Study Days 68 and 71, respectively. The cause of death is unknown (with no microscopic examination) but these macroscopic findings were also observed in the female dam found dead at 200 mg/kg/day in the pilot study and in one 50 mg/kg/day dam in this study.</td></tr>
<tr><td>F1 clinical observations</td><td>Unremarkable</td></tr>
<tr><td>F1 body weight</td><td>Unremarkable</td></tr>
</table>

F1 developmental landmarks	**150 mg/kg/day:** Static righting reflex occurred earlier (mean 2.1 days) compared to controls (mean 2.3 days). Air drop righting reflex was higher (16.4 days) compared to controls (16.2 days). These differences were statistically significant and outside of the historical control range, but of small magnitude and not considered adverse.
Auditory startle response, locomotor activity, FOB, etc	Unremarkable
Reproductive performance	Unremarkable
Necropsy Findings	**150 mg/kg/day:** 1/62 male pups on Day 28 have undeveloped renal papillae; 1/57 female pups had hepatodiaphragmatic nodule in the liver. **≥ 100 mg/kg/day:** Pups had absolute and relative liver weight decreases of -3 to -6%.
F2 Generation	Not tested

5.5.5. Other Toxicology Studies

No new information is provided in the current submission

X
Pharmacology-Toxicology Reviewer

X
Pharmacology-Toxicology Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

Regulatory Authorities Assessment:
The proposed starting dose of acalabrutinib in the current supplement is 100 mg orally approximately every 12 hours with or without food in patients with CLL or SLL. The efficacy and safety of the proposed dose were supported by the results of Phase 3 Study ELEVATE-TN, which evaluated 3 randomized (1:1:1) treatment arms (100 mg acalabrutinib BID monotherapy vs. 100 mg acalabrutinib BID + obinutuzumab vs. chlorambucil + obinutuzumab) in patients with previously untreated CLL (N=535). The Applicant updated the population PK analysis for acalabrutinib and ACP-5862 (active metabolite) PK with the data from patients with CLL. The PK data in CLL were similar to the PK observed in the currently approved mantle cell lymphoma (MCL) population. No drug-drug interaction was observed with acalabrutinib + obinutuzumab combination treatment. The Applicant also updated the labeling to recommend "avoid use" in patients with severe hepatic impairment based on Applicant's submitted severe hepatic impairment trial results (Study ACE-HI-102). From a clinical pharmacology perspective, this supplemental NDA is approvable.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

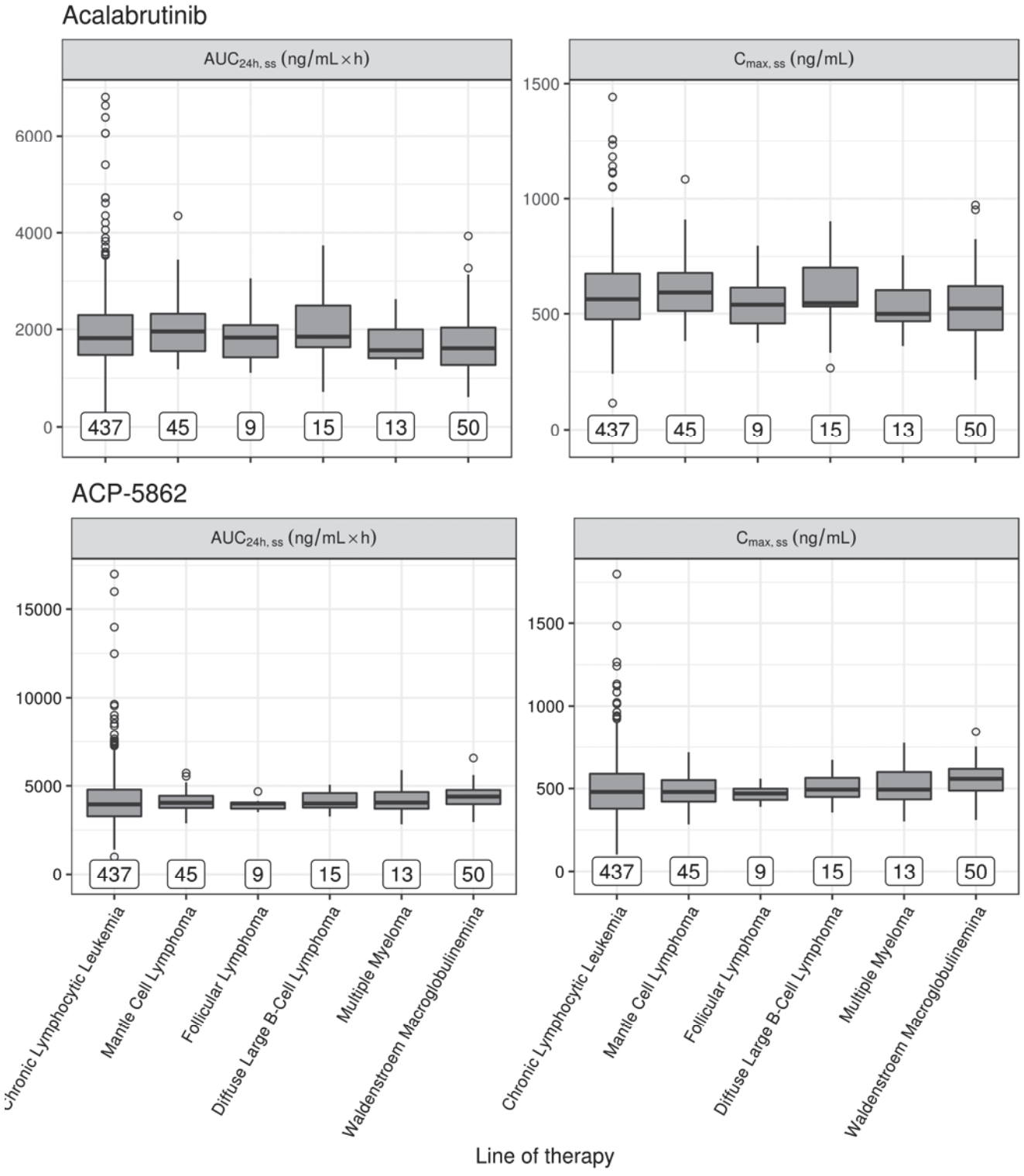
New PK results as of the data cutoff date of 08 February 2019 from ELEVATE-TN provided in this sNDA are as follows: in general, acalabrutinib plasma concentrations at 1-, 2- and 4-hours postdose were comparable between Cycle 1 and Cycle 2, suggesting achievement of steady state levels following the first dose. Also, the mean acalabrutinib and ACP-5862 (pharmacologically active metabolite) concentrations (and therefore exposures; Table 3) were similar following administration of acalabrutinib in combination with obinutuzumab versus as monotherapy, consistent with the lack of effect of obinutuzumab on acalabrutinib/ ACP-5862 PK. Overall, the mean pre- and postdose concentrations (and therefore exposures) of acalabrutinib/ACP-5862 were comparable to those observed in other studies/indications (Figure 1), and expected to maintain >90% BTK occupancy throughout the dosing interval.

Table 3: Comparison of Steady State Acalabrutinib and ACP-5862 Exposures Following Administration of Acalabrutinib as Monotherapy (Arm C) or in Combination with Obinutuzumab (Arm B)

Analyte	PK Parameter	Arm B (Acalabrutinib + Obinutuzumab)	Arm C (Monotherapy)
		Geometric Mean (Geometric CV%)	
Acalabrutinib	$AUC_{24h,ss}$ (ng.h/mL)	1822 (41)	1772 (34)
	$C_{max,ss}$ (ng/mL)	565.2 (28)	556.4 (24)
ACP-5862	$AUC_{24h,ss}$ (ng.h/mL)	3817 (46)	3878 (46)
	$C_{max,ss}$ (ng/mL)	439.4 (54)	453.2 (51)

Source: Module 5.3.5.3, Exposure-Efficacy Report: D8220C00010, Table 4.

Figure 1: Comparison of Steady State Acalabrutinib and ACP-5862 Exposures Across Various B-cell Malignancies, Including CLL and MCL



Notes: Boxplot of acalabrutinib exposures (top) and ACP-5862 exposures (bottom) versus indication. The black line within the box shows the median and the box's upper and lower edges show the IQR. Whiskers extend to the highest value that is within 1.5*IQR. Data outside whiskers are shown as circles.
Source: Module 5.3.5.3 from Population Pharmacokinetics Report (D8220C00009), Appendix 7, Figure 9.

The Applicant's Position:
Reference is made to original acalabrutinib NDA 210259 submitted on 13 June 2017 and approved by the US FDA on 31 October 2017. The previously approved data support a fixed 100 mg BID acalabrutinib dose for the treatment of patients with CLL.

Regulatory Authorities Assessment:
The regulatory authorities agree with Applicant's Position. The PK parameters of acalabrutinib and its active metabolite (ACP-5862) in Section 12.3 Pharmacokinetics of USPI were further updated based on post-hoc PK estimates from Applicant's updated population PK analysis (Population Pharmacokinetics Report D8220C00009).

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:
Reference is made to original acalabrutinib NDA 210259 submitted on 13 June 2017 and approved by US FDA on 31 October 2017. Key changes submitted in this sNDA include results from the pivotal study ELEVATE-TN (ACE-CL-007), the Phase 1 study in severe hepatic impairment population (ACE-HI-102), an updated population pharmacokinetic model, and exposure-response characterization for acalabrutinib and its active metabolite, ACP-5862.

The Applicant's Position:
The acalabrutinib dose of 100 mg BID was identified as the recommended dose based on a review of all available safety, tolerability, pharmacokinetic, pharmacodynamic, and efficacy data in the Phase 1 component of Study ACE-CL-001. In addition, ensuring maximal BTK occupancy over 24 hours may reduce development of resistance mechanisms and reduce the rate of tumor escape. The exposure-efficacy analyses confirmed a lack of relationship between acalabrutinib/ACP-5862 exposure and various efficacy endpoints in study ELEVATE-TN, indicating that the 100 mg BID regimen produced robust and consistent therapeutic effects across the exposure range observed. Moreover, there was a lack of exposure-safety relationships over a wide exposure range, suggesting modest effects of intrinsic/extrinsic factors on acalabrutinib and ACP-5862 PK and response.

Regulatory Authorities Assessment:
The regulatory authorities agree with Applicant's Position.

6.2.2.2. Therapeutic Individualization

Data:

Specific Populations:

Patients with severe hepatic impairment:
Acalabrutinib was evaluated in subjects with severe hepatic impairment (HI) in study ACE-HI-102. This was a Phase 1, open-label, single-dose study to investigate the influence of severe hepatic impairment on the pharmacokinetics of acalabrutinib and its metabolite (ACP-5862). The primary objective of this study was to compare the plasma pharmacokinetics of acalabrutinib and its metabolite ACP-5862 in subjects with severe HI with that in matched-control subjects following a single-dose administration of 50 mg acalabrutinib. The concentration-time profiles of total acalabrutinib and ACP-5862 were well characterized and the PK parameters observed in normal hepatic function subjects were comparable with historical data (median T_{max} of 0.75 hour and $t_{1/2}$ ranging from 0.9 to 2.8 hours reported in the Calquence product label). Total (AUC) and peak (C_{max}) exposure to acalabrutinib was approximately 5-fold higher in subjects with severe HI than in subjects with normal hepatic function.

The secondary objective of this study was to evaluate the safety and tolerability of acalabrutinib in subjects with severe HI after a single-dose administration of 50 mg acalabrutinib.

There were no deaths, SAEs, or subject discontinuations due to AEs in this study. There were no notable findings in the assessments for ECG, vital signs, clinical laboratory values, or physical examinations with respect to subject safety.

The Applicant's Position:

Total and peak exposure to total and unbound acalabrutinib increased approximately 5-fold and 3.6-fold, respectively, in subjects with severe HI when compared with healthy subjects. Higher bilirubin levels and prothrombin time values were associated with higher total acalabrutinib exposure parameters while higher albumin levels were associated with lower total acalabrutinib exposure parameters. The metabolism of acalabrutinib was affected by severe HI leading to increased systemic exposure and decreased systemic clearance. However, the total and peak exposure to total and unbound ACP-5862 was similar in subjects with severe HI and subjects with normal hepatic function. This is likely due to presystemic (intestinal-mediated) metabolism. No apparent trends were observed between Child-Pugh scores, albumin or bilirubin levels, prothrombin time and total ACP-5862 exposure PK parameters. A single 50-mg oral dose of acalabrutinib appeared to be safe and well tolerated by this group of male and female subjects with severe HI; however it is not recommended to administer acalabrutinib in patients with severe hepatic impairment (Child Pugh class C).

Regulatory Authorities Assessment:
The regulatory authorities agree with Applicant's Position. Acalabrutinib and ACP-5862 PK

results from Study ACE-HI-102 are provided below :

Table 4: Statistical Comparisons of Total Plasma Acalabrutinib PK Parameters – Severe HI vs. Normal Hepatic Function

	Geometric Mean (%CV)		GMR (90% CI) vs. Normal hepatic function	
	$AUC_{0-\infty}$ (ng·h/mL)	C_{MAX} (ng/mL)	$AUC_{0-\infty}$	C_{MAX}
Severe HI	1169 (54%) [n=8]	726 (56%) [n=8]	5.16 (3.29, 8.08)	4.92 (2.50, 9.66)
Normal hepatic function	227 (55%) [n=8]	148 (117%) [n=8]	N/A	N/A

Source: Reviewer's analysis based on data from Applicant's Study ACE-HI-102 CSR

Table 5: Statistical Comparisons of Unbound Plasma Acalabrutinib PK Parameters – Severe HI vs. Normal Hepatic Function

	Geometric Mean (%CV)		GMR (90% CI) vs. Normal hepatic function	
	AUC_{0-last} (ng·h/mL)	C_{MAX} (ng/mL)	$AUC_{0-\infty}$	C_{MAX}
Severe HI	12 (32%) [n=8)	4.4 (39%) [n=8]	3.56 (2.50, 5.05)	3.77 (2.55, 5.56)
Normal hepatic function	3.2 (45%) [n=7]	1.2 (48%) [n=7]	N/A	N/A

Source: Reviewer's analysis based on data from Applicant's Study ACE-HI-102 CSR

Table 6: Statistical Comparisons of Total Plasma ACP-5862 PK Parameters – Severe HI vs. Normal Hepatic Function

	Geometric Mean (%CV)		GMR (90% CI) vs. Normal hepatic function	
	$AUC_{0-\infty}$ (ng·h/mL)	C_{MAX} (ng/mL)	$AUC_{0-\infty}$	C_{MAX}
Severe HI	782 (22%) [n=6]	169 (30%) [n=8]	0.96 (0.73, 1.26)	1.01 (0.63, 1.62)
Normal hepatic function	817 (37%) [n=8]	167 (75%) [n=8]	N/A	N/A

Source: Reviewer's analysis based on data from Applicant's Study ACE-HI-102 CSR

Table 7: Statistical Comparisons of Unbound Plasma ACP-5862 PK Parameters – Severe HI vs. Normal Hepatic Function

	Geometric Mean (%CV)		GMR (90% CI) vs. Normal hepatic function	
	AUC_{0-last} (ng·h/mL)	C_{MAX} (ng/mL)	$AUC_{0-\infty}$	C_{MAX}
Severe HI	5.4 (27%) [n=7]	1.5 (44%) [n=7]	0.96 (0.60, 1.54)	0.88 (0.51, 1.51)
Normal hepatic function	5.6 (68%) [n=7]	1.7 (75%) [n=7]	N/A	N/A

Source: Reviewer's analysis based on data from Applicant's Study ACE-HI-102 CSR

The labeling has been updated to reflect "avoid use" in patients with severe hepatic impairment and descriptive PK results are provided in Section 12.

Note that Study ACE-HI-102 fulfills the following PMR issued at the time of original NDA accelerated approval:

- PMR 3291-3: Conduct a clinical PK trial to determine an appropriate safe dose of acalabrutinib in patients with severe hepatic impairment. This trial should be designed and conducted in accordance with the FDA Guidance for Industry entitled "PK in

Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

6.2.2.3. Outstanding Issues

Data:

PMR 3291-3 Study ACE-HI-102, a Phase 1, Open-Label, Single-Dose Study to investigate the influence of severe hepatic impairment on the pharmacokinetics of acalabrutinib and its metabolite (ACP-5862) has completed enrollment according to projected enrollment rates. This trial was designed and conducted in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labelling."

The Applicant's Position:
PM3921-3, the Final CSR for Study ACE-HI-102 is submitted in this sNDA. Patients with severe hepatic impairment are not recommended for treatment with acalabrutinib.

Regulatory Authorities Assessment:
There are no outstanding clinical pharmacology-related issues in the current submission. Study ACE-HI-102 CSR fulfills PMR 3291-3, as noted in Section 6.2.2.2 Therapeutic Individualization of this Assessment Aid.

6.3. Comprehensive Clinical Pharmacology Review

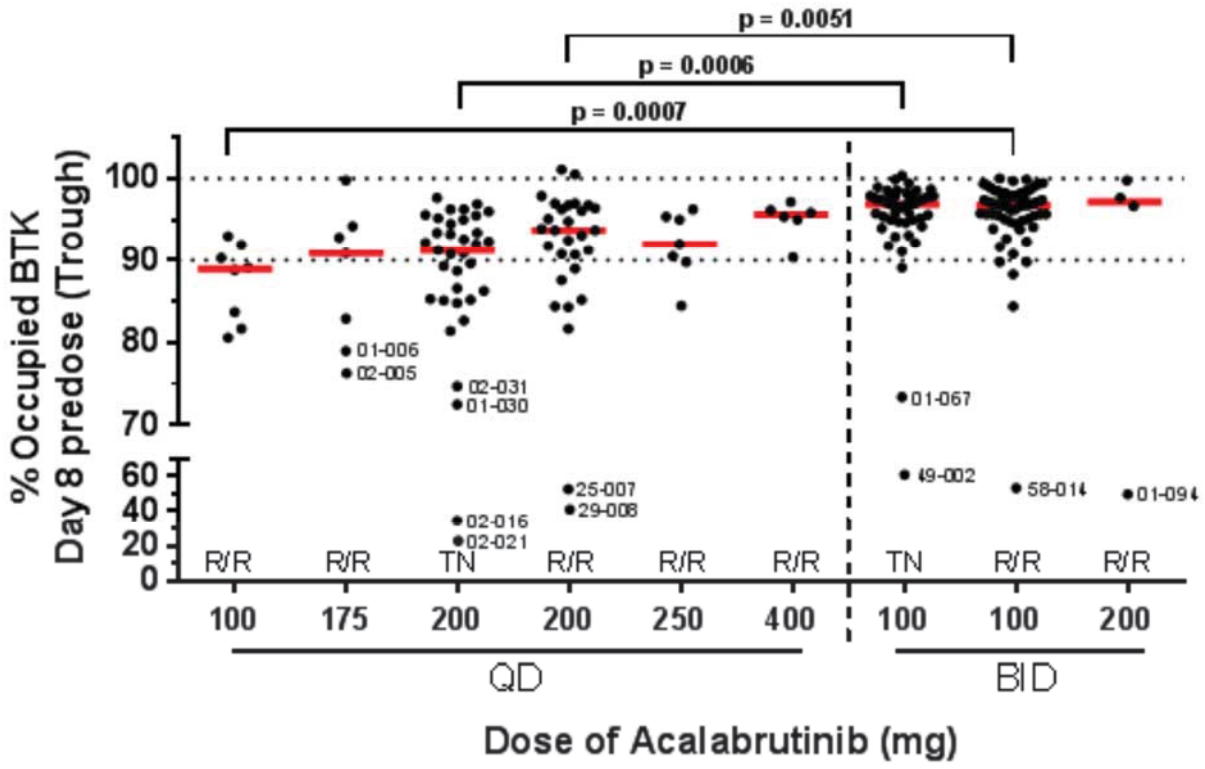
6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

Reference is made to the original acalabrutinib NDA 210259 submitted on 13 June 2017 and approved on 31 October 2017.

Acalabrutinib 100 mg BID dose provided maximal BTK occupancy with least interpatient variability at trough for subjects with R/R and TN CLL (Study ACE-CL-001); 95% of subjects maintained >90% BTK occupancy at the trough timepoint (i.e., 12 hour post-dose; (Figure 2).

Figure 2: BTK Occupancy (%) in Subjects with R/R and Treatment-Naive (TN) CLL at Trough



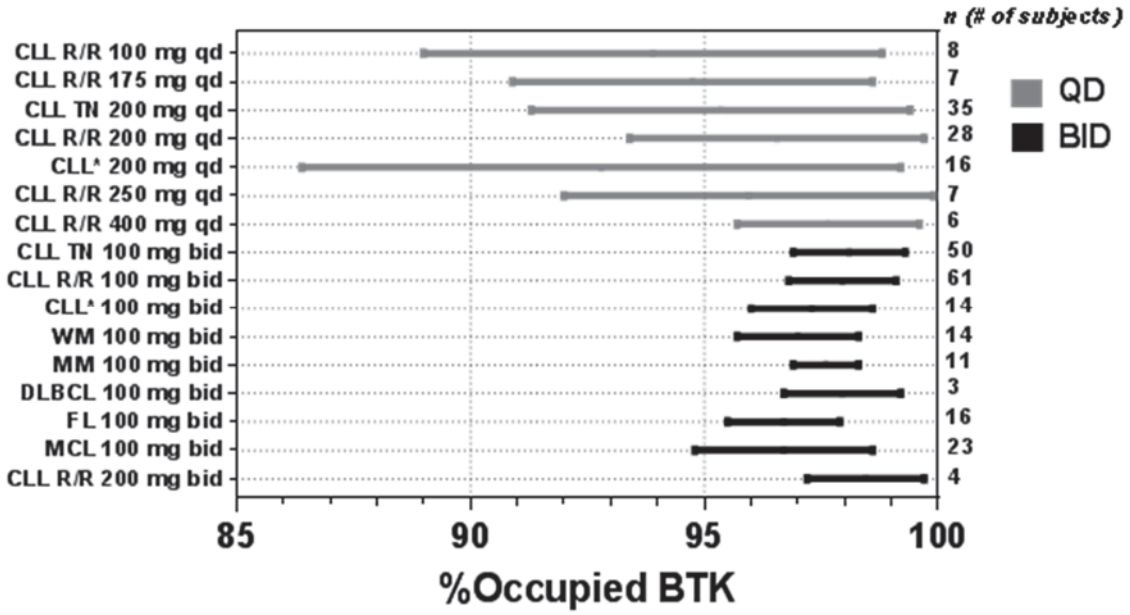
Percent BTK occupancy at trough on Day 8

	100 mg QD R/R	175 mg QD R/R	200 mg QD TN	200 mg QD R/R	250 mg QD R/R	400 mg QD R/R	100 mg BID TN	100 mg BID R/R	200 mg BID R/R
Median	89.0	90.9	91.3	93.7	92.0	95.7	96.9	96.8	97.2
Mean	87.4	88.0	86.6	89.8	91.9	95.0	95.3	95.3	86.0
SD	4.7	8.7	15.7	12.9	4.1	2.4	6.3	6.2	24.2
CV%	5.4	9.9	18.1	14.4	4.5	2.5	6.6	6.5	28.1
n	8	7	35	29	7	6	51	62	4

BID=twice daily; BTK=Bruton tyrosine kinase; CLL=chronic lymphocytic leukemia; CV=coefficient of variation; n=number of subjects; QD=once daily; R/R=relapsed/refractory; SD=standard deviation; TN=treatment naïve. Horizontal lines depict median values; (unpaired, parametric, 2 tailed t-test used for statistical testing); values in red are p-values <0.05.
Source: Module 2.7.2 Summary of Clinical Pharmacology Studies, Section 3.4.2, Figure 36.

Additionally, the BTK occupancy with the 100-mg BID dose was consistently high (≥95%) across multiple B-cell malignancies, including CLL and MCL (Figure 3). Overall, the results support acalabrutinib dose of 100mg BID appropriate for use in CLL indications.

Figure 3: Median BTK Occupancy Range Over the Daily Dosing Interval at Steady-State across All Studies Investigating Acalabrutinib in Subjects with B-cell Malignancies



BID=twice daily; CLL=chronic lymphocytic leukemia; DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; MCL=mantle cell lymphoma; MM=multiple myeloma; QD=once daily; R/R=relapsed/refractory; TN=treatment naive; WM=Waldenström Macroglobulinemia.
Notes: Grey lines represent QD dosing; black lines BID dosing.
The y-axis shows the B-cell malignancy and acalabrutinib dose for each study cohort. Percent of occupied BTK is displayed on the x-axis; lines represent the range of BTK occupancy from trough level to peak level (4 hours postdose) for each cohort, with the left cap representing the median occupancy at trough and right cap representing the median occupancy at peak.
Source: Module 2.7.2 Summary of Clinical Pharmacology Studies, Section 3.4.2 Figure 38.

The reports for population PK (D8220C00009), exposure versus efficacy (D8220C00010), and exposure versus safety (D8220C00011) analyses, including supporting programs and datasets, will be included in the submission package.

The key modeling changes, compared to previous submission for MCL indication, are described in the Table 8 below.

Table 8: Key changes in modeling between current (CLL) and previous (MCL) filing

Modeling Change	CLL	MCL
Population PK	• Plasma concentrations of acalabrutinib and ACP-5862, and relevant covariate data from 13 clinical trials, including data from 182 healthy subjects and 569 subjects with B-cell malignancies, were analyzed • A simultaneous population model characterizing the PK of acalabrutinib and ACP-5862 was developed • Acalabrutinib absorption was modeled using D1 and Ka. To adequately characterize the absorption profile, a mixture model on relative bioavailability (F1) with the mixture defined for each dosing occasion, and between occasion variability on duration of zero-order input (D1) was implemented • Covariates in the final model included health group (healthy versus patient), acid reducing agents (proton pump inhibitors), ECOG (eastern cooperative oncology group) status and body weight	• Plasma concentrations of acalabrutinib and relevant covariate data from 12 clinical trials were analyzed, including data from 285 healthy subjects and 292 subjects with B-cell malignancies • Only acalabrutinib PK was characterized • Acalabrutinib absorption was characterized using lag time, D1 and Ka. No random effects were included on absorption parameters. • Covariates in the final model included health group (healthy versus patient), dose, eGFR, acid reducing agents, sex, race, hepatic impairment and body weight
Exposure-Efficacy Analyses	• Data from a total of 274 subjects with previously untreated CLL in Study ACE-CL-007 were included • Acalabrutinib and ACP-5862 steady state AUC was used as the exposure metric. To account for contribution of the major active metabolite, ACP-5862, to overall activity acalabrutinib and ACP-5862 molar exposures were adjusted with respective BTK potency and protein binding, and expressed as 'total active AUC' (exposure metric for the total active moiety),	• Data from Study ACE-LY-004 in patients with MCL (n=45) were included • Acalabrutinib steady state AUC and C_{max} used as exposure metric
Exposure-Safety Analyses	• Pooled data from 8 clinical studies, involving a total of 567 subjects with B-cell malignancies were included • Acalabrutinib, ACP-5862, and total active steady state AUC used as exposure metric	• Pooled data from 6 clinical studies including a total of 292 subjects with B-cell malignancies were included • Acalabrutinib steady state AUC and C_{max} used as exposure metric

<u>The Applicant's Position:</u>

The clinical pharmacology and PK data submitted in the original NDA supports a fixed 100 mg BID acalabrutinib dose for the treatment of patients with CLL. Results from additional bioanalytical and PopPK data remain consistent with the data provided in the original NDA.

Regulatory Authorities Assessment:
The regulatory authorities agree with Applicant's Position. The Applicant's updated PopPK analysis (Population Pharmacokinetics Report D8220C00009) resulted in different PK parameter estimates as compared to the numbers reported in the original NDA. The PK parameters of acalabrutinib and its active metabolite (ACP-5862) in Section 12.3 Pharmacokinetics of USPI were further updated based on post-hoc PK estimates from the updated PopPK analysis. Refer to 19.4 OCP Appendices (Technical documents supporting OCP recommendations) for details.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:
Yes. The evidence of effectiveness of acalabrutinib was demonstrated in the original NDA 210259 approved on 31 October 2017.

The Applicant's Position:
The results from ELEVATE-TN are consistent with previously observed efficacy results.

Regulatory Authorities Assessment:
The regulatory authorities agree with Applicant's Position. Refer to Section 8 Statistical and Clinical Evaluation of this Assessment Aid for detailed efficacy results from Study ELEVATE-TN.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:
Yes. The safety profile of the proposed dosing regimen is appropriate. Reference is made to original acalabrutinib NDA 210259 submitted on 13 June 2017 and approved on 31 October 2017. Dose selection was based on results of phase 2 dose-finding study (ACE-CL-001), which evaluated acalabrutinib dosing regimens of 100 to 400 mg QD and 100 to 200 mg BID in patients with CLL. High response rates were observed across all doses, however based on BTK occupancy, 100 mg BID resulted in maximal BTK occupancy with the least inter-patient variability at steady-state trough.

The Applicant's Position:
The dosing regimen is suitable for the proposed patient population in CLL.

Regulatory Authorities Assessment:
The regulatory authorities agree with Applicant's Position. The Applicant's proposed acalabrutinib doing regimen of 100 mg BID in patients with CLL/SLL was additionally supported by the comparable acalabrutinib exposure as in patients with MCL, and generally flat exposure-

response relationships for both efficacy endpoints (progression-free survival [PFS], best overall response [BOR] and lesion size), and safety measurements (any Grade ≥3 TEAEs, any Grade ≥2 TEAEs of clinically special interest, including anemia, cardiac event, hypertension, infection, neutropenia, and thrombocytopenia) at acalabrutinib 100 mg BID monotherapy or in combination with obinutuzumab in patients with CLL. Refer to Section 8 Statistical and Clinical Evaluation of this Assessment Aid for detailed safety results from Study ELEVATE-TN.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Data:

Age, Race, and Body Weight

Age (42 to 90 years), sex, race (Caucasian, African American), and body weight did not have clinically meaningful effects on the PK of acalabrutinib and its active metabolite, ACP-5862, based on population PK analysis.

Renal Impairment

Acalabrutinib undergoes minimal renal elimination. Based on population PK analysis, no clinically relevant PK difference was observed in 543 patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥ 30 mL/min/1.73m^2, as estimated by (modification of diet in renal disease equation (MDRD). Acalabrutinib PK has not been evaluated in patients with severe renal impairment (eGFR < 29 mL/min/1.73m^2, MDRD) or renal impairment requiring dialysis.

Hepatic Impairment

Acalabrutinib is metabolized in the liver. In hepatic impairment studies, compared to subjects with normal liver function (n=6), acalabrutinib exposure (AUC) was increased by 1.9-fold, 1.5-fold, and 5.3-fold in subjects with mild (n=6) (Child-Pugh A), moderate (n=6) (Child-Pugh B) and severe (n=8) (Child-Pugh C) hepatic impairment, respectively. Based on a population PK analysis, no clinically relevant PK difference was observed in subjects with mild (n=79) or moderate (n=6) hepatic impairment (total bilirubin between 1.5 to 3 times the upper limit of normal [ULN] and any AST) relative to subjects with normal (n=651) hepatic function (total bilirubin and AST within ULN).

The Applicant's Position:

There are no dose modifications recommended for patients with mild or moderate hepatic impairment (Child-Pugh class A or Child-Pugh class B), however it is not recommended to administer acalabrutinib in patients with severe hepatic impairment (Child Pugh class C).

Regulatory Authorities Assessment:

The regulatory authorities agree with Applicant's Position. The labeling has been updated to reflect "avoid use" in patients with severe hepatic impairment. The FDA recommends no dose adjustments for patients with mild or moderate hepatic impairment (NCI or Child-Pugh class).

The Applicant's updated population PK model supports no need for dose adjustment based on patients' age (32 to 90 years), sex, weight (40 to 149 kg), race (Caucasian, African American), mild to moderate renal impairment (eGFR ≥ 30 mL/min/1.73m^2, as estimated by MDRD), and mild to moderate hepatic impairment (total bilirubin less and equal to upper limit of normal [ULN] and AST greater than ULN, or total bilirubin greater than ULN and any AST) relative to patients with normal hepatic function (total bilirubin and AST within ULN), which is consistent with the original labeling recommendation.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:

No new food effect was observed with acalabrutinib. Acalabrutinib can be taken with or without food as stated in the original NDA 210259.

The Applicant's Position:

No new information regarding food-drug or drug-drug interactions have been identified in this sNDA submission. The currently labelled food-drug or drug-drug interactions remain applicable.

Regulatory Authorities Assessment:

The Applicant submitted various in vitro metabolism and transporter DDI reports to support the following labeling updates:

- Acalabrutinib
  - **Metabolism:** not an inhibitor of UGT1A1 or UGT2B7
  - **Transporter:** substrate of BCRP, not an inhibitor of MATE2-K or MATE1
- ACP-5862
  - **Metabolism:** not an inhibitor of UGT1A1 or UGT2B7
  - **Transporter:** substrate of P-gp and BCRP, not a substrate of OATP1B1 or OATP1B3, not an inhibitor of P-gp, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE2-K, BCRP, and may be a MATE1 inhibitor (clinical relevance not likely since only 0.5% of ACP-5862 is excreted renally)

The regulatory authorities agree with the labeling updates based on the submitted in vitro metabolism and transporter DDI reports.

X
Clinical Pharmacology Reviewer

X
Clinical PharmacologyTeam Leader

X
Pharmacometrics Reviewer

X
Pharmacometrics Team Leader

7 Sources of Clinical Data

Data are submitted for a total of 11 clinical studies. Five of these studies evaluated acalabrutinib in patients with CLL, 5 studies evaluated acalabrutinib in patients with other hematologic malignancies, and 1 study evaluated acalabrutinib in volunteers with severe hepatic impairment. Details of the studies that support efficacy and safety for the pivotal study ELEVATE-TN are provided in Table 9 below.

7.1. Table of Clinical Studies

Data:

Table 9: Listing of Clinical Trials Relevant to this NDA: (Module 5.2)

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
ELEVATE-TN (ACE-CL-007)	NCT 02475681	Phase 3, randomized, OL	Arm A: Obinutuzumab IV 100 mg (Day 1 of Cycle 1), 900 mg (Day 2 of Cycle 1), and 1000mg (Day 8 and 15 of Cycle 1, Day 1 of Cycles 2-6) + chlorambucil 0.5mg/kg orally (Day 1 and 15 of Cycles 1-6) Arm B: Acalabrutinib 100 mg BID, starting on Cycle 1 Day 1 + obinutuzumab IV 100 mg starting on Cycle 2 Day 1 for no more than 6 cycles. Arm C: Acalabrutinib 100 mg BID, starting on Cycle 1 Day 1 Administered orally in 28-day cycles until disease progression or unacceptable drug-related toxicity	PFS, response, safety	Until PD or unacceptable toxicity.	535	Previously untreated CLL	142 sites in 18 countries
Studies to Support Safety								
15-H-0016	NCT 02337829	Phase 2 OL, randomized	Acalabrutinib 200 mg QD or 100 mg BID Administered orally in 28-day cycles until disease progression or unacceptable drug-related toxicity	Response, safety, PD	Until PD or unacceptable toxicity	48	CLL/SLL	1 center in 1 country

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
ACE-CL-001	NCT 02029443	Phase 1 (escalation): OL, sequential group, dose escalation Phase 2 (expansion): OL	Phase 1: Acalabrutinib 100 to 400 mg QD; 100 or 200 mg BID Phase 2: Acalabrutinib 200 mg QD or 100 mg BID Administered orally in 28-day cycles until disease progression or unacceptable drug-related toxicity	MTD, response, safety, PK, PD	Until PD or unacceptable toxicity	306	CLL/SLL, RS, PLL	12 centers in 3 countries
ACE-CL-003	NCT 02296918	Phase 1, OL	Cohort 1 and 2: Acalabrutinib 100 mg BID orally + obinutuzumab IV 100 mg (Day 1 of Cycle 2), 900 mg (Day 2 of Cycle 2), and 1000mg (Day 8 and 15 of Cycle 2, Day 1 of Cycles 3-7). For subjects treated at dose level -1, obinutuzumab IV 100 mg (Day 1 of Cycle 2), 650 mg (Day 2 of Cycle 2), and 750mg (Day 8 and 15 of Cycle 2, Day 1 of Cycles 3-7) Cohort 3: Acalabrutinib 100 mg BID orally + rituximab 375 mg/m^2 IV (Day 1, 8, 15, 22 of Cycle 2 and Day 1 of Cycles 3-7) + venetoclax orally 400mg/day following a weekly dose ramp-up (Cycle 3), 400mg/day until end of Cycle 15 Cohort 4: Acalabrutinib 100 mg BID orally + rituximab 375 mg/m^2 IV (Day 1, 2, 8, 15 of Cycle 2 and Day 1 of Cycles 3-7) + venetoclax orally 400 mg/day following a weekly dose ramp-up (Cycle 3), 400mg/day until end of Cycle 15 Treatment administered in 28-day	Response, safety, PK, PD	Until PD or unacceptable toxicity	70	CLL/SLL/PLL	1 center in 1 country

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
			cycles until disease progression or unacceptable drug related toxicity					
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacology studies)								
ACE-HI-102	NCT 03968848	Phase I, OL, single dose	Single, oral, 50-mg dose of acalabrutinib	PK (intrinsic factor), safety	7-27 days	16	Severe hepatic impairment	3 centers in 1 country

Abbreviations: ABC DLBCL = activated B-cell diffuse large B-cell lymphoma; bid = twice daily; CLL = chronic lymphocytic leukemia; CSR = clinical study report; DCO = data cut-off; IV = intravenous; MTD = maximum tolerated dose; OL = open-label; PD = pharmacodynamics; PK = pharmacokinetics; PLL = prolymphocytic leukemia; qd = once daily; R/R = relapsed or refractory; qd = once daily; qw = once weekly; RS = Richter's syndrome; SLL = small lymphocytic leukemia; WM = Waldenström macroglobulinemia.

The Applicant's Position:

The primary study supporting the evaluation of efficacy in this sNDA is ELEVATE-TN, which compared acalabrutinib 100 mg BID in combination with obinutuzumab vs. chlorambucil plus obinutuzumab vs. acalabrutinib 100 mg BID monotherapy. A detailed description of the results is provided in the sections below.

Regulatory Authorities Assessment:

The regulatory authorities agree with the Applicant's position and has provided further information below.

ELEVATE-TN is the primary study supporting both efficacy and safety, with a cut-off date of 08 February 2019. Cut-off dates for supportive studies are provided in Section 8.2.2. However, the Applicant's table of clinical studies is missing two key supportive safety studies, which are summarized in the table below: ASCEND (ACE-CL-309), the pivotal randomized trial in relapsed or refractory CLL and the basis for NDA210259 S-006, and ACE-LY-004, the pivotal single-arm trial in relapsed or refractory MCL.

Table 10: Additional Clinical Trials Relevant to this NDA

Trial Identity	Design	Regimen	Study Endpoints	No. of patients enrolled	No. of Sites
Controlled trials supporting safety					

Trial Identity	Design	Regimen	Study Endpoints	No. of patients enrolled	No. of Sites
ASCEND (ACE-CL-309) NCT02970318	Phase 3, randomized, open-label trial in patients with relapsed or refractory CLL	Arm A: Acalabrutinib 100 mg BID, starting on Cycle 1 Day 1 Administered orally in 28-day cycles until disease progression or unacceptable drug-related toxicity Arm B: Idelalisib 150 mg orally BID until disease progression or unacceptable toxicity + rituximab 375 mg/m^2 IV (Day 1 of Cycle 1), 500 mg/m^2 every 2 wks for 4 doses and then every 4 wks for 3 doses for a total of 8 infusions. or Bendamustine 70mg/m^2 IV, Day 1 and 2 of each cycle for up to 6 cycles. + rituximab 375 mg/m^2 IV (Day 1 of Cycle 1) and 500 mg/m^2 (Day 1 of Cycle 2-6).	PFS, response, safety	310	102 sites in 25 countries
Other trials supporting safety					
ACE-LY-004 NCT02213926	Phase 2, single-arm trial in MCL after 1-5 prior therapies	Acalabrutinib monotherapy 100 mg BID until disease progression or unacceptable toxicity.	ORR	124	40 sites, 9 countries

Source: FDA

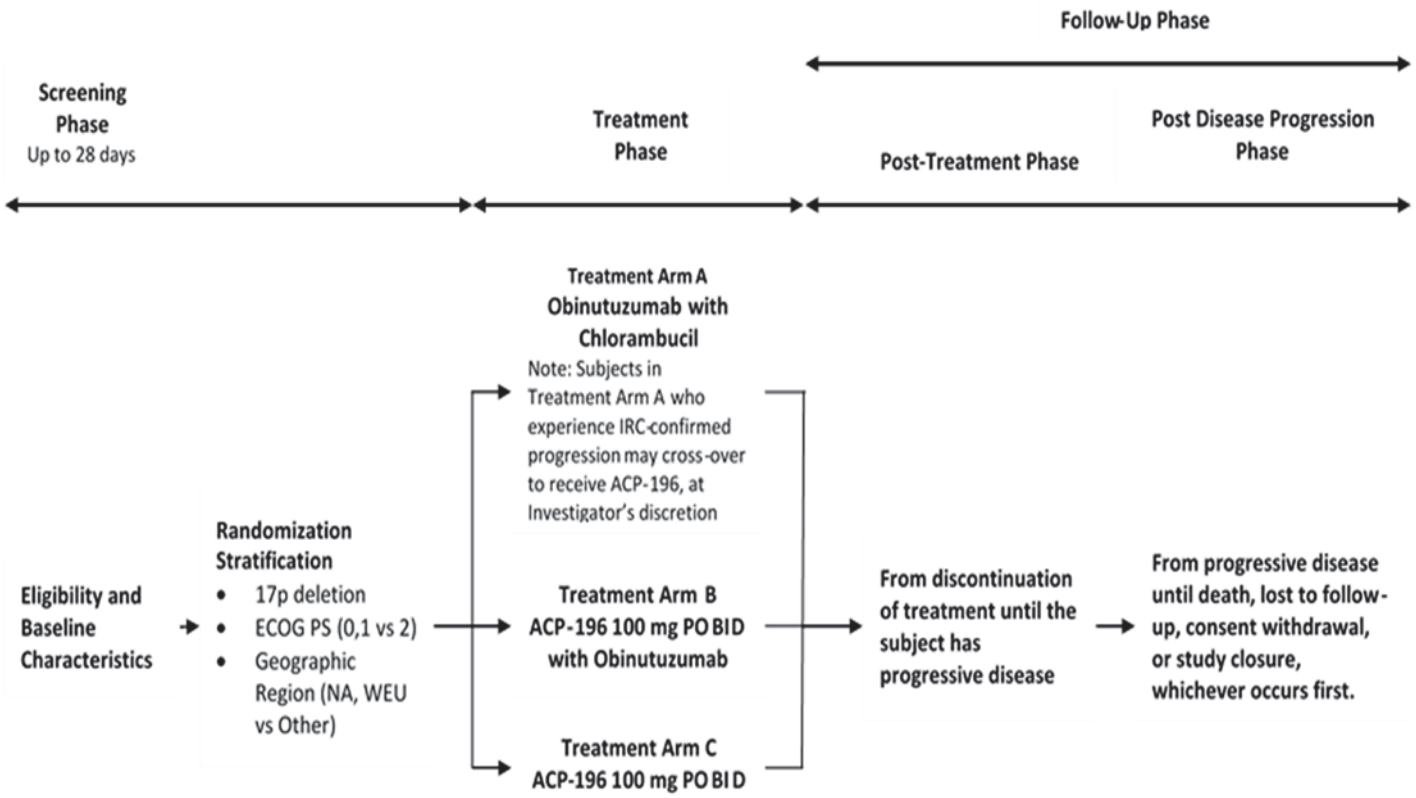
8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. ELEVATE-TN (ACE-CL-007)

The Applicant's Description:

Figure 4: Trial Design of ELEVATE-TN



BID=twice-daily, ECOG=Eastern Cooperative Oncology Group; IRC=Independent Review Committee; NA=North America; PO=oral; PS=performance status; WEU=Western Europe.

ELEVATE-TN is an ongoing Phase 3 open-label, randomized study in subjects with documented CD20–positive CLL who had not received any prior systemic treatment for CLL.

Subjects were randomized in a 1:1:1 ratio into 3 arms. Subjects randomized to Arm A received obinutuzumab+chlorambucil, subjects randomized to Arm B received acalabrutinib+ obinutuzumab, and subjects randomized to Arm C received acalabrutinib monotherapy.

Subjects were randomized based on the following stratification factors: presence of 17p deletion, Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 versus 2), and geographic region (North America and Western Europe versus Other).

Each treatment cycle was 28 days (4 weeks). Subjects in Arms A and C received acalabrutinib 100 mg BID orally starting Cycle 1 Day 1 until unacceptable drug-related toxicity or disease progression. Subjects in Arms A and B received 100-1000 mg of obinutuzumab as an intravenous (IV) infusion starting on Cycle 1 Day 1 for a total of 6 cycles. Subjects in Arm A received chlorambucil 0.5 mg/kg orally on Days 1 and 15 of Cycles 1 through 6.

After progression, subjects were followed for subsequent anticancer therapy (with start date of therapy and IWCLL indication for treatment initiation), additional malignancy occurrence, and survival status. Subjects were followed until death, loss to follow-up, consent withdrawal, or study closure, whichever occurred first.

Key Inclusion Criteria:

Key exclusion criteria as specified in ELEVATE-TN Protocol Amendment 5.0 (Global) are as follows:

- Men and women ≥65 years of age OR >18 and <65 years of age, provided that they met at least 1 of the following criteria:
    a. Creatinine clearance 30 to 69 mL/min using the Cockcroft-Gault equation.
    b. A score higher than 6 on the Cumulative Illness Rating Score-Geriatric (CIRS-G) (Protocol Amendment 5.0 [Global], Appendix M).
- ECOG performance status of 0, 1, or 2
- Diagnosis of CD20+ CLL that met published diagnostic criteria (Hallek et al. 2008): monoclonal B cells (either kappa or lambda light chain restricted) that were clonally co-expressing ≥ 1 B-cell marker (CD19, CD20, or CD23) and CD5; prolymphocytes may have comprised ≤55% of blood lymphocytes; presence of ≥5 x 10^9 B lymphocytes/L (5000 µL) in the peripheral blood (at any point since diagnosis).
- Active disease that met ≥1 of the following IWCLL 2008 criteria for requiring treatment: evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia (hemoglobin <10 g/dL) and/or thrombocytopenia (platelets <100,000/µL); massive (i.e., ≥6 cm below the left costal margin), progressive, or symptomatic splenomegaly; massive nodes (i.e., ≥10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy; progressive lymphocytosis with an increase of >50% over a 2-month period or a lymphocyte doubling time (LDT) of <6 months. LDT may have been obtained by linear regression extrapolation of absolute lymphocyte count (ALC) obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In subjects with initial blood lymphocyte counts of <30x10^9/L (30,000/µL), LDT should not have been used as a single parameter to define indication for treatment. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (e.g., infections) should have been excluded; autoimmune anemia and/or thrombocytopenia that was poorly responsive to

standard therapy; or constitutional symptoms documented in the subject's chart with supportive objective measures, as appropriate, defined as ≥1 of the following disease related symptoms or signs: unintentional weight loss ≥10% within the previous 6 months before Screening; significant fatigue (ECOG performance score 2; inability to work or perform usual activities); fevers higher than 100.5°F or 38.0°C for ≥2 weeks before Screening without evidence of infection; or night sweats for >1 month before Screening without evidence of infection.

- Met the following laboratory parameters:
  - Absolute neutrophil count (ANC) ≥750 cells/µL ($0.75x10^9$/L), or ≥500 cells/µL ($0.50x10^9$/L) in subjects with documented bone marrow involvement, and independent of growth factor support 7 days before assessment.
  - Platelet count ≥50,000 cells/µL ($50x10^9$/L), or ≥30,000 cells/µL ($30x10^9$/L) in subjects with documented bone marrow involvement, and without transfusion support 7 days before assessment. Subjects with transfusion dependent thrombocytopenia were excluded.
  - Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0 x upper limit of normal (ULN).
  - Total bilirubin ≤1.5 x ULN.
  - Estimated creatinine clearance (i.e., eGFR using Cockcroft-Gault) ≥30 mL/min.

Key Exclusion Criteria:

Key exclusion criteria as specified in ELEVATE-TN Protocol Amendment 5.0 (Global) are as follows:

- Any prior systemic treatment for CLL (note: prior localized radiotherapy was allowed).
- Known central nervous system (CNS) lymphoma or leukemia; prolymphocytic leukemia or history of or currently suspected Richter's syndrome.
- Missing or incomplete documentation of FISH results reflecting the presence or absence of 17p del and the percentage of cells with the deletion in subject records before randomization.
- Uncontrolled active systemic fungal, bacterial, viral, or other infection; uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura
- Corticosteroid use >20 mg within 1 week before first dose of study drug, except as indicated for other medical conditions such as inhaled steroid for asthma, topical steroid use, or as premedication for administration of study drug or contrast.
- History of prior malignancy except for the following:
  - Malignancy treated with curative intent and with no evidence of active disease present for more than 3 years before Screening and felt to be at low risk for recurrence by treating physician.
  - Adequately treated lentigo maligna melanoma without current evidence of disease or adequately controlled non-melanomatous skin cancer.
  - Adequately treated cervical carcinoma in situ without current evidence of disease.

- Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or QTc >480 msec at Screening.
- Known history of infection with HIV, serologic status reflecting active hepatitis B or C infection; history of stroke or intracranial hemorrhage within 6 months before randomization.
- Known history of a bleeding diathesis (e.g., hemophilia, von Willebrand disease); presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before Screening .
- Required treatment with proton-pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole), a strong CYP3A inhibitor/inducer; Required or received anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) within 7 days of first dose of study drug..

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's description for the study design.

Study Endpoints:

The Applicant's Description:

The primary efficacy endpoint is PFS comparing obinutuzumab+chlorambucil and acalabrutinib+ obinutuzumab, defined as the time from date of randomization to the date of first IRC-assessed disease progression or death due to any cause, whichever occurred first, as assessed by the IRC per IWCLL 2008 criteria.

The key secondary efficacy endpoint is PFS comparing obinutuzumab+chlorambucil and acalabrutinib monotherapy, defined as the time from date of randomization to the date of first IRC-assessed disease progression or death due to any cause, whichever occurred first, as assessed by the IRC per IWCLL 2008 criteria.

Other secondary efficacy endpoints were evaluated to compare acalabrutinib+obinutuzumab versus obinutuzumab+chlorambucil and acalabrutinib monotherapy versus obinutuzumab+ chlorambucil as described below:

- IRC-assessed ORR per IWCLL 2008 criteria: ORR was defined as the proportion of subjects who achieved a best response of CR, complete response with incomplete bone marrow recovery (Cri), nodular partial response (nPR), or PR at or before initiation of subsequent anticancer therapy as assessed by IRC. ORR including PRL was defined as the proportion of subjects who achieved a best response of CR, CRi, nPR, PR, or partial response with lymphocytosis (PRL) at or before initiation of subsequent anticancer therapy as assessed by IRC.
- Time to Next Treatment (TTNT): defined as the time from date of randomization to the

start date of non-protocol specified subsequent anticancer treatment for CLL (or first dose date of acalabrutinib for obinutuzumab+chlorambucil subjects who crossed over to receive acalabrutinib monotherapy) or death due to any cause, whichever occurred first.

- Overall Survival (OS): defined as the time from the date of randomization to date of death due to any cause.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's description for study endpoints.

The study design of ELEVATE-TN employs a control arm (obinutuzumab plus chlorambucil) that is a fixed treatment duration of 6 cycles versus 2 treatment arms that include acalabrutinib given continuously until disease progression or unacceptable toxicity. The differences in treatment exposure by design, with the acalabrutinib treatment arms having substantially longer exposure, directly affects the clinical interpretation of the primary endpoint of progression-free survival, and should be taken into consideration.

Statistical Analysis Plan and Amendments

The Applicant's Description:
The statistical analysis plan was discussed with FDA and finalized before the conduct of the pre-specified interim analysis of the ELEVATE-TN study, at which time the Applicant was unblinded to treatment randomization assignment at the aggregate level.

The primary efficacy analysis was based on assessment from an Independent Review Committee (IRC). The IRC reviewed radiologic evaluations assessed by independent central radiologists. Assessment of response and progression was conducted in accordance with the IWCLL 2008 criteria for CLL (Hallek et al. 2008), with the modification that treatment-related lymphocytosis in the absence of other signs or symptoms of disease progression was not considered progressive disease (Cheson et al. 2012). The investigator evaluated sites of disease by radiological imaging (primary), physical examination or other procedures as necessary, review of hematology results, and disease-related symptoms. The same methods of assessment used to assess disease at baseline were used throughout the study. A central laboratory performed all hematology testing for the primary endpoint analysis. Confirmation of CR required bone marrow analysis and radiologic tumor assessment. Baseline tumor assessments were performed at screening, and response evaluations were done every 12 weeks (±14 days) through Cycle 25, and then every 24 weeks (±14 days) thereafter.

Analysis Populations
The ITT population was defined as all randomized subjects, to be analyzed according to the arm to which they were randomly assigned, following "intent to treat" principle.

All efficacy analyses, except that for OS, were performed on the intent to treat (ITT) population and were analyzed as randomized and included data prior to crossover for obinutuzumab+

chlorambucil subjects who crossed over to acalabrutinib monotherapy. OS was analyzed based on the ITT population during the entire study including the crossover period.

Power and Sample Size

The study was expected to enroll approximately 510 subjects with a 1:1:1 randomization ratio between the 3 treatment arms (approximately 170 subjects per arm).

The study was sized to achieve approximately 90% power to detect a hazard ratio (acalabrutinib+obinutuzumab/obinutuzumab+chlorambucil) of 0.60 for PFS which, under the model assumptions, translates into a 67% relative and 17.8 months absolute increase in median PFS time: a median of 26.7 months for subjects in the obinutuzumab+chlorambucil arm vs. 44.5 months for subjects in the acalabrutinib+obinutuzumab arm. Given the study assumptions, the minimum detectable treatment difference at the final analysis of PFS corresponds to a hazard ratio of approximately 0.735.

Analysis Methods

All efficacy analyses were performed at the 2-sided significance level.

The following 3 randomization stratification factors (collected via IWRS) were used for all stratified analyses: presence or absence of 17p deletion; ECOG performance score (0 or 1 versus 2); and geographic region (North America and Western Europe versus Other). For the primary efficacy analysis of IRC-assessed PFS, if there was at least one stratum that had fewer than 2 events (where a stratum was defined as stratification factor 1 * stratification factor 2 * stratification factor 3), stratification factors were to be collapsed until all strata had at minimum 2 events for the primary endpoint. The stratification factors were collapsed in the following order:

1. Geographic region (North America and Western Europe versus Other)
2. ECOG performance score (0 or 1 versus 2)

Based on the unblinded data as of data cutoff date, Geographic region and ECOG status were collapsed according to the pre-specified rule. Thus, only the presence of 17p deletion was used as a stratification factor in the stratified analysis. The same stratification factor was applied for all stratified analyses.

The primary efficacy analysis was to compare PFS as assessed by IRC between obinutuzumab+chlorambucil and acalabrutinib+obinutuzumab in the ITT population. The primary efficacy analysis was performed using a stratified log rank test adjusting for randomization stratification factors. The estimate of the HR (acalabrutinib+ obinutuzumab/ obinutuzumab+chlorambucil) and the corresponding 95% CI was computed using a Cox Proportional Hazards model stratified by randomization stratification factors. Randomization stratification factors were based on IWRS assignment. A Kaplan-Meier (KM) curve was used to estimate the distribution of PFS. The proportions of subjects who are progression free were

estimated based on KM method and its corresponding 95% CI were calculated at selected timepoints for each treatment arm. A summary of PFS events was provided by treatment arm. A summary of PFS events was provided by treatment arm. Sensitivity analyses in support of the primary analysis of PFS included unstratified analysis, analysis including PFS without censoring for subsequent anticancer therapy, analysis including PFS events after 2 or more consecutively missed visits, and the exclusion of subjects with important protocol deviations from the analysis. Selected subgroup analyses were also performed.

The key secondary efficacy endpoint was IRC-assessed PFS between obinutuzumab+ chlorambucil and acalabrutinib monotherapy in the ITT population. The analysis method was the same method used for the primary efficacy analysis; subgroup and sensitivity analyses were also performed in the same manner.

Sensitivity Analyses

The following sensitivity analyses were conducted for IRC-assessed PFS between acalabrutinib+ obinutuzumab arm versus obinutuzumab+chlorambucil arm and obinutuzumab+chlorambucil arm versus acalabrutinib monotherapy arm in support of the primary and key secondary efficacy analyses: unstratified analysis, subjects with the use of any subsequent anticancer therapy prior to the first IRC confirmed progressive disease or death due to any cause were censored at the last adequate assessment prior to the start date of the subsequent anticancer therapy, subjects with PFS events after 2 or more consecutively missed visits were not censored at the last adequate assessment. IRC-confirmed progressive disease or death after 2 or more consecutively missed visits were included as a PFS event, and excluding subjects with important protocol deviations from the analysis

Additional efficacy endpoints comparing acalabrutinib+obinutuzumab versus obinutuzumab+ chlorambucil and acalabrutinib monotherapy versus obinutuzumab+ chlorambucil included IRC-assessed ORR, ORR with PRL, TTNT, and OS. ORR was summarized by number and percentage of subjects, and the corresponding 95% CI was calculated based on normal approximation (using Wilson's score). ORR was analyzed using the Cochran-Mantel-Haenszel (CMH) test adjusting for randomization stratification factors. ORR including PRL was analyzed using the same methods. TTNT and OS were analyzed using in the same fashion as the primary analysis.

Subgroup Analysis

Subgroup analyses were performed using potential prognostic variables at screening or baseline to investigate the consistency and robustness of PFS and ORR as assessed by the IRC between acalabrutinib+obinutuzumab versus obinutuzumab+ chlorambucil and acalabrutinib monotherapy versus obinutuzumab+chlorambucil: randomization stratification factors per IWRS recording (presence of 17p deletion mutation [yes vs. no], ECOG score at randomization [0, 1 vs. 2], and geographic region [North America and Western Europe vs. Other]); region (North America, South America, Western Europe, Central and Eastern Europe, Australia and New Zealand); age group (age <65 vs ≥65 years and age <75 vs ≥75 years); sex (male vs female); race (White vs Non-white); Rai Stage at screening (Stage 0-II vs. III-IV); Bulky disease (longest

diameter of lymph node <5 cm vs. ≥5 cm at baseline); β2-microglobulin at baseline (≤3.5 mg/L vs. >3.5 mg/L); presence of 11q deletion mutation (yes vs. no); TP53 mutation (mutated vs. unmutated); 17p del or TP53 mutation (yes vs. no); 17p del and TP53 mutation (yes vs. no); IgHV (mutated vs. unmutated); del17p, TP53 mutation, del11q, or unmutated IgHV; del17p, TP53 mutation, or del11q; and complex karyotype (yes vs no).

The hazard ratio (HR; acalabrutinib+obinutuzumab arm/obinutuzumab+chlorambucil arm) and its corresponding 95% CI for each subgroup was calculated based on an unstratified Cox regression model and displayed graphically in a forest plot.

Multiplicity Adjustments

To control the overall Type I error at 0.05 level, the Lan-DeMets alpha-spending function based on the O'Brien-Fleming boundary was used to split α into α1 and α2 for interim and final analyses, respectively. The nominal α1 and α2 levels was determined based on the actual information fraction at the time of the interim analysis. Within each analysis, the fixed sequence procedure was utilized to adjust for multiple comparisons.

If the primary efficacy endpoint, PFS as assessed by IRC in Arm B versus Arm A, achieved statistical significance, the following secondary efficacy endpoints was to be tested in a fixed sequential hierarchical manner for interim and final analyses:

1. PFS as assessed by IRC between Arms C and A
2. ORR as assessed by IRC between Arms B and A
3. ORR as assessed by IRC between Arms C and A
4. OS between Arms B and A
5. OS between Arms C and A

The fixed sequence procedure performed the testing of PFS between Arms B and A first. If the p-value is ≤ αi (i=1 for interim and 2 for final), the procedure will proceed to test PFS between Arms C and A at the same αi (i=1 for interim and 2 for final) level (testing 1).

If the testing of IRC-assessed PFS achieve statistical significance at interim analysis, the IRC-assessed ORR was to be tested at an alpha level of 0.05 (testing 2 and 3), given that almost all responses will have been observed at that time.

The OS was to be tested at the same alpha level as the primary endpoint (testing 4 and 5), thus nominal α1 and α2 for interim and final analyses, respectively.

Following the fixed sequence testing procedure, if a p-value was not statistically significant, the p-value for subsequent tests was presented as descriptive.

Table 11: SAP Amendments Summary

Version/Date	Summary of Major Changes and Rationale
Version 1.0, 8 July 2015	Original SAP
Version 2.0, 6 August 2015	1. Removed "withdrawal from study treatment due to toxicity" from the TTNT calculation formula so it will be consistent with the text description in based on feedback from the Ethics Committee in Spain—Section 7.2.2.
Version 3.0, 23 March 2018	1. Added details for primary and key secondary analysis. Same method will be applied to both. 2. Moved molecular remission (MRD negative) from secondary to exploratory endpoint – Section 2.3 3. Added ORR as assessed by IRC and OS into multiplicity adjustment plan. – Section 2.7 4. Removed PRO analysis. PRO analysis will be described in a separate SAP. – Section 7.5 5. Clarified TEAE and ECI definition. – Section 8.1
Version 4.0, 6 March 2019	1. Added clarification language around interim analysis, hierarchical testing procedure for the key secondary endpoints – Sections 2.4 and 2.6 2. Removed crossover population – Section 3 3. Added definitions for subsequent anticancer therapy, added language to clarify definitions on crossover subjects –Section 4 4. Clarified the definition of treatment-emergent period and treatment-emergent adverse events – Section 4.1.6, Section 8.1.1 5. Add language around collapse of stratification factors –Section 7. 6. Clarified the censoring rule for primary analysis for 7. IRC-assessed PFS, added analysis table for IRC-PFS censoring – Section 7.1 8. Added operational definition of the last adequate IRC assessment – Section 7.1 9. Updated the planned sensitivity and subgroup analyses for primary efficacy endpoint – Section 7.3, Section 7.4 10. Removed comparison of Treatment Arm B and Arm C from exploratory analysis, removed analysis of clonal evaluation rate and MRR from exploratory efficacy analysis; analysis will be described separately if applicable – Section 7.5 11. Added language around analysis of clinical laboratory and ECG – Section 8.3.2 and Section 8.6

Source: SAP Revision History Table ELEVATE-TN Appendix 16.1.9.

Regulatory Authorities Assessment:

The regulatory authorities agree with Applicant's proposed sample size and power calculation based on independent review committee (IRC) assessed progression-free survival (PFS), the analysis population and statistical analysis methods for the efficacy endpoints. The proposed Lan and DeMets alpha-spending function with O'Brien-Fleming boundaries is acceptable for calculating the efficacy stopping boundaries at interim and final analysis for IRC-assessed PFS. Though the statistical analysis plan (SAP) described that if the testing of IRC-assessed PFS achieve statistical significance at interim analysis, the IRC-assessed ORR was to be tested at an

alpha level of 0.05, the key secondary endpoints, including IRC-assessed ORR should have been tested based on the closed-testing procedure, i.e. the same alpha level that was allocated for the IRC-assessed PFS interim analysis to control the overall type I error rate.

However, the Applicant did not provide sufficient information on overall survival (OS) (e.g., number of OS events, desired power, assumed true difference in OS between the treatment arms, number of planned analyses, timing of these analyses, etc.). It is unlikely that there is sufficient power to test OS benefit given the information fraction of PFS and OS is different at the analysis time.

Protocol Amendments

The Applicant's Description:
There were 5 global protocol amendments to the ELEVATE-TN study. Table 12 summarizes relevant changes to the protocol. These changes have not significantly impacted the trial integrity or interpretation of the results.

Table 12: Protocol Amendments

Number (date of internal approval)	Reasons for Amendment[a]
Amendment 1.0 (Global) (01 April 2015) Amendment made before the start of subject recruitment	• Text revised to reduce the number of required peripheral blood samples from the FISH panel, cytogenetics and genetic molecular prognostic markers, and Biomarker samples and Exploratory Endpoints were revised to state that the exploratory endpoint of clonal evolution be evaluated by FISH only
Amendment 2.0 (Global) (27 April 2015) Amendment made before the start of subject recruitment	• Text was revised to remove any reference to Torsades de Pointes as no QTc prolongation risks have been identified with acalabrutinib • Text added to provide clarification regarding eligibility, scheduled visits, and assessments for subjects prior to cross over from Arm A to acalabrutinib monotherapy. • Text was revised to clarify window between obinutuzumab or chlorambucil doses and to clarify the start of obinutuzumab or chlorambucil dosing. • Text revised for clarity on discontinuation of study drug and also revised to provide guidance regarding possible re-escalation of acalabrutinib following dose reduction. • Text was revised to provide guidance on monitoring frequency for hepatitis B reactivation. • Text was revised to add a footnote window around CT scan response evaluation.
Amendment 3.0 (Global) (16 March 2016)	• Text was updated to reflect data from the most recent data cut of Study ACE-CL-001 and to match the acalabrutinib Investigator Brochure and the Byrd et al. 2016 publication. • Text was revised with additional documentation required prior to enrollment to the crossover arm • Inclusion criteria were revised to align with Hallek 2008 CLL diagnostic criteria or disease-related symptoms listed in IWCLL 2008 criteria.

Number (date of internal approval)	Reasons for Amendment[a]
	• Exclusion criteria were revised to exclude required treatment with a strong cytochrome P450 3A (CYP3A) inhibitor/inducer and presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening. • Text was updated with ASCO recommendation for the use of WBC growth factors from Smith et al. 2006 to Smith et al. 2015. • Revised text to provide flexibility in the reporting period for suspected disease progression, and for the use of samples from local laboratories if central testing was unavailable. • Revised text to provide clarity on statistical methods for the interim and final analyses and to align with the SAP.
Amendment 4.0 (Global) (06 March 2017)	• Text was revised with new requirements for the Early Termination visit. • Secondary Objective was revised to change the endpoint on molecular remission to an exploratory endpoint. • Exploratory Objectives was revised with new endpoints regarding molecular remission. • Text added to extend radiology reports and CT/MRI documentation requirement from 28 days to 60 days. • Inclusion criterion revised to accommodate variability in organization of sites and allow use of external facilities that conducted ancillary study procedures. • Assessment of Toxicity was revised to change dose modifications decisions being based on CTCAE v 4.03 or higher. • Text was revised to remove nodal disease needing to be documented. • Secondary Endpoints and Methods Minimal Residual Disease was revised to remove the molecular remission endpoint. • Safety Analysis was revised to indicate both hematologic and nonhematologic AEs will be graded by CTCAE.
Amendment 5.0 (Global) (04 December 2017)	• Text was revised to reflect change in monitoring of HBV. • Text was revised with updated language on contraception and updates based on new safety data regarding how long a subject must use contraception following the last dose of the study treatments.

Source: Table 8 from ELEVATE-TN CSR (section 9.9.1)

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's description.

8.1.2. Study Results

Compliance with Good Clinical Practices

Data:
ELEVATE-TN study was conducted in compliance with ICH Good Clinical Practice Regulations and ethical principles from the Declaration of Helsinki. The original protocol and protocol amendments were approved by an independent IRB/Ethics Committee associated with each

study center. Signed Informed consent was obtained from all participants prior to enrollment in the study. Additional details are provided within the CSR.

The Applicant's Position:
ELEVATE-TN study was conducted in compliance with Good Clinical Practice Regulation.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's position.

Financial Disclosure

Data:

Financial disclosure information was collected from 1601 investigators participating in the pivotal ELEVATE-TN study. Additional details are provided in Section 19.2 in this AA.

The Applicant's Position:
None of the disclosures submitted revealed a potential conflict of interest.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's position. Additional details are provided in Section 19.2.

Patient Disposition

Data:

Subject disposition for ELEVATE-TN is summarized in Table 13. A total of 535 subjects were enrolled and randomized, and 526 subjects were treated. As of the data cutoff date of 08 February 2019, 163 subjects (91.1%) in the acalabrutinib+obinutuzumab arm and 152 subjects (85.9%) in the obinutuzumab+chlorambucil arm have completed 6 cycles of obinutuzumab and 137 subjects (77.4%) in the obinutuzumab+ chlorambucil arm completed 6 cycles of chlorambucil.

A total of 146 subjects [81.6%] in the acalabrutinib+obinutuzumab arm and 142 subjects [79.3%] in the acalabrutinib monotherapy arm were still receiving acalabrutinib treatment as of the data cutoff date.

The primary reason for discontinuing acalabrutinib was AEs or SAEs (18 subjects (10.1%) in the acalabrutinib+obinutuzumab arm and 16 subjects (8.9%) in the acalabrutinib monotherapy arm). In the acalabrutinib+obinutuzumab arm, the primary reason for discontinuing obinutuzumab was AEs or SAEs (11 subjects [6.1%]). In the obinutuzumab+chlorambucil arm

the primary reason for discontinuing obinutuzumab was AEs or SAEs (10 subjects [5.6%]). In this arm the primary reason for discontinuing chlorambucil was AEs or SAEs (24 subjects [13.6%]).

Table 13: Subject Disposition (ITT Population)

	No. (%) of Subjects			
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab +Chlorambucil (N=177)**	**Total (N=535)**
Subjects randomized (ITT Population)	179 (100.0)	179 (100.0)	177 (100.0)	535 (100.0)
Treated with ≥1 study drug	179 (100.0)	178 (99.4)	169 (95.5)	526 (98.3)
Randomized but not treated[a]	0	1 (0.6)	8 (4.5)	9 (1.7)
Acalabrutinib				
Subjects treated with study drug	179 (100.0)	178 (99.4)	–	–
Subjects who discontinued study drug	33 (18.4)	36 (20.1)	–	–
Death	1 (0.6)	3 (1.7)	–	–
Lost to follow-up	0	1 (0.6)	–	–
Withdrawal of consent	1 (0.6)	1 (0.6)	–	–
AE/SAE	18 (10.1)	16 (8.9)	–	–
CLL progressive disease	6 (3.4)	7 (3.9)	–	–
Investigator's discretion	3 (1.7)	5 (2.8)	–	–
Pregnancy	0	0	–	–
Other	4 (2.2)[e]	3 (1.7)[f]	–	–
Chlorambucil				
Subjects treated with study drug	–	–	169 (95.5)	–
Subjects who discontinued study drug	–	–	169 (95.5)	–
Death	–	–	1 (0.6)	–
Lost to follow-up	–	–	1 (0.6)	–
Withdrawal of consent	–	–	1 (0.6)	–
AE/SAE	–	–	24 (13.6)	–
CLL progressive disease	–	–	4 (2.3)	–
Investigator's discretion	–	–	1 (0.6)	–
Pregnancy	–	–	0	–
Completed Study Regimen	–	–	137 (77.4)	–
Other	–	–	0	–
Obinutuzumab				
Subjects treated with study drug	179 (100.0)	–	169 (95.5)	–
Subjects who discontinued study drug	179 (100.0)	–	168 (94.9)[d]	–
Death	1 (0.6)	–	1 (0.6)	–
Lost to follow-up	0	–	1 (0.6)	–
Withdrawal of consent	0	–	0	–

	No. (%) of Subjects			
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab +Chlorambucil (N=177)**	**Total (N=535)**
AE/SAE	11 (6.1)	–	10 (5.6)	–
CLL progressive disease	2 (1.1)	–	3 (1.7)	–
Investigator's discretion	2 (1.1)	–	1 (0.6)	–
Pregnancy	0	–	0	–
Completed Study Regimen	163 (91.1)	–	152 (85.9)	–
Other	0	–	0	–
Subjects who discontinued all study treatment[b]	33 (18.4)	36 (20.1)	168 (94.9)	237 (44.3)
Subjects who exited study	16 (8.9)	22 (12.3)	32 (18.1)	70 (13.1)
Death	6 (3.4)	9 (5.0)	16 (9.0)	31 (5.8)
Lost to follow-up	1 (0.6)	3 (1.7)	2 (1.1)	6 (1.1)
Withdrawal of consent	6 (3.4)	9 (5.0)	12 (6.8)	27 (5.0)
Investigator's discretion	3 (1.7)	1 (0.6)	0	4 (0.7)
Other	0	0	2 (1.1)[g]	2 (0.4)
Time on study (months)[c]				
Mean (SD)	28.2 (7.18)	28.0 (7.75)	26.5 (9.40)	27.6 (8.18)
Median	28.5	28.4	28.0	28.3
Min, Max	1.7, 40.3	0.1, 40.8	0.0, 40.4	0.0, 40.8
Time from randomization to first dose (days)				
n	179	178	169	526
Mean (SD)	3.7 (2.40)	3.9 (2.45)	4.6 (3.27)	4.1 (2.75)
Median	3.0	3.0	4.0	3.0
Min, Max	1.0, 14.0	1.0, 15.0	1.0, 21.0	1.0, 21.0

AE=adverse events; CLL=chronic lymphocytic leukemia; ITT=intent to treat; Max=maximum; Min=minimum; SAE=serious adverse event; SD=standard deviation.

[a] Subjects randomized but did not receive any study treatments.

[b] Discontinued all study treatment based on randomized treatment assignment.

[c] Time on study = (study exit date or last visit date) – date of randomization + 1 day.

[d] End of treatment eCRF was not completed for 1 subject.

[e] For one subject, acalabrutinib was interrupted on Day 90 for 3 AEs (Grade 2 AE of anemia, Grade 1 AE of arthralgia, and Grade 1 AE of myalgia; all 3 events were related to acalabrutinib only). Following the subject's improvement, the investigator re-started acalabrutinib on Day 266 without informing the sponsor. Once the sponsor was alerted, the investigator was instructed to discontinue acalabrutinib. One subject discontinued acalabrutinib due to bleeding risk concerns while taking clopidogrel and acetylsalicylic acid as directed by the subject's cardiologist; the subject is continuing in the survival follow-up. One subject discontinued acalabrutinib due to a consecutive interruption of study drug >28 days. One subject discontinued acalabrutinib because the subject wanted to stop the study drug (ELEVATE-TN clinical report, Listing 16.2.1.1).

[f] One subject discontinued acalabrutinib due to a consecutive interruption of study drug >28 days. One subject discontinued acalabrutinib due to Richter's transformation. One subject discontinued acalabrutinib because the subject decided to stop treatment (ELEVATE-TN clinical report, Listing 16.2.1.1).

[g] One subject was randomized but discontinued the study before receiving study drug because the subject was ineligible for the study upon sponsor review of eligibility criteria. One subjects discontinued study drug for progressive disease and discontinued the study due to "other" reasons (progressive disease) (ELEVATE-TN clinical report, Listing 16.2.1.1).

Source: ELEVATE-TN clinical report, Table 14.1.1.3

The Applicant's Position:

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the Regulatory Authorities.

The median time on study for subjects in the acalabrutinib+obinutuzumab arm was 28.5 months, 28.4 months for the acalabrutinib monotherapy arm, and 28.0 months for the obinutuzumab+ chlorambucil arm. The primary reason for study exit was death (6 subjects (3.4%) for the acalabrutinib+obinutuzumab arm, 9 subjects (5.0%) for the acalabrutinib monotherapy arm, and 16 subjects (9.0%) for the obinutuzumab+chlorambucil arm. A total of 45/177 subjects (25.4%) crossed over from the obinutuzumab+chlorambucil arm to acalabrutinib 100 mg PO BID, 41/45 (91.1%) of whom are continuing on acalabrutinib monotherapy treatment as of the data cutoff date (08 February 2019).

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's description for patient disposition.

Protocol Violations/Deviations

Data:

Important protocol deviations were identified and classified prior to database lock. Protocol deviations are summarized for ELEVATE-TN in Table 14. A total of 78 subjects (14.6%) had important protocol deviations, the most common being those involving informed consent (22 subjects [4.1%]) and study treatment administration/dispense (22 subjects [4.1%]). Across all 78 important protocol deviations, the most common deviations were informed consent (22 subjects), study treatment administration/dispense (22 subjects), and study procedures/assessments (17 subjects). A total of 14 subjects (2.6%) had protocol deviations related to inclusion criteria. Of these 14 subjects, 11 subjects were less than 65 years of age and did not meet the requirement to either have a creatinine clearance of 30 to 69 mL/min or a CRIS-G score >6 (inclusion criteria).

Table 14: Summary of Important Protocol Deviations (ITT Population)

	No. (%) of Subjects			
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab +Chlorambucil (N=177)**	**Total (N=535)**
Subjects with any important protocol deviations	33 (18.4)	17 (9.5)	28 (15.8)	78 (14.6)
Informed consent	8 (4.5)	4 (2.2)	10 (5.6)	22 (4.1)
Study treatment administration/dispense[a]	8 (4.5)	6 (3.4)	8 (4.5)	22 (4.1)
Study procedures/assessments	9 (5.0)	2 (1.1)	6 (3.4)	17 (3.2)
Inclusion criteria	5 (2.8)	5 (2.8)	4 (2.3)	14 (2.6)
Concomitant medications	2 (1.1)	2 (1.1)	0	4 (0.7)
Missing endpoint assessments	3 (1.7)	0	1 (0.6)	4 (0.7)
Exclusion criteria	1 (0.6)	0	2 (1.1)	3 (0.6)

	No. (%) of Subjects			
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab +Chlorambucil (N=177)**	**Total (N=535)**
Withdrawal/termination criteria	2 (1.1)	0	0	2 (0.4)

Note: Subjects with >1 deviation were summarized once at each deviation.
[a] Refers to subjects under dosed, subjects administered invalid study drug, or subjects administered study drug incorrectly.
Source: ELEVATE-TN clinical report, Table 14.1.1.4.

The Applicant's Position:
A sensitivity analysis conducted on PFS excluding subjects with important protocol deviations did not demonstrate a significant impact on the overall interpretation of efficacy results for this study and the subjects with the important protocol deviations were retained in the analysis population.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's description for protocol deviations/violations. The reasons for protocol deviations/violations appear to be balanced between treatment arms and do not appear to be a significant cause of bias influencing the study results.

Demographic Characteristics

Data:
Subject demographics are summarized for ELEVATE-TN in Table 15. The median age for all subjects in the study was 70.0 years (range: 41.0 to 91.0 years). The majority of all subjects (83.7%) were ≥65 years old, and over half (61.3%) were male. Almost all subjects (93.3%) were white, and not Hispanic or Latino (89.9%).

Table 15: Subject Demographics (ITT Population)

	No. (%) of Subjects			
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab+ Chlorambucil (N=177)**	**Total (N=535)**
Age (years)				
Mean (SD)	70.2 (8.02)	69.8 (7.57)	70.8 (7.56)	70.3 (7.72)
Median	70.0	70.0	71.0	70.0
Min, Max	41.0, 88.0	44.0, 87.0	46.0, 91.0	41.0, 91.0
Age group				
<65	35 (19.6)	28 (15.6)	24 (13.6)	87 (16.3)
≥65	144 (80.4)	151 (84.4)	153 (86.4)	448 (83.7)
<75	126 (70.4)	129 (72.1)	125 (70.6)	380 (71.0)

	No. (%) of Subjects			
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab+ Chlorambucil (N=177)**	**Total (N=535)**
≥75	53 (29.6)	50 (27.9)	52 (29.4)	155 (29.0)
Sex, n (%)				
Male	111 (62.0)	111 (62.0)	106 (59.9)	328 (61.3)
Female	68 (38.0)	68 (38.0)	71 (40.1)	207 (38.7)
Region				
North America	64 (35.8)	70 (39.1)	61 (34.5)	195 (36.4)
South America	5 (2.8)	8 (4.5)	7 (4.0)	20 (3.7)
Western Europe	49 (27.4)	42 (23.5)	52 (29.4)	143 (26.7)
Central/Eastern Europe	48 (26.8)	46 (25.7)	40 (22.6)	134 (25.0)
Australia/New Zealand	13 (7.3)	13 (7.3)	17 (9.6)	43 (8.0)
Ethnicity, n (%)				
Hispanic or Latino	2 (1.1)	11 (6.1)	11 (6.2)	24 (4.5)
Not Hispanic or Latino	169 (94.4)	156 (87.2)	156 (88.1)	481 (89.9)
Not reported	8 (4.5)	12 (6.7)	10 (5.6)	30 (5.6)
Race, n (%)				
American Indian or Alaska Native	0	0	1 (0.6)	1 (0.2)
Asian	3 (1.7)	0	0	3 (0.6)
Black or African American	5 (2.8)	4 (2.2)	4 (2.3)	13 (2.4)
Native Hawaiian or Other Pacific Islander	0	0	1 (0.6)	1 (0.2)
White	164 (91.6)	170 (95.0)	165 (93.2)	499 (93.3)
Not reported	7 (3.9)	5 (2.8)	6 (3.4)	18 (3.4)

ITT=intent to treat; Max=maximum; Min=minimum; SD=standard deviation.
Source: ELEVATE-TN clinical report, Table 14.1.2.1.

The Applicant's Position:
There were no noteworthy differences in demographics across the 3 treatment arms.

Regulatory Authorities Assessment:
The regulatory authorities agree with Applicant's position and description of demographic characteristics between treatment arms. The demographics of the three arms appears to be balanced.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:
Almost all subjects (93.6%) has an ECOG score of 0 or 1. The median time from initial CLL diagnosis to the first dose of study treatment was 27.6 months (range 0.3–284.5 months). Almost all subjects (97.8%) had measurable lymph nodes at baseline with less than a third of subjects presenting with lymph nodes measuring ≥5 cm. Over half of the subjects (52.3%) had a

baseline Rai stage of I-II (intermediate risk). Baseline and disease characteristics are summarized for ELEVATE-TN in Table 16.

Table 16: Baseline and Disease Characteristics (ITT Population)

	No. (%) of Subjects			
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab +Chlorambucil (N=177)**	**Total (N=535)**
ECOG performance status				
0-1	169 (94.4)	165 (92.2)	167 (94.4)	501 (93.6)
2	10 (5.6)	14 (7.8)	10 (5.6)	34 (6.4)
Time from initial diagnosis to randomization (months)				
Mean (SD)	47.5 (51.93)	42.1 (45.10)	46.3 (48.67)	45.3 (48.61)
Median	30.5	24.4	30.7	27.6
Min, Max	0.4, 284.5	0.4, 242.6	0.3, 247.0	0.3, 284.5
Age <65 years	35 (19.6)	28 (15.6)	24 (13.6)	87 (16.3)
Creatinine clearance 30–69 mL/min	2 (1.1)	4 (2.2)	7 (4.0)	13 (2.4)
CIRS-G >6	30 (16.8)	21 (11.7)	15 (8.5)	66 (12.3)
Any of the above[a]	31 (17.3)	24 (13.4)	20 (11.3)	75 (14.0)
Creatine Clearance (mL/min)				
N	176	178	174	528
Median	76.5	75.0	70.0	75.0
Min, Max	28.0, 187.0	29.0, 245.0	30.0, 205.0	28.0, 245.0
Bulky disease (per investigator)				
Subjects with measurable lymph nodes[b]	177 (98.9)	175 (97.8)	171 (96.6)	523 (97.8)
<5 cm	131 (73.2)	107 (59.8)	116 (65.5)	354 (66.2)
≥5 cm	46 (25.7)	68 (38.0)	55 (31.1)	169 (31.6)
No measurable lymph nodes	2 (1.1)	4 (2.2)	6 (3.4)	12 (2.2)
Rai stage				
0	3 (1.7)	0	1 (0.6)	4 (0.7)
I	54 (30.2)	48 (26.8)	50 (28.2)	152 (28.4)
II	36 (20.1)	44 (24.6)	48 (27.1)	128 (23.9)
III	48 (26.8)	50 (27.9)	40 (22.6)	138 (25.8)
IV	38 (21.2)	37 (20.7)	38 (21.5)	113 (21.1)
Cytogenetics/FISH Category				
17p deletion – yes	17 (9.5)	16 (8.9)	16 (9.0)	49 (9.2)
11q deletion – yes	31 (17.3)	31 (17.3)	33 (18.6)	95 (17.8)
TP53 mutated	21 (11.7)	19 (10.6)	21 (11.9)	61 (11.4)
IgHV Mutated	74 (41.3)	58 (32.4)	59 (33.3)	191 (35.7)
High-risk features				
Del 17p, TP53 mutation, del 11q, or unmutated IgHV	117 (65.4)	129 (72.1)	129 (72.9)	375 (70.1)
Complex Karyotype - yes	29 (16.2)	31 (17.3)	32 (18.1)	92 (17.2)

	No. (%) of Subjects			
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab +Chlorambucil (N=177)**	**Total (N=535)**
Beta-2 microglobulin				
>3.5 mg/L	132 (73.7)	140 (78.2)	132 (74.6)	404 (75.5)
≤3.5 mg/L	44 (24.6)	38 (21.2)	42 (23.7)	124 (23.2)
Missing	3 (1.7)	1 (0.6)	3 (1.7)	7 (1.3)
Cytopenia at baseline				
Neutropenia: ANC≤1.5x10^9/L	9 (5.0)	10 (5.6)	5 (2.8)	24 (4.5)
Anemia: HGB≤11g/dL	67 (37.4)	68 (38.0)	69 (39.0)	204 (38.1)
Thrombocytopenia: platelets ≤100x10^9/L	44 (24.6)	33 (18.4)	34 (19.2)	111 (20.7)
All of the above	2 (1.1)	2 (1.1)	2 (1.1)	6 (1.1)
Any of the above	93 (52.0)	85 (47.5)	77 (43.5)	255 (47.7)
Prior RBC transfusion within 28 days before randomization	6 (3.4)	6 (3.4)	4 (2.3)	16 (3.0)
Prior platelet transfusion within 28 days before randomization	0	1 (0.6)	0	1 (0.2)
Constitutional symptoms				
Subjects with any constitutional symptoms	96 (53.6)	104 (58.1)	88 (49.7)	288 (53.8)
Weight loss	19 (10.6)	26 (14.5)	23 (13.0)	68 (12.7)
Fever	9 (5.0)	8 (4.5)	2 (1.1)	19 (3.6)
Night sweats	79 (44.1)	82 (45.8)	71 (40.1)	232 (43.4)
Fatigue	29 (16.2)	36 (20.1)	26 (14.7)	91 (17.0)

ANC=absolute neutrophil count; Del=deletion; CIRS-G=Cumulative Illness Rating Scale-Geriatric; ECOG=Eastern Cooperative Oncology Group; FISH=fluorescence in situ hybridization; HGB=hemoglobin; IgHV=immunoglobulin heavy-chain variable region gene; ITT=intent to treat; Max=maximum; Min=minimum; NA=not applicable; RBC=red blood cell; SD=standard deviation.

[a] Eleven subjects did not meet eligibility criteria related to creatinine clearance and CIRS-G criteria for subjects <65 years of age (ELEVATE-TN clinical report, Listing 16.2.2). In one subject, eligibility was confirmed prior to dosing, but the date of entry of the corrected eligibility information was after dosing;

[b] Only target lesions >1.5 cm in the longest diameter were assessed.

Source: ELEVATE-TN Table 14.1.2.1, Table 14.1.2.2.

The Applicant's Position:

There were no noteworthy differences in baseline disease characteristics between the 3 treatment arms.

Regulatory Authorities Assessment:

The regulatory authorities agree with Applicant's position and description of the baseline disease characteristics. The disease baseline characteristics of the three arms appear to be balanced.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Exposure to acalabrutinib was similar across the 2 acalabrutinib treatment arms (acalabrutinib+ obinutuzumab and acalabrutinib monotherapy). The median relative acalabrutinib dose intensity was 98.3% for the acalabrutinib+obinutuzumab arm and 99.2% for the acalabrutinib monotherapy arm. Exposure to obinutuzumab was also similar across the 2 treatment arms.

Obinutuzumab+Chlorambucil (Arm A): The median duration of obinutuzumab treatment for the obinutuzumab+chlorambucil arm was 5.6 months ([0.9-7.1 months]). The median duration of chlorambucil treatment was 5.5 months [0.9–7.1 months]). The median relative obinutuzumab dose intensity was 100% and the median relative chlorambucil dose intensity was 95.2%.

Acalabrutinib+Obinutuzumab (Arm B): The median duration of acalabrutinib treatment was 27.7 months (range 0.7–40.3 months) for the acalabrutinib+obinutuzumab arm. The median duration of obinutuzumab treatment was 5.5 months ([0.9-7.1 months]) for the acalabrutinib+ obinutuzumab arm. The median relative acalabrutinib dose intensity was 98.3% for the acalabrutinib+obinutuzumab arm, and the median obinutuzumab dose intensity was 100%.

Acalabrutinib Monotherapy (Arm C): The median duration of acalabrutinib treatment was 27.7 months for the acalabrutinib monotherapy arm (range 0.3–40.2 months). The median relative acalabrutinib dose intensity was 99.2% for the acalabrutinib monotherapy arm.

Concomitant Medications:
All subjects (100%) in the acalabrutinib+obinutuzumab arm were reported to have used a concomitant medication. The most frequently reported concomitant medications by preferred term taken by >25% of acalabrutinib+obinutuzumab subjects were paracetamol (87.7%), allopurinol (72.1%), dexamethasone (49.2%), acyclovir (31.8%), diphenhydramine (29.6%), and acetylsalicylic acid (26.3%).

In the acalabrutinib monotherapy arm, a total of 97.8% (175/179) of subjects were reported to have used a concomitant medication. The most frequently reported concomitant medications by preferred term taken by >25% of acalabrutinib monotherapy subjects were allopurinol (52.0%), paracetamol (36.9%), and acetylsalicylic acid (30.7%).

In the obinutuzumab+chlorambucil arm, a total of 95.5% (169/177) of subjects were reported to have used a concomitant medication. The most frequently reported concomitant medications by preferred term taken by >25% of obinutuzumab+chlorambucil subjects were paracetamol (84.7%), allopurinol (72.3%), dexamethasone (49.2%), ondansetron (34.5%), acyclovir (27.7%), diphenhydramine (27.7%), acetylsalicylic acid (25.4%), and sulfamethoxazole trimethoprim (25.4%).

The Applicant's Position:
Overall, the concomitant treatments administered were representative of those commonly prescribed for patients of the target population and were not considered to have impacted the study results.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's position and description.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Primary Variable: PFS as Assessed by IRC

The primary analysis to compare IRC-assessed PFS between the obinutuzumab+chlorambucil arm and acalabrutinib+obinutuzumab arm was conducted using a log-rank test, stratified by 17p deletion status as recorded in IXRS.

With a median follow-up of 28.5 months in the acalabrutinib+obinutuzumab arm and 28.0 months in the obinutuzumab+chlorambucil arm, the median estimated PFS for acalabrutinib+obinutuzumab was not reached; the median estimated PFS for obinutuzumab+ chlorambucil was 22.6 months (95% CI: 20.2–27.6). Based on the stratified analysis, acalabrutinib+obinutuzumab demonstrated a statistically significant improvement in IRC-assessed PFS compared with obinutuzumab+chlorambucil, with a 90% reduction in risk of disease progression or death (HR=0.10 [95% CI: 0.06–0.17]; p<0.0001) (Table 17;

Regulatory Authorities Assessment:

The efficacy assessment is conducted at the pre-specified interim analysis. FDA does not agree that the KM Estimates of PFS by timepoint should be presented in Table 17. These estimates can be misleading because they only present estimates at one single time point and cannot represent the overall effect of the treatment.

FDA conducted additional analysis on censoring patterns by arm and by time intervals. The censoring patterns are similar between arms.

	Acalabrutinib+ Obinutuzumab		Acalabrutinib		Obinutuzumab+ Chlorambucil	
Time	N=179		N=179		N=177	
	event	censored	event	censored	event	censored
0 -6 months	2	7	7	11	5	15
6-12 months	5	2	5	3	20	1

12-18 months	2	2	4	1	30	4
18-24 months	3	47	4	41	27	29
24-30 months	2	61	4	56	10	23
30-36 months	0	42	2	37	1	9
>= 36 months	0	4	0	4	0	3
Total	**14**	165	**26**	153	**93**	84

[Source: FDA statistics reviewer's analysis]

Figure 5).

The KM estimate of the proportion of subjects without a PFS event at 12 months was 95.9% (95% CI: 91.7–98.0) for acalabrutinib+obinutuzumab and 84.6% (95% CI: 78.0–89.3) for obinutuzumab+chlorambucil. The KM estimate of the proportion of subjects without a PFS event at 36 months was 89.6% (95% CI: 82.0–94.1) for acalabrutinib+obinutuzumab and 31.3% (95% CI: 21.8–41.3) for obinutuzumab+chlorambucil (Table 17; ;

Regulatory Authorities Assessment:

The efficacy assessment is conducted at the pre-specified interim analysis. FDA does not agree that the KM Estimates of PFS by timepoint should be presented in Table 17. These estimates can be misleading because they only present estimates at one single time point and cannot represent the overall effect of the treatment.

FDA conducted additional analysis on censoring patterns by arm and by time intervals. The censoring patterns are similar between arms.

	Acalabrutinib+ Obinutuzumab		Acalabrutinib		Obinutuzumab+ Chlorambucil	
Time	N=179		N=179		N=177	
	event	censored	event	censored	event	censored

0 -6 months	2	7	7	11	5	15
6-12 months	5	2	5	3	20	1
12-18 months	2	2	4	1	30	4
18-24 months	3	47	4	41	27	29
24-30 months	2	61	4	56	10	23
30-36 months	0	42	2	37	1	9
>= 36 months	0	4	0	4	0	3
Total	**14**	165	**26**	153	**93**	84

[Source: FDA statistics reviewer's analysis]

Figure 5).

Figure 6 displays the KM plot for PFS by IRC for acalabrutinib+obinutuzumab versus obinutuzumab+chlorambucil in the ITT population.

Table 17: Analysis of Progression-Free Survival by IRC Assessment (ITT Population) – Primary Endpoint

	No. (%) of Subjects	
	Acalabrutinib+ Obinutuzumab (N=179)	**Obinutuzumab+ Chlorambucil (N=177)**
Subject Status		
Events	14 (7.8)	93 (52.5)
Death	5 (2.8)	11 (6.2)
Progressive Disease	9 (5.0)	82 (46.3)
Censored	165 (92.2)	84 (47.5)
No Event Before Data Cutoff	154 (86.0)	64 (36.2)
No Postbaseline Assessment	1 (0.6)	11 (6.2)
No Event Before Taking Subsequent Anti-Cancer Therapy	3 (1.7)	3 (1.7)
Death or Progressive Disease After 2 or More Consecutive Missed Visits	2 (1.1)	1 (0.6)
No Event Before Study Exit	5 (2.8)	5 (2.8)

	No. (%) of Subjects	
	Acalabrutinib+ Obinutuzumab (N=179)	Obinutuzumab+ Chlorambucil (N=177)
Progression Free Survival (Months)		
Q1 (95% CI)	NE (NE, NE)	14.4 (13.9, 16.6)
Median (95% CI)	NE (NE, NE)	22.6 (20.2, 27.6)
Q3 (95% CI)	NE (NE, NE)	NE (33.1, NE)
Min, Max	0.0+, 39.4+	0.0+, 39.6+
Stratified Analysis[a]		
Hazard Ratio (95% CI)[b]	0.10 (0.06, 0.17)	–
p-value[c]	<0.0001	–
Unstratified Analysis		
Hazard Ratio (95% CI)[b]	0.10 (0.06, 0.18)	–
p-value[c]	<0.0001	–
KM Estimates of PFS[d] by Timepoint		
6 Months (95% CI)	98.9 (95.5, 99.7)	97.0 (92.9, 98.7)
12 Months (95% CI)	95.9 (91.7, 98.0)	84.6 (78.0, 89.3)
18 Months (95% CI)	94.8 (90.2, 97.2)	65.6 (57.7, 72.4)
24 Months (95% CI)	92.7 (87.4, 95.8)	46.7 (38.5, 54.6)
30 Months (95% CI)	89.6 (82.0, 94.1)	34.2 (25.3, 43.2)
36 Months (95% CI)	89.6 (82.0, 94.1)	31.3 (21.8, 41.3)

CI=confidence interval; IRC=Independent Review Committee; ITT=intent-to-treat; KM=Kaplan-Meier; Max=maximum; Min=minimum; NE=not estimable; PFS=progression-free survival; Q1=quartile 1; Q3=quartile 3.

[a] Stratified by 17p deletion status (yes vs. no).

[b] Estimated based on stratified or unstratified Cox Proportional Hazards model for Hazard Ratio (95% CI), respectively.

[c] Estimated based on stratified or unstratified log-rank test for p-value, respectively.

[d] KM estimate of the proportion of subjects who were progression free at the timepoint.

Note: Time to event (or time to censor for censored subjects) was calculated as date of disease progression or death (censoring date for censored subjects) – randomization date + 1. Months were derived as days / 30.4375.

Note: "+" indicates a value from a censored subject.

Source: ELEVATE-TN clinical report, Table 14.2.1.

Regulatory Authorities Assessment:

The efficacy assessment is conducted at the pre-specified interim analysis. FDA does not agree that the KM Estimates of PFS by timepoint should be presented in Table 17. These estimates can be misleading because they only present estimates at one single time point and cannot represent the overall effect of the treatment.

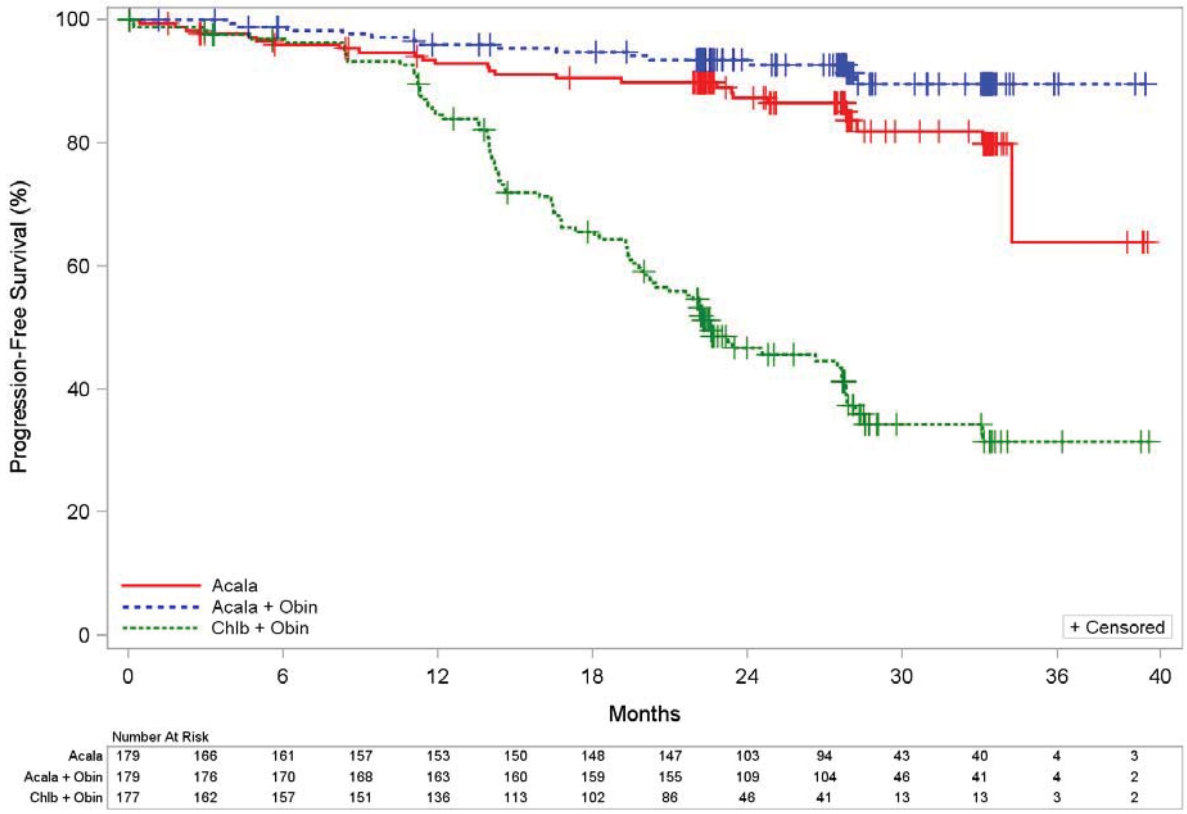
FDA conducted additional analysis on censoring patterns by arm and by time intervals. The censoring patterns are similar between arms.

	Acalabrutinib+ Obinutuzumab	Acalabrutinib	Obinutuzumab+ Chlorambucil
Time	N=179	N=179	N=177

	event	censored	event	censored	event	censored
0 -6 months	2	7	7	11	5	15
6-12 months	5	2	5	3	20	1
12-18 months	2	2	4	1	30	4
18-24 months	3	47	4	41	27	29
24-30 months	2	61	4	56	10	23
30-36 months	0	42	2	37	1	9
>= 36 months	0	4	0	4	0	3
Total	**14**	165	**26**	153	**93**	84

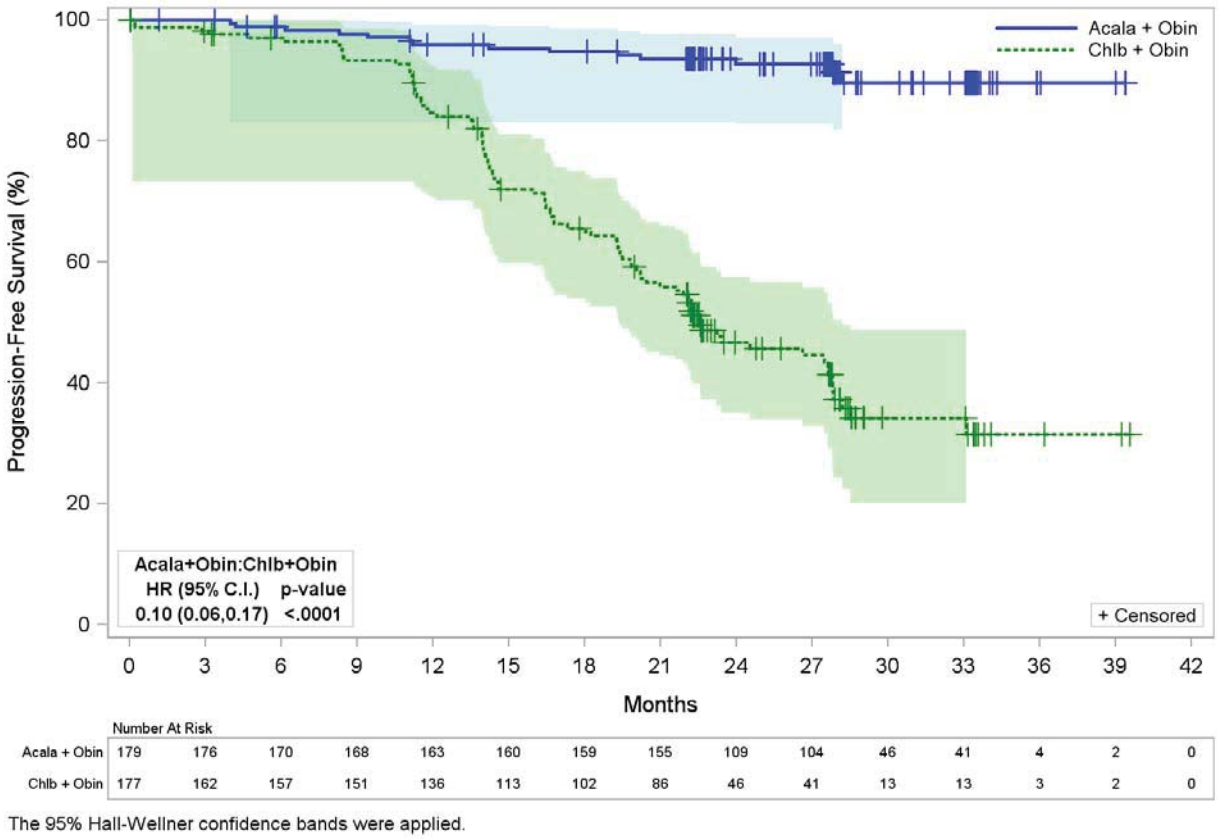
[Source: FDA statistics reviewer's analysis]

Figure 5: Kaplan-Meier Plot for Progression-Free Survival by IRC Assessment (ITT Population) – Primary Endpoint



IRC=Independent Review Committee; ITT=intent-to-treat.
Source: ELEVATE-TN clinical report, Figure 14.2.1.6.

Figure 6: Kaplan-Meier Plot for Progression-Free Survival by IRC for Acalabrutinib+ Obinutuzumab versus Obinutuzumab+Chlorambucil (ITT Population)



IRC=Independent Review Committee; ITT=intent-to-treat.
Source: Ad-hoc figure from ELEVATE-TN per FDA Request.

Examination of Subgroups

Subgroup analysis of the primary endpoint are provided in Table 18.

Table 18: Subgroup Analysis of Progression-Free Survival by IRC Assessment (ITT Population) – Primary Endpoint

	Responders/Subjects		
	Acalabrutinib+ Obinutuzumab (N=179)	**Obinutuzumab+ Chlorambucil (N=177)**	**Hazard Ratio (95% CI)**
	Number of Events/Subjects	Number of Events/Subjects	
Overall			
Primary analysis	14/179	93/177	0.10 (0.06, 0.17)
Presence of 17p deletion[a]			

	Responders/Subjects		
	Acalabrutinib+ Obinutuzumab (N=179)	**Obinutuzumab+ Chlorambucil (N=177)**	**Hazard Ratio (95% CI)**
Yes	3/21	11/117	0.13 (0.04, 0.46)
No	11/158	82/160	0.09 (0.05, 0.17)
ECOG at randomization[a]			
0, 1	12/169	86/168	0.09 (0.05, 0.17)
2	2/10	7/9	0.16 (0.03, 0.79)
Geographic region[a]			
North America and Western Europe	6/104	50/103	0.08 (0.03, 0.18)
Other	8/75	43/74	0.13 (0.06, 0.27)
Region			
North America	5/64	30/61	0.10 (0.04, 0.26)
South America	0/5	4/7	NE (NE, NE)
Western Europe	3/49	25/52	0.09 (0.03, 0.30)
Central and Eastern Europe	5/48	23/40	0.12 (0.04, 0.31)
Australia and New Zealand	1/13	11/17	0.09 (0.01, 0.73)
Age group			
<65	1/35	16/24	0.02 (0.00, 0.17)
≥65	13/144	77/153	0.13 (0.07, 0.23)
<75	8/126	66/125	0.08 (0.04, 0.16)
≥75	6/53	27/52	0.17 (0.07, 0.42)
Sex			
Male	8/111	58/106	0.09 (0.04, 0.18)
Female	6/68	35/71	0.12 (0.05, 0.29)
Race			
White	14/164	88/165	0.11 (0.06, 0.19)
Non-white	0/15	5/12	NE (NE, NE)
Rai stage at screening			
Stage 0-II	3/93	54/99	0.04 (0.01, 0.12)
Stage III-IV	11/86	39/78	0.18 (0.09, 0.35)
Bulky disease			
<5 cm	10/131	53/116	0.12 (0.06, 0.24)
≥5 cm	4/46	39/55	0.07 (0.02, 0.19)
B2-microglobin at baseline			
≤3.5 mg/L	2/44	14/42	0.11 (0.03, 0.49)
>3.5 mg/L	12/132	78/132	0.10 (0.05, 0.18)
Presence of 11q deletion			
Yes	4/31	26/33	0.09 (0.03, 0.26)
No	10/148	66/143	0.10 (0.05, 0.20)
TP53 mutation			
Yes	2/21	14/21	0.04 (0.01, 0.22)
No	12/158	78/155	0.11 (0.06, 0.20)
17p deletion or TP53 mutation			
Yes	3/25	16/25	0.10 (0.03. 0.34)
No	11/154	77/152	0.10 (0.05, 0.18)
17p deletion and TP53 mutation			
Yes	2/13	9/12	0.02 (0.00, 0.24)

	Responders/Subjects		
	Acalabrutinib+ Obinutuzumab (N=179)	**Obinutuzumab+ Chlorambucil (N=177)**	**Hazard Ratio (95% CI)**
No	12/166	84/165	0.10 (0.05, 0.18)
IgHV			
Mutated	3/74	14/59	0.15 (0.04, 0.52)
Unmutated	11/103	78/116	0.08 (0.04, 0.16)
17p deletion, TP53 mutation, 11q deletion, or unmutated IgHV			
Yes	11/117	83/129	0.08 (0.04, 0.15)
No	3/62	10/48	0.22 (0.06, 0.79)
17p deletion, TP53 mutation, or 11q deletion			
Yes	7/53	41/55	0.10 (0.04, 0.22)
No	7/126	52/122	0.09 (0.04, 0.21)
Complex karyotype			
Yes	3/29	20/32	0.09 (0.03, 0.29)
No	9/126	59/121	0.11 (0.05, 0.21)

ECOG=Eastern Cooperative Oncology Group; ITT=intent-to-treat; NE=not estimable.

[a] Per Interactive voice/web response system (IXRS) record.

Source: ELEVATE-TN clinical report, Figure 14.2.1.9.1.

Sensitivity Analyses

The following sensitivity analyses were performed for acalabrutinib+obinutuzumab compared with obinutuzumab+chlorambucil: unstratified analysis, inclusion of PFS without censoring for subsequent anticancer therapy, inclusion of PFS events after 2 or more consecutively missed visits, and exclusion of subjects with important protocol deviations (Table 19, Figure 7).

The key sensitivity analysis of PFS without censoring for subsequent anticancer therapy was consistent with the primary analysis and showed similar improvement in PFS for acalabrutinib+ obinutuzumab compared with obinutuzumab+chlorambucil (stratified: HR=0.11 [95% CI: 0.06–0.18]; p<0.0001 and unstratified: HR=0.11 [95% CI: 0.06–0.19]; p<0.0001). All other sensitivity analyses were also consistent with the primary analysis, with HR ranging from 0.08–0.11, which was statistically significant for all analyses (p<0.0001) (Table 19, Figure 7).

Per the Agency's request, sensitivity analysis was performed on IRC-assessed PFS using weighted log-rank test (Harrington-Fleming), stratified by del17p status as recorded in IXRS, to compare between obinutuzumab+chlorambucil arm and acalabrutinib+obinutuzumab arm. The results remain consistent with the primary analysis result, and confirm the robustness of the primary analysis (Table 20).

Table 19: Sensitivity Analyses of Progression-Free Survival by IRC Assessment (ITT Population) – Primary Endpoint

	No. (%) of Subjects	
Sensitivity Analysis	**Arm B Acalabrutinib+ Obinutuzumab (N=179)**	**Arm A Obinutuzumab+ Chlorambucil (N=177)**
Include PFS Without Censoring for Subsequent Anticancer Therapy		
Events	15 (8.4)	93 (52.5)
Death	6 (3.4)	11 (6.2)
Disease Progression	9 (5.0)	82 (46.3)
Censored	164 (91.6)	84 (47.5)
Progression-free survival (months)		
Median (95% CI)	NE (NE, NE)	22.6 (20.2, 27.8)
Min, Max	0.0+, 39.4+	0.0+, 39.6+
Stratified analysis[a]		
Hazard ratio (95% CI)[b]	0.11 (0.06, 0.18)	–
p-value[c]	<0.0001	–
Unstratified Analysis		
Hazard ratio (95% CI) [b]	0.11 (0.06, 0.19)	–
p-value[c]	<0.0001	–
Include PFS Events After ≥2 Consecutively Missed Visits		
Events	16 (8.9)	94 (53.1)
Death	7 (3.9)	12 (6.8)
Disease Progression	9 (5.0)	82 (46.3)
Censored	163 (91.1)	83 (46.9)
Progression-free survival (months)		
Median (95% CI)	NE (NE, NE)	22.6 (20.2, 27.6)
Min, Max	0.0+, 39.4+	0.0+, 39.6+
Stratified analysis[a]		
Hazard ratio (95% CI)[b]	0.11 (0.06, 0.19)	–
p-value[c]	<0.0001	–
Exclude Subjects with Important Protocol Deviation		
Events	10/146 (6.8)	82/149 (55.0)
Death	4/146 (2.7)	10/149 (6.7)
Disease Progression	6/146 (4.1)	72/149 (48.3)
Censored	136/146 (93.2)	67/149 (45.0)
Progression-free survival (months)		
Median (95% CI)	NE (NE, NE)	22.3 (19.8, 27.5)
Min, Max	0.0+, 39.4+	0.0+, 39.6+
Stratified analysis[a]		
Hazard ratio (95% CI)[b]	0.08 (0.04, 0.15)	–
p-value[c]	<0.0001	–

CI=confidence interval; IRC=Independent Review Committee; ITT=intent-to-treat; Max=maximum; Min=minimum; NE=not estimable; PFS=progression-free survival.

[a] Stratified by 17p deletion status (yes vs. no).

[b] Estimated based on stratified or unstratified Cox Proportional Hazards model for Hazard Ratio (95% CI), respectively.

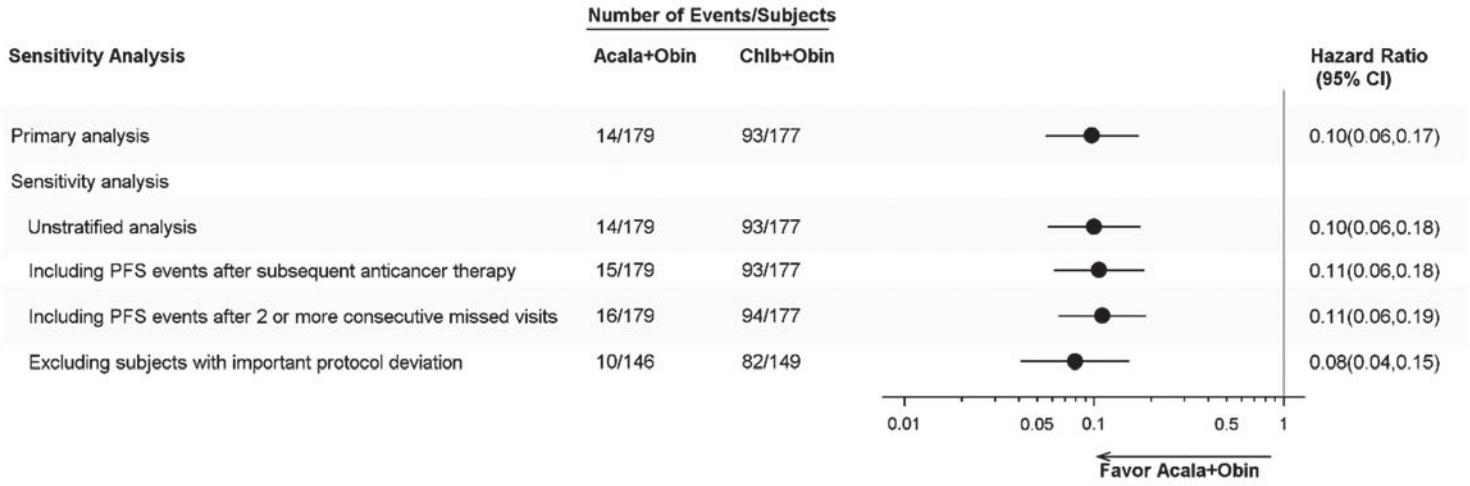
[c] Estimated based on stratified or unstratified log-rank test for p-value, respectively.

Note: Time to event (or time to censor for censored subjects) was calculated as date of disease progression or death (censoring date for censored subjects) – randomization date + 1. Months were derived as days / 30.4375.
Note: "+" indicates a value from a censored subject.
Source: ELEVATE-TN clinical report, Table 14.2.1.1, Table 14.2.1.2, Table 14.2.1.3.

Regulatory Authorities Assessment:

The FDA does not agree that p-values should be included in Table 19. These sensitivity analyses are exploratory and do not have alpha allocation. All p-values presented in Table 19 are nominal. There are no outlier subgroups identified.

Figure 7: Forest Plot for Sensitivity Analysis of Progression Free Survival by IRC Assessment (ITT Population)– Primary Endpoint



IRC=Independent Review Committee; ITT=intent-to-treat; PFS=progression-free survival.
Source: ELEVATE-TN clinical report, Figure 14.2.1.8.1.

Regulatory Authorities Assessment:

These analyses are exploratory.

Table 20: Progression Free Survival (PFS) by Independent Review Committee (IRC) Assessment by Weighted Log-Rank Test (Harrington-Fleming) ITT Population

	Acala + Obin (N=179)	Acala (N=179)	Chlb + Obin (N=177)
Subject Status			
Events[a] - n(%)	14 (7.8%)	26 (14.5%)	93 (52.5%)
Death	5 (2.8%)	6 (3.4%)	11 (6.2%)

	Acala + Obin (N=179)	Acala (N=179)	Chlb + Obin (N=177)
PD	9 (5.0%)	20 (11.2%)	82 (46.3%)
Censored[b] - n(%)	165 (92.2%)	153 (85.5%)	84 (47.5%)
No event before data cutoff	154 (86.0%)	139 (77.7%)	64 (36.2%)
No post-baseline assessment	1 (0.6%)	5 (2.8%)	11 (6.2%)
No event before taking subsequent anti-cancer therapy	3 (1.7%)	2 (1.1%)	3 (1.7%)
Death or PD after 2 or more consecutive missed visits	2 (1.1%)	3 (1.7%)	1 (0.6%)
No event before study exit	5 (2.8%)	4 (2.2%)	5 (2.8%)
Progression Free Survival (months)			
Q1 (95% CI)	NE (NE , NE)	34.2 (28.2, NE)	14.4 (13.9, 16.6)
Median (95% CI)	NE (NE , NE)	NE (34.2, NE)	22.6 (20.2, 27.6)
Q3 (95% CI)	NE (NE , NE)	NE (NE , NE)	NE (33.1, NE)
Min, Max	0.0+, 39.4+	0.0+, 39.5+	0.0+, 39.6+
Fleming(0,0)			
Stratified Analysis (vs. Chlb + Obin)			
Chi-Square	110.5814	79.7391	
DF	1	1	
p-value[c]	<.0001	<.0001	
Unstratified Analysis (vs. Chlb + Obin)			
Chi-Square	108.7877	78.9684	
DF	1	1	
p-value[d]	<.0001	<.0001	
Fleming(0,1)			
Stratified Analysis (vs. Chlb + Obin)			
Chi-Square	104.9434	75.9452	
DF	1	1	
p-value[c]	<.0001	<.0001	
Unstratified Analysis (vs. Chlb + Obin)			
Chi-Square	104.9124	77.3464	
DF	1	1	
p-value[d]	<.0001	<.0001	
Fleming(0,2)			
Stratified Analysis (vs. Chlb + Obin)			
Chi-Square	71.3089	45.6989	
DF	1	1	
p-value[c]	<.0001	<.0001	
Unstratified Analysis (vs. Chlb + Obin)			
Chi-Square	73.5456	49.1702	
DF	1	1	
p-value[d]	<.0001	<.0001	
Fleming(0,3)			
Stratified Analysis (vs. Chlb + Obin)			
Chi-Square	45.6659	25.0731	
DF	1	1	
p-value[c]	<.0001	<.0001	
Unstratified Analysis (vs. Chlb + Obin)			

	Acala + Obin (N=179)	Acala (N=179)	Chlb + Obin (N=177)
Chi-Square	50.1171	29.3579	
DF	1	1	
p-value[d]	<.0001	<.0001	
Fleming(0,4)			
Stratified Analysis (vs. Chlb + Obin)			
Chi-Square	28.8144	13.1613	
DF	1	1	
p-value[c]	<.0001	0.0003	
Unstratified Analysis (vs. Chlb + Obin)			
Chi-Square	34.7713	17.3748	
DF	1	1	
p-value[d]	<.0001	<.0001	
Fleming(0,5)			
Stratified Analysis (vs. Chlb + Obin)			
Chi-Square	18.1301	6.6952	
DF	1	1	
p-value[c]	<.0001	0.0097	
Unstratified Analysis (vs. Chlb + Obin)			
Chi-Square	24.8627	10.3424	
DF	1	1	
p-value[d]	<.0001	0.0013	
K-M Estimates of PFS by Timepoint			
6 Months PFS Rate (95% CI)	98.9 (95.5, 99.7)	95.9 (91.6, 98.0)	97.0 (92.9, 98.7)
12 Months PFS Rate (95% CI)	95.9 (91.7, 98.0)	92.9 (87.8, 95.9)	84.6 (78.0, 89.3)
18 Months PFS Rate (95% CI)	94.8 (90.2, 97.2)	90.5 (84.9, 94.1)	65.6 (57.7, 72.4)
24 Months PFS Rate (95% CI)	92.7 (87.4, 95.8)	87.3 (80.9, 91.7)	46.7 (38.5, 54.6)
30 Months PFS Rate (95% CI)	89.6 (82.0, 94.1)	81.9 (73.3, 88.0)	34.2 (25.3, 43.2)
36 Months PFS Rate (95% CI)	89.6 (82.0, 94.1)	63.9 (29.4, 84.9)	31.3 (21.8, 41.3)

[a] Based on the earliest contributing assessment.

[b] Based on the latest contributing assessment.

[c] Based on stratified weighted log-rank test (Harrington-Fleming), stratified by del 17p status as recorded in IXRS.

[d] Based on unstratified weighted log-rank test (Harrington-Fleming).

Time to event (or time to censor for censored subjects) is calculated as date of disease progression or death (censoring date for censored subjects) - randomization date + 1. Months are derived as days/30.4375. NE: not estimable.

Source: Ad-hoc table from ELEVATE-TN per FDA Request

Regulatory Authorities Assessment:

FDA does not agree that the p-values and the KM Estimates of PFS by timepoint should be presented in Table 20. These estimates can be misleading because they only present estimates at one single time point and cannot represent the overall effect of the treatment. These

sensitivity analyses are exploratory and do not have alpha allocation. All p-values presented in Table 20 are nominal.

The Applicant's Position:
The acalabrutinib+obinutuzumab arm demonstrated a statistically significant improvement in IRC-assessed PFS compared with the obinutuzumab+chlorambucil arm. The PFS benefit of acalabrutinib+obinutuzumab compared with obinutuzumab+chlorambucil was consistent across all prespecified subgroups, including age, race, sex, geographic region, presence of chromosomal abnormalities, and baseline disease status, with HR ranging from 0.02–0.22. The key sensitivity analysis of PFS without censoring for subsequent anticancer therapy was consistent with the primary analysis and showed similar improvement in PFS for acalabrutinib+obinutuzumab compared with obinutuzumab+chlorambucil.

Regulatory Authorities Assessment:

Please see comments under Tables 17, 19, 20 and Figure 7.

The acalabrutinib+obinutuzumab arm showed statistically significant improvement in IRC-assessed PFS compared with the obinutuzumab+chlorambucil arm. The results were consistent across subgroup analyses and sensitivity analyses.

Data Quality and Integrity

Data:
Not applicable

The Applicant's Position:
No issues were identified with the data quality or integrity from ELEVATE-TN which could affect the efficacy results.

Regulatory Authorities Assessment:

The data quality is acceptable. In general, the FDA reviewer was able to conduct the review based on the data package submitted by the Applicant.

Efficacy Results – Secondary and other relevant endpoints

Data:

PFS by IRC Assessment

See

Regulatory Authorities Assessment:

The efficacy assessment is conducted at the pre-specified interim analysis. FDA does not agree that the KM Estimates of PFS by timepoint should be presented in Table 17. These estimates can be misleading because they only present estimates at one single time point and cannot represent the overall effect of the treatment.

FDA conducted additional analysis on censoring patterns by arm and by time intervals. The censoring patterns are similar between arms.

	Acalabrutinib+ Obinutuzumab		Acalabrutinib		Obinutuzumab+ Chlorambucil	
Time	N=179		N=179		N=177	
	event	censored	event	censored	event	censored
0 -6 months	2	7	7	11	5	15
6-12 months	5	2	5	3	20	1
12-18 months	2	2	4	1	30	4
18-24 months	3	47	4	41	27	29
24-30 months	2	61	4	56	10	23
30-36 months	0	42	2	37	1	9
>= 36 months	0	4	0	4	0	3
Total	**14**	165	**26**	153	**93**	84

[Source: FDA statistics reviewer's analysis]

Figure 5 for the KM curve for acalabrutinib monotherapy compared to obinutuzumab+ chlorambucil in "Primary Variable: PFS as Assessed by IRC" in Section 8.1.2 above.

With a median follow-up of 28.4 months in the acalabrutinib monotherapy arm and 28.0 months in the obinutuzumab+chlorambucil arm, the median estimated PFS for acalabrutinib monotherapy was not reached; the median estimated PFS for obinutuzumab+chlorambucil was 22.6 months (95% CI: 20.2–27.6).

Based on the stratified analysis, acalabrutinib monotherapy demonstrated a statistically significant improvement in IRC-assessed PFS compared with obinutuzumab+ chlorambucil, with an 80% reduction in risk of disease progression or death (HR=0.20 [95% CI: 0.13–0.30]; p<0.0001) (Table 21).

The KM estimate of the proportion of subjects without a PFS event at 12 months was 92.9% (95% CI: 87.8–95.9) for acalabrutinib monotherapy and 84.6% (95% CI: 78.0–89.3) for obinutuzumab+chlorambucil. The KM estimate of the proportion of subjects without a PFS event at 36 months was 63.9% (95% CI: 29.4–84.9) for acalabrutinib monotherapy and 31.3% (95% CI: 21.8–41.3) for obinutuzumab+chlorambucil (Table 21).

The results from the sensitivity analyses of IRC-assessed PFS based on the weighted log rank tests (Table 20) remain consistent with the primary analysis result, and confirm the robustness of the primary analysis.

Figure 8 displays the KM plot for PFS by IRC for acalabrutinib monotherapy versus obinutuzumab+ chlorambucil in the ITT population.

Table 21: Analysis of Progression-Free Survival by IRC Assessment (ITT Population) – Key Secondary Endpoint

	No. (%) of Subjects	
	Arm C Acalabrutinib Monotherapy (N=179)	**Arm A Obinutuzumab+ Chlorambucil (N=177)**
Subject Status		
Events	26 (14.5)	93 (52.5)
Death	6 (3.4)	11 (6.2)
Progressive Disease	20 (11.2)	82 (46.3%)
Censored	153 (85.5)	84 (47.5)
No Event Before Data Cutoff	139 (77.7)	64 (36.2)
No Postbaseline Assessment	5 (2.8)	11 (6.2)
No Event Before Taking Subsequent Anti-Cancer Therapy	2 (1.1)	3 (1.7)
Death or Progressive Disease After 2 or More Consecutive Missed Visits	3 (1.7)	1 (0.6)
No Event Before Study Exit	4 (2.2)	5 (2.8)
Progression Free Survival (Months)		
Q1 (95% CI)	34.2 (28.2, NE)	14.4 (13.9, 16.6)

	No. (%) of Subjects	
	Arm C Acalabrutinib Monotherapy (N=179)	**Arm A Obinutuzumab+ Chlorambucil (N=177)**
Median (95% CI)	NE (34.2, NE)	22.6 (20.2, 27.6)
Q3 (95% CI)	NE (NE, NE)	NE (33.1, NE)
Min, Max	0.0+, 39.5+	0.0+, 39.6+
Stratified Analysis[a]		
Hazard Ratio (95% CI)[b]	0.20 (0.13, 0.30)	–
p-value[c]	<0.0001	–
Unstratified Analysis		
Hazard Ratio (95% CI)[b]	0.20 (0.13, 0.31)	–
p-value[c]	<0.0001	–
KM Estimates of PFS[d] by Timepoint		
6 Months (95% CI)	95.9 (91.6, 98.0)	97.0 (92.9, 98.7)
12 Months (95% CI)	92.9 (87.8, 95.9)	84.6 (78.0, 89.3)
18 Months (95% CI)	90.5 (84.9, 94.1)	65.6 (57.7, 72.4)
24 Months (95% CI)	87.3 (80.9, 91.7)	46.7 (38.5, 54.6)
30 Months (95% CI)	81.9 (73.3, 88.0)	34.2 (25.3, 43.2)
36 Months (95% CI)	63.9 (29.4, 84.9)	31.3 (21.8, 41.3)

CI=confidence interval; IRC=Independent Review Committee; ITT=intent-to-treat; KM=Kaplan-Meier; Max=maximum; Min=minimum; NE=not estimable; PFS=progression-free survival; Q1=quartile 1; Q3=quartile 3.

[a] Stratified by 17p deletion status (yes vs. no).

[b] Estimated based on stratified or unstratified Cox Proportional Hazards model for Hazard Ratio (95% CI), respectively.

[c] Estimated based on stratified or unstratified log-rank test for p-value, respectively.

[d] KM estimate of the proportion of subjects who were progression free at the timepoint.

Note: Time to event (or time to censor for censored subjects) was calculated as date of disease progression or death (censoring date for censored subjects) – randomization date + 1. Months were derived as days / 30.4375.

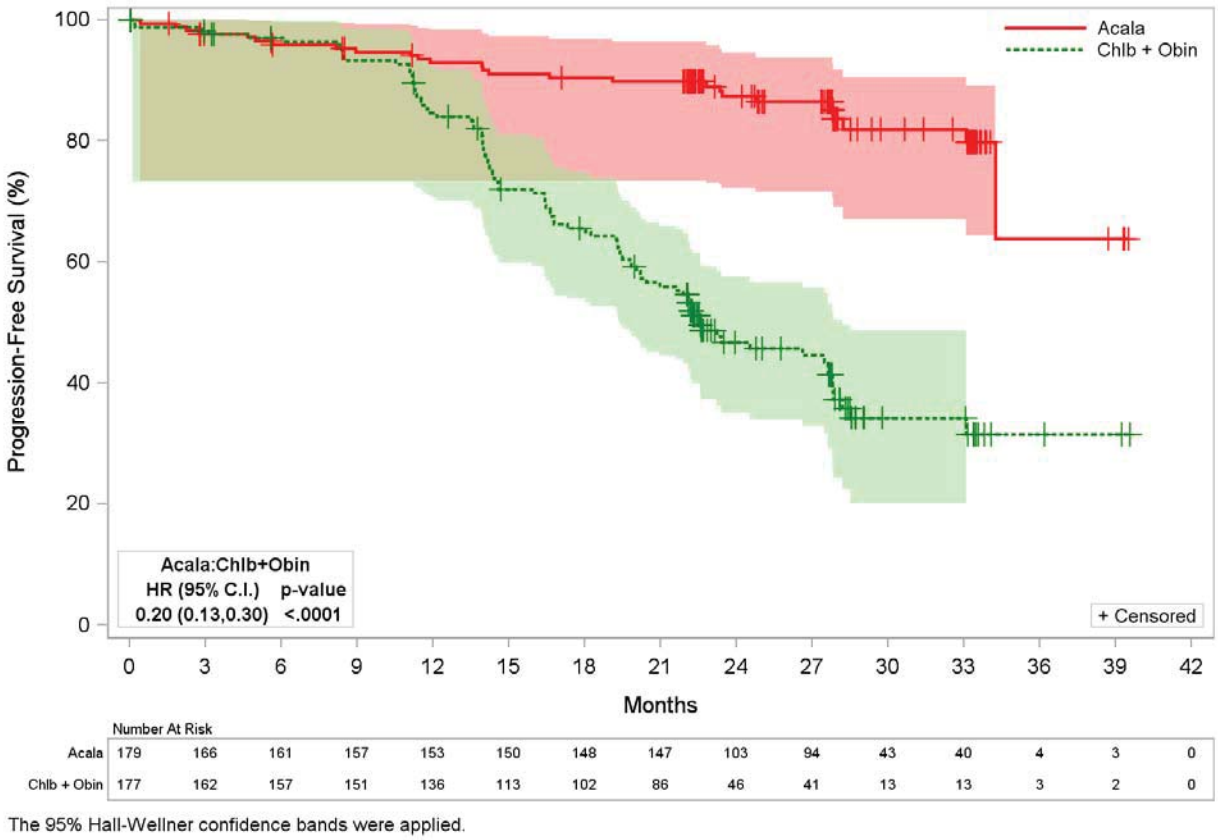
Note: "+" indicates a value from a censored subject.

Source: ELEVATE-TN clinical report, Table 14.2.1.

Regulatory Authorities Assessment:

FDA does not agree that the KM Estimates of PFS by timepoint should be presented in Table 21. These estimates can be misleading because they only present estimates at one single time point and cannot represent the overall effect of the treatment.

Figure 8: Kaplan-Meier Plot for Progression-Free Survival by IRC for Acalabrutinib Monotherapy versus Obinutuzumab+Chlorambucil (ITT Population)



IRC=Independent Review Committee; ITT=intent-to-treat.
Source: Ad-hoc figure from ELEVATE-TN per FDA Request.

Examination of Subgroups

Subgroup analysis of the key secondary endpoint are provided in Table 22.

Table 22: Subgroup Analysis of Progression-Free Survival by IRC Assessment (ITT Population) – Key Secondary Endpoint

	Responders/Subjects		
	Arm C Acalabrutinib Monotherapy (N=179)	**Arm A Obinutuzumab+ Chlorambucil (N=177)**	**Hazard Ratio (95% CI)**
Overall			
Primary analysis	26/179	93/177	0.20 (0.13, 0.30)
Presence of 17p deletion[a]			
Yes	4/19	11/117	0.20 (0.06, 0.64)

	Responders/Subjects		
	Arm C Acalabrutinib Monotherapy (N=179)	**Arm A Obinutuzumab+ Chlorambucil (N=177)**	**Hazard Ratio (95% CI)**
No	22/160	82/160	0.20 (0.12, 0.31)
ECOG at randomization[a]			
0, 1	21/167	86/168	0.18 (0.11, 0.28)
2	5/12	7/9	0.48 (0.15, 1.52)
Geographic region[a]			
North America and Western Europe	21/105	50/103	0.30 (0.18, 0.51)
Other	5/74	43/74	0.08 (0.03, 0.21)
Region			
North America	14/70	30/61	0.30 (0.16, 0.56)
South America	0/8	4/7	NE (NE, NE)
Western Europe	8/42	25/52	0.29 (0.13, 0.65)
Central and Eastern Europe	3/46	23/40	0.07 (0.02, 0.24)
Australia and New Zealand	1/13	11/17	0.10 (0.01, 0.79)
Age group			
<65	5/28	16/24	0.19 (0.07, 0.52)
≥65	21/151	77/153	0.20 (0.12, 0.32)
<75	16/129	66/125	0.15 (0.09, 0.27)
≥75	10/50	27/52	0.35 (0.17, 0.72)
Sex			
Male	19/111	58/106	0.23 (0.14, 0.39)
Female	7/68	35/71	0.14 (0.06, 0.32)
Race			
White	24/170	88/165	0.18 (0.12, 0.29)
Non-white	2/9	5/12	0.62 (0.12, 3.19)
Rai stage at screening			
Stage 0-II	7/92	54/99	0.10 (0.04, 0.21)
Stage III-IV	19/87	39/78	0.34 (0.19, 0.59)
Bulky disease			
<5 cm	15/107	53/116	0.23 (0.13, 0.40)
≥5 cm	10/68	39/55	0.14 (0.07, 0.27)
B2-microglobin at baseline			
≤3.5 mg/L	4/38	14/42	0.26 (0.09, 0.79)
>3.5 mg/L	22/140	78/132	0.18 (0.11, 0.30)
Presence of 11q deletion			
Yes	3/31	26/33	0.07 (0.02, 0.22)
No	23/148	66/143	0.26 (0.16, 0.41)
TP53 mutation			
Yes	5/19	14/21	0.15 (0.05, 0.46)
No	21/160	78/155	0.20 (0.12, 0.32)
17p deletion or TP53 mutation			
Yes	6/23	16/25	0.23 (0.09, 0.61)
No	20/156	77/152	0.19 (0.11, 0.31)
17p deletion and TP53 mutation			
Yes	2/12	9/12	0.03 (0.00, 0.28)

	Responders/Subjects		
	Arm C Acalabrutinib Monotherapy (N=179)	**Arm A Obinutuzumab+ Chlorambucil (N=177)**	**Hazard Ratio (95% CI)**
No	24/167	84/165	0.21 (0.13, 0.33)
IgHV			
Mutated	10/58	14/59	0.69 (0.31, 1.56)
Unmutated	16/119	78/116	0.11 (0.07, 0.19)
17p deletion, TP53 mutation, 11q deletion, or unmutated IgHV			
Yes	18/129	83/129	0.13 (0.08, 0.21)
No	8/50	10/48	0.76 (0.30, 1.92)
17p deletion, TP53 mutation, or 11q deletion			
Yes	8/52	41/55	0.11 (0.05, 0.24)
No	18/127	52/122	0.26 (0.15, 0.45)
Complex karyotype			
Yes	3/31	20/32	0.10 (0.03, 0.33)
No	20/117	59/121	0.27 (0.16, 0.46)

ECOG=Eastern Cooperative Oncology Group; del=deletion; IgHV=immunoglobulin heavy-chain variable; IRC=Independent Review Committee; ITT=intent-to-treat; NE=not estimable.

[a] Per Interactive voice/web response system (IXRS) record.

Source: ELEVATE-TN clinical report Figure 14.2.1.9.2.

Sensitivity Analyses

The following sensitivity analyses were performed for obinutuzumab+chlorambucil compared with acalabrutinib monotherapy: unstratified analysis, inclusion of PFS without censoring for subsequent anticancer therapy, inclusion of PFS events after 2 or more consecutively missed visits and exclusion of subjects with important protocol deviations (Table 23, Figure 9).

The key sensitivity analysis of PFS without censoring for subsequent anticancer therapy was consistent with the key secondary analysis and showed similar improvement in PFS for acalabrutinib monotherapy compared with obinutuzumab+chlorambucil (stratified: HR=0.20 [95% CI: 0.13–0.30]; p<0.0001 and unstratified: HR=0.20 [95% CI: 0.13–0.31]; p<0.0001). All other sensitivity analyses were also consistent with the key secondary analysis, with HR ranging from 0.15–0.21, which was statistically significant for all analyses (p<0.0001) (Table 23, Figure 9).

Table 23: Sensitivity Analyses of Progression-Free Survival by IRC Assessment (ITT Population) – Key Secondary Endpoint

	No. (%) of Subjects	
	Arm C Acalabrutinib Monotherapy (N=179)	**Arm A Obinutuzumab+ Chlorambucil (N=177)**
Include PFS Without Censoring for Subsequent Anticancer Therapy		
Events	26 (14.5)	93 (52.5)
Death	6 (3.4)	11 (6.2)
Disease Progression	20 (11.2)	82 (46.3)
Censored	153 (85.5)	84 (47.5)
Progression-free survival (months)		
Median (95% CI)	NE (34.2, NE)	22.6 (20.2, 27.8)
Min, Max	0.0+, 39.5+	0.0+, 39.6+
Stratified analysis[a]		
Hazard ratio (95% CI)[b]	0.20 (0.13, 0.30)	–
p-value[c]	<0.0001	–
Unstratified Analysis		
Hazard ratio (95% CI)[b]	0.20 (0.13, 0.31)	–
p-value[c]	<0.0001	–
Include PFS Events After ≥2 Consecutively Missed Visits		
Events	29 (16.2)	94 (53.1)
Death	9 (5.0)	12 (6.8)
Disease Progression	20 (11.2)	82 (46.3)
Censored	150 (83.8)	83 (46.9)
Progression-free survival (months)		
Median (95% CI)	NE (34.2, NE)	22.6 (20.2, 27.6)
Min, Max	0.0+, 39.5+	0.0+, 39.6+
Stratified analysis[a]		
Hazard ratio (95% CI)[b]	0.21 (0.14, 0.33)	–
p-value[c]	<0.0001	–
Exclude Subjects with Important Protocol Deviation		
Events	20/162 (12.3)	82/149 (55.0)
Death	5/162 (3.1)	10/149 (6.7)
Disease Progression	15/162 (9.3)	72/149 (48.3)
Censored	142/162 (87.7)	67/149 (45.0)
Progression-free survival (months)		
Median (95% CI)	34.2 (33.1, NE)	22.3 (19.8, 27.5)
Min, Max	0.0+, 39.4+	0.0+, 39.6+
Stratified analysis[a]		
Hazard ratio (95% CI)[b]	0.15 (0.09, 0.25)	–
p-value[c]	<0.0001	–

CI=confidence interval; IRC=Independent Review Committee; ITT=intent-to-treat; Max=maximum; Min=minimum; NE=not estimable; PFS=progression-free survival.

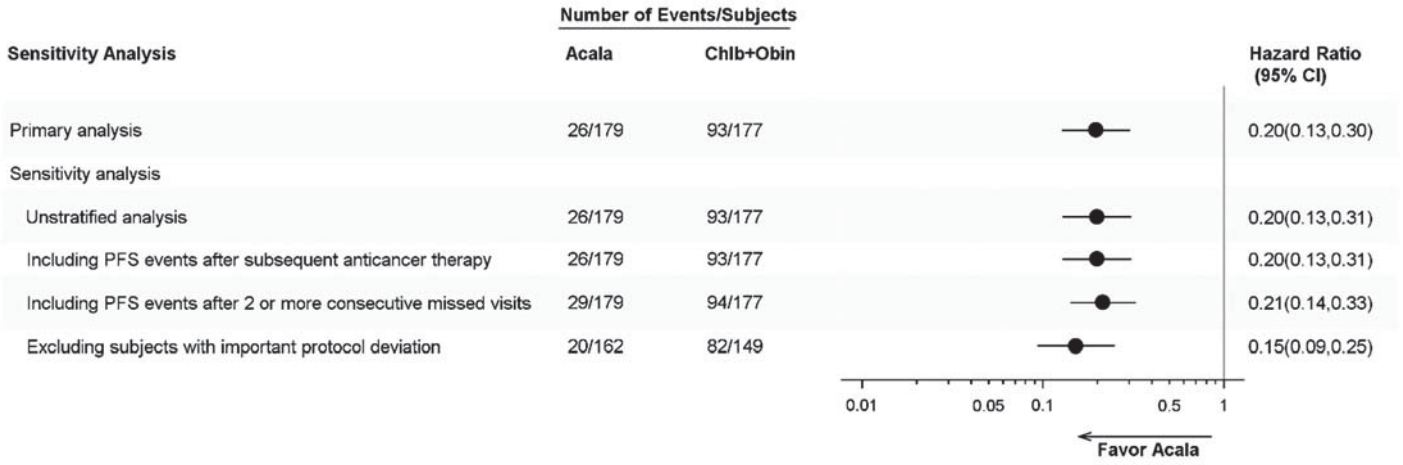
[a] Stratified by 17p deletion status (yes vs. no).

[b] Estimated based on stratified or unstratified Cox Proportional Hazards model for Hazard Ratio (95% CI), respectively.
[c] Estimated based on stratified or unstratified log-rank test for p-value, respectively.
Note: Time to event (or time to censor for censored subjects) was calculated as date of disease progression or death (censoring date for censored subjects) – randomization date + 1. Months were derived as days / 30.4375.
Note: "+" indicates a value from a censored subject.
Source: ELEVATE-TN clinical report, Table 14.2.1.1, Table 14.2.1.2, Table 14.2.1.3.

Regulatory Authorities Assessment:

FDA does not agree that the p-values should be presented in Table 23. These sensitivity analyses are exploratory and do not have alpha allocation. All p-values presented in Table 23 are nominal.

Figure 9: Forest Plot for Sensitivity Analysis of Progression Free Survival by IRC Assessment (ITT Population) – Key Secondary Endpoint



IRC=Independent Review Committee; ITT=intent-to-treat; PFS=progression-free survival.
Source: ELEVATE-TN clinical report, Figure 14.2.1.8.2.

Regulatory Authorities Assessment:

These analyses are exploratory.

PFS by Investigator Assessment

The analysis of the investigator-assessed PFS was consistent with the primary analysis. Based on the stratified analysis, both acalabrutinib+obinutuzumab and acalabrutinib monotherapy demonstrated a statistically significant improvement in investigator-assessed PFS compared with obinutuzumab+chlorambucil (HR=0.12 [95% CI: 0.07–0.21]; p<0.0001) and (HR=0.16 [95% CI: 0.10–0.27]; p<0.0001), respectively. The unstratified analysis was also statistically significant for both treatment arms (p<0.0001). As of the data cutoff date, the median estimated PFS for

acalabrutinib+ obinutuzumab and acalabrutinib monotherapy was not reached; the median estimated PFS for obinutuzumab+chlorambucil was 27.8 months (95% CI: 22.6–28.8) (Table 24).

The KM estimate of the proportion of responders without an investigator-assessed PFS event at 12 months was 95.4% (95% CI: 91.1–97.7) for acalabrutinib+obinutuzumab, 94.7% (95% CI: 90.1–97.2) for acalabrutinib monotherapy, and 85.5% (95% CI: 79.1–90.0) for obinutuzumab+ chlorambucil. The KM estimate of the proportion of responders without a PFS event at 36 months was 90.9% (95% CI: 85.3–94.5), 87.6% (95% CI: 81.0–92.1), and 36.9% (95% CI: 26.6–47.1) for acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+ chlorambucil, respectively (Table 24).

Table 24: Investigator-Assessed PFS (ITT Population)

	No. (%) of Subjects		
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab+ Chlorambucil (N=177)**
Subject Status			
Events	15 (8.4)	19 (10.6)	86 (48.6)
Death	6 (3.4)	7 (3.9)	11 (6.2)
Progressive Disease	9 (5.0)	12 (6.7)	75 (42.4)
Censored	164 (91.6)	160 (89.4)	91 (51.4)
PD after Subsequent anticancer therapy	0	0	1 (0.6)
No event before data cutoff	155 (86.6)	147 (82.1)	74 (41.8)
No postbaseline assessment	0	1 (0.6)	6 (3.4)
No event before taking subsequent anti-cancer therapy	2 (1.1)	4 (2.2)	2 (1.1)
Death or PD after 2 or more consecutive missed visits	1 (0.6)	1 (0.6)	1 (0.6)
No event before study exit	6 (3.4)	7 (3.9)	7 (4.0)
Progression Free Survival (months)			
Q1 (95% CI)	NE (NE, NE)	NE (NE, NE)	16.4 (14.1, 18.2)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)	27.8 (22.6, 28.8)
Q3 (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Min, Max	1.1, 39.4+	0.0+, 39.5+	0.0+, 39.6+
Stratified Analysis[a]			
Hazard Ratio (95% CI)[b]	0.12 (0.07, 0.21)	0.16 (0.10, 0.27)	–
p-value[c]	<0.0001	<0.0001	–
Unstratified Analysis			
Hazard Ratio (95% CI)[b]	0.13 (0.07, 0.22)	0.17 (0.10, 0.27)	–
p-value[c]	<0.0001	<0.0001	–
KM Estimates of PFS[d] by Timepoint			

	No. (%) of Subjects		
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab+ Chlorambucil (N=177)**
6 Months (95% CI)	98.3 (94.8, 99.5)	97.1 (93.2, 98.8)	95.2 (90.7, 97.6)
12 Months (95% CI)	95.4 (91.1, 97.7)	94.7 (90.1, 97.2)	85.5 (79.1, 90.0)
18 Months (95% CI)	94.3 (89.6, 96.9)	92.9 (87.8, 95.9)	68.8 (61.0, 75.3)
24 Months (95% CI)	91.9 (86.7, 95.1)	90.4 (84.9, 94.0)	54.7 (46.7, 62.0)
30 Months (95% CI)	90.9 (85.3, 94.5)	87.6 (81.0, 92.1)	39.9 (30.6, 49.1)
36 Months (95% CI)	90.9 (85.3, 94.5)	87.6 (81.0, 92.1)	36.9 (26.6, 47.1)

CI=confidence interval; ITT=intent-to-treat; KM=Kaplan-Meier; Max=maximum; Min=minimum; NE=not estimable; PFS=progression free survival; Q1=quartile 1; Q3=quartile 3.

[a] Stratified by 17p deletion status (yes vs. no).

[b] Estimated based on stratified or unstratified Cox Proportional Hazards model for Hazard Ratio (95% CI), respectively.

[c] Estimated based on stratified or unstratified log-rank test for p-value, respectively.

[d] KM estimate of the proportion of subjects who were progression free at the timepoint.

Note: Time to event (or time to censor for censored subjects) was calculated as date of disease progression or death (censoring date for censored subjects) – randomization date + 1. Months were derived as days / 30.4375.

Note: "+" indicates a value from a censored subject.

Source: ELEVATE-TN clinical report, Table 14.2.5.1.

Regulatory Authorities Assessment:

FDA does not agree that the p-values and the KM Estimates of PFS by timepoint should be presented in Table 24. These estimates can be misleading because they only present estimates at one single time point and cannot represent the overall effect of the treatment. These sensitivity analyses are exploratory and do not have alpha allocation. All p-values presented in Table 24 are nominal.

Concordance Between IRC-Assessed and Investigator-Assessed PD

The overall concordance rates between the IRC-assessed and investigator-assessed PD for acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+chlorambucil were 96.6%, 93.3%, and 89.3%, respectively (Table 25).

Table 25: Concordance between IRC-and Investigator-Assessed Progressive Disease (ITT Population)

	No. (%) of Subjects		
	PD by Investigator		
Progressive Disease by IRC	**Yes**	**No**	**Total**
Arm B: Acalabrutinib+ Obinutuzumab (N=179)			
Yes	6 (3.4)	3 (1.7)	9 (5.0)
No	3 (1.7)	167 (93.3)	170 (95.0)
Total	9 (5.0)	170 (95.0)	179 (100.0)
Overall concordance rate	96.6	–	–

	No. (%) of Subjects		
	PD by Investigator		
Progressive Disease by IRC	**Yes**	**No**	**Total**
Arm C: Acalabrutinib Monotherapy (N=179)			
Yes	10 (5.6)	10 (5.6)	20 (11.2)
No	2 (1.1)	157 (87.7)	159 (88.8)
Total	12 (6.7)	167 (93.3)	179 (100.0)
Overall concordance rate	93.3	–	–
Arm A: Obinutuzumab+ Chlorambucil (N=177)			
Yes	69 (39.0)	13 (7.3)	82 (46.3)
No	6 (3.4)	89 (50.3)	95 (53.7)
Total	75 (42.4)	102 (57.6)	177 (100.0)
Overall concordance rate	89.3	–	–

IRC=Independent Review Committee; ITT=intent-to-treat; PD=progressive disease.
Source: ELEVATE-TN clinical report, Table 14.2.5.2.

Investigator-Assessed and IRC-assessed ORR

The investigator-assessed ORR for acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+chlorambucil was 96.1% (95% CI: 92.1–98.1), 89.4% (95% CI: 84.0–93.1), and 82.5% (95% CI: 76.2–87.4), respectively. Per investigator assessment, CR was achieved in 38 subjects in the acalabrutinib+obinutuzumab arm, 13 subjects in acalabrutinib monotherapy arm, and 23 subjects in the obinutuzumab+ chlorambucil arm. The investigator-assessed ORR including PRL for acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+ chlorambucil was 96.6% (95% CI: 92.9–98.5), 92.2% (95% CI: 87.3–95.3), and 82.5% (95% CI: 76.2–87.4) (Table 26) .

Table 26: Best Overall Response by Investigator Assessment (ITT Population)

	No. (%) of Subjects		
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab+ Chlorambucil (N=177)**
Best Overall Response			
CR	38 (21.2)	13 (7.3)	23 (13.0)
CRi	5 (2.8)	1 (0.6)	0
nPR	12 (6.7)	8 (4.5)	11 (6.2)
PR	117 (65.4)	138 (77.1)	112 (63.3)
PRL	1 (0.6)	5 (2.8)	0
Stable Disease	1 (0.6)	4 (2.2)	16 (9.0)
Progressive Disease	1 (0.6)	3 (1.7)	3 (1.7)
UNK	0	1 (0.6)	0
Not Evaluable[a]	4 (2.2)	6 (3.4)	12 (6.8)
ORR (CR+CRi+nPR+PR)	172 (96.1)	160 (89.4)	146 (82.5)
95% CI[b]	(92.1, 98.1)	(84.0, 93.1)	(76.2, 87.4)

	No. (%) of Subjects		
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab+ Chlorambucil (N=177)**
ORR Difference (vs. obinutuzumab+chlorambucil)	13.6	6.9	–
95% CI[b]	(7.3, 19.9)	(-0.3, 14.1)	–
p-value[c]	<0.0001	0.0522	–
ORR+PRL (CR+CRi+nPR+PR+PRL)	173 (96.6)	165 (92.2)	146 (82.5)
95% CI[b]	(92.9, 98.5)	(87.3, 95.3)	(76.2, 87.4)
ORR+PRL Difference (vs. obinutuzumab+chlorambucil)	14.2	9.7	–
95% CI[b]	(8.0, 20.4)	(2.8, 16.5)	–
p-value[c]	<0.0001	0.0048	–

CI=confidence interval; CR=complete response; CRi=CR with incomplete blood count recovery; ITT=intent-to-treat; nPR=nodular partial response; ORR=overall response rate; PR=partial response; PRL=partial response with lymphocytosis; UNK=unknown.

[a] A total of 22 subjects were not evaluable for the investigator-assessed ORR and investigator-assessed ORR including PRL. Of the 22 subjects, 20 subjects discontinued the study before the first response assessment (Cycle 4): 15 subjects withdrew consent; 4 subjects died (One subject died in a car accident before receiving the first dose of study medication; one subject died of sepsis before receiving the first dose of study medication; one subject died due to bilateral pneumonia caused by aspergillus; and one subject died due to bacterial sepsis), and 1 subject was a randomization error (one subject did not receive a dose of study medication). Of the 22 subjects, 2 subjects discontinued study medication before the first response assessment (Cycle 4) and have been followed up on survival only. One subject had a Grade 4 nonserious AE of thrombocytopenia (related to acalabrutinib); acalabrutinib was withdrawn. One subject discontinued obinutuzumab due to a Grade 4 SAE of infusion-related reaction (related to obinutuzumab) and discontinued acalabrutinib due to cardiologist's concern of bleeding risk with the concomitant medications of clopidogrel and acetylsalicylic acid (ELEVATE-TN clinical report, Listing 16.2.1.1 and Listing 16.2.7.1).

[b] 95% confidence interval based on Normal approximation (with use of Wilson's score).

[c] Based on Cochran-Mantel-Haenzel test with adjustment for 17p deletion status (yes vs no).

Source: ELEVATE-TN clinical report, Table 14.2.6.

Regulatory Authorities Assessment:

The IRC-assessed ORR should be presented before the investigator-assessed ORR. The IRC-assessed ORR is the secondary endpoint included in the pre-specified hierarchical testing order, while the investigator-assessed ORR is exploratory and not included in the hierarchical testing order.

FDA does not agree that the p-values should be presented in Table 26. The investigator-assessed ORR analyses are exploratory and do not have alpha allocation. All p-values presented in Table 26 are nominal.

The IRC-assessed ORR for acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+chlorambucil was 93.9% (95% CI: 89.3–96.5), 85.5% (95% CI: 79.6–89.9), and 78.5% (95% CI: 71.9–83.9), respectively. Per IRC assessment, CR was achieved in 23 subjects in the acalabrutinib+obinutuzumab arm, 1 subject in acalabrutinib monotherapy arm, and 8 subjects in the obinutuzumab+chlorambucil arm. IRC-assessed ORR including PRL for acalabrutinib+ obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+chlorambucil was 93.9% (95% CI: 89.3–96.5), 86.6% (95% CI: 80.8–90.8), and 78.5% (95% CI: 71.9–83.9), respectively (Table 27).

Table 27: Best Overall Response by IRC Assessment (ITT Population)

	No. (%) of Subjects		
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab+ Chlorambucil (N=177)**
Best Overall Response			
CR	23 (12.8)	1 (0.6)	8 (4.5)
CRi	1 (0.6)	0	0
nPR	1 (0.6)	2 (1.1)	3 (1.7)
PR	143 (79.9)	150 (83.8)	128 (72.3)
PRL	0	2 (1.1)	0
Stable Disease	4 (2.2)	8 (4.5)	15 (8.5)
Non-PD	1 (0.6)	0	2 (1.1)
NED	0	0	1 (0.6)
Progressive Disease	0	3 (1.7)	0
UNK[a]	6 (3.4)	12 (6.7)	12 (6.8)
Not Evaluable[b]	0	1 (0.6)	8 (4.5)
ORR (CR+CRi+nPR+PR)	168 (93.9)	153 (85.5)	139 (78.5)
95% CI[c]	(89.3, 96.5)	(79.6, 89.9)	(71.9, 83.9)
ORR Difference (vs. obinutuzumab+chlorambucil)	15.3	6.9	–
95% CI[c]	(8.3, 22.3)	(-1.0, 14.9)	–
p-value[d]	<0.0001	0.0763	–
ORR+PRL (CR+CRi+nPR+PR+PRL)	168 (93.9)	155 (86.6)	139 (78.5)
95% CI[c]	(89.3, 96.5)	(80.8, 90.8)	(71.9, 83.9)
ORR+PRL Difference (vs. obinutuzumab+chlorambucil)	15.3	8.1	–
95% CI[c]	(8.3, 22.3)	(0.2, 15.9)	–
p-value[d]	<0.0001	0.0376	–

CI=confidence interval; CR=complete response; CRi=CR with incomplete blood count recovery; IRC=Independent Review Committee; ITT=intent-to-treat; NED=no evaluable disease; Non-PD=not meeting criteria for progressive disease and not UNK; nPR=nodular partial response; ORR=overall response rate; PR=partial response; PRL=partial response with lymphocytosis; UNK=unknown.

[a] "UNK" category included 17 subjects with IRC global assessment as "Not Applicable" whereas their IRC timepoint assessments included "PR" at either a single timepoint or at nonconsecutive timepoints.
[b] These 9 subjects with no evaluable disease were those 9 subjects who were randomized to study drug but did not receive study drug.
[c] 95% confidence interval based on Normal approximation (with use of Wilson's score).
[d] Based on Cochran-Mantel-Haenzel test with adjustment for 17p deletion status (yes vs no).
Note: CR, Cri, nPR, and PR were based on IRC global assessment; other response categories are derived from IRC assessment at each timepoint.
Source: ELEVATE-TN clinical report, Table 14.2.2.

Regulatory Authorities Assessment:

The IRC-assessed ORR is a secondary endpoint to be tested if the test for PFS is statistically significant according to the SAP and study protocol.

FDA does not agree that the p-values for the ORR+PRL Difference should be presented in Table 27. These analyses are exploratory and do not have alpha allocation. The p-values for the ORR+PRL Difference in Table 27 are nominal.

Subgroup Analysis of ORR by IRC Assessment
Subgroup analysis for ORR by IRC assessment is provided in Table 28.

Table 28: Overall Response Rate by IRC Assessment by for Selected Subgroups (ITT Population)

	No. (%) of Subjects					
	Arm B Acalabrutinib+ Obinutuzumab (N=179)		Arm C Acalabrutinib Monotherapy (N=179)		Arm A Obinutuzumab+ Chlorambucil (N=177)	
	Responders/ Subjects	ORR (%) (95% CI)	Responders/ Subjects	ORR (%) (95% CI)	Responders/ Subjects	ORR (%) (95% CI)
Overall	168/179	93.9 (89.3, 96.5)	153/179	85.5 (79.6, 89.9)	139/177	78.5 (71.9, 83.9)
Presence of 17p deletion[a]						
Yes	18/21	85.7 (65.4, 95.0)	14/19	73.7 (51.2, 88.2)	9/17	52.9 (31.0, 73.8)
No	150/158	94.9 (90.3, 97.4)	139/160	86.9 (80.8, 91.3)	130/160	81.3 (74.5, 86.5)
ECOG PS at randomization						
0, 1	160/169	94.7 (90.2, 97.2)	145/167	86.8 (80.9, 91.1)	134/168	79.8 (73.1, 85.1)
2	8/10	80.0 (49.0, 94.3)	8/12	66.7 (39.1, 86.2)	5/9	55.6 (26.7, 81.1)
Age group						
<65	35/35	100 (90.1, 100)	23/28	82.1 (64.4, 92.1)	17/24	70.8 (50.8, 85.1)
≥65	133/144	92.4 (86.8, 95.7)	130/151	86.1 (79.7, 90.7)	122/153	79.7 (72.2, 85.3)
<75	123/126	97.6 (93.2, 99.2)	114/129	88.4 (81.7, 92.8)	95/125	76.0 (67.8, 82.6)
≥75	45/53	84.9 (72.9, 92.1)	39/50	78.0 (64.8, 87.2)	44/52	84.6 (72.5, 92.0)
Sex						
Male	107/111	96.4 (91.1, 98.6)	94/111	84.7 (76.8, 90.2)	85/106	80.2 (71.6, 86.7)
Female	61/68	89.7 (80.2, 94.9)	59/68	86.8 (76.7, 92.9)	54/71	76.1 (65.0, 84.5)
Race						
White	153/164	93.3 (88.4, 96.2)	146/170	85.9 (79.9, 90.3)	130/165	78.8 (71.9, 84.3)
Non-white	15/15	100 (79.6, 100)	7/9	77.8 (45.3, 93.7)	9/12	75.0 (46.8, 91.1)
Rai stage at screening						
Stage 0-II	92/93	98.9 (94.2, 99.8)	85/92	92.4 (85.1, 96.3)	82/99	82.8 (74.2, 89.0)
Stage III-IV	76/86	88.4 (79.9, 93.6)	68/87	78.2 (68.4, 85.5)	57/78	73.1 (62.3, 81.7)
Bulky disease						
<5 cm	123/131	93.9 (88.4, 96.9)	95/107	88.8 (81.4, 93.5)	92/116	79.3 (71.1, 85.7)
≥5 cm	43/46	93.5 (82.5, 97.8)	57/68	83.8 (73.3, 90.7)	43/55	78.2 (65.5, 87.1)
B2-microglobin at baseline						
≤3.5 mg/L	43/44	97.7 (88.2, 99.6)	31/38	81.6 (66.6, 90.8)	27/42	64.3 (49.2, 77.0)
>3.5 mg/L	124/132	93.9 (88.5, 96.9)	121/140	86.4 (79.8, 91.1)	109/132	82.6 (75.2, 88.1)

	No. (%) of Subjects					
	Arm B Acalabrutinib+ Obinutuzumab (N=179)		Arm C Acalabrutinib Monotherapy (N=179)		Arm A Obinutuzumab+ Chlorambucil (N=177)	
	Responders/ Subjects	ORR (%) (95% CI)	Responders/ Subjects	ORR (%) (95% CI)	Responders/ Subjects	ORR (%) (95% CI)
Complex karyotype						
Yes	27/29	93.1 (78.0, 98.1)	26/31	83.9 (67.4, 92.9)	20/32	62.5 (45,3, 77.1)
No	118/126	93.7 (88.0, 96.7)	98/117	83.3 (76.0, 89.4)	98/121	81.0 (73.1, 87.0)
Presence of 11q deletion						
Yes	31/31	100 (89.0, 100)	27/31	87.1 (71.1, 94.9)	27/33	81.8 (65.6, 91.4)
No	137/148	92.6 (87.2, 95.8)	126/148	85.1 (78.5, 90.0)	111/143	77.6 (70.1, 83.7)
TP53 mutation						
Yes	18/21	85.7 (65.4, 95.0)	16/19	84.2 (62.4, 94.5)	10/21	47.6 (28.3, 67.6)
No	150/158	94.9 (90.3, 97.4)	137/160	85.6 (79.4, 90.2)	128/155	82.6 (75.8, 87.7)
IgHV						
Mutated	68/74	91.9 (83.4, 96.2)	44/58	75.9 (63.5, 85.0)	48/59	81.4 (69.6, 89.3)
Unmutated	98/103	95.1 (89.1, 97.9)	107/119	89.9 (83.2, 94.1)	89/116	76.7 (68.3, 83.5)
17p deletion, TP53 mutation, 11q deletion, or unmutated IgHV						
Yes	110/117	94.0 (88.2, 97.1)	114/129	88.4 (81.7, 92.8)	97/129	75.2 (67.1, 81.8)
No	58/62	93.5 (84.6, 97.5)	39/50	78.0 (64.8, 87.2)	42/48	87.5 (75.3, 94.1)

ECOG PS=Eastern Cooperative Oncology Group performance status; IgHV=immunoglobulin heavy-chain variable; IRC=Independent Review Committee; ITT=intent-to-treat.

[a] Per Interactive voice/web response system (IXRS) record.

Source: ELEVATE-TN clinical report, Figure 14.2.2.1.

Richter's Transformation

One subject in the acalabrutinib+obinutuzumab arm, 5 subjects in the acalabrutinib monotherapy arm, and 1 subject in the obinutuzumab+chlorambucil arm had Richter's transformation during the study including the crossover period.

Concordance Between IRC-Assessed and Investigator-Assessed CR/CRi and Best Overall Response

The overall concordance rates between the IRC-assessed and investigator-assessed CR/CRi for acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+ chlorambucil were 86.0%, 92.7%, and 90.4%, respectively (Table 29).

Table 29: Concordance between IRC-and Investigator-Assessed CR/CRi and Best Overall Response (ITT Population)

	No. (%) of Subjects		
	CR/CRi by Investigator		
CR/CRi by IRC	**Yes**	**No**	**Total**
Acalabrutinib+ Obinutuzumab (N=179)			
Yes	21 (11.7)	3 (1.7)	24 (13.4)
No	22 (12.3)	133 (74.3)	155 (86.6)
Total	43 (24.0)	136 (76.0)	179 (100.0)
Overall concordance rate	86.0	–	–
Acalabrutinib Monotherapy (N=179)			
Yes	1 (0.6)	0	1 (0.6)
No	13 (7.3)	165 (92.2)	178 (99.4)
Total	14 (7.8)	165 (92.2)	179 (100.0)
Overall concordance rate	92.7	–	–
Obinutuzumab+ Chlorambucil (N=177)			
Yes	7 (4.0)	1 (0.6)	8 (4.5)
No	16 (9.0)	153 (86.4)	169 (95.5)
Total	23 (13.0)	154 (87.0)	177 (100.0)
Overall concordance rate	90.4	–	–
	Best Overall Response by Investigator		
Best Overall Response by IRC	**Yes**	**No**	**Total**
Acalabrutinib+ Obinutuzumab (N=179)			
Yes	168 (93.9)	0	168 (93.9)
No	4 (2.2)	7 (3.9)	11 (6.1)
Total	172 (96.1)	7 (3.9)	179 (100.0)
Overall concordance rate	97.8	–	–
Acalabrutinib Monotherapy (N=179)			
Yes	150 (83.8)	3 (1.7)	153 (85.5)
No	10 (5.6)	16 (8.9)	26 (14.5)
Total	160 (89.4)	19 (10.6)	179 (100.0)
Overall concordance rate	92.7	–	–
Obinutuzumab+ Chlorambucil (N=177)			
Yes	128 (72.3)	11 (6.2)	139 (78.5)
No	18 (10.2)	20 (11.3)	38 (21.5)
Total	146 (82.5)	31 (17.5)	177 (100.0)

	No. (%) of Subjects		
Overall concordance rate	83.6	–	–

Best Overall Response=CR+Cri+nPR+PR; CR=complete response; CRi=CR with incomplete blood count recovery; IRC=Independent Review Committee; ITT=intent-to-treat; PD=progressive disease; PR=Partial Response; nPR=nodular PR.
Source: ELEVATE-TN clinical report, Table 14.2.6.1, Table 14.2.6.2.

Overall Survival

The median OS was not reached in any of the treatment arms, with an HR of 0.47 (95% CI: 0.21–1.06; p=0.0577) for the acalabrutinib+obinutuzumab arm and an HR of 0.60 (95% CI: 0.28–1.27; p=0.1556) for the acalabrutinib monotherapy arm compared with obinutuzumab+chlorambucil arm (Table 30,Figure 10).

Table 30: Overall Survival (ITT Population)

	No. (%) of Subjects		
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab+ Chlorambucil (N=177)**
Subject Status			
Events[a]	9 (5.0)	11 (6.1)	17 (9.6)
Death	9 (5.0)	11 (6.1)	17 (9.6)
Censored[b]	170 (95.0)	168 (93.9)	160 (90.4)
Alive	170 (95.0)	168 (93.9)	160 (90.4)
Overall Survival (months)			
Q1 (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Q3 (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Min, Max	1.7, 40.4+	0.1+, 40.8+	0.0+, 40.7+
Stratified Analysis[c]			
Hazard Ratio (95% CI)[d]	0.47 (0.21, 1.06)	0.60 (0.28, 1.27)	–
p-value[e]	0.0577	0.1556	–
KM Estimates of OS[f] by Timepoint			
6 Months (95% CI)	98.3 (94.9, 99.5)	98.9 (95.5, 99.7)	97.1 (93.2, 98.8)
12 Months (95% CI)	96.1 (91.9, 98.1)	98.3 (94.8, 99.4)	96.5 (92.4, 98.4)
18 Months (95% CI)	94.9 (90.5, 97.3)	97.1 (93.2, 98.8)	94.7 (90.1, 97.2)
24 Months (95% CI)	94.9 (90.5, 97.3)	94.7 (90.2, 97.2)	91.7 (86.3, 95.0)
30 Months (95% CI)	94.9 (90.5, 97.3)	93.5 (88.6, 96.3)	89.9 (83.9, 93.7)
36 Months (95% CI)	94.9 (90.5, 97.3)	93.5 (88.6, 96.3)	88.1 (80.7, 92.8)

CI=confidence interval; ITT=intent-to-treat; KM=Kaplan-Meier; Max=maximum; Min=minimum; NE=not estimable; OS=overall survival; Q1=quartile 1; Q3=quartile 3.

[a] Included all deaths on study, including deaths after crossover for obinutuzumab+chlorambucil subjects who crossed over.
[b] Based on subject's last known date of alive on study.
[c] Stratified by 17p deletion status (yes vs. no).
[d] Estimated based on stratified Cox Proportional Hazards model for Hazard Ratio (95% CI).
[e] Estimated based on stratified log-rank test for p-value.
[f] KM estimate of proportion subjects who were alive at the timepoint.

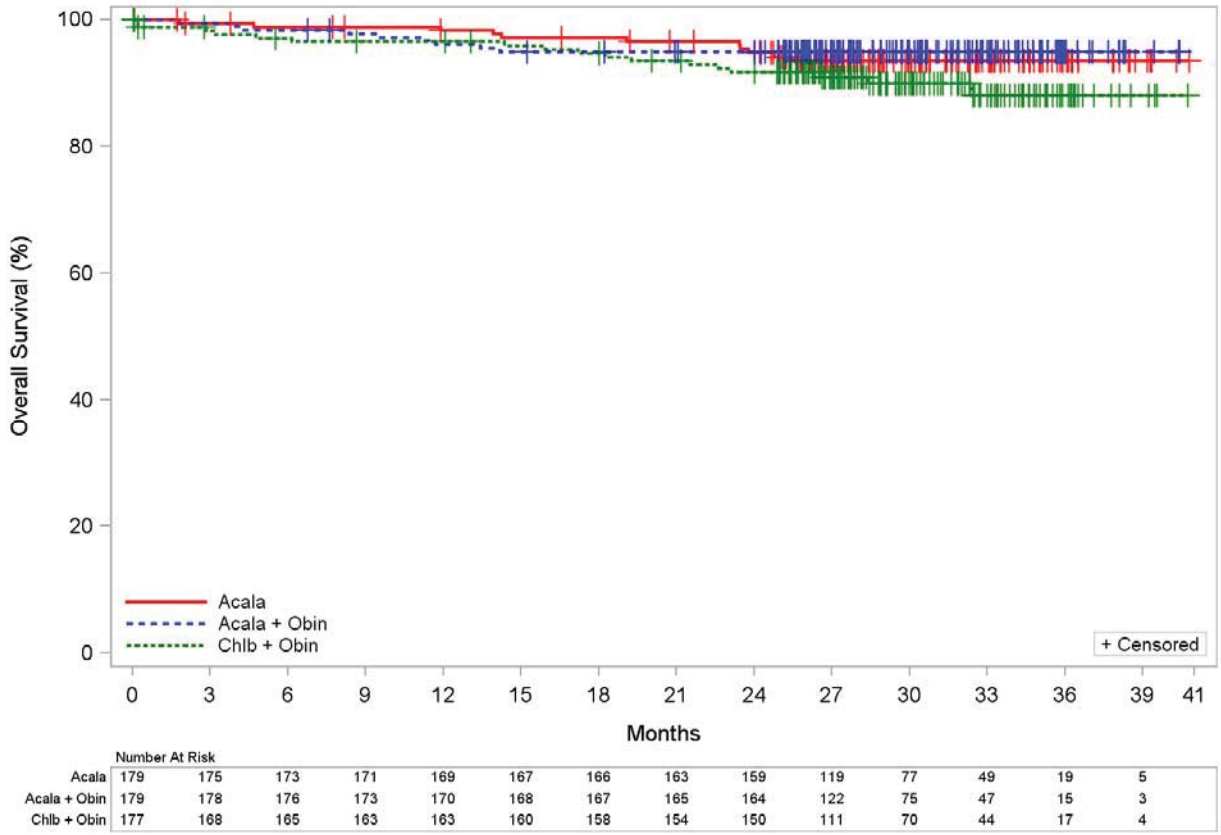
Note: Time to event (or time to censor for censored subjects) was calculated as date of death (censoring date for censored subjects) – randomization date + 1; Months are derived as days / 30.4375.
Note: "+" indicates a value from a censored subject.
Source: ELEVATE-TN clinical report, Table 14.2.4.

Regulatory Authorities Assessment:

FDA does not agree that the KM Estimates of OS by timepoint should be presented in Table 30. The KM estimates can be misleading because they only present estimates at one single time point and cannot represent the overall effect of the treatment.

FDA also does not agree that the p-values should be presented in Table 30. According to the protocol, OS is to be tested if the test for PFS and ORR for both comparisons of the acalabrutinib+ obinutuzumab arm and acalabrutinib alone arm with the obinutuzumab+ chlorambucil arm are statistically significant. However, the ORR test for the acalabrutinib alone arm with the obinutuzumab+ chlorambucil arm is not statistically significant at the pre-specified alpha level. There is no alpha allocation left to test OS. The p-values presented in Table 30 are nominal. In addition, the number of events in OS is low and the OS data is immature.

Figure 10: Kaplan-Meier Plot for OS – ITT Population



Source: ELEVATE-TN clinical report, Figure 14.2.4.1.

Time to Next Treatment

As of the data cutoff date, the TTNT was significantly prolonged compared with obinutuzumab+chlorambucil for both acalabrutinib+obinutuzumab HR=0.14 [95% CI: 0.08–0.26]; p<0.0001) and acalabrutinib monotherapy (HR=0.24 [95% CI: 0.15–0.40]; p<0.0001). The median TTNT was not reached for acalabrutinib+obinutuzumab (range: 1.3–40.3+ months), acalabrutinib monotherapy (range: 0.1+–40.1+ months), or obinutuzumab+chlorambucil (range: 0.0+–39.6+ months) (Table 31).

Table 31: Time to Next Treatment (ITT Population)

	No. (%) of Subjects		
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab+ Chlorambucil (N=177)**
Subject Status			
Events	13 (7.3)	21 (11.7)	70 (39.5)
Death	8 (4.5)	10 (5.6)	15 (8.5)
Crossover Treatment	0	0	45 (25.4)
Subsequent Anticancer Therapy	5 (2.8)	11 (6.1)	10 (5.6)
Censored	166 (92.7)	158 (88.3)	107 (60.5)
No event before data cutoff	166 (92.7)	158 (88.3)	107 (60.5)
Time to Next Treatment (months)			
Q1 (95% CI)	NE (NE, NE)	NE (NE, NE)	19.9 (17.2, 21.5)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (28.9, NE)
Q3 (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Min, Max	1.3, 40.3+	0.1+, 40.1+	0.0+, 39.6+
Stratified Analysis[a]			
Hazard Ratio (95% CI)[b]	0.14 (0.08, 0.26)	0.24 (0.15, 0.40)	–
p-value[c]	<0.0001	<0.0001	–
KM Estimates of TTNT[d] by Timepoint			
6 Months (95% CI)	97.8 (94.2, 99.2)	96.6 (92.6, 98.5)	95.3 (90.9, 97.6)
12 Months (95% CI)	94.9 (90.5, 97.3)	94.3 (89.7, 96.9)	92.9 (87.9, 95.9)
18 Months (95% CI)	93.2 (88.4, 96.1)	92.6 (87.5, 95.6)	78.5 (71.5, 84.0)
24 Months (95% CI)	93.2 (88.4, 96.1)	90.2 (84.7, 93.8)	67.0 (59.2, 73.6)
30 Months (95% CI)	93.2 (88.4, 96.1)	87.9 (81.8, 92.1)	55.5 (46.5, 63.5)
36 Months (95% CI)	90.0 (80.0, 95.2)	86.3 (79.2, 91.1)	50.2 (40.3, 59.3)

CI=confidence interval; ITT=intent-to-treat; KM=Kaplan-Meier; Max=maximum; Min=minimum; NE=not estimable; Q1=quartile 1; Q3=quartile 3; TTNT=time to next treatment.

[a] Stratified by 17p deletion status (yes vs. no).

[b] Estimated based on stratified Cox Proportional Hazards model for Hazard Ratio (95% CI).

[c] Estimated based on stratified log-rank test for p-value.

[d] Kaplan-Meier estimates of proportion of subjects who have not received next treatment at timepoint.

Note: Time to event (or time to censor for censored subjects) was calculated as date of death (censoring date for censored subjects) – randomization date + 1; Months were derived as days / 30.4375.

Source: ELEVATE-TN clinical report, Table 14.2.3.

Regulatory Authorities Assessment:

FDA does not agree that the KM Estimates of TTNT by timepoint should be presented in Table 31. The KM estimates can be misleading because they only present estimates at one single time point and cannot represent the overall effect of the treatment.

FDA also does not agree that the p-values should be presented in Table 31. TTNT is not included in the pre-specified hierarchical testing order. There is no alpha allocation for TTNT. The p-values presented in Table 31 are nominal.

Subsequent Anticancer Therapy

The most common subsequent anticancer therapies used by subjects in the acalabrutinib+ obinutuzumab arm were anti-CD20 monoclonal antibodies (4 [2.2%] subjects) and investigational drugs (2 [1.1%] subjects). The most common subsequent anticancer therapies used by subjects in the acalabrutinib monotherapy arm were anti-CD20 monoclonal antibodies (5 [2.8%] subjects), RCHOP (4 [2.2%] subjects), bendamustine, obinutuzumab plus chlorambucil, and venetoclax (2 [1.1%] subjects each). The most common subsequent anticancer therapies used by subjects in the obinutuzumab+chlorambucil arm were ibrutinib (6 [3.4%] subjects), anti-CD20 monoclonal antibodies (5 [2.8%] subjects), and bendamustine (3 [1.7%] subjects) (Table 32).

Table 32: Subsequent Anticancer Therapy for CLL (ITT Population)

	No. (%) of Subjects		
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab+ Chlorambucil (N=177)**
Subjects with ≥1 Subsequent Anticancer Therapy	5 (2.8)	11 (6.1)	10 (5.6)
Time from First Dose to Subsequent Anticancer Therapy (months)			
n	5	11	10
Mean (SD)	13.1 (13.02)	11.0 (10.36)	15.5 (9.61)
Median	12	7	19
Min, Max	1, 35	2, 32	2, 28
Number of Subsequent Anticancer Therapies			
1	5 (2.8)	4 (2.2)	7 (4.0)
2	0	5 (2.8)	2 (1.1)
3	0	1 (0.6)	1 (0.6)
≥4	0	1 (0.6)	0
n	5	11	10
Mean (SD)	1.0 (0.00)	1.9 (0.94)	1.4 (0.70)
Median	1	2	1
Min, Max	1, 1	1, 4	1, 3
Type of Subsequent Anticancer Therapy			
Bendamustine	1 (0.6)	2 (1.1)	3 (1.7)
Anti-CD20 monoclonal antibodies	4 (2.2)	5 (2.8)	5 (2.8)
Ibrutinib	0	1 (0.6)	6 (3.4)
Venetoclax	0	2 (1.1)	0

	No. (%) of Subjects		
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab+ Chlorambucil (N=177)**
Immunosuppressives[a]	0	1 (0.6)	0
RCHOP[b,c]	0	4 (2.2)	0
FCR	0	1 (0.6)	0
CVP	1 (0.6)	1 (0.6)	0
Investigational drugs[d]	2 (1.1)	0	0
Steroids	0	1 (0.6)	1 (0.6)
Obinutuzumab and Chlorambucil	0	2 (1.1)	0
PI3K	1 (0.6)	1 (0.6)	0
Other	0	2 (1.1)	0
Methotrexate	0	1 (0.6)	0
Radiotherapy[e]	0	1 (0.6)	0
Vindesine	0	1 (0.6)	0

CLL=chronic lymphocytic leukemia; CVP=cyclophosphamide, vincristine sulfate, prednisone; DLBCL=diffuse large B-cell lymphoma; FCR=fludarabine, cyclophosphamide, rituximab; ITT=intent-to-treat; Max=maximum; Min=minimum; PI3K=phosphoinositide 3-kinase; RCHOP=rituximab, cyclophosphamide, hydroxydaunomycin, oncovin, prednisone; SD=standard deviation.

[a] One subject received cyclosporine.

[b] RCHOP was administered for Richter's transformation.

[c] Three subjects were administered RCHOP for DLBCL One subject was administered RCHOP for CLL.

[d] One subject received the investigational drug umbralisib and one subject received the investigational drug umbralisib+pembrolizumab+ublituximab.

[e] One subject was also treated with radiotherapy for "other" reasons: subcutaneous papillary erythematous skin nodule.

Note: Subjects who received combination therapies were counted under each listed category respectively.

Note: Acalabrutinib was not considered a subsequent anticancer therapy for obinutuzumab+chlorambucil subjects who crossed over.

Source: ELEVATE-TN clinical report, Table 14.1.3.3.

PROs by FACIT-Fatigue

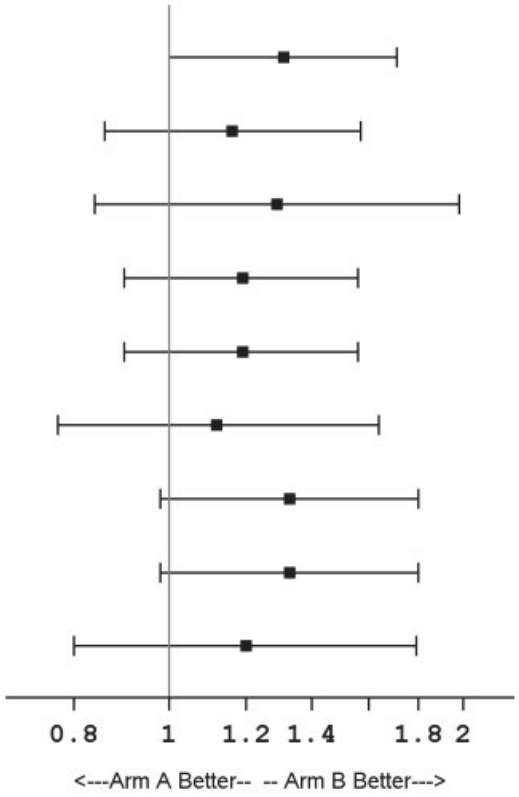
At Week 96 (timepoint for primary analysis), 34 subjects in Arm B (acalabrutinib+ obinutuzumab), 33 subjects in Arm C (acalabrutinib monotherapy), and 11 subjects in Arm A (chlorambucil+obinutuzumab) completed FACIT-Fatigue questionnaires meeting the minimum requirements for scoring (unadjusted completion rate=64.2%, 58.9%, and 26.2%, respectively, adjusted completion rate=73.9%, 70.2%, and 68.8%, respectively). Time to improvement in FACIT-Fatigue scores was slightly shorter for Arm B (acalabrutinib+obinutuzumab) for all thresholds, however, not nominally significant. Overall, TTFI in EORTC QLQ-C30 was similar between Arm B (acalabrutinib+ obinutuzumab) and Arm A (chlorambucil+obinutuzumab), except for constipation, which was shorter for Arm B with 19.43 months versus not yet reached for Arm A (chlorambucil+obinutuzumab) (p=0.0075), and financial difficulties, which was significantly shorter for Arm A (chlorambucil+obinutuzumab) with 22.34 months versus not yet reached for Arm B (acalabrutinib+ obinutuzumab) (p=0.0154). For EQ-5D median (95% CI) time to improvement was 1.91 (1.12-2.89) months for subjects in Arm A (chlorambucil+ obinutuzumab) compared with 1.87.

Time to improvement in FACIT-Fatigue scores was slightly shorter for Arm C (acalabrutinib monotherapy) for most thresholds, however, not nominally significant. Overall TTFI in EORTC QLQ-C30 was similar between Arm C (acalabrutinib monotherapy) and Arm A (chlorambucil+ obinutuzumab); no differences were observed. For EQ-5D median (95% CI) time to improvement was 1.91 (1.12-2.89) months for subjects in Arm A (chlorambucil+obinutuzumab) and 1.84 (1.12-2.07) months for Arm C (acalabrutinib monotherapy). Corresponding HR (95% CI): 1.12 (0.70-1.77; p=0.6364); (1.12-2.07) months for Arm B (acalabrutinib+ obinutuzumab) Corresponding HR (95% CI) was 1.16 (0.73-1.85; p=0.5362 (Figure 11).

Figure 11: Time to First Improvement in FACIT-Fatigue Scores

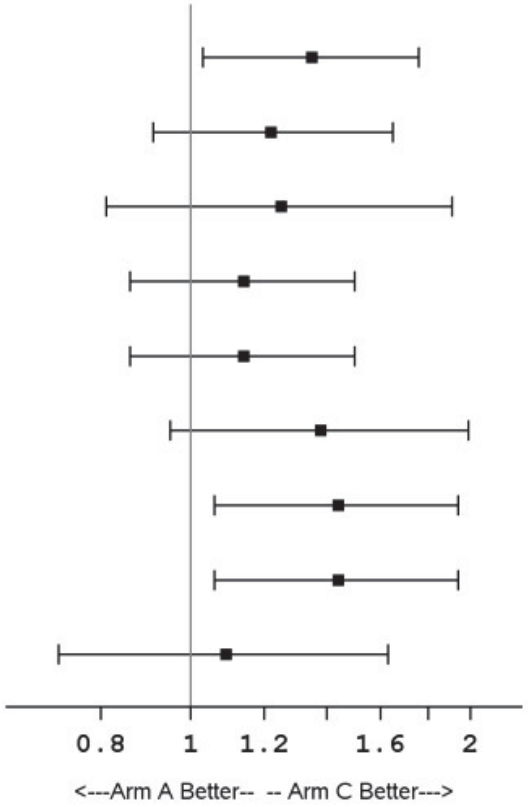
A. Arm B (Acala+Obin) versus Arm A (Chlb+Obin)

Domain	No. of Events Arm A/Arm B	Median (Months) Arm A/Arm B	HR [95% CI]	p-value
Global Fatigue Score - Primary	99/121	2.83/1.97	1.31 [1.00; 1.71]	0.0527
Global Fatigue Score - Sensitivity 1	81/94	4.93/2.96	1.16 [0.86; 1.57]	0.3292
Global Fatigue Score - Sensitivity 2	37/51	NYR/NYR	1.29 [0.84; 1.98]	0.2385
Fatigue Symptom Score - Primary	99/116	2.79/2.07	1.19 [0.90; 1.56]	0.2162
Fatigue Symptom Score - Sensitivity 1	99/116	2.79/2.07	1.19 [0.90; 1.56]	0.2162
Fatigue Symptom Score - Sensitivity 2	49/60	NYR/NYR	1.12 [0.77; 1.64]	0.5475
Fatigue Impact Score - Primary	75/97	11.24/2.73	1.33 [0.98; 1.80]	0.0678
Fatigue Impact Score - Sensitivity 1	75/97	11.24/2.73	1.33 [0.98; 1.80]	0.0678
Fatigue Impact Score - Sensitivity 2	43/55	NYR/NYR	1.20 [0.80; 1.79]	0.3831



B. Arm C (Acala) versus Arm A (Chlb+Obin)

Domain	No. of Events Arm A/Arm C	Median (Months) Arm A/Arm C	HR [95% CI]	p-value
Global Fatigue Score - Primary	99/122	2.83/2.00	1.35 [1.03; 1.76]	0.0316
Global Fatigue Score - Sensitivity 1	81/99	4.93/2.89	1.22 [0.91; 1.65]	0.1821
Global Fatigue Score - Sensitivity 2	37/52	NYR/NYR	1.25 [0.81; 1.91]	0.3112
Fatigue Symptom Score - Primary	99/112	2.79/2.07	1.14 [0.86; 1.50]	0.3658
Fatigue Symptom Score - Sensitivity 1	99/112	2.79/2.07	1.14 [0.86; 1.50]	0.3658
Fatigue Symptom Score - Sensitivity 2	49/69	NYR/NYR	1.38 [0.95; 1.99]	0.0888
Fatigue Impact Score - Primary	75/103	11.24/2.86	1.44 [1.06; 1.94]	0.0177
Fatigue Impact Score - Sensitivity 1	75/103	11.24/2.86	1.44 [1.06; 1.94]	0.0177
Fatigue Impact Score - Sensitivity 2	43/54	NYR/NYR	1.09 [0.72; 1.63]	0.6936



Source: ELEVATE-TN PRO report, Table 11.1.2; Figures 11.1.2.1 and 11.1.2.2.

Regulatory Authorities Assessment:

The results for PRO analyses are considered to be exploratory.

The Applicant's Position:

Acalabrutinib+obinutuzumab demonstrated a statistically significant improvement in IRC-assessed PFS compared with obinutuzumab+chlorambucil, with a 90% reduction in risk of disease progression or death (HR=0.10 [95% CI: 0.06–0.17]; p<0.0001). The acalabrutinib monotherapy arm demonstrated a statistically significant improvement in IRC-assessed PFS compared with the obinutuzumab+chlorambucil arm, with an 80% reduction in risk of disease progression or death (HR=0.20 [95% CI: 0.13–0.30]; p<0.0001). IRC-assessed ORR (CR+CRi+nPR+PR) for acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+chlorambucil was 93.9%, 85.5%, and 78.5%, respectively. TTNT was significantly prolonged compared with obinutuzumab+chlorambucil for both acalabrutinib+obinutuzumab HR=0.14 [95% CI: 0.08–0.26]; p<0.0001) and acalabrutinib monotherapy (HR=0.24 [95% CI: 0.15–0.40]; p<0.0001). Both acalabrutinib+obinutuzumab and acalabrutinib monotherapy demonstrated a statistically significant improvement in investigator-assessed PFS compared with obinutuzumab+chlorambucil (HR=0.12 [95% CI: 0.07–0.21]; p<0.0001) and (HR=0.16 [95% CI: 0.10–0.27]; p<0.0001), respectively. The investigator-assessed ORR for acalabrutinib+ obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+chlorambucil was 96.1%, 89.4%, and 82.5%, respectively. The investigator-assessed ORR including PRL for acalabrutinib+ obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+chlorambucil was 96.6%, 92.2%, and 82.5%.

Regulatory Authorities Assessment:
The results of the secondary endpoints support the primary analysis.

Dose/Dose Response

Data:
See Section 6.2.1.

The Applicant's Position:
Dose response was evaluated using population pharmacokinetic and exposure-response analyses (see Section 6.2.1).

Regulatory Authorities Assessment:
Please refer to Section 6.2.1 as noted above.

Durability of Response

Data:
See above described Efficacy Results – Primary Endpoint (Including Sensitivity Analyses) and Efficacy Results – Secondary and other relevant endpoints.

The Applicant's Position:
Durability of response for 100mg tablets BID daily regimen in ELEVATE-TN was demonstrated by superior PFS versus the control group as discussed above under Efficacy Results – Primary Endpoint (Including Sensitivity Analyses) and Efficacy Results – Secondary and other relevant endpoints.

Regulatory Authorities Assessment:
Based upon FDA review of the ADTTE dataset, per Kaplan-Meier method, the median duration of response for responders receiving acalabrutinib plus obinutuzumab was not reached (range 2.8 to 36.5 months) with a median follow-up of 24.8 months. In the acalabrutinib plus obinutuzumab arm, of 168 patients who achieved an objective response (CR, CRi, nPR, PR), 158 patients (94%) had a response ≥ 12 months, 147 patients (88%) with a response ≥ 18 months, and 99 patients (59%) with a response ≥ 24 months. In the acalabrutinib monotherapy arm, the median duration of response was 31.5 months (range 2.8 to 36.4 months) with a median follow-up of 24.5 months. Of 153 patients who achieved an objective response (CR, CRi, nPR, PR), 144 patients (94%) had a response ≥ 12 months, 125 patients (82%) with a response ≥ 18 months, and 70 patients (46%) with a response ≥ 24 months. The results are summarized in the following table.

Duration of Response	Acalabrutinib+ Obinutuzumab	Acalabrutinib	Obinutuzumab+ Chlorambucil
	N=168	N=153	N=139
Median	NE	31.5	20.3
95% CI of Median	(NE, NE)	(31.5, NE)	(17.0, 24.9)
Range	(2.8, 36.6)	(2.8, 36.4)	(2.8, 36.4)
Number of Ongoing Response (%)	159 (94.6%)	136 (88.9%)	63 (45.3%)
Response ≥ 12 months (%)	158 (94.1%)	144 (94.1%)	101 (72.7%)
Response ≥ 18 months (%)	147 (87.5%)	125 (81.7%)	71 (51.1%)
Response ≥ 24 months (%)	99 (58.9%)	70 (45.8%)	37 (26.6%)

Source: FDA analysis of ADTTE dataset

Persistence of Effect

Data:
See above described Efficacy Results- Secondary and other relevant endpoints.

The Applicant's Position:
Persistence of effect over time after treatment with acalabrutinib in the ELEVATE-TN study was demonstrated by a trend for prolonged OS (Efficacy Results –Secondary and other relevant endpoints).

Regulatory Authorities Assessment:
FDA does not agree that any conclusion can be drawn based on the current OS data. The OS data is immature.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:
Statistical results for exploratory endpoints were considered descriptive. Exploratory analyses were performed using the ITT population unless otherwise specified.

The Applicant's Position:

There was a trend toward an improvement in (absence of) constitutional symptoms during treatment across all 3 treatment arms for any constitutional symptoms as well as for individual constitutional symptoms (Table 33).

Table 33: Disease-Related Symptoms (Constitutional Symptoms) (ITT Population)

	No. (%) of Subjects		
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab+ Chlorambucil (N=177)**
Any Constitutional Symptom			
Present at Baseline	96 (100.0)	104 (100.0)	88 (100.0)
Absent at Cycle 2 Day 1	57 (59.4)	70 (67.3)	53 (60.2)
Absent at Cycle 3 Day 1	68 (70.8)	74 (71.2)	65 (73.9)
Absent at Cycle 4 Day 1	76 (79.2)	81 (77.9)	70 (79.5)
Absent at Cycle 5 Day 1	73 (76.0)	78 (75.0)	68 (77.3)
Absent at Cycle 6 Day 1	75 (78.1)	84 (80.8)	67 (76.1)
Absent at Cycle 7 Day 1	76 (79.2)	85 (81.7)	69 (78.4)
Absent at Cycle 10	80 (83.3)	86 (82.7)	69 (78.4)
Absent at Cycle 13	75 (78.1)	86 (82.7)	61 (69.3)
Absent at Cycle 16	78 (81.3)	84 (80.8)	64 (72.7)
Absent at Cycle 19	76 (79.2)	85 (81.7)	55 (62.5)
Absent at Cycle 22	76 (79.2)	85 (81.7)	47 (53.4)
Absent at Cycle 25	78 (81.3)	83 (79.8)	52 (59.1)
Absent at Cycle 31	63 (65.6)	66 (63.5)	46 (52.3)
Absent at Cycle 37	23 (24.0)	21 (20.2)	21 (23.9)
Absent at Cycle 43	3 (3.1)	2 (1.9)	1 (1.1)

ITT=intent-to-treat.

Note: Disease-related symptoms at post baseline timepoints were assessed for the subset of subjects with respective symptom present at baseline.
Source: ELEVATE-TN clinical report Table 14.2.7.

Sustained hematologic improvement in subjects with cytopenia at baseline was similar in the acalabrutinib+obinutuzumab arm and acalabrutinib monotherapy arm, but lower in the obinutuzumab+chlorambucil for ANC, hemoglobin, and platelet count (Table 34).

Table 34: Sustained Hematologic Improvement (ITT Population; Subjects with Cytopenia[s] Present at Baseline)

	No. (%) of Subjects		
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab+ Chlorambucil (N=177)**
Present at Baseline			
Neutropenia (ANC)	9 (5.0)	10 (5.6)	6 (3.4)
Anemia (Hgb)	67 (37.4)	68 (38.0)	73 (41.2)
Thrombocytopenia (platelet counts)	44 (24.6)	33 (18.4)	36 (20.3)
Any 2 of the above	25 (14.0)	24 (13.4)	31 (17.5)
Any of the above	93 (52.0)	85 (47.5)	81 (45.8)
Sustained Hematologic Improvement			
Neutropenia (ANC)	8/9 (88.9)	9/10 (90.0)	3/6 (50.0)
Anemia (Hgb)	52/67 (77.6)	44/68 (64.7)	36/73 (49.3)
Thrombocytopenia (platelet counts)	36/44 (81.8)	29/33 (87.9)	18/36 (50.0)
Any 2 of the above	18/25 (72.0)	17/24 (70.8)	12/31 (38.7)
Any of the above	76/93 (81.7)	63/85 (74.1)	45/81 (55.6)

ANC=absolute neutrophil count; Hgb=hemoglobin; ITT=intent-to-treat.
Note: Sustained hematologic improvement was defined as hematologic improvement that persisted continuously for ≥56 days (8 weeks) without blood transfusion or growth factors.
Note: Sustained hematologic improvement was assessed for subset of subjects with respective hematologic condition(s) present at baseline.
Source: Table 14.2.8 from ELEVATE-TN CSR.

Medical resource utilization was lower in the acalabrutinib monotherapy arm compared with the acalabrutinib+ obinutuzumab arm and the obinutuzumab+chlorambucil arm for the number of hospitalizations per person-year (0.225, 0.294, and 0.335, respectively), number of emergency department visits per person-year (0.215, 0.229, and 0.261, respectively), number of plasma, whole blood, and packed RBC transfusions per person-year (0.134, 0.147, and 0.178, respectively), and number of use of hematopoietic growth factors per person-year (0.116, 0.255, and 0.641, respectively). The number of platelet transfusions per person-year was higher in the acalabrutinib monotherapy arm compared with the acalabrutinib+obinutuzumab arm and the obinutuzumab+chlorambucil arm (0.035, 0.017, and 0.019, respectively) (Table 35).

Table 35: Medical Resource Utilization (ITT Population)

	No. (%) of Subjects		
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab+ Chlorambucil (N=177)**
Number of hospitalizations per person-year	0.294	0.225	0.335
Number of emergency department visits per person-year	0.229	0.215	0.261
Number of plasma, whole blood, and packed RBC transfusions per person-year	0.147	0.134	0.178
Number of platelet transfusions per person-year	0.017	0.035	0.019
Number of use(s) of hematopoietic growth factors per person-year	0.255	0.116	0.641

ITT=intent-to-treat: RBC=red blood cell.
Note: Number of incidences per person-year was calculated as total number of incidences of the specific category divided by the sum of total person in the ITT population.
Source: ELEVATE-TN clinical report, Table 14.2.9.

See PROs by FACIT-Fatigue under Secondary Efficacy and other relevant endpoints for effect on PRO endpoints.

Regulatory Authorities Assessment:
The data on disease-related symptoms, sustained hematologic improvement, and medical resource utilization are descriptive.

Additional Analyses Conducted on the Individual Trial

Data:
No other analyses were conducted for the ELEVATE-TN trial.

The Applicant's Position:
Not applicable

Regulatory Authorities Assessment:
Not applicable

8.1.3. Integrated Review of Effectiveness

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's position for the majority of primary analysis and secondary analyses. However, the FDA does not agree with the following items:

- The efficacy assessment for PFS per IRC was conducted at the pre-specified interim analysis. Although, FDA does not agree that the KM Estimates of PFS by timepoint

should be presented. These estimates can be misleading because they only present estimates at one single time point and cannot represent the overall effect of the treatment.

- The FDA does not agree that p-values should be included in for sensitivity analyses for PFS per IRC. These sensitivity analyses are exploratory and do not have alpha allocation. All p-values presented in this context are nominal. There were no outlier subgroups identified.
- The FDA does not agree that the p-values for the ORR + PRL difference should be presented. These analyses are exploratory and do not have alpha allocation. The p-values for the ORR + PRL difference are nominal.
- The FDA does not agree that the p-values should be presented for overall survival. According to the protocol, OS is to be tested if the test for PFS and ORR for both comparisons of the acalabrutinib plus obinutuzumab arm and acalabrutinib monotherapy arm with the obinutuzumab plus chlorambucil arm are statistically significant. However, the ORR test for the acalabrutinib monotherapy arm with the obinutuzumab plus chlorambucil arm is not statistically significant at the pre-specified alpha level. There is no alpha allocation left to test OS. The p-values presented for OS are nominal. In addition, the number of events in OS is low (≤10 % overall) and the OS data is immature.
- The FDA does not agree that the KM Estimates of time to next treatment by timepoint should be presented. The KM estimates can be misleading because they only present estimates at one single time point and cannot represent the overall effect of the treatment.
- The FDA also does not agree that the p-values should be presented for TTNT. TTNT is not included in the pre-specified hierarchical testing order. There is no alpha allocation for TTNT and the p-values presented are nominal.

8.1.4. Assessment of Efficacy Across Trials

ASCEND Study (ACE-CL-309)

ASCEND is an ongoing Phase 3 open-label, randomized study in subjects with documented CD20-positive CLL who had received ≥1 prior treatment regimen. The primary endpoint was to evaluate the efficacy of acalabrutinib monotherapy (Arm A) compared with IR or BR (Arm B) based on IRC assessment of PFS per IWCLL 2008 criteria (Hallek et al. 2008) with incorporation of the clarification for treatment-related lymphocytosis (Cheson et al. 2012) in subjects with R/R CLL.

The ITT population included a total of 310 subjects: 155 subjects in the acalabrutinib monotherapy arm and 155 subjects in the IR/BR arm.

The median duration of exposure of acalabrutinib was 15.7 months (range: 1.1-22.4) with 85.7% of subjects receiving ≥1 year of therapy. The median follow-up of 16.1 months in the acalabrutinib arm and 15.7 months in the IR/BR arm.

Data

The median estimated PFS for acalabrutinib was not reached; the median estimated PFS for IR/BR was 16.5 months (95% CI: 14.0, 17.1). Acalabrutinib monotherapy demonstrated a statistically significant improvement in IRC-assessed PFS compared with IR/BR, with a 69% reduction in risk of disease progression or death (HR=0.31 [95% CI: 0.20, 0.49]; p<0.0001) (Table 36).

Table 36: ASCEND: Analysis of Progression-Free Survival by IRC Assessment (ITT Population)

	Arm A Acalabrutinib (N=155)	Arm B IR or BR (N=155)
Subject Status		
Events,[a] n (%)	27 (17.4%)	68 (43.9%)
Death	8 (5.2%)	9 (5.8%)
Disease progression	19 (12.3%)	59 (38.1%)
Censored,[b] n (%)	128 (82.6%)	87 (56.1%)
Randomization	2 (1.3%)	4 (2.6%)
Last adequate assessment before data cutoff	123 (79.4%)	82 (52.9%)
Last adequate assessment before subsequent anticancer therapy	3 (1.9%)	1 (0.6%)
Progression-free survival (months)		
Median (95% CI)	NE (NE, NE)	16.5 (14.0, 17.1)
Min, Max	0.0+, 22.4+	0.0+, 20.0+
Stratified analysis (versus Arm B)		
Hazard ratio (95% CI)[c]	0.31 (0.20, 0.49)	
p-value[d]	<0.0001	
Unstratified analysis (versus Arm B)		
Hazard ratio (95% CI)[e]	0.30 (0.19, 0.48)	
p-value[f]	<0.0001	
KM estimates of PFS by timepoint (%)		
6 Months PFS Rate (95% CI)	96.1 (91.5, 98.2)	93.9 (88.6, 96.8)
9 Months PFS Rate (95% CI)	92.7 (87.3, 95.9)	82.4 (75.0, 87.7)
12 Months PFS Rate (95% CI)	87.8 (81.3, 92.1)	68.0 (59.4, 75.1)
15 Months PFS Rate (95% CI)	82.6 (75.0, 88.1)	54.9 (45.4, 63.5)
18 Months PFS Rate (95% CI)	79.0 (69.7, 85.8)	38.6 (27.3, 49.8)

BR=bendamustine/rituximab; CI=confidence interval; IR=idelalisib/rituximab; IRC=Independent Review Committee; ITT=intent-to-treat; IXRS=interactive voice/web response system; KM=Kaplan-Meier; Max=maximum; Min=minimum; NE=not estimable; PFS=progression-free survival.

[a] Based on the earliest contributing assessment.
[b] Based on the latest contributing assessment.
[c] Based on stratified Cox proportional hazards model, stratified by randomization stratification factors as recorded in IXRS (see ASCEND clinical report, Table 14.2.1.14).
[d] Based on stratified log-rank test, stratified by randomization stratification factors as recorded in IXRS (see ASCEND clinical report, Table 14.2.1.14).
[e] Based on unstratified Cox proportional hazards model.
[f] Based on unstratified log-rank test.
Time to event (or time to censor for censored subjects) is calculated as date of disease progression or death (censoring date for censored subjects) - randomization date + 1. Months are derived as days/30.4375.
Source: ASCEND clinical report,Table 14.2.1.

The Applicant's Position:
ASCEND demonstrated statistically significant and clinically meaningful improvements in progression-free survival. ASCEND was supported by and consistent with the efficacy results of the supporting studies.

Regulatory Authorities Assessment:

FDA does not agree that the KM Estimates of PFS by timepoint should be presented in Table 36. The KM estimates can be misleading because they only present estimates at one single time point and cannot represent the overall effect of the treatment.

Secondary and Other Endpoints

Data:
Key secondary efficacy endpoints in the Phase 3 pivotal study ASCEND included investigator-assessed PFS, IRC-assessed ORR, TTNT, OS, DOR, PROs and are summarized in Table 37.

In R/R subjects (ASCEND), acalabrutinib demonstrated a statistically significant improvement in investigator-assessed PFS compared with IR/BRs (HR=0.28 [95% CI: 0.18, 0.45]; p<0.0001). With a median follow-up of 16.1 months in the acalabrutinib arm and 15.7 months in the IR/BR arm, the median estimated PFS for acalabrutinib was not reached; the median estimated PFS for IR/BR was 16.2 months (95% CI: 14.0, not reached).

In R/R subjects (ASCEND), the IRC-assessed ORR for acalabrutinib and IR/BR was 81.3% (95% CI: 74.4, 86.6) and 75.5% (95% CI: 68.1, 81.6), respectively (p=0.2248). PR was achieved in 126 (81.3%) subjects in the acalabrutinib group 115 (74.2%) subjects in the IR/BR group. No acalabrutinib subjects and 2 IR/BR subjects achieved a CR. The ORR including PRL for acalabrutinib and IR/BR subjects, respectively, was 88.4% (95% CI: 82.4, 92.5) and 77.4% (95% CI: 70.2, 83.3), with a statistically significant difference between arms of 11.0% (95% CI: 2.7, 19.3; p=0.0110).

Investigator-assessed ORR was a secondary endpoint in ASCEND. Per investigator assessment, the ORR for acalabrutinib and IR/BR was 79.4% (95% CI: 72.3, 85.0) and 83.2% (95% CI: 76.6,

88.3), respectively (p=0.3453). PR was achieved in 116 (74.8%) acalabrutinib subjects and 123 (79.4%) IR/BR subjects. Two acalabrutinib subjects and 5 IR/BR subjects achieved a CR. The ORR including PRL for acalabrutinib and IR/BR was 92.9% (95% CI: 87.7, 96.0) and 87.1% (95% CI: 80.9, 91.5), respectively (p=0.0849).

In R/R subjects (ASCEND), with a median follow-up of 16.1 months in the acalabrutinib arm and 15.7 months in the IR/BR arm, 15 (9.7%) subjects in the acalabrutinib arm and 18 (11.6%) subjects in the IR/BR arm had died. The median OS was not reached in either treatment arm, with a HR of 0.84 (95% CI: 0.42, 1.66; p=0.6089). The estimated 18-month OS rate for acalabrutinib and IR/BR was 89.7% (95% CI: 83.4, 93.7) and 88.1 % (95% CI: 81.4, 92.5), respectively.

IRC- and investigator-assessed DOR were secondary objectives in ASCEND. In R/R subjects, acalabrutinib demonstrated an improvement in IRC-assessed DOR (HR=0.33 [95% CI: 0.19, 0.59]) and investigator-assessed DOR (HR=0.20 [95% CI: 0.10, 0.42]) compared with IR/BR. The median DOR was not reached based on IRC assessment (range: 0.0+ to 19.6+ months for acalabrutinib and 2.1+ to 16.8+ months for IR/BR) or investigator assessment (range: 0.0+ to 19.6+ months for acalabrutinib and 0.0+ to 16.8+ months for IR/BR). Based on IRC assessment, disease progression in the acalabrutinib and IR/BR arms occurred in 9.5% and 35.9% of subjects, respectively, and based on investigator assessment, disease progression in the acalabrutinib and IR/BR arms occurred in 5.7% and 34.1% of subjects, respectively.

Table 37: ASCEND: Summary of Primary and Selected Secondary Efficacy Endpoints in the Pivotal Phase 3 Studies (ITT Population)

	ASCEND Study ACE-CL-309[a] (R/R CLL)	
	Acalabrutinib monotherapy (N=155)	**IR or BR (N=155)**
IRC-assessed PFS		
Median (95% CI)	NE (NE, NE)	16.5 (14.0, 17.1)
Hazard ratio (95% CI)[b]	0.31 (0.20, 0.49)	
p-value[c]	<0.0001	
INV-assessed PFS		
Median (95% CI)	NE (NE, NE)	16.2 (14.0, NE)
Hazard ratio (95% CI)[b]	0.28 (0.18, 0.45)	
p-value[c]	<0.0001	
Best Overall Response (IRC-assessed), n (%)		
CR	0	2 (1.3%)
CRi	0	0
nPR	0	0
PR	126 (81.3%)	115 (74.2%)
ORR (CR+CRi+nPR+PR)	126 (81.3%)	117 (75.5%)
95% CI[d]	(74.4, 86.6)	(68.1, 81.6)
ORR difference[e]	5.8%	

	ASCEND Study ACE-CL-309[a] (R/R CLL)	
	Acalabrutinib monotherapy (N=155)	**IR or BR (N=155)**
95% CI[d]	(-3.3, 14.9)	
p-value[f]	0.2248	
Overall Survival		
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
Hazard Ratio (95% CI)[b]	0.84 (0.42, 1.66)	
p-value[c]	0.6089	
TTNT (months)		
Median (95% CI)	NE (NE, NE)	NE (18.4, NE)
Hazard ratio (95% CI)[b]	0.35 (0.21, 0.58)	
p-value[c]	<0.0001	

Acala=acalabrutinib; BR=bendamustine+rituximab; chlb=chlorambucil; CI=confidence interval; CR=complete response; CRi=complete response with incomplete blood count recovery; INV=investigator; IR=idelalisib+rituximab; IRC=Independent Review Committee; ITT=intent-to-treat; NE=not estimable; nPR=nodular partial response; obin=obinutuzumab; ORR=overall response rate; PFS=progression-free survival; PR=partial response; PrevUnt=previously untreated; R/R=relapsed/refractory.

[a] Data shown are through the data cutoff dates of 15 January 2019 (ACE-CL-309) and 08 February 2019 (ACE-CL-007).

[b] Estimated based on stratified Cox proportional hazards model for Hazard Ratio (95% CI). In ACE-CL-007, analysis was stratified by 17p deletion status (yes versus no). In ACE-CL-309, analysis was stratified by number of prior therapies (1-3 versus ≥4) and 17p deletion status (yes versus no).

[c] Estimated based on stratified log-rank test for p-value.

[d] 95% CI based on Normal approximation (with use of Wilson's score).

[e] Difference versus the IR/BR arm in ACE-CL-309, and versus the obin+chlb arm in ACE-CL-007.

[f] Based on Cochran-Mantel-Haenszel test with adjustment for 17p deletion status in ACE-CL-007, and for number of prior therapies and 17p deletion status in ACE-CL-309.

"+" indicates a value from a censored subject.

Source: ASCEND clinical report, Table 14, Table 16, Table 18, Table 20, Table 22, and Table 23.

The Applicant's Position:

Results from secondary efficacy endpoints from ASCEND were consistent with the results from ELEVATE-TN.

Regulatory Authorities Assessment:

FDA also does not agree that the p-values for TTNT should be presented in Table 37. TTNT is not included in the pre-specified hierarchical testing order. FDA does not agree that the p-value for OS should be presented in Table 37-. Since IRC-assessed ORR did not cross the efficacy boundary, no further hypothesis testing should be conducted and the result from OS analysis is considered exploratory and should only be described descriptively. The median OS was not reached in either treatment arm due to the early timing of analysis.

Subpopulations

Data

In ASCEND, the PFS benefit of acalabrutinib compared with IR/BR was consistent across all prespecified as summarized in Table 38.

Table 38: ASCEND Study: Subgroup Analysis of Progression-Free Survival by IRC Assessment (ITT Population)

	Responders/Subjects		
	Arm A Acalabrutinib	**Arm B IR or BR**	**Hazard Ratio (95% CI)**
Overall			
Primary analysis	27/155	68/155	0.30 (0.19, 0.48)
Presence of 17p deletion			
Yes	4/28	12/26	0.21 (0.07, 0.68)
No	23/127	56/129	0.33 (0.21, 0.54)
ECOG at randomization			
0, 1	24/137	60/135	0.30 (0.18, 0.48)
2	3/18	8/20	0.36 (0.10, 1.37)
Age group			
<65	7/58	27/57	0.20 (0.09, 0.46)
≥65	20/97	41/98	0.40 (0.23, 0.68)
<75	19/121	55/124	0.26 (0.15, 0.44)
≥75	8/34	13/31	0.54 (0.22, 1.30)
Sex			
Male	22/108	45/100	0.34 (0.20, 0.57)
Female	5/47	23/55	0.21 (0.08, 0.57)
Race			
White	24/145	63/141	0.28 (0.18, 0.45)
Non-white	3/10	5/14	0.61 (0.14, 2.56)
Region			
Asia	2/7	3/7	0.44 (0.07, 2.64)
Australia and New Zealand	2/9	2/7	0.50 (0.07, 3.61)
Central and Eastern Europe	18/99	45/99	0.31 (0.18, 0.54)
North America	0/8	4/9	NE (NE, NE)
Western Europe	5/32	14/33	0.32 (0.12, 0.89)
Rai stage at screening			
Stage 0-II	16/90	35/90	0.36 (0.20, 0.66)
Stage III-IV	11/65	33/64	0.24 (0.12, 0.47)
Bulky disease			
<5 cm	14/79	28/80	0.36 (0.19, 0.69)
≥5 cm	13/76	40/75	0.26 (0.14, 0.49)
B2-microglobin at baseline			
≤3.5 mg/L	4/32	9/25	0.25 (0.07, 0.82)
>3.5 mg/L	23/120	59/126	0.33 (0.20, 0.53)
Presence of 11q deletion			
Yes	6/39	20/44	0.28 (0.11, 0.70)
No	21/116	40/92	0.31 (0.19, 0.53)
TP53 mutation			
Yes	8/39	20/34	0.24 (0.11, 0.56)

	Responders/Subjects		
	Arm A Acalabrutinib	**Arm B IR or BR**	**Hazard Ratio (95% CI)**
No	19/113	48/119	0.33 (0.20, 0.57)
17p deletion or TP53 mutation			
Yes	8/45	23/42	0.21 (0.09, 0.48)
No	19/108	45/111	0.36 (0.21, 0.61)
17p deletion and TP53 mutation			
Yes	4/22	7/13	0.20 (0.06, 0.69)
No	23/132	60/141	0.32 (0.20, 0.52)
IgHV			
Mutated	5/33	10/26	0.32 (0.11, 0.94)
Unmutated	22/118	56/125	0.32 (0.19, 0.52)
17p deletion, TP53 mutation, 11q deletion, or unmutated IgHV			
Yes	23/135	63/137	0.27 (0.17, 0.44)
No	4/19	4/15	0.84 (0.21, 3.37)
17p deletion, TP53 mutation, or 11q deletion			
Yes	14/79	39/78	0.27 (0.15, 0.49)
No	13/75	29/75	0.35 (0.18, 0.68)
Complex karyotype			
Yes	12/50	24/46	0.32 (0.16, 0.63)
No	12/97	40/92	0.23 (0.12, 0.44)

ECOG=Eastern Cooperative Oncology Group; del=deletion; IGHV=immunoglobulin heavy-chain variable; IRC=Independent Review Committee; ITT=intent-to-treat.
Source: Figure 14.2.1.11 from ASCEND CSR.

IRC-assessed ORR was also consistent across most prespecified subgroups (Table 39).

Table 39: ASCEND Study: Overall Response Rate by IRC Assessment by for Selected Subgroups (ITT Population)

	Arm A Acalabrutinib		**Arm B IR or BR**	
	Responders/ Subjects	**ORR (%) (95% CI)**	**Responders/ Subjects**	**ORR (%) (95% CI)**
Overall	126/155	81.3 (74.2, 87.1)	117/155	75.5 (67.9, 82.0)
Presence of 17p deletion				
Yes	25/28	89.3 (71.8, 97.7)	19/26	73.1 (52.2, 88.4)
No	101/127	79.5 (71.5, 86.2)	98/129	76.0 (67.7, 83.1)
ECOG PS at randomization				
0, 1	114/137	83.2 (75.9, 89.0)	102/135	75.6 (67.4, 82.5)
2	12/18	66.7 (41.0, 86.7)	15/20	75.0 (50.9, 91.3)
Number of prior therapies				
1-3	116/139	83.5 (76.2, 89.2)	105/138	76.1 (68.1, 82.9)
≥4	10/16	62.5 (35.4, 84.8)	12/17	70.6 (44.0, 89.7)
Age group				

	Arm A Acalabrutinib		Arm B IR or BR	
	Responders/ Subjects	**ORR (%) (95% CI)**	**Responders/ Subjects**	**ORR (%) (95% CI)**
<65	49/58	84.5 (72.6, 92.7)	40/57	70.2 (56.6, 81.6)
≥65	77/97	79.4 (70.0, 86.9)	77/98	78.6 (69.1, 86.2)
<75	100/121	82.6 (74.7, 88.9)	95/124	76.6 (68.2, 83.7)
≥75	26/34	76.5 (58.8, 89.3)	22/31	71.0 (52.0, 85.8)
Sex				
Male	87/108	80.6 (71.8, 87.5)	75/100	75.0 (65.3, 83.1)
Female	39/47	83.0 (69.2, 92.4)	42/55	76.4 (63.0, 86.8)
Race				
White	119/145	82.1 (74.8, 87.9)	106/141	75.2 (67.2, 82.1)
Non-white	7/10	70.0 (34.8, 93.3)	11/14	78.6 (49.2, 95.3)
Rai stage at screening				
Stage 0-II	72/90	80.0 (70.2, 87.7)	70/90	77.8 (67.8, 85.9)
Stage III-IV	54/65	83.1 (71.7, 91.2)	46/64	71.9 (59.2,82.4)
Bulky disease				
<5 cm	62/79	78.5 (67.8, 86.9)	59/80	73.8 (62.7, 83.0)
≥5 cm	64/76	84.2 (74.0, 91.6)	58/75	77.3 (66.2, 86.2)
B2-microglobulin at baseline				
≤3.5 mg/L	22/32	68.8 (50.0, 83.9)	19/25	76.0 (54.9, 90.6)
>3.5 mg/L	101/120	84.2 (76.4, 90.2)	96/126	76.2 (67.8, 83.3)
Complex karyotype				
Yes	40/50	80.0 (66.3, 90.0)	31/46	67.4 (52.0, 80.5)
No	79/97	81.4 (72.3, 88.6)	74/92	80.4 (70.9, 88.0)
Presence of 11q deletion				
Yes	29/39	74.4 (57.9, 87.0)	32/44	72.7 (57.2, 85.0)
No	97/116	83.6 (75.6, 89.8)	84/110	76.4 (67.3, 83.9)
TP53 mutation				
Yes	34/39	87.2 (72.6, 95.7)	24/34	70.6 (52.5, 84.9)
No	89/113	78.8 (70.1, 85.9)	92/119	77.3 (68.7, 84.5)
IGHV				
Mutated	25/33	75.8 (57.7, 88.9)	21/26	80.8 (60.6, 93.4)
Unmutated	98/118	83.1 (75.0, 89.3)	94/125	75.2 (66.7, 82.5)
17p deletion, TP53 mutation, 11q deletion, or unmutated IGHV				
Yes	112/135	83.0 (75.5, 88.9)	104/137	75.9 (67.9, 82.8)
No	13/19	68.4 (43.4, 87.4)	12/15	80.0 (51.9, 95.7)

BR=bendamustine/rituximab; CI=confidence interval; del=deletion; IR=idelalisib/rituximab; ITT=intent-to-treat; IXRS=interactive voice/web response system; ECOG PS=Eastern Cooperative Oncology Group performance status; IGHV=immunoglobulin heavy-chain variable; IRC=Independent Review Committee; ITT=intent-to-treat.
Source: Figure 14.2.2.3 from ASCEND CSR.

The Applicant's Position:

Results of the subgroup analyses from ASCEND were consistent with the results from ELEVATE-TN.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's position.

8.1.5. Integrated Assessment of Effectiveness

Data:
Not applicable

The Applicant's Position:
The varying study designs and differences in primary endpoint in this pivotal ELEVATE-TN study (IRC assessed PFS) compared to the supporting studies does not allow for integration of efficacy assessment.

Regulatory Authorities Assessment:
In adult patients with previously untreated CLL, age 65 years or older or between 18 and 65 years of age with a total Cumulative Illness Rating Scale (CIRS) >6 or creatinine clearance of 30 to 69 mL/min, Study ACE-CL-007/ELEVATE-TN, a Phase 3, randomized, multicenter, open-label, actively controlled, 3-arm trial demonstrated that treatment with acalabrutinib in combination with obinutuzumab or acalabrutinib monotherapy resulted in a statistically significant improvement in PFS per IRC compared to obinutuzumab in combination with chlorambucil.

A total of 535 patients were randomized in a 1:1:1 ratio, stratified by 17p deletion mutation status and ECOG performance status, to receive acalabrutinib plus obinutuzumab, acalabrutinib monotherapy, or obinutuzumab plus chlorambucil. The median age was 70 years (range: 41 to 91 years), nearly half had Rai stage III or IV disease (47%), 63% had unmutated IGVH, 9% had 17p deletion, 18% had 11q deletion, and 11% with TP53 mutation.

The analysis of PFS per IRC demonstrated statistically significant improvement in PFS with acalabrutinib plus obinutuzumab [hazard ratio of 0.10 (95% CI: 0.06, 0.17); two-sided stratified log-rank test p<0.0001] and acalabrutinib monotherapy [hazard ratio 0.20 (95% CI 0.13, 0.30); two-sided stratified log-rank test p-value <0.0001] compared to the comparator arm of obinutuzumab plus chlorambucil. In addition, the key secondary endpoint of overall response rate was demonstrated to statistically significantly improved in the acalabrutinib plus obinutuzumab arm compared to obinutuzumab plus chlorambucil (94% versus 79%, p -value <0.0001). The analysis of overall response rate between acalabrutinib monotherapy versus obinutuzumab plus chlorambucil (86% vs. 79%) was not statistically significant (p=0.0763). At the time of the analysis, there were fewer than 10% overall survival events, thus the OS data is immature.

The study design of ELEVATE-TN employs a control arm (obinutuzumab plus chlorambucil) that is a fixed treatment duration of 6 cycles versus 2 treatment arms that include acalabrutinib

given continuously until disease progression or unacceptable toxicity. The differences in treatment exposure by design, with the acalabrutinib treatment arms having substantially longer exposure, directly affects the clinical interpretation of the primary endpoint of progression-free survival. Nevertheless, the results of the ELEVATE-TN trial are supportive of regular approval for acalabrutinib in patients with previously untreated CLL due to the disease setting, consistent demonstration of superiority across multiple efficacy endpoints, and robust efficacy results on statistical evaluation. The recommended indication for acalabrutinib includes patients with small lymphocytic lymphoma because it is the same disease as chronic lymphocytic leukemia.

The ELEVATE-TN trial and ASCEND trial, in combination, support regular approval for acalabrutinib for the treatment of adult patients with CLL or SLL.

Per FDA and TGA assessment, it justifiable to extend the indication to SLL, because SLL represents the same disease process as CLL. Thus, their recommended indication for acalabrutinib is for the treatment of adult patients with CLL or SLL. (b) (4)

The recommended indications for approval of acalabrutinib in Canada are in combination with obinutuzumab or as monotherapy for the treatment of patients with previously untreated CLL, and as monotherapy for the treatment of patients with CLL who have received at least one prior therapy.

8.2. **Review of Safety**

The Applicant's Position:
The safety review of acalabrutinib 100 mg BID for this sNDA is primarily based on results from the ASCEND and ELEVATE-TN studies, with supporting data provided from the eight additional CLL and other hematologic malignancies studies.

The integrated safety analyses demonstrated the safety profile for acalabrutinib 100 mg BID is consistent with that observed in the studies presented in the original NDA. No new safety concerns were observed with the acalabrutinib 100mg BID dose in the CLL studies.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's position that the safety review primarily focuses on the randomized studies, ELEVATE-TN and ASCEND, with additional, relevant, supportive safety data. For this sNDA, the primary safety results are based upon the ELEVATE-TN trial. The regulatory authorities agree that the safety profile in ELEVATE-TN for acalabrutinib, as monotherapy or in combination, is similar to the known safety profile of

acalabrutinib across multiple clinical trials and no new safety signals were identified.

The integrated safety analyses presented by the Applicant include patients with Waldenström macroglobulinemia (WM), multiple myeloma (MM), follicular lymphoma (FL), and diffuse large B-cell lymphoma (DLBCL) who received various dose-schedules of acalabrutinib and some with limited exposure (MM, FL, DLBCL). For the CALQUENCE USPI Warnings and Precautions, the denominator consists of patients with sufficient exposure to acalabrutinib 100 mg approximately every 12 hours as monotherapy or in combination with obinutuzumab. Refer to Section 8.2.2 for a description of the revised safety population.

8.2.1. Safety Review Approach

The Applicant's Position:

The safety population is defined as all subjects who received ≥1 dose of study drug (N=178 for acalabrutinib+obinutuzumab, N=179 for acalabrutinib monotherapy, and N=169 for obinutuzumab+chlorambucil). These safety results are presented in the sections below.

The clinical review of safety for this NDA is based on the following:

- Clinical study report for studies ELEVATE-TN, ASCEND, ACE-CL-001, 15-H-0016, ACE-CL-003, ACE-LY-002, ACE-LY-003, ACE-LY-004, ACE-MY-001, and ACE-WM-001
- Statistical analysis plan for the Integrated Summary of Safety
- Integrated datasets from the studies listed in Section 8.2.2 below.
- Case report forms and safety narratives
- Summary of Clinical Safety
- Proposed labeling for Calquence

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's position. The safety population for ELEVATE-TN is the primary safety population, however the FDA included the 45 patients that crossed over from the obinutuzumab+chlorambucil arm upon IRC-confirmed disease progression to receive acalabrutinib monotherapy until progressive disease or unacceptable toxicity in certain sections of the safety review (e.g., deaths). For those indicated sections, the denominator for safety by treatment arm in ELEVATE-TN is N=178 for acalabrutinib+obinutuzumab, N=224 for acalabrutinib monotherapy, and N=169 for obinutuzumab+chlorambucil.

FDA conducted the primary safety analyses using the study-specific, rather than integrated, data analysis datasets, supplemented by the CSR and safety narratives. FDA also performed an integrated safety analysis focusing on selected events of clinical interest (ECIs), using a subset of the integrated datasets described above. However, as previously noted, FDA tailored the integrated safety analysis to patients with CLL or SLL, MCL, and WM who received acalabrutinib

100 mg approximately every 12 hours as monotherapy or in combination with obinutuzumab (N = 1029). This safety population is defined in Section 8.2.2.

FDA's safety analysis considers all-causality treatment-emergent AEs (TEAEs) in recipients of any study drug. TEAEs were defined as AEs that are new or worsened from baseline grade or are unknown to have worsened from baseline. Laboratory grading is based on CTCAE rather than Hallek 2008 criteria. The primary safety window (on-treatment period) for ELEVATE-TN is approximately 30 days after last study drug, with censoring for subsequent anticancer therapy. For increased sensitivity, FDA used a combination of individual MedDRA preferred terms (PTs) and custom groupings of PTs as defined in the Appendix 19.5, which the Applicant agreed to in the Assessment Aid and labeling for reporting the results of ELEVATE-TN.

8.2.2. Review of Safety Database

The Applicant's Position:

The clinical safety data supporting the proposed indication of acalabrutinib for adult subjects with CLL is based on acalabrutinib-treated subjects from 10 open-label Phase 1, 2, and 3 clinical studies of acalabrutinib in hematologic malignancies (Table 40).

The safety review was conducted using the integrated datasets from clinical studies ELEVATE-TN, ASCEND, ACE-CL-001, 15-H-0016, ACE-CL-003, ACE-LY-002, ACE-LY-003, ACE-LY-004, ACE-MY-001, and ACE-WM-001. A data pool including patients with previously untreated CLL, R/R CLL, activated B-cell diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, multiple myeloma, and Waldenström macroglobulinemia was used to develop the safety profile of acalabrutinib 100 mg BID in patients with hematologic malignancies. Additionally, data pools consisting of patients receiving acalabrutinib monotherapy from the pivotal CLL studies, CLL patients receiving acalabrutinib monotherapy, or CLL patients receiving acalabrutinib in combination with obinutuzumab were analyzed. Furthermore, a data pool consisting of CLL patients receiving acalabrutinib monotherapy or acalabrutinib in combination with obinutuzumab was analyzed. The safety review will focus on data from CLL patients from the individual pivotal studies, as well as the pooled population of all CLL patients receiving acalabrutinib monotherapy.

Table 40 provides the total number of subjects and brief study details for all studies that contributed safety data to the submission.

Table 41 provides a summary of treatment exposure for all studies that contributed safety data to the submission.

Table 40: Total Subjects From Clinical Studies That Contributed Safety Data to This Submission

	Total N[a]	Pivotal Studies		CLL Supportive Studies			Hematologic Malignancies Supportive Studies				
		ACE-CL-007	ACE-CL-309	ACE-CL-001	15-H-0016	ACE-CL-003	ACE-LY-002	ACE-LY-003[b]	ACE-LY-004	ACE-MY-001[b]	ACE-WM-001
Phase		3	3	1/2	2	1/2	1b	2	2	1b	2
Status		Ongoing	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing
Data cutoff date		08Feb2019	15Jan2019	04Jan2019	07Dec2018	01Nov2018	30Oct2017	01Jan2019	12Feb2018	30Apr2018	01Nov2018
Indication		CLL	CLL	CLL/SLL /RS/PLL	CLL/SLL	CLL/SLL	ABC/DLBCL	FL	MCL	MM	WM
Acalabrutinib Monotherapy Pivotal Population	**333**	179	154	NA	NA	NA	NA	NA	NA	NA	NA
Acalabrutinib Monotherapy CLL Population	**762[c]**	224	190	301	48	NA	NA	NA	NA	NA	NA
Combination CLL Population	**223**	178	NA	NA	NA	45	NA	NA	NA	NA	NA
Total Acalabrutinib CLL Population	**985[c]**	402	190	301	48	45	NA	NA	NA	NA	NA
Acalabrutinib Monotherapy Hematologic Malignancies Population	**1040[c]**	224	190	301	48	NA	21	14	124	13	106
Treatment Arm											
Acalabrutinib Monotherapy		179	154	301	48	NA	21	14	124	13	106
Acalabrutinib + Obinutuzumab		178	NA	NA	NA	45	NA	NA	NA	NA	NA
Crossover from Control Arm to Acalabrutinib		45	36								

[a] The total number is based on the actual number of subjects treated with acalabrutinib.

[b] Other combination groups are not included in the analysis.

[c] Subjects who crossed over from control arm to acalabrutinib monotherapy are included in this pooled population.

ABC DLBCL=activated B-cell diffuse large B-cell lymphoma; CLL=chronic lymphocytic leukemia; FL=follicular lymphoma; MCL=mantle cell lymphoma; MM=multiple myeloma; NA=not applicable: PLL=prolymphocytic leukemia; RS=Richter's syndrome; SLL=small lymphocytic leukemia; WM=Waldenström macroglobulinemia.
Source: Table 1 from Module 2.7.4.

Overall Exposure

The Applicant's Position:

In the pivotal study ELEVATE-TN, for subjects in the acalabrutinib monotherapy arm, 81.6% of subjects completed at least 24 months of acalabrutinib treatment, with a median duration of exposure of 27.7 months (range: 0.3 to 40.2 months). Treatment exposure for the safety pools is summarized in Table 41.

Table 41: Summary of Treatment Exposure From Clinical Studies That Contributed Safety Data to This Submission

	Mono Pivotals (N=333)	Mono CLL (N=762)	Combo CLL (N=223)	Total CLL (N=985)	Mono HemMalig (N=1040)
Duration of Exposure (months)[a]					
n	333	760	223	983	1038
Mean (SD)	21.0 (9.48)	24.9 (15.35)	28.5 (9.33)	25.8 (14.29)	23.6 (15.20)
Median	19.3	24.9	29.8	27.1	24.6
Min, Max	0.3, 40.2	0.0, 58.5	0.7, 44.9	0.0, 58.5	0.0, 58.5
Patient Year	581.9	1579.3	530.1	2109.4	2037.7
<= 6 months	24 (7.2%)	107 (14.0%)	10 (4.5%)	117 (11.9%)	188 (18.1%)
> 6 to <= 12 months	23 (6.9%)	68 (8.9%)	11 (4.9%)	79 (8.0%)	96 (9.2%)
> 12 to <= 24 months	141 (42.3%)	191 (25.1%)	14 (6.3%)	205 (20.8%)	226 (21.7%)
> 24 to <= 36 months	132 (39.6%)	177 (23.2%)	150 (67.3%)	327 (33.2%)	273 (26.3%)
> 36 months	13 (3.9%)	217 (28.5%)	38 (17.0%)	255 (25.9%)	255 (24.5%)

Source: ISS Table 4.1.

Acalabrutinib was well tolerated and showed an acceptable safety profile that is consistent with the other acalabrutinib clinical trials.

Regulatory Authorities Assessment:

The FDA acknowledges the exposure data for the safety pool as presented above. Within ELEVATE-TN and the safety pool, the number of patients exposed and the duration of exposure was adequate for safety review.

The review of the safety data in subsequent sections is primarily focused on the safety data from the ELEVATE-TN trial. Therefore, for ELEVATE-TN, exposure by treatment arm is presented in Table 42. The median exposure of acalabrutinib in both, the acalabrutinib+obinutuzumab arm and acalabrutinib monotherapy arm was 27.7 months (range 0.3-0.7 to 40 months), with 95% and 92%, 89% and 86%, and 84% and 82% with at least 6 months, 12 months, and 24 months of exposure, respectively. The median number of cycles was 6 for obinutuzumab and chlorambucil, with 84-85% and 70% of patients receiving 6 cycles, respectively. The addition of obinutuzumab to acalabrutinib did not substantially alter the relative dose intensity (RDI) of acalabrutinib with a mean RDI of 95% (standard deviation 10.5%), with 87% of patients achieving an acalabrutinib RDI ≥ 90%.

Table 42: Summary of Exposure by Treatment Arm in ELEVATE-TN

Parameter		Acalabrutinib+ Obinutuzumab N=178	Acalabrutinib N=179	Obinutuzumab+ Chlorambucil N=169
Acalabrutinib/ Chlorambucil exposure duration, months	Median	27.7	27.7	5.5
	Range	0.7, 40	0.3, 40	0.5, 7.2
Obinutuzumab exposure duration, months	Median	5.5	N/A	5.6
	Range	0.9, 7.1	N/A	0.9, 7.4
Relative Dose Intensity				
Acalabrutinib/ Chlorambucil	Mean (SD)	94.6 (10.5)	96.8 (8.0)	83.4 (24.6)
	≥90%	87%	93%	62%
	≥80%	92%	96%	69%
Obinutuzumab	Mean (SD)	94.5 (18.4)	N/A	93.8 (19.0)
	≥90%	85%	N/A	84%
	# of cycles <3 3 to <6 ≥6	 5% 10% 85%	 N/A N/A N/A	 5% 11% 84%
Patients on treatment by month	≥2 months	99%	96%	96%
	≥3 months	98%	93%	95%
	≥6 months	95%	92%	90%
	≥12 months	89%	86%	N/A
	≥18 months	85%	84%	N/A
	≥24 months	84%	82%	N/A

N/A: Not applicable, SD: Standard deviation
Source: FDA review of ADEX dataset

Exposure following crossover

There were 45 patients randomized to the obinutuzumab + chlorambucil arm, who had IRC-confirmed disease progression and crossed over to receive treatment with acalabrutinib 100 mg twice daily until disease progression or unacceptable toxicity. For the 45 patients, the median exposure of acalabrutinib was 11 months (range 2 to 23.5 months). Table 43 summarizes exposure for the crossover patients.

Table 43: Summary of Acalabrutinib Exposure in Crossover Patients

Parameter		Acalabrutinib N=45
Acalabrutinib exposure duration, months	Median	11
	Range	2.0 , 23.5
Relative Dose Intensity Acalabrutinib	Mean (SD)	96 (7.6)
	≥90%	84%
	≥80%	88%
Patients on treatment by month	≥2 months	96%
	≥3 months	89%
	≥6 months	78%
	≥12 months	38%
	≥18 months	22%
	≥24 months	0%

Relevant characteristics of the safety population:
The Applicant's Position:

Demographic and baseline characteristics were generally similar across the 5 analysis populations (Table 44). Among Mono HemMalig subjects, the mean age was 66.6 years (median: 67.0 years), with a range of 32 to 90 years. Most subjects were white (88.8%) and male (67.7%). Mean calculated BMI was 27.2 kg/m2, and most subjects (93.0%) had a baseline ECOG status of 0 or 1. Subjects reported a median of 1 prior systemic treatment regimen.

Discussion of the subject populations in the 10 pooled studies (inclusion/exclusion criteria and subject characteristics) is provided within the individual CSRs.

Table 44: Demographic and Baseline Characteristics

	Mono Pivotals (N=333)	Mono CLL (N=762)	Combo CLL (N=223)	Total CLL (N=985)	Mono HemMalig (N=1040)
Age (years)					
Mean (SD)	68.5 (8.82)	66.4 (9.36)	68.6 (8.97)	66.9 (9.31)	66.6 (9.86)
Median	69.0	67.0	69.0	68.0	67.0
Min, Max	32, 89	32, 89	41, 88	32, 89	32, 90
<65, n (%)	85 (25.5)	288 (37.8)	61 (27.4)	349 (35.4)	388 (37.3)
≥65 and <75, n (%)	164 (49.2)	318 (41.7)	104 (46.6)	422 (42.8)	424 (40.8)
≥75, n (%)	84 (25.2)	156 (20.5)	58 (26.0)	214 (21.7)	228 (21.9)
Sex, n (%)					

	Mono Pivotals (N=333)	Mono CLL (N=762)	Combo CLL (N=223)	Total CLL (N=985)	Mono HemMalig (N=1040)
Male	217 (65.2)	508 (66.7)	143 (64.1)	651 (66.1)	704 (67.7)
Female	116 (34.8)	254 (33.3)	80 (35.9)	334 (33.9)	336 (32.3)
Race, n (%)					
American Indian or Alaska Native	0	1 (0.1)	0	1 (0.1)	1 (0.1)
Asian	7 (2.1)	14 (1.8)	3 (1.3)	17 (1.7)	16 (1.5)
Black or African American	4 (1.2)	26 (3.4)	5 (2.2)	31 (3.1)	34 (3.3)
Native Hawaiian or Other Pacific Islander	0	1 (0.1)	0	1 (0.1)	1 (0.1)
White	314 (94.3)	698 (91.6)	208 (93.3)	906 (92.0)	923 (88.8)
Other	0	11 (1.4)	0	11 (1.1)	15 (1.4)
Missing/NA	8 (2.4)	11 (1.4)	7 (3.1)	18 (1.8)	50 (4.8)
Ethnicity, n (%)					
Hispanic	12 (3.6)	21 (2.8)	3 (1.3)	24 (2.4)	29 (2.8)
Non-Hispanic	303 (91.0)	715 (93.8)	212 (95.1)	927 (94.1)	943 (90.7)
Missing/NA	18 (5.4)	26 (3.4)	8 (3.6)	34 (3.5)	68 (6.5)
Geographic region, n (%)					
North America	78 (23.4)	400 (52.5)	109 (48.9)	509 (51.7)	508 (48.8)
South America	7 (2.1)	8 (1.0)	5 (2.2)	13 (1.3)	8 (0.8)
Western Europe	75 (22.5)	140 (18.4)	48 (21.5)	188 (19.1)	286 (27.5)
Central and Eastern Europe	144 (43.2)	177 (23.2)	48 (21.5)	225 (22.8)	199 (19.1)
Australia and New Zealand	22 (6.6)	28 (3.7)	13 (5.8)	41 (4.2)	30 (2.9)
Asia	7 (2.1)	9 (1.2)	0	9 (0.9)	9 (0.9)
Weight (kg)					
n	333	760	223	983	1037
Mean (SD)	79.7 (18.29)	80.2 (17.82)	80.5 (18.24)	80.3 (17.91)	79.6 (17.50)
Median	78.2	79.4	79.0	79.3	78.5
Min, Max	41, 149	39, 155	47, 142	39, 155	39, 155
Body Mass Index (kg/m^2)					
n	328	746	219	965	1014
Mean (SD)	27.7 (5.20)	27.4 (5.11)	27.9 (5.44)	27.5 (5.19)	27.2 (5.05)
Median	27.1	26.7	27.0	26.7	26.5
Min, Max	17.6, 48.5	15.6, 48.5	18.1, 50.5	15.6, 50.5	15.6, 48.5
ECOG Status, n (%)					
0	148 (44.4)	292 (38.3)	104 (46.6)	396 (40.2)	437 (42.0)
1	152 (45.6)	415 (54.5)	110 (49.3)	525 (53.3)	530 (51.0)
2	33 (9.9)	54 (7.1)	9 (4.0)	63 (6.4)	71 (6.8)
3	0	1 (0.1)	0	1 (0.1)	2 (0.2)
Number of prior anticancer therapies					
N	333	762	223	985	1026
Mean (SD)	0.88 (1.30)	1.36 (1.94)	0.27 (1.03)	1.11 (1.83)	1.62 (1.93)
Median	0.00	1.00	0.00	0.00	1.00
Min, Max	0, 8	0, 13	0, 9	0, 13	0, 13

CLL=chronic lymphocytic leukemia; ECOG=Eastern Cooperative Oncology Group; Max=maximum; Min=minimum; NA=not available; SD=standard deviation

Summarized for safety population by actual treatment arm.
Body mass index was calculated as weight (kg)/height in m^2
Source: Module 5.3.5.3, ISS Table 2, and ISS Table 3.

There were no noteworthy differences in demographics between the studies.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's position.

For the ELEVATE-TN trial, the baseline characteristics of the ELEVATE-TN safety population are nearly identical to the ELEVATE-TN efficacy or ITT population. See Table 15 and Table 16 for a summary of demographics, baseline, and disease characteristics by treatment arm. The baseline characteristics were balanced amongst the treatment arms.

For the integrated safety analysis presented in the FDA assessments and in the USPI Warnings and Precautions, FDA revised the denominator to

- exclude patients with acalabrutinib dosing other than 100 mg every 12 hours,
- add recipients of combination therapy (acalabrutinib + obinutuzumab), and
- exclude patients with MM, DLBCL, and FL because of their limited exposure duration (median exposure 1 month, 2 months, and 6 months, respectively)

The table below summarizes the integrated safety population of 1029 patients, consisting of the majority of the total acalabrutinib CLL population (N = 805), patients with MCL (N = 124), and patients with WM (N = 100). In this revised safety population (median age, 68), the median duration of exposure to acalabrutinib (excluding 2 patients with missing data) was 26.1 months (Q1, Q3: 13.8, 34.6), with 901 patients (75%) treated for ≥ 6 months, 808 (67%) for ≥ 1 year, 588 (49%) for ≥ 2 years, and 194 (16%) for ≥ 3 years.

Table 45: Revised Integrated Safety Population for FDA Analysis (N = 1029)

	Total treated (from 1216)	Randomized Studies		CLL Supportive Studies			Other HM Supportive Studies	
		ACE-CL-007 (ELEVATE)	ACE-CL-309 (ASCEND)	ACE-CL-001	15-H-0016	ACE-CL-003	ACE-LY-004	ACE-WM-001
Phase		3	3	1/2	2	1/2	2	2
Data cutoff date		8Feb2019	15Jan2019	4Jan2019	7Dec2018	1Nov2018	12Feb2018	1Nov2018
Disease		CLL	CLL	CLL/SLL[b]	CLL/SLL	CLL/SLL	MCL	WM
Acala monotherapy, excluding crossover	**749**	179	154	159	24	NA	124	100
Acala monotherapy, after crossover from control arm	**80**	45	35	–	–	–	–	–
Acala + obinutuzumab	**209**	178	NA	NA	NA	31	NA	NA

Summary [a]	
Total CLL population	**805**
Monotherapy	596
With obinutuzumab	209
Other HM (all monotherapy)	**224**

[a] Acalabrutinib dose is 100 mg approximately every 12 hours for all patients.
[b] Excludes transformed CLL (RS, PLL) because of different acalabrutinib dosing.

Adequacy of the safety database:

The Applicant's Position:
The size of the database for the pivotal ELEVATE-TN safety pool is adequate to provide an estimate of adverse reactions that may be associated with acalabrutinib use in the CLL population. The database from the total pooled population (N=1040) includes patients with other hematologic malignancies (CLL, NHL, WM) and provides supportive safety. Demographic and baseline characteristics of subjects treated with acalabrutinib 100 mg BID were generally representative of the CLL population. Treated subjects varied with regards to age, sex, race, and ethnicity. The duration of treatment in the Total CLL Population is adequate to provide assessment of adverse reactions.

The safety database of acalabrutinib is considered to be adequate to assess the safety of the 100 mg BID dose.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's position.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No issues were identified regarding data integrity or submission quality that had an effect on the clinical safety review. The submission included adequate narratives for events of clinical interest as agreed with FDA. No safety update is required.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's position.

Categorization of Adverse Event

The Applicant's Position:
AEs and serious adverse (SAEs) were coded using the MedDRA reporting system, version 21.1. AEs were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03. AEs were summarized by treatment arm as treated. Treatment-emergent adverse events (TEAEs) were defined as any event with an onset date on or after the first dose date of study drug or any ongoing event that worsened in severity after the first dose date of study drug, and prior to 30 days after the date of the last dose of study drug or the first date starting new anticancer therapy. All AEs and SAEs discussed in this AA are treatment-emergent unless otherwise specified.

Selected AEs for additional analyses (events of clinical interest [ECIs]) have been identified based on nonclinical findings, emerging data from clinical studies relating to acalabrutinib, and pharmacological effects of an approved BTK inhibitor. The AEs selected for dedicated analysis were evaluated using Standardized MedDRA Queries, where available, by SOC, or by Applicant-defined baskets of MedDRA Adverse Event Grouped Terms. The following ECIs were summarized: cardiac events (including subsets of atrial fibrillation and ventricular tachyarrhythmias), cytopenias (anemia, leukopenia [including subsets of neutropenia and other leukopenia], thrombocytopenia), hemorrhage (including subset of major hemorrhage), hepatotoxicity, hypertension, infections, interstitial lung disease/pneumonitis, second primary malignancies (including subset of second primary malignancies excluding non-melanoma skin), and tumor lysis syndrome.

Adverse events were collected as specified in the ELEVATE-TN protocol.

Routine Clinical Tests

The Applicant's Position:

ELEVATE-TN protocol prespecified the various clinical laboratory evaluations to be performed before study entry, throughout the study, and at the follow-up evaluation. Hematology tests included a complete blood count (CBC) with white blood cell differential and determination of absolute T/B/NK counts. Chemistry tests included albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), calcium, creatinine, glucose, lactate dehydrogenase (LDH), phosphate/ phosphorus, potassium, sodium, total bilirubin, and uric acid. Sparse PK samples and serum immunoglobulins/beta2 microglobulins were also collected.

Laboratory assessments were carried out as specified in the ELEVATE-TN protocol.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's position. For increased sensitivity, the FDA and Applicant used agreed upon custom groupings of preferred terms as defined in Appendix 19.5.

8.2.4. Safety Results

Deaths
The Applicant's Position:

Summary of deaths is provided in Table 46. Eight subjects (4.5%) in the acalabrutinib+ obinutuzumab arm, 12 subjects (6.7%) in the acalabrutinib monotherapy arm, and 13 subjects (7.7%) in the obinutuzumab+chlorambucil arm died, including 2 deaths (4.4%) during the crossover period. Deaths within 30 days of the last study drug occurred in 3 subjects (1.7%) in both the acalabrutinib + obinutuzumab and acalabrutinib monotherapy arms, and in 2 subjects (1.2% in the obinutuzumab + chlorambucil arm. Deaths more than 30 days after the last dose of study drug occurred in 5 subjects (2.8%) in the acalabrutinib+ obinutuzumab arm, 9 subjects (5.0%) in the acalabrutinib monotherapy arm, and 11 subjects (6.5%) in the obinutuzumab+ chlorambucil arm.

The primary cause of death in all treatment groups was AEs (2.2%, 3.4%, 5.9% for acalabrutinib +obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+chlorambucil, respectively). Narratives for all subjects who received acalabrutinib and died are provided.

Table 46: Summary of Deaths (Safety Population)

	No. (%) of Subjects		
	Arm B Acalabrutinib+ Obinutuzumab (N=178)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab+ Chlorambucil (N=169)**
Deaths	8 (4.5)	12 (6.7)	13 (7.7)
Primary cause of death			
Adverse event	4 (2.2)	6 (3.4)	10 (5.9)
Disease progression	2 (1.1)	1 (0.6)	1 (0.6)

	No. (%) of Subjects		
	Arm B Acalabrutinib+ Obinutuzumab (N=178)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab+ Chlorambucil (N=169)**
Richter's transformation	0	1 (0.6)	0
Other	0	3 (1.7)	0
Unknown	2 (1.1)	1 (0.6)	2 (1.2)
Within 30 days of last dose	3 (1.7)	3 (1.7)	2 (1.2)
More than 30 days after last dose	5 (2.8)	9 (5.0)	11 (6.5)

Source: Table 14.3.3.2 from ELEVATE-TN CSR.

Grade 5 (fatal) TEAEs occurred in 5 subjects (2.8%) in the acalabrutinib+obinutuzumab treatment arm, 6 subjects (3.4%) in the acalabrutinib monotherapy treatment arm, and 4 subjects (2.4%) in the obinutuzumab+chlorambucil treatment arm. No Grade 5 TEAEs by preferred term occurred in more than 1 subject, with the exception of 2 subjects (1.1%) in the acalabrutinib+obinutuzumab arm who had Grade 5 events of sepsis, not related to study drug.

Table 47: Treatment Emergent Adverse Events Resulting in Death (Safety Population)

System Organ Class /Preferred Term	**Acala + Obin (N=178)**	**Acala (N=179)**	**Chlb + Obin (N=169)**
Number of subjects with fatal adverse events – n(%)	5 (2.8%)	6 (3.4%)	4 (2.4%)
Blood and lymphatic system disorders	0	1 (0.6%)	0
Febrile neutropenia	0	1 (0.6%)	0
Cardiac disorders	0	0	1 (0.6%)
Cardiac arrest	0	0	1 (0.6%)
Endocrine disorders	0	1 (0.6%)	0
Goitre	0	1 (0.6%)	0
Infections and infestations	3 (1.7%)	2 (1.1%)	1 (0.6%)
Sepsis	2 (1.1%)	0	0
Pneumonia	1 (0.6%)	0	0
Bacterial sepsis	0	0	1 (0.6%)
Bronchopulmonary aspergillosis	0	1 (0.6%)	0
Septic shock	0	1 (0.6%)	0
Musculoskeletal and connective tissue disorders	0	1 (0.6%)	0
Myositis	0	1 (0.6%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.1%)	0	2 (1.2%)
Gastric cancer stage IV	1 (0.6%)	0	0
Metastases to bone	1 (0.6%)	0	0
Acute myelomonocytic leukaemia	0	0	1 (0.6%)
Lung adenocarcinoma	0	0	1 (0.6%)
Nervous system disorders	0	1 (0.6%)	0
Parkinson's disease	0	1 (0.6%)	0

SOURCE: Ad-hoc analysis of ELEVATE-TN datasets
MedDRA version: 21.1
A subject with multiple severity grades for a given TEAE was counted only once under the maximum severity.

Acalabrutinib was well tolerated and showed an acceptable safety profile that is consistent with the other acalabrutinib clinical trials.

Regulatory Authorities Assessment:
Upon review of patient narratives and adverse event datasets for all deaths occurring during the ELEVATE-TN trial, The regulatory authorities agree with the Applicant's position. To provide further supportive information, Table 48 summarizes deaths within 30 days of last dose of study treatment and Table 49 summarizes deaths greater than 30 days from last dose of study treatment. The most common cause of death within 30 days of last dose of study treatment for the both acalabrutinib treatment arms was infection, most often due to sepsis and pneumonia.

Table 48: Deaths within 30 Days of Last Dose of Study Treatment

Primary cause of death per FDA analysis	n
Acalabrutinib+Obinutuzumab (N = 178)	
Total deaths, n (%)	**3 (1.7%)**
Fatal adverse event, n (%)	**3 (1.7%)**
Infection	
Sepsis	2
Pneumonia	1
Progressive disease	**0**
Acalabrutinib (N = 224, includes crossover patients)	
Total deaths, n (%)	**5 (2.2%)**
Fatal adverse event, n (%)	**5 (2.2%)**
Cardiac arrest	2
Sepsis	1
Bronchopulmonary aspergillosis	1
Polymyositis	1
Progressive disease	**0**
Obinutuzumab+Chlorambucil (N = 169)	
Total deaths, n (%)	**2 (1.2%)**
Fatal adverse event, n (%)	**2 (1.2%**
Sepsis	1
Cardiac arrest	1
Progressive disease	**0**
Source: FDA analysis of ADAE and ADDTH datasets	

Table 49: Deaths After 30 Days From Last Dose of Study Treatment

Primary cause of death per FDA analysis	n
Acalabrutinib+Obinutuzumab (N = 178)	
Total deaths, n (%)	**6 (3.4%)**
Fatal adverse event, n (%)	**4 (1.7%)**
SPM - Squamous cell carcinoma, gastric cancer	2
Bacteremia	1
Unknown	1
Progressive disease, n (%)	**2 (1.1%)**
Acalabrutinib (N = 224, includes crossover patients)	
Total deaths, n (%)	**9 (4.0%)**
Fatal adverse event, n (%)	**5 (2.2%)**
Stroke	1
Cardiac failure	1
Respiratory insufficiency	1
SPM – Glioblastoma multiforme	1
Parkinson's disease	1
Progressive disease, n (%)	**4 (1.8%)**
Obinutuzumab+Chlorambucil (N = 169)	
Total deaths, n (%)	**11 (6.5%)**
Fatal adverse event, n (%)	**10 (5.9%)**
SPM- AML, lung adenocarcinoma, cholangiocarcinoma, brain tumor	4
Duodenal hemorrhage, intracranial hemorrhage	2
Progressive multifocal leukoencephalopathy	1
Sepsis	1
Pneumonia	1
Unknown	1
Progressive disease, n (%)	**1 (<1%)**
Abbreviations: SPM: Second primary malignancy Source: FDA analysis of ADAE and ADDTH datasets	

Serious Adverse Events

The Applicant's position:

SAEs occurred in 38.8%, 31.8%, 21.9% of subjects who received acalabrutinib + obinutuzumab, acalabrutinib monotherapy, and obinutuzumab + chlorambucil, respectively, and most SAEs were Grade ≥3. In the acalabrutinib+obinutuzumab arm, the most common SAEs were pneumonia (12 subjects [6.7%]) and infusion-related reactions (4 subjects [2.2%]). In the acalabrutinib monotherapy arm the most common SAEs were pneumonia (5 subjects [2.8%])

and anemia (4 subjects [2.2%]). In the obinutuzumab + chlorambucil arm, the most common SAEs was febrile neutropenia (7 subjects [4.1%]) and pneumonia (3 subjects [1.8%]) (Table 50).

Table 50: Serious Treatment-Emergent Adverse Events Reported in ≥2% of Subjects in the Acalabrutinib Arm (Safety Population)

	Acala + Obin (N=178)		Acala (N=179)		Chlb + Obin (N=169)	
System Organ Class /Preferred Term	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Subjects with at least one Serious TEAE – n(%)	69 (38.8%)	58 (32.6%)	57 (31.8%)	53 (29.6%)	37 (21.9%)	33 (19.5%)
Blood and lymphatic system disorders	5 (2.8%)	5 (2.8%)	9 (5.0%)	9 (5.0%)	9 (5.3%)	9 (5.3%)
Anaemia	3 (1.7%)	3 (1.7%)	4 (2.2%)	4 (2.2%)	0	0
Febrile neutropenia	3 (1.7%)	3 (1.7%)	2 (1.1%)	2 (1.1%)	7 (4.1%)	7 (4.1%)
Cardiac disorders	10 (5.6%)	8 (4.5%)	10 (5.6%)	9 (5.0%)	3 (1.8%)	2 (1.2%)
Gastrointestinal disorders	8 (4.5%)	6 (3.4%)	3 (1.7%)	2 (1.1%)	0	0
General disorders and administration site conditions	3 (1.7%)	2 (1.1%)	4 (2.2%)	1 (0.6%)	4 (2.4%)	1 (0.6%)
Infections and infestations	35 (19.7%)	28 (15.7%)	22 (12.3%)	21 (11.7%)	9 (5.3%)	9 (5.3%)
Pneumonia	12 (6.7%)	8 (4.5%)	5 (2.8%)	4 (2.2%)	3 (1.8%)	3 (1.8%)
Injury, poisoning and procedural complications	9 (5.1%)	6 (3.4%)	7 (3.9%)	7 (3.9%)	4 (2.4%)	4 (2.4%)
Infusion related reaction	4 (2.2%)	3 (1.7%)	0	0	2 (1.2%)	2 (1.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (5.1%)	5 (2.8%)	5 (2.8%)	4 (2.2%)	2 (1.2%)	2 (1.2%)
Nervous system disorders	4 (2.2%)	3 (1.7%)	5 (2.8%)	3 (1.7%)	1 (0.6%)	0
Renal and urinary disorders	4 (2.2%)	4 (2.2%)	2 (1.1%)	2 (1.1%)	1 (0.6%)	1 (0.6%)
Respiratory, thoracic and mediastinal disorders	4 (2.2%)	3 (1.7%)	4 (2.2%)	4 (2.2%)	5 (3.0%)	3 (1.8%)

MedDRA version: 21.1
A subject with multiple severity grades for a given TEAE was counted only once under the maximum severity.
Source: Ad-hoc analysis of ELEVATE-TN datasets.

Acalabrutinib was well tolerated and showed an acceptable safety profile that is consistent with the other acalabrutinib clinical trials.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's position and has provided supplemental information on SAEs below.

Table 51 summarizes the FDA analysis of SAEs by treatment arm in ELEVATE-TN using preferred terms or grouped preferred terms (Appendix 19.5). The use of grouped preferred terms identified some notable discrepancies in serious adverse events, with FDA analysis demonstrating an incidence of Grade ≥3 SAEs in the acalabrutinib monotherapy arm of pneumonia (4%), myocardial ischemia or infarction (2%), and cardiac failure (2%), and in the acalabrutinib + obinutuzumab arm of sepsis (3%) and myocardial ischemia or infarction (2%).

Table 51: Serious Adverse Events in ≥ 2% by Preferred Term or Grouped Preferred Term in Acalabrutinib Treatment Arms

Event	Acalabrutinib+ Obinutuzumab N = 178		Acalabrutinib N = 179		Obinutuzumab+ Chlorambucil N = 169	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Pneumonia	7%	5%	4%	4%	2%	2%
Sepsis	4%	3%	1%	1%	2%	2%
Febrile neutropenia	2%	2%	1%	1%	4%	4%
Myocardial ischemia or infarction	2%	2%	2%	2%	<1%	0
Infusion-related reaction	2%	2%	0	0	1%	1%
Anemia	2%	2%	3%	3%	<1%	<1%
Lower respiratory tract infection	2%	1%	<1%	<1%	0	0
Upper respiratory tract infection	2%	<1%	0	0	<1%	<1%
Urinary tract infection	1%	<1%	2%	2%	0	0
Tumor lysis syndrome	<1%	<1%	0	0	5%	5%
Cardiac failure	0	0	2%	2%	0	0
Dyspnea	0	0	2%	2%	<1%	<1%

Source: FDA analysis of ADAE dataset
Includes all-cause events reported up to 30 days after last dose of study treatment.

Treatment Modifications

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

TEAEs that led to discontinuation of acalabrutinib treatment occurred in 19 subjects (10.7%) in the acalabrutinib+obinutuzumab arm and 17 subjects (9.5%) in the acalabrutinib monotherapy arm. Events which led to acalabrutinib discontinuation in more than 1 subject were hepatitis B reactivation and sepsis (2 subjects [1.1%] each), all in the acalabrutinib+ obinutuzumab arm. TEAEs that led to discontinuation of obinutuzumab treatment occurred in 11 subjects (6.2%) in the acalabrutinib+obinutuzumab arm and 10 subjects (5.9%) in the obinutuzumab+ chlorambucil arm. Common TEAEs leading to obinutuzumab discontinuation were infusion-related reaction (2 subjects [1.1%] each in the acalabrutinib+ obinutuzumab and obinutuzumab+chlorambucil arms) and neutropenia (2 subjects [1.1%] and 3 subjects [1.8%] in the acalabrutinib+obinutuzumab and obinutuzumab+chlorambucil arms, respectively). TEAEs that led to discontinuation of chlorambucil occurred in 24 subjects (14.2%) discontinued chlorambucil treatment due to TEAEs. Common TEAEs leading to chlorambucil discontinuation were neutropenia (11 subjects [6.5%]), thrombocytopenia and upper respiratory tract infection

(2 subjects [1.1%] each). A summary of adverse events leading to discontinuation is presented below (Table 52).

Table 52: Adverse Events Leading to Discontinuation of Study Treatment in ≥2 Subjects in Any Treatment Arm (Safety Population)

	No. (%) of Subjects					
	Arm B Acalabrutinib+ Obinutuzumab (N=178)		Arm C Acalabrutinib Monotherapy (N=179)		Arm A Obinutuzumab+ Chlorambucil (N=169)	
Preferred Term	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Subjects with ≥1 TEAE leading to discontinuation of **acalabrutinib**	19 (10.7)	12 (6.7)	17 (9.5)	16 (8.9)	--	--
Hepatitis B reactivation	2 (1.1)	0	0	0	--	--
Sepsis	2 (1.1)	2 (1.1)	0	0	--	--
Subjects with ≥1 TEAE leading to discontinuation of **obinutuzumab**	11 (6.2)	9 (5.1)	--	--	10 (5.9)	10 (5.9)
Infusion related reaction	2 (1.1)	2 (1.1)	--	--	2 (1.2)	2 (1.2)
Neutropenia	2 (1.1)	2 (1.1)	--	--	3 (1.8)	3 (1.8)
Subjects with ≥1 TEAE leading to discontinuation of **chlorambucil**	--	--	--	--	24 (14.2)	22 (13.0)
Neutropenia	--	--	--	--	11 (6.5)	11 (6.5)
Thrombocytopenia	--	--	--	--	2 (1.2)	1 (0.6)
Upper respiratory tract infection	--	--	--	--	2 (1.2)	1 (0.6)

TEAE=treatment-emergent adverse event.
TEAEs coded with MedDRA Version 21.1.
A subject with multiple severity grades for a given TEAE was counted only once under the maximum severity.
Source: ELEVATE-TN clinical report, Table 14.3.5.1, Table 14.3.5.2, Table 14.3.5.3, Table 14.3.5.4, and Table 14.3.5.5.

Acalabrutinib was well tolerated and showed an acceptable safety profile that is consistent with the other acalabrutinib clinical trials.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's position and has provided supplemental information.

In the acalabrutinib monotherapy arm, the most common reason for discontinuation was infection, with 1 patient discontinuing due to bacterial pneumonia, 1 patient with pulmonary aspergillosis, and 1 patient with disseminated cryptococcosis.

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

A total of 33.7% of subjects in the acalabrutinib+obinutuzumab arm and 15.6% of subjects in the acalabrutinib monotherapy arm had ≥1 dose withholding due to TEAEs. A total of 19.7% of subjects in the acalabrutinib+obinutuzumab arm and 13.4% of subjects in the acalabrutinib monotherapy arm had a dose reduction to 100 mg QD. The main reasons for dose reduction were TEAE (7.9% and 2.8% for acalabrutinib+obinutuzumab and acalabrutinib monotherapy arms, respectively) and subject error (10.1% and 7.3% for acalabrutinib+obinutuzumab and acalabrutinib monotherapy arms, respectively).

Acalabrutinib was well tolerated and showed an acceptable safety profile that is consistent with the other acalabrutinib clinical trials.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's position and has provided supplemental information.

In the acalabrutinib + obinutuzumab arm, 7% of patients dose reduced acalabrutinib due to an adverse event, most often due to gastrointestinal toxicity, neutropenia, and thrombocytopenia.

In the acalabrutinib monotherapy arm, 4% of patients dose reduced due to an adverse event, most often due to gastrointestinal toxicity and headache.

Significant Adverse Events

The Applicant's Position:

ECIs categories reported in ≥25% of subjects in the acalabrutinib+obinutuzumab arm were infections (69.1%), leukopenia (33.1%), and neutropenia (32.0%). ECI categories reported in ≥25% of subjects in the acalabrutinib monotherapy arm were infections (65.4%). ECIs categories reported in ≥25% of subjects in the obinutuzumab+ chlorambucil arm were leukopenia (49.7%), neutropenia (49.1%), and infections (43.8%). No subjects in this study had an ECI of ventricular tachyarrhythmia (Table 53).

Table 53: Summary of Treatment-Emergent Events by ECI Category and FDA Grouped Preferred Terms (Safety Population)

	Acala + Obin (N=178)		Acala (N=179)		Chlb + Obin (N=169)	
Category Subcategory	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥3**
Cardiac events	**25 (14.0%)**	**8 (4.5%)**	**25 (14.0%)**	**9 (5.0%)**	**13 (7.7%)**	**3 (1.8%)**
Atrial fibrillation or flutter[1]	6 (3.4%)	1 (0.6%)	7 (3.9%)	0	1 (0.6%)	0
Ventricular arrhythmias[1]	0	0	0	0	0	0
Cardiac arrhythmias[1]	13 (7.3%)	2 (1.1%)	10 (5.6%)	0	8 (4.7%)	2 (1.2%)
Myocardial ischemia or infarction[1]	5 (2.8%)	4 (2.2%)	5 (2.8%)	4 (2.2%)	1 (0.6%)	0
Supraventricular tachycardia[1]	8 (4.5%)	1 (0.6%)	7 (3.9%)	0	2 (1.2%)	0
Anemia[1]	**25 (14.0%)**	**11 (6.2%)**	**29 (16.2%)**	**14 (7.8%)**	**22 (13.0%)**	**13 (7.7%)**
Leukopenia	**59 (33.1%)**	**56 (31.5%)**	**21 (11.7%)**	**19 (10.6%)**	**84 (49.7%)**	**78 (46.2%)**
Neutropenia[1]	57 (32.0%)	54 (30.3%)	19 (10.6%)	17 (9.5%)	81 (47.9%)	75 (44.4%)
Febrile neutropenia[1]	4 (2.2%)	4 (2.2%)	2 (1.1%)	2 (1.1%)	9 (5.3%)	9 (5.3%)
Other Leukopenia	1 (0.6%)	1 (0.6%)	0	0	4 (2.4%)	3 (1.8%)
Thrombocytopenia[1]	**27 (15.2%)**	**16 (9.0%)**	**17 (9.5%)**	**6 (3.4%)**	**26 (15.4%)**	**22 (13.0%)**
Hemorrhage or hematoma[1]	**36 (20.2%)**	**3 (1.7%)**	**35 (19.6%)**	**3 (1.7%)**	**10 (5.9%)**	**0**
Major hemorrhage	5 (2.8%)	3 (1.7%)	3 (1.7%)	3 (1.7%)	2 (1.2%)	0
Gastrointestinal hemorrhage[1]	6 (3.4%)	3 (1.7%)	3 (1.7%)	0	2 (1.2%)	0
Hemorrhage intracranial[1]	1 (0.6%)	0	1 (0.6%)	1 (0.6%)	1 (0.6%)	0
Hepatotoxicity	**16 (9.0%)**	**9 (5.1%)**	**4 (2.2%)**	**1 (0.6%)**	**8 (4.7%)**	**5 (3.0%)**
Hepatitis[1]	3 (1.7%)	1 (0.6%)	1 (0.6%)	0	0	0
Hyperbilirubinemia[1]	3 (1.7%)	1 (0.6%)	2 (1.1%)	0	2 (1.2%)	1 (0.6%)
Hypertension[1]	**11 (6.2%)**	**5 (2.8%)**	**8 (4.5%)**	**4 (2.2%)**	**6 (3.6%)**	**5 (3.0%)**
Infections	**123 (69.1%)**	**37 (20.8%)**	**117 (65.4%)**	**25 (14.0%)**	**74 (43.8%)**	**14 (8.3%)**
Cytomegalovirus infection[1]	0	0	0	0	0	0
Gastroenteritis[1]	2 (1.1%)	0	11 (6.1%)	1 (0.6%)	1 (0.6%)	1 (0.6%)
Herpesvirus infection[1]	0	0	0	0	0	0
Lower respiratory tract infection[1]	27 (15.2%)	3 (1.7%)	25 (14.0%)	1 (0.6%)	7 (4.1%)	0
Pneumonia[1]	20 (11.2%)	11 (6.2%)	17 (9.5%)	7 (3.9%)	5 (3.0%)	3 (1.8%)
Respiratory tract infection[1]	2 (1.1%)	0	2 (1.1%)	0	0	0
Sepsis[1]	8 (4.5%)	8 (4.5%)	2 (1.1%)	2 (1.1%)	4 (2.4%)	4 (2.4%)
Upper respiratory tract infection[1]	69 (38.8%)	5 (2.8%)	62 (34.6%)	0	29 (17.2%)	2 (1.2%)
Urinary tract infection[1]	26 (14.6%)	3 (1.7%)	27 (15.1%)	5 (2.8%)	9 (5.3%)	1 (0.6%)
Interstitial lung disease/Pneumonitis	**1 (0.6%)**	**0**	**2 (1.1%)**	**0**	**1 (0.6%)**	**0**
Pneumonitis[1]	1 (0.6%)	0	0	0	1 (0.6%)	0
Second primary malignancies	**19 (10.7%)**	**7 (3.9%)**	**15 (8.4%)**	**2 (1.1%)**	**6 (3.6%)**	**3 (1.8%)**

	Acala + Obin (N=178)		Acala (N=179)		Chlb + Obin (N=169)	
Category Subcategory	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥3**
Second primary malignancies excluding non-melanoma skin	10 (5.6%)	6 (3.4%)	5 (2.8%)	2 (1.1%)	3 (1.8%)	2 (1.2%)
Nonmelanoma skin cancer[1]	9 (5.1%)	1 (0.6%)	10 (5.6%)	0	4 (2.4%)	1 (0.6%)
Tumor lysis syndrome	**3 (1.7%)**	**2 (1.1%)**	**0**	**0**	**15 (8.9%)**	**13 (7.7%)**

[1] FDA grouped preferred terms

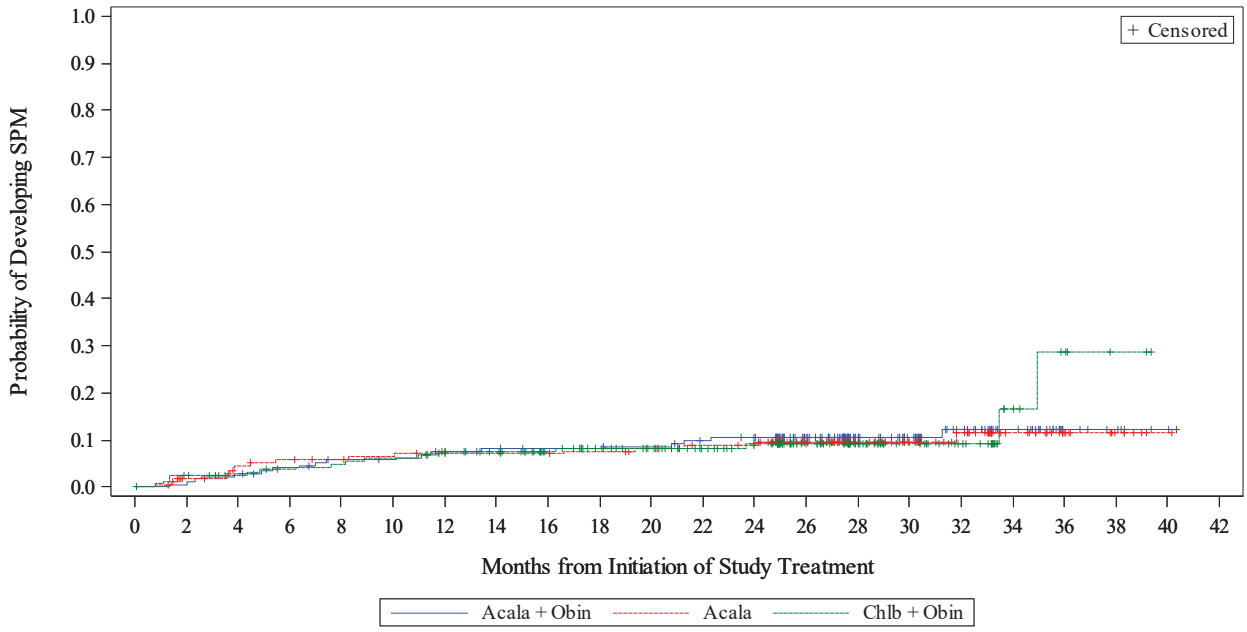
MedDRA version: 21.1

A subject with multiple severity grades for a given TEAE was counted only once under the maximum severity.

Source: Ad-hoc analysis of ELEVATE-TN datasets.

Second primary malignancies (any grade) occurred in 19 (10.7%), 15 (8.4%), and 6 (3.6%) subjects in the acalabrutinib+obinutuzumab arm, acalabrutinib monotherapy arm, and obinutuzumab+chlorambucil arm, respectively. Basal cell carcinoma was the most frequent second primary malignancy (any grade) in the acalabrutinib+obinutuzumab and acalabrutinib monotherapy treatment arms (7 subjects [3.9%] and 8 subjects [4.5%], respectively). All Grade ≥3 events of second primary malignancies (by preferred term) occurred in ≤2 subjects with the exception of basal cell carcinoma. Figure 12 below provides estimated cumulative incidences based on a time-to-first event analysis.

Figure 12 Time to Onset of Second Primary Malignancies (SPM) Event – Failure Plot (Safety Population)



Number of Subjects at Risk

Acala + Obin	178	177	173	169	164	163	158	155	153	153	151	147	144	118	79	66	49	30	9	6	2	0
Acala	179	170	162	159	157	155	151	151	150	148	145	141	139	108	78	63	47	26	14	6	1	0
Chlb + Obin	169	163	158	154	152	150	144	141	127	118	111	99	91	65	46	32	24	9	5	2	0	

Source: Ad-hoc analysis of ELEVATE-TN datasets.

Acalabrutinib was well tolerated and showed an acceptable safety profile that is consistent with the other acalabrutinib clinical trials.

Regulatory Authorities Assessment:

The regulatory authorities agree with the Applicant's position. The events of clinical interest including cardiac arrhythmias, hemorrhage, neutropenia, infection, and second primary malignancies are further evaluated in Section 8.2.5.

Treatment Emergent Adverse Events and Adverse Reactions

The Applicant's Position:

Treatment-related TEAEs were reported less frequently in the acalabrutinib monotherapy treatment arm than in either of the acalabrutinib+obinutuzumab (65.9% versus 80.9%, respectively) or obinutuzumab+chlorambucil (65.9% versus 91.1%, respectively) treatment arms. Subjects in the acalabrutinib monotherapy treatment arm also had notably lower rates of most Grade ≥3 TEAEs compared to the other 2 treatment arms.

Common TEAEs that occurred in ≥20% of acalabrutinib+obinutuzumab arm subjects were headache (39.9%), diarrhea (38.8%), neutropenia (31.5%), fatigue (28.1%), contusion (23.6%),

arthralgia (21.9%), cough (21.9%), upper respiratory tract infection (21.3%), and nausea (20.2%). Most of these common TEAEs were Grade 1 or 2, with the exception of neutropenia (most TEAEs were Grade 3-4) (Table 54).

Common TEAEs that occurred in ≥20% of acalabrutinib monotherapy arm subjects were headache (36.9%), diarrhea (34.6%), and nausea (22.3%). Almost all of these frequent TEAEs were Grade 1 or 2, with the exception of 2 subjects (1.1%) with Grade 3 TEAEs of headache, and 1 subject (0.6%) with a Grade 3 AE of diarrhea. None of these frequent TEAEs were Grade 4 (Table 54).

Common TEAEs that occurred in ≥20% of obinutuzumab+chlorambucil subjects were neutropenia (45.0%), infusion-related reaction (39.6%), nausea (31.4%), diarrhea (21.3%), and pyrexia (20.7%). Most of these frequent TEAEs were Grade 1 or 2, with the exception of neutropenia (most TEAEs were Grade 3-4) (Table 54).

Table 54: Treatment Emergent Adverse Events in ≥10% of Subjects in the Acalabrutinib Arm (Safety Population)

	Acala + Obin (N=178)		Acala (N=179)		Chlb + Obin (N=169)	
System Organ Class /Preferred Term	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Subjects with at least one TEAE – n(%)	171 (96.1%)	125 (70.2%)	170 (95.0%)	89 (49.7%)	167 (98.8%)	118 (69.8%)
Blood and lymphatic system disorders	80 (44.9%)	67 (37.6%)	56 (31.3%)	32 (17.9%)	92 (54.4%)	80 (47.3%)
Neutropenia	56 (31.5%)	53 (29.8%)	19 (10.6%)	17 (9.5%)	76 (45.0%)	70 (41.4%)
Thrombocytopenia	23 (12.9%)	15 (8.4%)	13 (7.3%)	5 (2.8%)	24 (14.2%)	20 (11.8%)
Anaemia	21 (11.8%)	10 (5.6%)	25 (14.0%)	12 (6.7%)	20 (11.8%)	12 (7.1%)
Cardiac disorders	25 (14.0%)	8 (4.5%)	25 (14.0%)	9 (5.0%)	13 (7.7%)	3 (1.8%)
Ear and labyrinth disorders	20 (11.2%)	1 (0.6%)	11 (6.1%)	0	7 (4.1%)	0
Eye disorders	26 (14.6%)	3 (1.7%)	26 (14.5%)	4 (2.2%)	11 (6.5%)	2 (1.2%)
Gastrointestinal disorders	115 (64.6%)	17 (9.6%)	118 (65.9%)	4 (2.2%)	85 (50.3%)	6 (3.6%)
Diarrhoea	69 (38.8%)	8 (4.5%)	62 (34.6%)	1 (0.6%)	36 (21.3%)	3 (1.8%)
Nausea	36 (20.2%)	0	40 (22.3%)	0	53 (31.4%)	0
Constipation	25 (14.0%)	0	20 (11.2%)	0	17 (10.1%)	1 (0.6%)
Vomiting	24 (13.5%)	1 (0.6%)	22 (12.3%)	1 (0.6%)	19 (11.2%)	1 (0.6%)
General disorders and administration site conditions	104 (58.4%)	6 (3.4%)	84 (46.9%)	5 (2.8%)	80 (47.3%)	6 (3.6%)
Fatigue	50 (28.1%)	3 (1.7%)	33 (18.4%)	2 (1.1%)	29 (17.2%)	1 (0.6%)
Pyrexia	23 (12.9%)	0	12 (6.7%)	1 (0.6%)	35 (20.7%)	1 (0.6%)
Oedema peripheral	22 (12.4%)	1 (0.6%)	16 (8.9%)	1 (0.6%)	12 (7.1%)	0
Chills	20 (11.2%)	0	8 (4.5%)	0	14 (8.3%)	1 (0.6%)
Infections and infestations	123 (69.1%)	37 (20.8%)	117 (65.4%)	25 (14.0%)	74 (43.8%)	14 (8.3%)
Upper respiratory tract infection	38 (21.3%)	4 (2.2%)	33 (18.4%)	0	14 (8.3%)	1 (0.6%)
Urinary tract infection	22 (12.4%)	1 (0.6%)	22 (12.3%)	3 (1.7%)	8 (4.7%)	0
Nasopharyngitis	20 (11.2%)	1 (0.6%)	17 (9.5%)	0	7 (4.1%)	0
Pneumonia	19 (10.7%)	10 (5.6%)	13 (7.3%)	4 (2.2%)	5 (3.0%)	3 (1.8%)
Injury, poisoning and procedural complications	80 (44.9%)	8 (4.5%)	52 (29.1%)	9 (5.0%)	73 (43.2%)	11 (6.5%)
Contusion	42 (23.6%)	0	27 (15.1%)	0	7 (4.1%)	0
Infusion related reaction	24 (13.5%)	4 (2.2%)	0	0	67 (39.6%)	9 (5.3%)
Investigations	52 (29.2%)	16 (9.0%)	34 (19.0%)	4 (2.2%)	33 (19.5%)	12 (7.1%)

	Acala + Obin (N=178)		Acala (N=179)		Chlb + Obin (N=169)	
System Organ Class /Preferred Term	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Metabolism and nutrition disorders	59 (33.1%)	16 (9.0%)	31 (17.3%)	7 (3.9%)	44 (26.0%)	25 (14.8%)
Decreased appetite	18 (10.1%)	0	10 (5.6%)	0	13 (7.7%)	1 (0.6%)
Musculoskeletal and connective tissue disorders	90 (50.6%)	7 (3.9%)	95 (53.1%)	8 (4.5%)	39 (23.1%)	6 (3.6%)
Arthralgia	39 (21.9%)	2 (1.1%)	28 (15.6%)	1 (0.6%)	8 (4.7%)	2 (1.2%)
Back pain	25 (14.0%)	1 (0.6%)	25 (14.0%)	2 (1.1%)	14 (8.3%)	1 (0.6%)
Pain in extremity	22 (12.4%)	1 (0.6%)	11 (6.1%)	0	7 (4.1%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	28 (15.7%)	8 (4.5%)	22 (12.3%)	5 (2.8%)	8 (4.7%)	3 (1.8%)
Nervous system disorders	101 (56.7%)	12 (6.7%)	96 (53.6%)	9 (5.0%)	51 (30.2%)	1 (0.6%)
Headache	71 (39.9%)	2 (1.1%)	66 (36.9%)	2 (1.1%)	20 (11.8%)	0
Dizziness	32 (18.0%)	0	21 (11.7%)	0	10 (5.9%)	0
Psychiatric disorders	29 (16.3%)	0	28 (15.6%)	3 (1.7%)	25 (14.8%)	1 (0.6%)
Renal and urinary disorders	34 (19.1%)	6 (3.4%)	33 (18.4%)	6 (3.4%)	19 (11.2%)	3 (1.8%)
Respiratory, thoracic and mediastinal disorders	79 (44.4%)	6 (3.4%)	76 (42.5%)	5 (2.8%)	45 (26.6%)	5 (3.0%)
Cough	39 (21.9%)	0	33 (18.4%)	1 (0.6%)	15 (8.9%)	0
Skin and subcutaneous tissue disorders	89 (50.0%)	6 (3.4%)	76 (42.5%)	2 (1.1%)	45 (26.6%)	2 (1.2%)
Rash	21 (11.8%)	1 (0.6%)	25 (14.0%)	1 (0.6%)	8 (4.7%)	0

MedDRA version: 21.1
A subject with multiple severity grades for a given TEAE was counted only once under the maximum severity.
Source: Ad-hoc analysis of ELEVATE-TN datasets.

The number of subjects with adverse drug reactions is provided in the table below in decreasing incidence by system organ class and preferred term.

Table 55: Subject Incidence of Acerta-Defined Adverse Drug Reactions by FDA Grouped Preferred Terms (Safety Population)

	Acala + Obin (N=178)		Acala (N=179)		Chlb + Obin (N=169)	
Grouped Term	**All Grades**	**Grades >=3**	**All Grades**	**Grades >=3**	**All Grades**	**Grades >=3**
Abdominal pain [1]	26 (14.6%)	3 (1.7%)	19 (10.6%)	0	19 (11.2%)	0
Bruising [1]	55 (30.9%)	0	37 (20.7%)	0	9 (5.3%)	0
Rash [1]	47 (26.4%)	4 (2.2%)	44 (24.6%)	1 (0.6%)	15 (8.9%)	1 (0.6%)
Hemorrhage or hematoma [1]	36 (20.2%)	3 (1.7%)	35 (19.6%)	3 (1.7%)	10 (5.9%)	0
Second Primary Malignancy [2]	19 (10.7%)	7 (3.9%)	15 (8.4%)	2 (1.1%)	6 (3.6%)	3 (1.8%)
Second Primary Malignancy, excluding non-melanoma skin [2]	10 (5.6%)	6 (3.4%)	5 (2.8%)	2 (1.1%)	3 (1.8%)	2 (1.2%)
Nonmelanoma skin cancer [1]	9 (5.1%)	1 (0.6%)	10 (5.6%)	0	4 (2.4%)	1 (0.6%)
Infection [2]	123 (69.1%)	37 (20.8%)	117 (65.4%)	25 (14.0%)	74 (43.8%)	14 (8.3%)
Atrial fibrillation or flutter [1]	6 (3.4%)	1 (0.6%)	7 (3.9%)	0	1 (0.6%)	0
Cytopenias						
Anemia [1]	25 (14.0%)	11 (6.2%)	29 (16.2%)	14 (7.8%)	22 (13.0%)	13 (7.7%)
Leukopenia [2]	59 (33.1%)	56 (31.5%)	21 (11.7%)	19 (10.6%)	84 (49.7%)	78 (46.2%)
Neutropenia [1]	57 (32.0%)	54 (30.3%)	19 (10.6%)	17 (9.5%)	81 (47.9%)	75 (44.4%)
Other Leukopenia [2]	1 (0.6%)	1 (0.6%)	0		4 (2.4%)	3 (1.8%)
Thrombocytopenia [1]	27 (15.2%)	16 (9.0%)	17 (9.5%)	6 (3.4%)	26 (15.4%)	22 (13.0%)

	Acala + Obin (N=178)		Acala (N=179)		Chlb + Obin (N=169)	
Grouped Term	All Grades	Grades >=3	All Grades	Grades >=3	All Grades	Grades >=3
Musculoskeletal pain [1]	65 (36.5%)	4 (2.2%)	58 (32.4%)	2 (1.1%)	27 (16.0%)	4 (2.4%)
Hypertension [1]	11 (6.2%)	5 (2.8%)	8 (4.5%)	4 (2.2%)	6 (3.6%)	5 (3.0%)
Diarrhea [1]	69 (38.8%)	8 (4.5%)	62 (34.6%)	1 (0.6%)	36 (21.3%)	3 (1.8%)
Dizziness [1]	35 (19.7%)	0	22 (12.3%)	0	11 (6.5%)	0
Fatigue [1]	60 (33.7%)	4 (2.2%)	42 (23.5%)	2 (1.1%)	41 (24.3%)	2 (1.2%)
Headache [1]	71 (39.9%)	2 (1.1%)	69 (38.5%)	2 (1.1%)	20 (11.8%)	0
Nausea [1]	36 (20.2%)	0	40 (22.3%)	0	53 (31.4%)	0

SOURCE: Ad-hoc analysis of ELEVATE-TN datasets
[1] FDA grouped terms
[2] As per Acerta ADR definition
MedDRA version: 21.1

Acalabrutinib was well tolerated and showed an acceptable safety profile that is consistent with the other acalabrutinib clinical trials.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's position and has provided supplemental information.

Table 56 summarizes common treatment emergent adverse events using preferred term or FDA grouped preferred terms. For the ELEVATE-TN trial, the most common TEAEs (incidence ≥30%) with acalabrutinib, in combination with obinutuzumab or as monotherapy, were neutropenia, thrombocytopenia, anemia, headache, diarrhea, upper respiratory infection, musculoskeletal pain, and fatigue.

Table 56: Treatment Emergent Adverse Events in ≥10% by Preferred Term or FDA Grouped Preferred Term

Event	Acalabrutinib+ Obinutuzumab N = 178		Acalabrutinib N = 179		Obinutuzumab+ Chlorambucil N = 169	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any Adverse Event	96%	70%	96%	50%	99%	70%
Adverse Events in ≥ 10% by Preferred Term or Grouped Preferred Term						
Neutropenia[1]	54%	36%	24%	13%	76%	47%
Thrombocytopenia[1]	49%	12%	28%	3%	60%	15%
Anemia[1]	48%	8%	44%	6%	49%	11%
Headache	40%	1%	39%	1%	12%	0
Diarrhea	39%	4%	35%	<1%	21%	2%
Upper respiratory tract infection	39%	3%	35%	0	17%	1%
Musculoskeletal pain	38%	2%	32%	1%	17%	3%

Event	Acalabrutinib+ Obinutuzumab N = 178		Acalabrutinib N = 179		Obinutuzumab+ Chlorambucil N = 169	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Fatigue	34%	2%	23%	1%	24%	1%
Bruising	28%	0	18%	0	4%	0
Rash	26%	2%	24%	<1%	9%	<1%
Cough	24%	0	24%	<1%	12%	0
Arthralgia	22%	1%	16%	<1%	5%	1%
Nausea	20%	0	22%	0	31%	0
Dizziness	20%	0	12%	0	7%	0
Edema	18%	<1%	16%	1%	11%	<1%
Lower respiratory tract infection	15%	2%	14%	<1%	4%	0
Abdominal pain	15%	2%	11%	0	11%	0
Constipation	14%	0	11%	0	10%	0
Infusion related reaction	13%	2%	0	0	40%	5%
Vomiting	13%	<1%	12%	<1%	11%	<1%
Urinary tract infection	13%	1%	15%	2%	5%	0
Dyspnea	12%	0	11%	2%	10%	2%
Lymphocytosis[1]	12%	11%	16%	15%	<1%	<1%
Haemorrhage	11%	2%	14%	1%	4%	0
Pneumonia	11%	6%	9%	4%	3%	2%
Respiratory tract infection	11%	2%	13%	1%	5%	<1%
Decreased appetite	10%	0	6%	0	8%	<1%
Hypotension	10%	<1%	4%	1%	4%	<1%

Source: FDA analysis of ADAE and ADLB dataset
[1]Combination of adverse event and laboratory data
Includes all-cause events reported up to 30 days after last dose of study treatment

For the ELEVATE-TN trial and ASCEND trial, in 511 patients with CLL exposed to acalabrutinib, with or without obinutuzumab, the most common adverse reactions (≥30%) were anemia, neutropenia, thrombocytopenia, leukocytosis, headache, upper respiratory tract infection, and diarrhea.

In the expanded safety population, consisting of 1209 patients exposed to acalabrutinib 100 mg approximately every 12 hours with or without obinutuzumab, the most common adverse events were similar to those described for the ELEVATE-TN and ASCEND trials.

Laboratory Findings

The Applicant's Position:

By Hallek 2008 criteria, subjects in the acalabrutinib monotherapy treatment arm had a lower incidence of Grade 3-4 TEAEs compared to the other 2 treatment arms: decreased ANC (11.7% acalabrutinib monotherapy versus 34.3% acalabrutinib+obinutuzumab and 46.7% obinutuzumab+chlorambucil) and decreased platelets (7.3% acalabrutinib monotherapy versus 15.2% acalabrutinib+obinutuzumab and 29.0% obinutuzumab+ chlorambucil) (Table 57).

Table 57: Subject Incidence of Neutrophil, Hemoglobin, Platelets Toxicities per Hallek 2008 Criteria (Safety Population)

Lab Test (Unit) (Direction of Change Relative to Baseline)	No. (%) of Subjects					
	Arm B Acalabrutinib+ Obinutuzumab (N=178)		Arm C Acalabrutinib Monotherapy (N=179)		Arm A Obinutuzumab+ Chlorambucil (N=169)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
ANC, hemoglobin, or platelets						
Any (decrease)	143 (80.3)	74 (41.6)	109 (60.9)	30 (16.8)	157 (92.9)	97 (57.4)
ANC (decrease)	108 (60.7)	61 (34.3)	53 (29.6)	21 (11.7)	138 (81.7)	79 (46.7)
Hemoglobin (decrease)	64 (36.0)	2 (1.1)	45 (25.1)	2 (1.1)	64 (37.9)	2 (1.2)
Platelets (decrease)	95 (53.4)	27 (15.2)	62 (34.6)	13 (7.3)	116 (68.6)	49 (29.0)

ANC=absolute neutrophil count.
The worst postbaseline severity grade was used for each subject.
Source: Table 14.3.7.1.1 from ELEVATE-TN CSR.

By CTCAE criteria, subjects in the acalabrutinib monotherapy treatment arm had a lower incidence of Grade 3-4 TEAEs compared to the other treatment arms for each hematology parameter except increased leukocytes (26.8% acalabrutinib monotherapy versus 32.6% acalabrutinib+obinutuzumab and 0.6% obinutuzumab+chlorambucil) and increase in ALC (12.8% acalabrutinib monotherapy versus 10.1% acalabrutinib+obinutuzumab and 0% obinutuzumab+chlorambucil) (Table 58).

The frequency of the following hematologic abnormalities was notably lower in subjects treated with acalabrutinib monotherapy compared with obinutuzumab + chlorambucil respectively: decreased ANC (23.5% vs. 75.7%), decreased platelets (27.9% vs. 59.8%), decreased leukocytes (12.3% vs. 79.3%), decreased ALC (8.9% vs. 82.2%) (Table 58).

The frequency of the following hematologic abnormalities was notably lower in subjects treated with acalabrutinib+ obinutuzumab compared with obinutuzumab + chlorambucil: decreased ANC (53.4% vs. 75.7%), decreased platelets (48.3% vs. 59.8%), decreased leukocytes (45.5% vs. 79.3%), and decreased ALC (44.9% vs. 82.2%) (Table 58).

Table 58: Treatment Emergent Laboratory Abnormality in Hematology by CTCAE Toxicity Grade (Safety Population)

Lab Test (Unit) (Direction of Change Relative to Baseline)	No. (%) of Subjects					
	Arm B Acalabrutinib+ Obinutuzumab (N=178)		Arm C Acalabrutinib Monotherapy (N=179)		Arm A Obinutuzumab+ Chlorambucil (N=169)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
ANC, hemoglobin, or platelets						
Any (decrease)	143 (80.3)	80 (44.9)	117 (65.4)	35 (19.6)	155 (91.7)	87 (51.5)
ANC (decrease)	95 (53.4)	63 (35.4)	42 (23.5)	23 (12.8)	128 (75.7)	80 (47.3)
Hemoglobin (decrease)	85 (47.8)	15 (8.4)	79 (44.1)	11 (6.1)	83 (49.1)	19 (11.2)
Platelets (decrease)	86 (48.3)	21 (11.8)	50 (27.9)	5 (2.8)	101 (59.8)	26 (15.4)
Leukocytes (decrease)	81 (45.5)	26 (14.6)	22 (12.3)	1 (0.6)	134 (79.3)	58 (34.3)
Leukocytes (increase)	58 (32.6)	58 (32.6)	48 (26.8)	48 (26.8)	1 (0.6)	1 (0.6)
ALC (decrease)	80 (44.9)	17 (9.6)	16 (8.9)	3 (1.7)	139 (82.2)	80 (47.3)
ALC (increase)	20 (11.2)	18 (10.1)	24 (13.4)	23 (12.8)	0	0

ALC=absolute leukocyte count; ANC=absolute neutrophil count; CTCAE=Common Terminology Criteria for Adverse Events
CTCAE version 4.03 was used.
The worst postbaseline severity grade was used for each subject.
Source: Table 14.3.7.1.2 from ELEVATE-TN CSR.

Most chemistry laboratory abnormalities were Grade 1 or 2. The most common Grade 3 or 4 chemistry laboratory abnormality was increased urate, reported in 29.2%, 22.3% and 37.3% of subjects in the acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+ chlorambucil treatment arms, respectively. Laboratory abnormalities that occurred notably less frequently in subjects treated with acalabrutinib monotherapy compared with obinutuzumab+ chlorambucil included: increased alanine aminotransferase (20.1% vs. 35.5%), decreased albumin (5.6% vs. 11.2%), increased aspartate aminotransferase (17.3% vs. 60.4%), decreased calcium (14% vs. 30.8%) (Table 59).

Laboratory abnormalities that occurred notably less frequently in subjects treated with acalabrutinib+obinutuzumab compared with obinutuzumab+chlorambucil included: increased aspartate aminotransferase: (37.6% vs. 60.4%) (Table 59).

Table 59: Treatment Emergent Laboratory Abnormality in Chemistry by CTCAE Toxicity Grade (Safety Population)

	No. (%) of Subjects					
	Arm B Acalabrutinib+ Obinutuzumab (N=178)		Arm C Acalabrutinib Monotherapy (N=179)		Arm A Obinutuzumab+ Chlorambucil (N=169)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Alanine Aminotransferase (U/L) (Increased)	54 (30.3)	13 (7.3)	36 (20.1)	2 (1.1)	60 (35.5)	10 (5.9)
Albumin (g/L) (Decreased)	14 (7.9)	1 (0.6)	10 (5.6)	0	19 (11.2)	0
Alkaline Phosphatase (U/L) (Increased)	31 (17.4)	2 (1.1)	33 (18.4)	0	36 (21.3)	1 (0.6)
Aspartate Aminotransferase (U/L) (Increased)	67 (37.6)	9 (5.1)	31 (17.3)	1 (0.6)	102 (60.4)	13 (7.7)
Bilirubin (µmol/L) (Increased	23 (12.9)	1 (0.6)	26 (14.5)	1 (0.6)	19 (11.2)	1 (0.6)
Calcium (mmol/L) (Decreased)	56 (31.5)	4 (2.2)	25 (14.0)	1 (0.6)	52 (30.8)	3 (1.8)
Calcium (mmol/L) (Increased)	3 (1.7)	0	7 (3.9)	0	3 (1.8)	0
Creatinine (µmol/L) (Increased)	113 (63.5)	0	112 (62.6)	1 (0.6)	112 (66.3)	1 (0.6)
Glucose (mmol/L) (Decreased)	5 (2.8)	2 (1.1)	4 (2.2)	0	4 (2.4)	0
Glucose (mmol/L) (Increased)	22 (12.4)	22 (12.4)	9 (5.0)	9 (5.0)	11 (6.5)	11 (6.5)
Phosphate (mmol/L) (Decreased)	43 (24.2)	6 (3.4)	28 (15.6)	4 (2.2)	19 (11.2)	1 (0.6)
Potassium (mmol/L) (Decreased)	15 (8.4)	4 (2.2)	7 (3.9)	2 (1.1)	6 (3.6)	0
Potassium (mmol/L) (Increased)	56 (31.5)	5 (2.8)	44 (24.6)	0	39 (23.1)	3 (1.8)
Sodium (mmol/L) (Decreased)	15 (8.4)	3 (1.7)	14 (7.8)	5 (2.8)	19 (11.2)	4 (2.4)
Sodium (mmol/L) (Increased)	46 (25.8)	0	37 (20.7)	0	24 (14.2)	0
Urate (µmol/L) (Increased)	52 (29.2)	52 (29.2)	40 (22.3)	40 (22.3)	63 (37.3)	63 (37.3)

CTCAE=Common Terminology Criteria for Adverse Events.
Note: The worst postbaseline severity grade is used for each subject. CTCAE version: 4.03.
Source: Table 14.3.7.2.1 from ELEVATE-TN CSR.

The median time to onset of lymphocytosis for subjects in the acalabrutinib+obinutuzumab and acalabrutinib monotherapy arms was 1.1 weeks each. No subjects in the obinutuzumab+ chlorambucil arm experienced lymphocytosis. Almost all subjects with lymphocytosis had

resolved events (99.0% and 96.4% for the acalabrutinib+obinutuzumab and acalabrutinib monotherapy arms, respectively) (Table 60).

Table 60: Summary of Lymphocytosis (Safety Population)

	No. (%) of Subjects		
	Arm B Acalabrutinib+ Obinutuzumab (N=178)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab+ Chlorambucil (N=169)**
Subjects with baseline and postbaseline ALC	178 (100.0)	176 (98.3)	168 (99.4)
Subjects with lymphocytosis[a]	103 (57.9)	111 (63.1)	0
95% CI[b]	(50.25, 65.21)	(55.48, 70.21)	(0.00, 2.17)
Time to lymphocytosis (weeks)[c]			
n	103	111	--
Mean (SD)	1.4 (0.69)	1.6 (1.40)	--
Median (Min, Max)	1.1 (1.0, 4.4)	1.1 (0.9, 12.1)	--
Duration of lymphocytosis (weeks)[d]			--
n	103	111	--
Resolved (event)	102 (99.0)	107 (96.4)	--
Not resolved (censored)	1 (1.0)	4 (3.6)	--
Median (95% CI)	4.1 (3.9, 4.1)	11.1 (7.1, 11.6)	--
Min, Max	1.1, 35.1	0.9, 107.1+	--

ALC=absolute lymphocyte count; Min=minimum; Max=maximum; SD=standard deviation.
Lymphocytosis was defined as ALC increasing ≥50% from baseline and achieving ≥5 x 10^9/L for subjects with lymphocytosis. Resolution of lymphocytosis occurred when ALC decreased to the baseline level or lower or achieving <5 x 10^9/L for subjects with lymphocytosis.

[a] Exact binomial confidence interval.

[b] Number of weeks from first dose date of study drug to first postbaseline ALC which met the lymphocytosis criteria. Descriptive statistics are present.

[c] Number of weeks from the first postbaseline ALC which met the lymphocytosis criteria to the earliest date of the following ALC which met the resolution of lymphocytosis criteria or date of censoring (date of last non-missing ALC). The Kaplan-Meier method was used to estimate the median time.

Note: "+" indicates a value from a censored subject who had not recovered at the last ALC measurement.
Source: Table 14.3.7.3 from ELEVATE-TN CSR.

Analysis of laboratory data from ELEVATE-TN showed that:

- The frequency of hematologic abnormalities (any grade and Grade ≥3) was notably lower in the acalabrutinib monotherapy arm, compared to the other 2 treatment arms.
- Lymphocytosis occurred in slightly more subjects in the acalabrutinib monotherapy arm than in either of the other 2 treatment arms. The median duration of lymphocytosis was 4.1 weeks (95% CI: 3.9, 4.1) and 11.1 weeks (95% CI: 7.1, 11.6) for the acalabrutinib+obinutuzumab and acalabrutinib monotherapy arms, respectively.
- A total of 6 subjects (2 subjects in each treatment arm) fulfilled the biochemical criteria for Hy's law (elevations ≥3×ULN in ALT or AST concurrent with total bilirubin ≥2×ULN).

Laboratory assessments were carried out as specified in the ELEVATE-TN Protocol. Acalabrutinib was well tolerated and showed an acceptable safety profile that is consistent with the other acalabrutinib clinical trials.

Among subjects treated with acalabrutinib, there were no clinically significant mean changes in hematology or clinical laboratory values, serum immunoglobulin values, T/B/NK cell counts, or vital sign values. In the obinutuzumab-containing treatment arms, there was a common trend toward worsening of baseline toxicity grade for the hematology parameters including decreased ALC, ANC, hemoglobin, platelets and leukocytes. In the acalabrutinib-containing treatment arms, the common trend toward worsening of baseline toxicity grade was limited to decreased ANC and platelets, and increased leukocytes.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's position. The FDA utilizes Common Terminology Criteria for Adverse Events (CTCAE) criteria to evaluate hematologic and non-hematologic toxicities for regulatory evaluation of safety. The Hallek 2008 criteria is not an established criteria for regulatory review of safety. The combined evaluation of adverse event data and laboratory data for hematologic toxicities are included in Table 56 displaying common treatment-emergent adverse events.

Vital Signs

The Applicant's Position:
Body temperature, heart rate (beats/min), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and weight were collected for study ELEVATE-TN. There were no notable differences between treatment arms in shifts in vital signs during the study.

There were no clinically important differences in mean systolic and diastolic blood pressure, heart rate, temperature, and body weight from baseline to last postbaseline values for any of the 3 treatment arms, and no notable differences between treatment arms.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's position.

Electrocardiograms (ECGs)

The Applicant's Position:
ECGs were performed at screening only. A total of 9 subjects met the exclusion criteria of QTcF or QTcB >480 msec at baseline. These 9 subjects were enrolled under Protocol Amendment 2.0 which did not have an exclusion for QTcF or QTcB >480 msec and were therefore not considered to be important protocol deviations. There were no exclusion criteria for QTc in Protocol Amendment 2.0, and this exclusion criterion was updated in Protocol Amendment 3.0. 5 subjects had clinically significant abnormal ECG at baseline: 3 subjects in the obinutuzumab + chlorambucil arm [1.8%], and 2 subjects [1.1%] in the acalabrutinib+obinutuzumab arm.

Acalabrutinib was well tolerated and showed an acceptable safety profile that is consistent with the other acalabrutinib clinical trials.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's position.

QT

The Applicant's Position:
Not applicable

Regulatory Authorities Assessment:
No QT studies were performed as part of the ELEVATE-TN trial.

Immunogenicity

The Applicant's Position:
Not applicable

Regulatory Authorities Assessment:
No immunogenicity assessments were conducted as part of the ELEVATE-TN trial.

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position:
No new potential safety issues were identified as a result of the safety review of acalabrutinib 100 mg BID.

Regulatory Authorities Assessment:
In the acalabrutinib treatment arms, the FDA evaluated the events of clinical interest including cardiac arrhythmias, hemorrhage, neutropenia, infection, second primary malignancies, and Richter's transformation, based on the known and potential risks of acalabrutinib, known class effects, previous clinical experience, and the underlying disease.

Cardiac Arrhythmias

Regulatory Authorities Assessment:
Events of cardiac arrhythmias were identified using the MedDRA high-level group term cardiac arrhythmias. Further, the specific preferred terms of atrial fibrillation and atrial flutter were combined and the high-level terms of supraventricular tachycardia (SVT) and ventricular arrhythmia were evaluated. Table 61 summarizes the events of cardiac arrhythmias reported in the ELEVATE-TN trial. In the acalabrutinib arms of the ELEVATE-TN trial, using the high-level group term cardiac arrhythmia, 13 patients (7%) in the acalabrutinib + obinutuzumab arm and 11 patients (6%) in the acalabrutinib monotherapy arm (including crossover patients) had a reported event. For the acalabrutinib + obinutuzumab arm, 6 patients (3%) experienced atrial fibrillation or flutter, 1 patient (<1%) experienced SVT, and 1 patient (<1%) experience a complete atrioventricular block. In the acalabrutinib monotherapy arm, 8 patients (4%) experienced atrial fibrillation or flutter and 1 patient (<1%) experienced SVT. There were no reported events of cardiac arrest in either of the acalabrutinib arms.

Table 61: Summary of Treatment Emergent Cardiac Arrhythmias in ELEVATE-TN

Cardiac event	Acalabrutinib+ Obinutuzumab N = 178		Acalabrutinib N = 224*		Obinutuzumab+ Chlorambucil N = 169	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Cardiac arrhythmias HLGT	7%	1%	5%	0	5%	1%
Atrial fibrillation or flutter	3%	<1%	4%	0	<1%	0
Tachycardia	2%	0	<1%	0	2%	0
Supraventricular tachycardia	<1%	0	<1%	0	<1%	0
Complete atrioventricular block	<1%	<1%	0	0	0	0
Myocardial ischemia or infarction	3%	2%	3%	2%	<1%	0

Abbreviations: HLGT: MedDRA High-level group term
*Includes 45 crossover patients
Source: FDA analysis of ADAE dataset

Hemorrhage

Regulatory Authorities Assessment:

Hemorrhage is a known risk with CALQUENCE. FDA evaluation of hemorrhage included grouped preferred terms (e.g., all preferred terms containing "hemorrhage" or "hemorrhagic" and all preferred terms contained in FDA's "Gastrointestinal hemorrhage"grouping) and excluded bruising, petechiae, and purpura as defined in Appendix 19.5. Major hemorrhage was defined as any serious, Grade ≥3, or CNS hemorrhage. Table 62 summarizes the events of hemorrhage reported in the ELEVATE-TN trial.

Major hemorrhages included gastrointestinal hemorrhage, gastric ulcer hemorrhage, hematemesis, and a subdural hemorrhage in the acalabrutinib + obinutuzumab arm. In the acalabrutinib monotherapy arm, major hemorrhages included a hemarthrosis and retinal hemorrhage. One crossover patient receiving acalabrutinib monotherapy experienced a major hemorrhage event, an intracranial hemorrhage.

Two patients receiving acalabrutinib experienced post-procedural bleeding complications, that included a post-surgical hematoma following back surgery, required surgical removal of the hematoma and rectal bleeding following a colonoscopy.

Table 62: Summary of Hemorrhage Events in ELEVATE-TN

Hemorrhage	Acalabrutinib+ Obinutuzumab N = 178		Acalabrutinib N = 224*		Obinutuzumab + Chlorambucil N = 169	
	n	%	n	%	n	%
Any grade	26	15%	30	13%	9	5%
Serious adverse event	3	2%	3	1%	1	<1%
Grade ≥3	3	2%	2	1%	0	0
Major hemorrhage (Serious, Grade ≥3, or CNS)	4	2%	3	1%	2	1%
Post-procedural hemorrhage or hematoma	1	<1%	1	<1%	0	0

*Includes 45 crossover patients
Source: FDA analysis of ADAE dataset

Neutropenia

Regulatory Authorities Assessment:

Using laboratory data, the incidence of Grade ≥3 neutropenia occurred in 35%, 13%, and 47% and Grade 4 neutropenia in 21%, 7%, and 18% for the acalabrutinib + obinutuzumab, acalabrutinib, and obinutuzumab + chlorambucil arms, respectively.
Per adverse event data, febrile neutropenia was reported in 2% and 1% in the acalabrutinib + obinutuzumab arm and acalabrutinib arms, respectively, compared to 5% in the obinutuzumab + chlorambucil arm.

Treatment discontinuation due to neutropenia occurred in 1% in the acalabrutinib + obinutuzumab arm compared to 7% in the obinutuzumab + chlorambucil arm. Dose reductions due to neutropenia occurred in 2% in the acalabrutinib + obinutuzumab arm compared to 19% in the obinutuzumab + chlorambucil arm

There were no discontinuations or dose reduction due to neutropenia in the acalabrutinib monotherapy arm.

Use of granulocyte colony-stimulating factor (G-CSF) for secondary prophylaxis occurred in 21% in the acalabrutinib + obinutuzumab arm, 7% in the acalabrutinib monotherapy arm, and 37% in the obinutuzumab + chlorambucil arm.

Infection and Opportunistic infections

Regulatory Authorities Assessment:

Table 63 summarizes treatment emergent infections in the ELEVATE-TN trial.

Table 63: Summary of Treatment Emergent Infection in ELEVATE-TN

Infections	Acalabrutinib+ Obinutuzumab N = 178	Acalabrutinib N = 179	Obinutuzumab + Chlorambucil N = 169
Any grade	69%	65%	44%
Grade ≥3	21%	14%	8%
Serious adverse event	20%	12%	5%
Treatment discontinuation	3%	2%	5%
Dose reduction	0	<1%	0
Most common infections (any grade)			
Upper respiratory tract infection	39%	35%	17%
Lower respiratory tract infection	15%	14%	4%
Urinary tract infection	13%	15%	5%
Pneumonia	11%	9%	3%
Most common Grade ≥3 infections			
Pneumonia	6%	4%	2%
Sepsis	4%	1%	3%
Upper respiratory tract infection	3%	0	1%
Urinary tract infection	1%	2%	0

*Grouped preferred terms, see Appendix 19.5
Source: FDA analysis of ADAE dataset

Opportunistic infections
In the acalabrutinib + obinutuzumab arm, two opportunistic infections were reported, one patient with esophageal candidiasis and one patient with fatal progressive multifocal leukoencephalopathy (PML). Additionally, 2 patients experienced hepatitis B reactivation.

In the acalabrutinib monotherapy arm, 3 opportunistic infection were reported with aspergillus infections in 2 patients and 1 patient with disseminated cryptococcosis.

In the obinutuzumab + chlorambucil arm, there were no opportunistic infection reported.

Reviewer Comment:
Based on the risk of serious infections (20% in the acalabrutinib plus obinutuzumab arm and 12% in the acalabrutinib monotherapy arm), including 1-2% incidence of fatal infections, and the incidence of opportunistic infections, the Warning and Precaution for infection was revised to "Serious and Opportunistic Infections." Further, a patient with untreated CLL in the ELEVATE-TN trial receiving acalabrutinib plus obinutuzumab developed fatal progressive multifocal leukoencephalopathy. Therefore, the risk of PML is conveyed in the Serious and Opportunistic Infections Warning and Precaution.

The overall risk of infection was evaluated in the integrated safety population (N=1029). Refer to the clinical review of NDA210259 S-06 in Section 8.2.4.

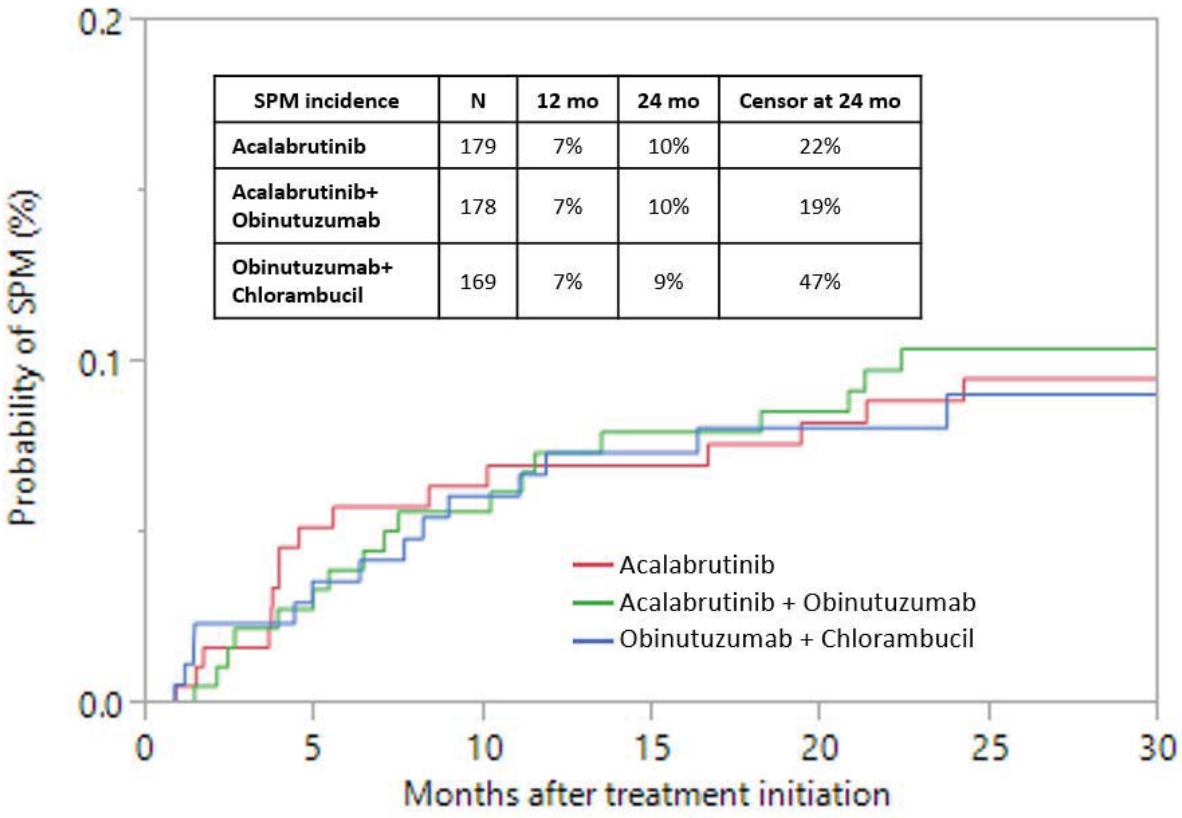
Second Primary Malignancy

Regulatory Authorities Assessment:

The rate of second primary malignancies (SPM) was comparable amongst the treatment arms (Figure 13). The most common malignancies seen in the acalabrutinib arms, after censoring for receipt of subsequent anti-cancer treatment, were basal cell carcinoma and squamous cell carcinoma of the skin.

Figure 13: Incidence of Second Primary Malignancies in ELEVATE-TN trial

SPM incidence	N	12 mo	24 mo	Censor at 24 mo
Acalabrutinib	179	7%	10%	22%
Acalabrutinib+ Obinutuzumab	178	7%	10%	19%
Obinutuzumab+ Chlorambucil	169	7%	9%	47%



Abbreviations: SPM: Second primary malignancy, Mo: months
Source: FDA analysis of ADSPM dataset

Richter's Transformation

Regulatory Authorities Assessment:

One patient in the acalabrutinib + obinutuzumab arm, 5 patients in the acalabrutinib monotherapy arm, and 1 crossover patient from the obinutuzumab + chlorambucil arm developed Richter's syndrome. However, only 2 patients had reports of Richter's

transformation with confirmation via biopsy results. There remains some residual uncertainty regarding the risk of Richter's transformation in patients with previously untreated CLL treated with acalabrutinib monotherapy due to a small number of events and lack of biopsy confirmation.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:
No safety related data were collected in the ELEVATE-TN PRO analyses.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's position.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's position:

Safety analyses were not conducted by demographic subgroups.

Regulatory Authorities Assessment:
The FDA notes that safety analyses were conducted by demographic subgroups as described in the summary of clinical safety (Section 5.1), which presents data for 1040 patients with hematologic malignancies who received acalabrutinib monotherapy at various doses. For TEAEs reported in ≥ 10% of patients,

- Patients age ≥ 65 had a numerically higher incidence of at least one grade ≥ 3 AE (58%; 379/652) than patients age < 65 (47%; 184/388).
- The incidence of at least one grade ≥ 3 AE was similar among White patients (54%; 494/923) and Non-White patients (58%; 59/101), and according to gender.

To inform labeling, FDA explored safety by age group in the 929 of 1209 patients in the FDA integrated safety population who had CLL, SLL, or MCL. This population was selected in order to permit use of the same population for safety and efficacy reporting in the prescribing information Section 8.3. In this group, 68% were age ≥ 65 and 24% were age ≥ 75. Compared to patients age < 65, patients age ≥ 65 had numerically higher incidences of grade ≥ 3 AEs and SAEs as shown in the table below.

Table 64: Safety by Age Group

Age group (from N of 929)	Grade ≥ 3 AEs	SAEs
≥ 65 (N = 629) [a]	373/629 (59%)	245/629 (39%)
< 65 (N = 300)	135/300 (45%)	76/300 (25%)

Source: FDA analysis
[a] 222 were age ≥ 75

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:
No new information is provided in the current submission.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's position.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development
The Applicant's Position:
No new information is provided in the current submission.

Regulatory Authorities Assessment:

The regulatory authorities agree with the Applicant's position.

Human Reproduction and Pregnancy
The Applicant's Position:
No new information is provided in the current submission.

Regulatory Authorities Assessment:
New information was received as part of this application regarding human reproduction or pregnancy and the potential risk for acalabrutinib to cause dystocia, based on animal data. The data informed a change in the Pregnancy section (Section 8.1) of the USPI.

Pediatrics and Assessment of Effects on Growth
The Applicant's Position:
No new information is provided in the current submission.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's position.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

There was no experience of overdose reported in the clinical studies of acalabrutinib. Acalabrutinib is intended to be prescribed by specialists in hematology and oncology.

There is no evidence that acalabrutinib produces physical or psychological dependence in patients with hematological malignancies.

Regulatory Authorities Assessment:

The regulatory authorities agree with the Applicant's position.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Calquence was first registered in the United States on 31 October 2017 at a dosage of 100 mg BID for the treatment of adult patients with MCL who have received at least one prior therapy. Calquence has since been approved in additional markets for the same indication and dosage cited above. The cumulative world-wide post-approval patient exposure since launch is estimated to be (b) (4) patient-years. Details are provided in the acalabrutinib PBRER, dated 21 June 2019. Cumulative review of all the safety data from this post-marketing period has not identified any new safety concerns.

No new safety concerns were identified from post- marketing experience that impact the safety profile of acalabrutinib as presented in the acalabrutinib PBRER, dated 21 June 2019. Acalabrutinib was well tolerated and showed an acceptable safety profile that is consistent with the other acalabrutinib clinical trials.

Regulatory Authorities Assessment:

The regulatory authorities agree with the Applicant's position.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Safety information collected from the post-market setting is expected to be consistent with data collected in the clinical trials.

Regulatory Authorities Assessment:

The regulatory authorities agree with the Applicant's position.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

In the Mono CLL population, approximately 85.7%, 76.8%, 51.7%, and 28.5% of subjects completed more than 6, 12, 24, and 36 months of acalabrutinib treatment, respectively, with a median duration of exposure of 24.9 months (range: 0 to 58.5months). Total exposure was 1579.3 patient-years. In the Mono HemMalig population, 850 (81.7%), 754 (72.5%), 528 (50.8%), and 255(24.5%) of subjects completed more than 6, 12, 24, and 36 months of acalabrutinib treatment, respectively, with a median duration of exposure of 24.6 months (range: 0 to 58.5 months). Total exposure was 2037.7 patient-years.

Safety data from the Mono Pivotals population demonstrated a well-tolerated and manageable safety profile which is favorable relative to the comparator arms. The majority of TEAEs observed were low grade and non-serious. These benefits are supported by the results seen in the broader CLL Mono and CLL Combo populations, and further supported by the results seen in the Mono HemMalig population.

Acalabrutinib 100 mg BID is associated with the following risks based on the safety profile that was observed in the Mono HemMalig population (N=1040), and is consistent with observations seen in the pivotal Phase 3 studies and the CLL Mono population:

- Atrial fibrillation/flutter of any grade severity was reported in 4.4% of subjects in the Mono HemMalig population. Grade ≥3 events were reported in 1.3% of subjects.

- Anemia, neutropenia, and thrombocytopenia were reported in 13.8%, 15.7%, and 8.9% of subjects in the Mono HemMalig population, respectively; febrile neutropenia was reported in 1.9% of subjects. Grade ≥3 cytopenias based on laboratory measurements included anemia (10.1%), neutropenia (20.7%), and thrombocytopenia (6.9%). SAEs of anemia were reported in 19 (1.8%) subjects. Twenty (1.9%) subjects had a neutropenia SAE; of these, 16 subjects had SAEs of febrile neutropenia and 3 subjects had SAEs of neutropenic sepsis. Four (0.4%) subjects had an SAE in the ECI category of thrombocytopenia.

- Major hemorrhage events, defined as Grade ≥3, SAE, and/or any grade or seriousness of CNS hemorrhage, were reported in 3.6% of subjects. The most frequently reported sites of major hemorrhage in the Mono HemMalig population were the GI tract (GI hemorrhage, gastric hemorrhage, hematemesis, rectal hemorrhage, and upper GI hemorrhage; 8 subjects) and the CNS (intracranial hemorrhage, cerebral microhemorrhage, intracranial hematoma, subarachnoid hemorrhage, and traumatic intracranial hemorrhage; 6 subjects), followed by the nose (epistaxis; 4 subjects).

- Grade ≥3 TEAEs of infection occurred in 17.6% of subjects in the Mono HemMalig population, with pneumonia as the most frequently reported Grade ≥3 infection (4.9%). Fatal infections were reported in 20 (1.9%) subjects.

- Second primary malignancies were reported in 12.2% of subjects in the Mono HemMalig population; the most frequent were skin malignancies, including basal cell carcinoma (3.8%) and squamous cell carcinoma of the skin (2.9%). Second primary malignancies (excluding nonmelanoma skin neoplasms) were reported in 6.5% of subjects in the Mono HemMalig population.

- The most common adverse reactions reported were of Grade 1 or 2 severity. These included headache, diarrhea, nausea, constipation, vomiting, bleeding events (hematuria, epistaxis, bruising), rash, musculoskeletal pain, fatigue and asthenia, dizziness, and arthralgia. One subject developed drug-induced TLS meeting the Howard's criteria.

While there are risks associated with taking acalabrutinib, active monitoring and preventive measures assist in their mitigation. Mitigation measures are provided in the product labeling.

Acalabrutinib was well tolerated and showed an acceptable safety profile that is consistent with the other acalabrutinib clinical trials.

In patients with CLL, acalabrutinib offers a favorable benefit-risk profile, with high response rates which were durable, and an acceptable safety profile. The data support acalabrutinib 100 mg BID as an important treatment option for patients with this serious and life-threatening disease.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Applicant's position that acalabrutinib, with or without obinutuzumab, has an acceptable safety profile in patients with CLL.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

Regulatory Authorities Assessment:
The ELEVATE-TN trial was a randomized, open-label, actively controlled, 3-arm trial of acalabrutinib plus obinutuzumab, acalabrutinib monotherapy compared to obinutuzumab plus chlorambucil. The primary endpoint was IRC-assessed PFS, and the key secondary endpoints included in the hierarchical testing order were ORR and OS. The study pre-specified an interim analysis using the O'Brien and Fleming method. The test results of the primary endpoint was statistically significant at the interim analysis. Both acalabrutinib plus obinutuzumab arm and acalabrutinib monotherapy arm demonstrated superiority in PFS when compared with the

obinutuzumab plus chlorambucil arm. The acalabrutinib plus obinutuzumab arm demonstrated superiority in ORR when compared with the obinutuzumab plus chlorambucil arm but the test comparing acalabrutinib monotherapy and obinutuzumab plus chlorambucil in ORR was not statistically significant. OS data was not mature at time of the analysis.

8.4. Conclusions and Recommendations

Regulatory Authorities Assessment:

The ELEVATE-TN trial, a randomized, open-label, actively controlled, 3-arm trial of acalabrutinib plus obinutuzumab, acalabrutinib monotherapy, compared to obinutuzumab plus chlorambucil in 535 patients with untreated CLL demonstrated that treatment with acalabrutinib plus obinutuzumab or acalabrutinib monotherapy resulted in longer progression-free survival compared to obinutuzumab plus chlorambucil. Additionally, overall response rate was improved in patients treated with acalabrutinib plus obinutuzumab compared to obinutuzumab plus chlorambucil. The evaluation of safety of acalabrutinib plus obinutuzumab and acalabrutinib monotherapy demonstrated an acceptable safety profile in patients with newly diagnosed CLL, and the overall safety profile is consistent with current labeling for acalabrutinib. The results of the ELEVATE-TN trial are supportive of regular approval for acalabrutinib in patients with previously untreated CLL due to the disease setting, consistent demonstration of superiority across multiple efficacy endpoints, and robust efficacy results on statistical evaluation. The recommended indication for acalabrutinib includes patients with small lymphocytic lymphoma because it is the same disease as chronic lymphocytic leukemia.

Therefore, the ELEVATE-TN trial, in combination with the ASCEND trial, supports regular approval for acalabrutinib for the treatment of adult patients with CLL or SLL.

X	X
Statistical Reviewer	Statistical Team Leader
X	X
Clinical Reviewer	Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

Regulatory Authorities Assessment:

This application was not presented to an advisory committee or external consultants because it did not raise significant efficacy or safety issues for the proposed indication.

10 Pediatrics

The Applicant's Position:
Not applicable.

Regulatory Authorities Assessment:
CALQUENCE is exempt from pediatric study requirements in 21 CFR 314.55 for patients with CLL. FDA granted Orphan Drug Designation for CALQUENCE for the following indication (date of designation): Treatment of patients with chronic lymphocytic leukemia (13 May 2015).

11 Labeling Recommendations

The following are FDA recommendations for the CALQUENCE prescribing information based on this review.

Table 65: Summary of Significant labeling changes

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
1: Indications and Usage	A broad chronic lymphocytic leukemia (CLL/SLL) indication is proposed, in addition to the already labelled Mantle Cell Lymphoma (MCL) indication	The recommended new indication for Calquence, with regular approval, is for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).
2.1: Dosage and Administration-Recommended Dosage	Added language about CALQUENCE combination therapy with obinutuzumab and obinutuzumab PI is referred for dosing Dosage and Administration within the Highlights section remain the same as there is no change to CALQUENCE dosage, administration, and toxicity management recommendations	For the recommended dosage, acalabrutinib monotherapy is specified for MCL, CLL, or SLL, whereas acalabrutinib in combination with obinutuzumab is specified for previously untreated CLL or SLL.
2.2: Dose Modifications	Dose Modifications are separated into the following 4 sections: • Section 2.2 Dose Modifications for Adverse Reactions • Section 2.3 Dose Modifications for Use with CYP3A Inhibitors or Inducers • Section 2.4 Concomitant Use with Gastric Acid Reducing Agents • Section 2.5 Dose Modifications for Use in Hepatic Impairment (new section) Note: No changes to text within sections 2.2, 2.3 and 2.4. Sec 2.5 is a newly added section	A new section on "Recommended Dosage for Hepatic Impairment" states to avoid administration of Calquence in patients with severe hepatic impairment; dose modifications are not required for patients with mild or moderate hepatic impairment. The organization of this section was revised to reflect the order in which prescribers will need the information.
6.1: Adverse Reactions-Clinical Trials Experience	Most common adverse reactions reported in MCL and CLL are separated by indication	In addition to separating the most common ARs by indication, FDA added text at the start of Section

	Proposal to use cutoff of ≥ 20% to define common adverse reactions	6.1 to describe the composition, exposure, and most common ARs in the expanded safety population that informs the Warnings and Precautions (N = 1209). Used agreed upon grouped preferred terms for more sensitive labeling
8.6: Use in Specific Populations-Hepatic Impairment	Added recommendations for severe hepatic impairment based on recent studies. Consistent with Sec 2.5 listed above	Regulatory authorities agree.
12.3 Pharmacokinetics	Updated text on acalabrutinib and ACP-5862 (its active metabolite) Population PK results. Absorption: Updated median time to peak plasma concentrations for ACP-5862 Distribution: Updated reversible binding to human plasma protein and in vitro mean blood-to-plasma ratio for ACP-5862 Elimination: Updated the median $t_{1/2}$ for ACP-5862 and mean apparent oral clearance (CL/F) for acalabrutinib and ACP-5862 Specific Populations: *Age, Race, and Body Weight*: added text for ACP-5862 *Renal Impairment:* Added data on mild or moderate renal impairment (eGFR ≥ 30 mL/min/1.73m^2 *Hepatic Impairment*: Added data on patients with mild, moderate, and severe hepatic impairment Drug Interaction Studies: *Metabolic Pathways:* Included additional metabolic pathways Drug Transporter Systems: Added text on ACP-5862 substrates and that ACP-5852 does not inhibit specific hepatic transporters. Added text on ACP-5862 and co-administration of MATE1 and BCRP substrates	Regulatory authorities agree.

The Applicant's Position:

Based on the findings and results from studies ASCEND and ELEVATE-TN, the Applicant is proposing the above mentioned significant changes in the CALQUENCE label.

Regulatory Authorities Assessment:

Additional FDA labeling recommendations are listed below:

- The denominator for Section 5 Warnings and Precautions was revised to include 1029 patients with hematologic malignancies exposed to acalabrutinib 100 mg approximately every 12 hours.
- Reordered Section 5 with Serious and Opportunistic Infections first followed by Hemorrhage, and further revised each Warning and Precaution to appropriately convey risk based on updated safety data.
- Updated Section 8.1 Pregnancy to convey the risk of dystocia with acalabrutinib, based on review of animal data
- Updated Section 8.5 Geriatric Use to highlight difference in safety based upon age and that no differences in efficacy were observed based on age.
- Revised efficacy results (Section 14) to remove results of exploratory subgroup analyses and revised OS data to state that OS data was immature at the time of analysis.

Health Canada's Assessment: (b) (4)

The recommended indications for approval in Canada are:

Calquence (acalabrutinib) is indicated:
- in combination with obinutuzumab or as monotherapy for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL)
- as monotherapy for the treatment of patients with CLL who have received at least one prior therapy.

12 Risk Evaluation and Mitigation Strategies (REMS)

Regulatory Authorities Assessment:
Based on the benefit-risk profile of acalabrutinib plus obinutuzumab and acalabrutinib monotherapy, safety issues can be adequately managed through appropriate labeling and routine post-marketing surveillance.

13 Postmarketing Requirements and Commitment

Regulatory Authorities Assessment:
The clinical review team determined that a safety PMR or PMC was not warranted based upon this review.

14 Division Director (DHOT)

X

Pharmacology-Toxiclogy Supervisor

15 Division Director (OCP)

X

Clinical Pharmacology Division Director

16 Division Director (OB)

X

Statistics Division Director

17 Division Director (Clinical)

(This section relies in part on the reviews of Drs. Angelo de Claro, Yvette Kasamon and Nicholas Richardson.)

Background: AstraZeneca UK Limited submitted concomitantly NDA 210259 (S-006) and NDA 210259 (S-007) on August 5, 2019, August 24, 2019, and September 24, 2019 (for S-006) and August 5, 2019, August 24, 2019, and September 23, 2019 for (S-007) respectively requesting that acalabrutinib (Calquence) be approved for the following indication: Treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). This request relied on the results of the ASCEND (ACE-CL-309) trial (S-006) and the ELEVATE-TN (NCT02475681) trial (S-007). Acalabrutinib had already been given Accelerated Approval for the following indication: Mantle cell lymphoma who have received at least one prior therapy.
The ASCEND trial enrolled 310 patients with CLL which is relapsed or refractory after ≥1 prior therapy who were randomized between acalabrutinib vs "investigator's choice": idelalisib with rituximab (IR=119 patients) or bendamustine with rituximab (BR=36 patients). The primary endpoint was independent review committee (IRC) assessed progression free survival (PFS).

The ELEVATE-TN trial randomized 535 patients with previously untreated CLL which was previously untreated between acalabrutinib with obinutuzumab, vs acalabrutinib alone vs obinutuzumab with chlorambucil. The primary endpoint was PFS by IRC.

Efficacy Results for ASCEND Trial: At the prespecified time of 16.1 months, the hazard ratio (HR) for IRC-assessed PFS for acalabrutinib vs investigators' choice was 0.31 (95% CI: 0.20, 0.49) p <0.0001 (stratified log rank test). The median PFS was not reached in the acalabrutinib arm and was 16.5 months (95% CI: 14.0, 17.1) in the investigator choice arm.

Efficacy for the ELEVATE-TN Trial: The results showed a statistically significant increase in PFS per IRC for both acalabrutinib with obinutuzumab (HR=0.1 (95% CI: 0.06, 0.17) p<0.0001 and acalabrutinib alone (HR=0.2 (95% CI: 0.13, 0.30) p<0.0001 when compared to obinutuzumab with chlorambucil.

Safety Results for ASCEND TRIAL: On the acalabrutinib arm, on study deaths were 2.6% and serious adverse events were observed in 29% of the patients. AEs led to permanent discontinuation in the acalabrutinib arm in 10% of the patients. The most common AEs (≥30%) included cytopenias.

Safety Results for ELEVATE-TN TRIAL: The safety population included 178 patients treated with acalabrutinib and obinutuzumab, 179 patients treated with acalabrutinib monotherapy, and 169 treated with obinutuzumab with chlorambucil. All 3 arms were similar with respect to the incidence of death within 30 days after the last dose of treatment (≤2%), serious adverse events (range was 22%-39%) and discontinuations due to toxicity (9% to 15%).

Benefit Risk: For treatment of CLL previously untreated or relapsed refractory after ≥1 prior therapy, the benefit risk profile was favorable.

Recommended Regulatory Action: This Supervisory Associate Division Director (Albert Deisseroth) agrees with the review divisions in their recommendation of approval of acalabrutinib for the therapy of CLL.

X

Clinical Division Director

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X _____

19 Appendices

19.1. References

The Applicant's References:

Burger JA, Tedeschi A, Barr PB, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. N Engl J Med 2015;373:2425-37.

Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med 2013;369:32-42.

Byrd JC, Stilgenbauer S, Flinn IW. Chronic lymphocytic leukemia. Am Soc Hematol Educ Program. 2004:163-183.

Cheson BD, Byrd JC, Rai KR, et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. J Clin Oncol 2012;30:2820-2.

Cheson BD, Wendtner CM, Pieper A, et al. Optimal use of bendamustine in chronic lymphocytic leukemia, non-Hodgkin lymphomas, and multiple myeloma: treatment recommendations from an international consensus panel. Clin Lymphoma Myeloma Leuk 2010;10:21-7.

Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26 (Suppl 5):v78-84.

Eichhorst BF, Busch R, Stilgenbauer S, et al. First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. Blood 2009 Oct 15;114(16):3382-3391.

Eichhorst et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol. 2016 Jul;17(7):928-942.

Fischer K, Cramer P, Busch R, et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter Phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 2011;29:3559-66.

Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med 2014;370:997-1007.

Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood 2018a;131:2745-60.

Hallek M, Shanafelt TD, Barbara Eichhorst B. Chronic lymphocytic leukaemia. Lancet 2018b;391:1524–37.

Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, Phase 3 trial. Lancet 2010;376:1164-74.

Hallek M, Cheson BD,Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008;111:5446-56. Erratum in: Blood 2008;112:5259.

Han T, Ezdinli EZ, Shimaoka K, Desai DV. Chlorambucil vs combined chlorambucil-corticosteroid therapy in chronic lymphocytic leukemia. Cancer 1973;31:502–08.

Hillmen P, Skotnicki AB, Robak T, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. J Clin Oncol 2007;25:5616-23.

Knospe WH, Loeb V Jr. Biweekly chlorambucil treatment of lymphocytic lymphoma. Cancer Clin Trials 1980;3:329–36.

Mato AR, Roeker LE, Allan JN, et al. Outcomes of front-line ibrutinib treated CLL patients excluded from landmark clinical trial. Am J Hematol 2018a;93:1394-401.

Mato AR, Nabhan C, Thompson MC, et al. Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis. Haematologica 2018b;103:874-9.

National Comprehensive Cancer Network (NCCN). Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia. Version 4.2019. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed 24 April 2019.

Noone AM, Howlader N, Krapcho M, et al (eds). SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER web site, April 2018.

O'Brien S, Jones JA, Coutre SE, et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. Lancet Oncol 2016;17:1409–18.

Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. N Engl J Med 2016;374:311–22.

Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med 2018;378:1107-20.

Shanafelt TD, Wang V, Kay NE, et al. A randomized Phase III study of ibrutinib (PCI-32765)-based therapy vs. standard fludarabine, cyclophosphamide, and rituximab (FCR) chemoimmunotherapy in untreated younger patients with chronic lymphocytic leukemia (CLL): a trial of the ECOG-ACRIN Cancer Research Group (E1912). Blood 2018;132:LBA-4.

Shanafelt TD, Wang V, Kay NE, et al. Ibrutinib–Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia N Engl J Med 2019;381:432-43.

Sharman JP, Coutre SE, Furman RR, et al. Final results of a randomized, Phase III study of rituximab with or without idelalisib followed by open-label idelalisib in patients with relapsed chronic lymphocytic leukemia. J Clin Oncol 2019;37:1391-402.

Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. Lancet Oncol 2016;17:768–78.

UK CLL Forum. Ibrutinib for relapsed/refractory chronic lymphocytic leukemia: a UK and Ireland analysis of outcomes in 315 patients. Haematologica 2016;101:1563-72.

Wiestner A. The role of B-cell receptor inhibitors in the treatment of patients with chronic lymphocytic leukemia. Haematologica 2015 Dec;100(12):1495-507.

Woyach JA, Smucker K, Smith LL, et al. Prolonged lymphocytosis during ibrutinib therapy is associated with distinct molecular characteristics and does not indicate a suboptimal response to therapy. Blood 2014;123:1810-7.

Woyach JA, Ruppert AS, Rai KR, et al. Impact of Age on Outcomes Following Initial Therapy with Chemotherapy and Different Chemoimmunotherapy Regimens in Patients with Chronic Lymphocytic Leukemia (CLL): Results of Sequential CALGB Studies Chemoimmunotherapy Regimens in Patients with Chronic Lymphocytic Leukemia (CLL): Results of Sequential CALGB Studies. J Clin Oncol 2013 Feb 1;31(4):440-447.

19.2. Financial Disclosure

The Applicant's Position:

All investigators participating in ELEVATE-TN study were assessed for equity interest, significant payments, proprietary interests and other compensation. 5 out of 1601 clinical investigators had financial information to disclose (0.31%). None of the disclosures submitted revealed a potential conflict of interest. Statements of due diligence in cases where the Applicant was unable to obtain a signed form from the investigator, is provided in the FDA Forms 3454 .

Regulatory Authorities Assessment:

The FDA agreed with the Applicant's position and has completed the table below on the provided data.

Covered Clinical Study (Name and/or Number):* ACE-CL-007/ELEVATE-TN

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1601		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 5		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the Applicant, and confirmed/edited by the FDA.

19.3. Nonclinical Pharmacology/Toxicology

Data:
See Section 5 above

The Applicant's Position:

See Section 5 above

Regulatory Authorities Assessment:
Refer to Section 5.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

Regulatory Authorities Assessment:
The Applicant updated the population PK analysis using 10,588 acalabrutinib and 2396 ACP-5862 (active metabolite) plasma concentrations from 182 healthy subjects in 5 Phase 1 trials and 569 patients with B-cell malignancies in 8 Phase 1b/2/3 trials. A simultaneous population PK model characterizing the PK of acalabrutinib and ACP-5862 was developed. Acalabrutinib concentration-time profile was characterized by a 2-compartment structural model with sequential zero- and first-order absorption and linear elimination, while ACP-5862 concentration-time profile was characterized by a 2-compartment structural model with a first-order production from acalabrutinib and linear elimination. The final population PK model was able to describe the acalabrutinib and ACP-5862 concentration-time profiles in patients with B-cell Malignancies .

Covariate analysis identified 6 statistically significant covariates on the PK parameters of acalabrutinib and ACP-5862, including concomitant use of proton pump inhibitors (PPI) on acalabrutinib relative bioavailability (F1) and duration of zero-order absorption (D1), subject type (healthy subject or patients with B-cell malignancies) and Eastern Cooperative Oncology Group (ECOG) score on acalabrutinib apparent clearance (CL/F), and body weight on ACP-5862 apparent clearance (CLM/F) and apparent central volume distribution (VcM/F). However, none of these covariates were considered clinically meaningful, given the generally flat exposure-response relationships for both efficacy endpoints (PFS, BOR and lesion size), and safety measurements (any Grade ≥3 TEAEs, any Grade ≥2 TEAEs of clinically special interest, including anemia, cardiac event, hypertension, infection, neutropenia, and thrombocytopenia) at acalabrutinib 100 mg BID in combination with obinutuzumab in patients with CLL.

The derived post-hoc PK parameter estimates of acalabrutinib and ACP-5862 in patients with B-cell malignancies from the final population PK analysis (Table 66) were included in Section 12.3 of USPI, as there was no significant difference in acalabrutinib and ACP-5862 PK exposures among patients with different types of B-cell malignancies, including CLL, MCL, FL, DLBCL, MM, and WM.

Table 66 Derived Post-hoc PK Parameter Estimates of Acalabrutinib and ACP-5862 from the Final Population PK Analysis in Patients with B-cell Malignancies following Acalabrutinib 100 mg twice daily

	PK parameter	Geometric mean (CV%)	Mean ± standard deviation	Median [min, max]
Acalabrutinib (n = 568)	AUC_{24h} (ng·h/mL)	1843 (38%)	1972 ± 801	1816 [284, 6807]
	C_{max} (ng/mL)	563 (29%)	585 ± 165	558 [115, 1442]
	C_{min} (ng/mL)	3.5 (79%)	4.6 ± 4.6	3.4 [0.1, 44]
	CL/F (L/h)	71 (35%)	75 ± 28	72 [19, 399]
	V_{ss} (L)	101 (52%)	122 ± 138	84 [69, 1757]
	$T_{1/2}$ (hour)	1 (59%)	1.2 ± 1.5	0.9 [0.3, 28]
	T_{max} (hour)	0.9 (24%)	0.9 ± 0.2	0.9 [0.5, 1.9]
ACP-5862 (n = 292)	AUC_{24h} (ng·h/mL)	3947 (43%)	4314 ± 2045	3832 [989, 17005]
	C_{max} (ng/mL)	451 (52%)	504 ± 240	470 [52, 1799]
	C_{min} (ng/mL)	47 (62%)	57 ± 44	44 [12, 386]
	CL/F (L/h)	13 (42%)	14 ± 6	14 [2.8, 60]
	V_{ss} (L)	67 (32%)	73 ± 52	63 [45, 796]
	$T_{1/2}$ (hour)	3.5 (24%)	3.6 ± 1.1	3.4 [2.1, 11]
	T_{max} (hour)	1.6 (20%)	1.6 ± 0.3	1.6 [0.9, 2.7]

AUC_{24h}: steady-state area under the plasma drug concentration over time curve from 0 to 24 h.
C_{max}: steady-state maximum plasma concentration.
C_{min}: steady-state minimum plasma concentration.
V_{SS}: steady-state volume of distribution.
$T_{1/2}$: terminal elimination half-life.
T_{max}: time to peak plasma concentrations.

19.5. FDA Grouped Preferred Terms

Regulatory Authorities Assessment:
The following grouping of terms was adopted for the primary safety analyses for ELEVATE-TN and ASCEND as well as the FDA integrated safety analysis (N = 1029) performed subsequently using ISS datasets. Underlined terms were added upon review of the ISS.

Note: Not all listed PTs appear in the NDA datasets.

FDA Grouped PT	Included in Grouping	Not Included
Abdominal pain	All PTs containing "abdominal pain", Abdominal discomfort, Abdominal tenderness, Epigastric discomfort	
Anemia	All PTs containing "anemia", RBC count decreased	
Atrial fibrillation or flutter	Atrial fibrillation, Atrial flutter, Cardiac flutter	
Bruising	All PTs containing "bruise," "contusion," or "ecchymosis"	Petechiae, Purpura
Cardiac arrhythmias	High-level group term, "Cardiac arrhythmias"	
Cardiac failure	All PTs containing "cardiac failure", Congestive cardiomyopathy, Cardiomyopathy, Left ventricular failure, Cor pulmonale, Cardiopulmonary failure Added with ISS: Cardiogenic shock, Ischemic cardiomyopathy	ISS: Cardiomegaly, Hypertrophic cardiomyopathy, Ejection fraction decreased
Chest pain	Chest discomfort, Chest pain, Angina pectoris	Noncardiac chest pain
Colitis	Colitis, Colitis microscopic, Colitis ulcerative, Colitis erosive, Enterocolitis, Enterocolitis hemorrhagic **Note:** For ASCEND and ISS, "Diarrhea or colitis" grouping used	Enteritis ISS: colitis ischemic, infectious colitis (e.g. C difficile)
Cough	All PTs containing "Cough"	
Cytomegalovirus infection	Cytomegalovirus infection, Cytomegalovirus viremia	
Diarrhea	Diarrhea, Diarrhea hemorrhagic, Defecation urgency **Note:** For ASCEND, "Diarrhea or colitis" grouping used	Post procedural diarrhea
Diarrhea or colitis (for ASCEND)	All terms under FDA's grouping of "Diarrhea" and "Colitis"	
Dizziness	All PTs containing "Dizziness" or "Vertigo"	
Dyspnea	All PTs containing "Dyspnea"	

FDA Grouped PT	Included in Grouping	Not Included
Edema	Edema, Generalized edema, Face edema, Swelling face, Edema peripheral, Fluid overload, Fluid retention, Pulmonary edema, Acute pulmonary edema, Pulmonary congestion	Edema blister, Localized sites of edema (e.g. Localized edema, Lip edema, Nasal edema, Periorbital edema, Eye swelling) With ISS: Angioedema, Gravitational edema, Soft tissue swelling
Fatigue	Asthenia, Fatigue, Lethargy, ECOG performance status worsened	
Febrile neutropenia	Febrile neutropenia, Febrile bone marrow aplasia, Neutropenic infection, Neutropenic sepsis* *** Note: Neutropenic sepsis is counted under both the "febrile neutropenia" and "sepsis" PTs**	
Gastroenteritis	Gastroenteritis and specific types (e.g. viral), Enteritis	Gastroenteritis radiation, Gastritis, Duodenitis
Gastrointestinal hemorrhage	All PTs containing "Gastrointestinal hemorrhage", Gastric hemorrhage, Gastric ulcer hemorrhage, Large intestinal ulcer hemorrhage, Hematochezia, Hematemesis, Intestinal hemorrhage, Intestinal hemorrhage, Melena, Hemorrhoidal hemorrhage, Rectal hemorrhage, Small intestinal hemorrhage	
Headache	All PTs containing "headache", Migraine With ISS: Head discomfort	
Hemorrhage or hematoma	All PTs containing "hemorrhage", "hemorrhagic", or "hematoma", all PTs contained in FDA's "Gastrointestinal hemorrhage" grouping, Menorrhagia, Hemarthrosis, Hemoptysis, Hematuria, Epistaxis ISS: Blood urine present, Extravasation blood Hematoma as separate category: All PTs containing "hematoma"	Petechiae, Purpura, FDA's grouping for "Bruising"
Hemorrhage intracranial	Includes but is not limited to: Hemorrhage intracranial, Subdural hematoma, Subdural hemorrhage, Cerebral hemorrhage, Hemorrhagic stroke, Subarachnoid hemorrhage	
Hepatitis	All PTs containing "hepatitis", Hepatocellular injury, Hepatotoxicity, Drug-induced liver injury, Liver injury	FDA's "Transaminase elevation" grouping, PTs containing "Hepatic failure", Hepatic encephalopathy

FDA Grouped PT	Included in Grouping	Not Included
Herpesvirus infection	High-level group term, "Herpes viral infection"	
Hyperbilirubinemia	Blood bilirubin increased, Hyperbilirubinemia, Jaundice	
Hypertension	Hypertension, Essential hypertension, Blood pressure increased, Blood pressure systolic increased. ISS: hypertensive crisis, Malignant hypertension	
Hypotension	Hypotension, Diastolic hypotension, Orthostatic hypotension, Blood pressure decreased	
Leukocytosis [a]	Leukocytosis, Hyperleukocytosis, White blood cell count increase	
Lower respiratory tract infection	All PTs containing "bronchitis" or "lower respiratory tract infection", Bronchiolitis, Tracheitis, Lung infection. ISS: Infective exacerbation of bronchiectasis	Bronchiectasis
Musculoskeletal pain	Back pain, Musculoskeletal chest pain, Noncardiac chest pain, Musculoskeletal pain, Musculoskeletal discomfort, Myofascial pain syndrome, Neck pain, Pain in extremity, Myalgia, Spinal pain, Bone pain	Arthralgia, Musculoskeletal stiffness
Myocardial ischemia or infarction	Acute myocardial infarction, Myocardial ischemia, Angina unstable, Troponin increased, Acute coronary syndrome, Myocardial infarction, Coronary artery stenosis or occlusion	Angina pectoris
Nausea	Nausea, Retching	Procedural nausea
Neutropenia	Neutropenia, Neutrophil count decreased, Granulocytopenia	Febrile neutropenia
Nonmelanoma skin cancer	Squamous cell carcinoma of skin, Basal cell carcinoma, Bowen's disease, Basosquamous carcinoma, Lip squamous cell carcinoma	ISS: Neuroendocrine carcinoma of the skin
Pneumonia	All PTs containing "pneumonia", including within another word (e.g. bronchopneumonia), Bronchopulmonary aspergillosis, Lung infiltration, Lung consolidation	Lung infection
Pneumonitis	Pneumonitis, Acute respiratory distress syndrome, Interstitial lung disease	
Rash	All PTs containing "rash", all PTs containing "dermatitis" except as noted, Drug eruption, Drug reaction with eosinophilia and systemic symptoms, Erythema, Erythema multiforme, Generalized erythema, Toxic skin eruption, Palmar erythema, Palmoplantar keratoderma, Palmar-plantar erythrodysesthesia syndrome, Skin reaction, Skin toxicity, Stevens-Johnson syndrome, Toxic epidermal necrolysis. ISS: acute febrile neutrophilic dermatosis	All PTs containing "Eczema", Actinic keratosis, Folliculitis, Urticaria, Lichen planus, Herpes dermatitis. ISS: Erythema nodosum, Erythema annulare, Dermatitis infected
Renal insufficiency	All PTs containing "renal failure" or "nephropathy", Acute kidney injury, Blood creatinine increase, Creatinine renal	

FDA Grouped PT	Included in Grouping	Not Included
	clearance decreased, Glomerular filtration rate decreased, Renal impairment, Hypercreatinemia, Chronic kidney disease. ISS: Renal injury	
Respiratory tract infection	Respiratory tract infection + specific types (e.g. respiratory tract infection viral, respiratory syncytial virus infection, influenza, Haemophilus infection), Influenza like illness, Sinobronchitis [b]	Upper respiratory tract infection, Lower respiratory tract infection [b]
Sepsis	All PTs containing "Bacteremia" or "Sepsis", including within another word (e.g. urosepsis) Septic shock *** Note: Neutropenic sepsis is counted under both the "febrile neutropenia" and "sepsis" PTs**	
Supraventricular tachycardia	High-level term, "Supraventricular arrhythmias"	
Thrombocytopenia	Thrombocytopenia, Platelet count decreased	Immune thrombocytopenic purpura
Thrombosis or thromboembolism	All PTs containing "thrombosis" except as noted, Peripheral embolism, Pulmonary embolism	Superficial thrombosis, Embolic cerebral infarction
Transaminase elevation	Alanine aminotransferase increased, Aspartate aminotransferase increased, Alanine aminotransferase, Aspartate aminotransferase, Transaminase increased, Hypertransaminasemia, Hepatic enzyme increased	PTs under FDA's "Hepatitis" grouping, PTs containing "hepatic failure", Hepatic function abnormal
Upper respiratory tract infection	All PTs containing "upper respiratory tract infection," "sinusitis," "laryngitis," "tonsillitis," or "pharyngitis," including within another word (e.g. nasopharyngitis), all PTs containing "rhinitis" except as noted, Rhinovirus infection, Human rhinovirus test positive	Rhinitis allergic ISS: Allergic sinusitis, Reflux laryngitis, Epiglossitis
Urinary tract infection	All PTs containing "cystitis" or "urinary tract infection", Pyelonephritis, Kidney infection	
Ventricular arrhythmia	High-level term, "Ventricular arrhythmias and cardiac arrest"	
Xerosis	Dry skin, Dry eye, Dry mouth, Xerosis	

Source: FDA analysis

[a] Grouping for other lab-related AEs is similar, e.g., hyperglycemia = hyperglycemia + blood glucose increased, hypokalemia = hypokalemia + blood potassium decreased, lymphopenia = lymphopenia + lymphocyte count decreased

[b] This grouping defines respiratory tract infection (RTI) of unspecified localization. Where designated, FDA also evaluated all "RTI" including the "Upper RTI" and "Lower RTI" grouping.

NDA 210259/S-006
NDA 210259/S-007

CALQUENCE (acalabrutinib)
Assessment Aid Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Natalie Simpson, PhD	OOD/DHOT	Section: 5	**Select one:** ☑ Authored ☐ Approved
	Signature: Natalie Simpson -S Digitally signed by Natalie Simpson -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, 0.9.2342.19200300.100.1.1 2000576562, cn Natalie Simpson -S Date 2019.11.14 17 30 23 -05'00'			
Nonclinical Team Leader (Acting)	Brenda Gehrke, PhD	OOD/DHOT	Section: 5	**Select one:** ☑ Authored ☑ Approved
	Signature: Brenda Gehrke -S Digitally signed by Brenda Gehrke -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Brenda Gehrke -S, 0.9.2342.19200300.100.1.1 0012062023 Date 2019.11.13 16 52 13 -05'00'			
Clinical Pharmacology Reviewer	Vicky Hsu, PhD	OCP/DCPV	Section: 6	**Select one:** ☑ Authored ☐ Approved
	Signature: Vicky Hsu -S Digitally signed by Vicky Hsu -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Vicky Hsu -S, 0.9.2342.19200300.100.1.1 2000996657 Date 2019.11.13 10 30 42 -05'00'			
Clinical Pharmacology Team Leader	Lanre Okusanya, PharmD	OCP/DCPV	Section: 6	**Select one:** ☑ Authored ☑ Approved
	Signature: Olanrewaju Okusanya -S Digitally signed by Olanrewaju Okusanya -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.23 2.19200300.100.1.1=2001 10838, cn=Olanrewaju Okusanya -S Date: 2019.11.20 09:06:52 -05'00'			
Pharmacometrics Reviewer	Liang Li, PhD	OCP/DPM	Section: 6	**Select one:** ☑ Authored ☐ Approved
	Signature: Liang Li -S Digitally signed by Liang Li -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Liang Li -S, 0.9.2342.19200300.100.1.1 2001459144 Date 2019.11.13 10 14 36 -05'00'			
Pharmacometrics Team Leader	Lian Ma, PhD	OCP/DPM	Section: 6	**Select one:** ☑ Authored ☑ Approved
	Signature: Lian Ma -S Digitally signed by Lian Ma -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Lian Ma -S, 0.9.2342.19200300.100.1.1 2000825336 Date 2019.11.20 09 41 34 -05'00'			
Clinical Reviewer (S-006)	Yvette Kasamon, MD	OOD/DHM2	Sections: 1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13	**Select one:** ☑ Authored ☐ Approved
	Signature: Yvette L. Kasamon -S Digitally signed by Yvette L. Kasamon -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, 0.9.2342.19200300.100.1.1 2001634199, cn Yvette L. Kasamon -S Date 2019.11.13 13 59 50 -05'00'			
Clinical Reviewer (S-007)	Nick Richardson, DO, MPH	OOD/DHM2	Sections: 1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13	**Select one:** ☑ Authored ☐ Approved
	Signature: Nicholas C. Richardson -S Digitally signed by Nicholas C. Richardson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.23 2.19200300.100.1.1=20020 0136, cn=Nicholas C. Richardson -S Date: 2019.11.1 10:27:31 -05'00'			

NDA 210259/S-006
NDA 210259/S-007

CALQUENCE (acalabrutinib)
Assessment Aid Signatures

Biometrics Reviewer (S-006)	Lola Luo, PhD	OB/DBIX	Section: 8	**Select one:** ☑ Authored ☐ Approved
	Signature: Lola Luo — Digitally signed by Lola Luo DN cn Lola Luo, o FDA, ou HHS, email lola.luo@fda.hhs.gov, c US Date 2019.11.13 10:50:55 -05'00'			
Biometrics Reviewer (S-007)	Vivian Yuan, PhD	OB/DBIX	Section: 8	**Select one:** ☑ Authored ☐ Approved
	Signature: Weishi Yuan -S — Digitally signed by Weishi Yuan -S Date: 2019.11.13 10:16:53 -05'00'			
Biometrics Team Leader	Jingjing Ye, PhD	OB/DBIX	Section: 8	**Select one:** ☑ Authored ☑ Approved
	Signature: Jingjing Ye -S — Digitally signed by Jingjing Ye -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Jingjing Ye -S, 0.9.2342.19200300.100.1.1 2000458157 Date 2019.11.18 13:53:03 -05'00'			
Division Director (OB)	Thomas Gwise, PhD	OB/DBIX	Section: 8	**Select one:** ☑ Authored ☑ Approved
	Signature: Thomas E. Gwise -S — Digitally signed by Thomas E. Gwise -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, 0.9.2342.19200300.100.1.1 1300369224, cn Thomas E. Gwise -S Date 2019.11.20 10:14:38 -05'00'			
Cross-Disciplinary Team Leader (CDTL)	R. Angelo de Claro, MD	OOD/DHM1	Sections: All	**Select one:** ☑ Authored ☑ Approved
	Signature: Romeo De Claro -S — Digitally signed by Romeo De Claro -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Romeo De Claro -S, 0.9.2342.19200300.100.1.1 2000486745 Date 2019.11.19 08:00:24 -05'00'			
Supervisory Associate Division Director (Clinical)	Albert Deisseroth, MD, PhD	ODE1/DHP	Sections: All	**Select one:** ☑ Authored ☑ Approved
	Signature: Albert B. Deisseroth -S — Digitally signed by Albert B. Deisseroth -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, 0.9.2342.19200300.100.1.1 2000589069, cn Albert B. Deisseroth -S Date 2019.11.14 14:12:57 -05'00'			

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JENNIFER J LEE
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ROMEO A DE CLARO
11/20/2019 03:23:44 PM

ALBERT B DEISSEROTH
11/20/2019 03:31:13 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210259Orig1s006
210259Orig1s007

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: Thursday, October 24, 2019

To: Jennifer Lee, Regulatory Project Manager
Division of Hematology Products (DHP)

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Nazia Fatima, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Brian Tran, Team Leader, OPDP

Subject: OPDP Labeling Comments for CALQUENCE® (acalabrutinib) capsules, for oral use

NDA: 210259/S-006 and S-007

The Office of Prescription Drug Promotion (OPDP) has reviewed the proposed product labeling (PI) and patient package insert (PPI) for CALQUENCE® (acalabrutinib) capsules, for oral use (Calquence) as requested by the Division of Hematology Products (DHP) consult dated September 19, 2019.

OPDP's comments on the proposed labeling are based on the draft PI and draft PPI send to OPDP on October 17, 2019. OPDP has reviewed the draft PI and has no comments. A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover.

Thank you for your consult. If you have any questions, please contact Nazia Fatima at 240-402-5041 or Nazia.Fatima@fda.hhs.gov.

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/s/

NAZIA FATIMA
10/24/2019 04:40:41 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 24, 2019
To:	Ann Farrell, MD Director **Division of Hematology Products (DHP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nazia Fatima, PharmD, MBA, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	CALQUENCE (acalabrutinib)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 210259
Supplement Number:	S-006 and S-007
Applicant:	AstraZeneca UK Limited c/o Acerta Pharma B.V.

1 INTRODUCTION

On September 24, 2019, AstraZeneca UK Limited c/o Acerta Pharma B.V., submitted for the Agency's review Prior Approval Supplements (PAS)-Efficacy to New Drug Application (NDA) 210259/S-006 and S-007 for CALQUENCE (acalabrutinib) capsules, for oral use. Supplement 007 provides for the "child" CALQUENCE (acalabrutinib) 100 mg oral capsule for the treatment of patients with chronic lymphocytic leukemia (CLL). Supplement 006 cross-references the "parent" sNDA, for the expanded usage of CALQUENCE for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). These supplement submissions are based on study results of ASCEND (ACE-CL-309) and ELEVATE-TN (ACE-CL-007) studies.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on September 18, 2019 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for CALQUENCE (acalabrutinib) capsules.

2 MATERIAL REVIEWED

- Draft CALQUENCE (acalabrutinib) capsules PPI received on September 24, 2019, revised by the Review Division throughout the review cycle, and received by DMPP on October 17, 2019.
- Draft CALQUENCE (acalabrutinib) capsules Prescribing Information (PI) received on September 24, 2019, revised by the Review Division throughout the review cycle, and received by OPDP on October 17, 2019.
- Approved CALQUENCE (acalabrutinib) capsules labeling dated October 31, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible

- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

5 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

SUSAN W REDWOOD
10/24/2019 07:57:07 AM

NAZIA FATIMA
10/24/2019 07:59:11 AM

BARBARA A FULLER
10/24/2019 08:20:33 AM

LASHAWN M GRIFFITHS
10/24/2019 09:11:52 AM

CLINICAL INSPECTION SUMMARY

Date	October 7, 2019
From	Anthony Orencia M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Nicholas Richardson, D.O., M.P.H., Medical Officer Yvette Kasamon, M.D., Ph.D., Medical Officer R. Angelo de Claro, M.D., Clinical Team Leader Ann Farrell, M.D., Director Jennifer J. Lee, Pharm.D., Project Manager Division of Hematology Products
NDA	210259 S-007
Applicant	AstraZeneca UK Limited
Drug	Acalabrutinib (Calquence®)
NME	No
Division Classification	Bruton tyrosine kinase inhibitor
Proposed Indication	Treatment of adult patients with Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)
Consultation Request Date	September 5, 2019
Summary Goal Date	October 25, 2019 (Breakthrough Therapy Priority Review)
Action Goal Date	November 21, 2019
PDUFA Date	February 25, 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The Sponsor's site (Acerta Pharma, LLC) was selected for inspection of Study ACE-CL-007 in NDA 210259 S-007.

The inspection found no significant deficiencies with monitoring of the trial. In general, the sponsor maintained adequate oversight of the clinical trial, and appeared to be in compliance with Good Clinical Practice.

Data from Study ACE-CL-007 are considered reliable. The study appears to have been conducted adequately in support of this application.

An inspection summary addendum will be generated, if conclusions change upon receipt and review of the pending Establishment Inspection Report.

II. BACKGROUND

Acalabrutinib is a tyrosine kinase inhibitor indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. The drug application received accelerated approval for this indication in 2017.

Study ACE-CL-007 was conducted to support the proposed indication of newly diagnosed chronic lymphocytic leukemia (that is, the following proposed indication is previously untreated chronic lymphocytic leukemia). This clinical investigative study will form the basis for the regulatory decision-making process for this application.

DHP requested inspection of the sponsor's conduct and oversight for data submitted from Study ACE-CL-007 to support the regulatory evaluation regarding this newly diagnosed/first line breakthrough drug indication, for chronic lymphocytic leukemia (CLL).

Study ACE-CL-007 (ELEVATE-TN)
Study ACE-CL-007 is a Phase 3, multicenter, open-label, 1:1:1 randomized ratio 3-arm study to evaluate the efficacy and safety of obinutuzumab in combination with chlorambucil (Arm A), acalabrutinib in combination with obinutuzumab (Arm B), and acalabrutinib (Arm C) in subjects with previously untreated CLL. This study deployed an Interactive Web Response System (IWRS) for randomization.

Subject participation included a Screening Phase, a Treatment Phase, Post-treatment Phase and a Post-disease Progression Phase. The Screening Phase lasted up to 28 days before the first dose of study drug, during which the subject's eligibility and baseline characteristics will be determined. The Treatment Phase lasted from randomization until study drug(s) discontinuation. Treatment with acalabrutinib may be continued until an unacceptable drug-related toxicity occurs or until disease progression. Assessment for tumor response and progression were performed in accordance with the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 criteria until disease progression. Disease assessments were assessed every 12 weeks through 24 months and then every 24 weeks thereafter for all subjects (including subjects who discontinued from the study due to an adverse event or any reason) until confirmation of disease progression or death, consent withdrawal, or lost to follow-up.

The primary efficacy objective of the trial was to evaluate the efficacy of obinutuzumab in combination with chlorambucil (Arm A) compared with acalabrutinib (ACP-196) in combination with obinutuzumab (Arm B) based on Independent Review Committee (IRC) assessment of progression-free survival (PFS) per International Workshop on Chronic Lymphocytic Leukemia criteria with incorporation of the clarification for treatment-related lymphocytosis —hereafter referred to as IWCLL 2008 criteria—in subjects with previously untreated chronic lymphocytic leukemia (CLL). The primary efficacy study endpoint of the study was progression free survival (PFS) as assessed by IRC review per IWCLL 2008 criteria. The primary analysis was a comparison of PFS between obinutuzumab in combination with chlorambucil (Arm A) and acalabrutinib (ACP-196) in combination with obinutuzumab (Arm B).

The study was conducted in 142 study centers in 18 countries across North America, Europe, Australia, New Zealand, and Latin America. A total of 535 subjects were randomized in the trial. Per sponsor, enrolled subjects were randomized between September 14, 2015 and February 8, 2017. Subjects completed enrolment on February 8, 2017. The study is currently ongoing. The data cut-off date for the submitted interim study report was on February 8, 2019.

III. RESULTS (by site):

Acerta Pharma, LLC
121 Oyster Point Blvd.
South San Francisco, CA 94080

Sponsor inspection dates: September 23 to 27, 2019

Acerta Pharma, LLC, a subsidiary of AstraZeneca which owns 55% of the firm, is the sponsor of Study ACE-CL-007.

This inspection evaluated compliance with the sponsor's responsibilities concerning the conduct of Study ACE-CL-007. The inspection included review of organizational charts, vendor list, vendor oversight, transfer of obligations, investigator agreements, financial disclosures, monitoring plans, monitoring reports, monitor qualifications, safety reports, adverse events, protocol deviations, and standard operating procedures.

Interim Site Visit Monitoring Reports for this clinical investigation were selected and reviewed for the following seven study sites: John Pagel, M.D., Site 048 (U.S.); Patricia Walker, M.D., Site 284 (Australia); Talha Munir, M.D., Site 295 (U.K.); Francesca Re, M.D., Site 323 (Italy); Arpad Illes, M.D., Site 324 (Hungary); Zsolt Nagy, M.D., Site 275 (Hungary) and David Simpson, M.D., Site 280 (New Zealand).

(b) (4) is the AstraZeneca (b) (4) that receives all domestic and foreign individual case study adverse event reports from data entry sites (e.g., doctor's office), and identifies which cases may need expedited reporting to FDA. (b) (4) then submits reportable adverse event to the Acerta Medical Safety Team. The Acerta Medical Safety Team conducts the case evaluation, processing, and submits qualifying adverse events to the FDA and all clinical sites involved in the study.

A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection. In general, the sponsor appeared to be in compliance with Good Clinical Practice.

{See appended electronic signature page}
Anthony Orencia, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Min Lu, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
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MIN LU
10/08/2019 08:26:02 AM

KASSA AYALEW
10/08/2019 09:53:58 AM