CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212526Orig1s000

MULTI-DISCIPLINE REVIEW

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

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	NDA - 505(b)(1)
Application Number(s)	212526
Priority or Standard	Priority
Submit Date(s)	December 18, 2018
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PDUFA Goal Date	August 18, 2019
Division/Office	CDER/OHOP/DOP1
Review Completion Date	*Electronic Stamp Date*
Established Name	Alpelisib
(Proposed) Trade Name	Piqray
Pharmacologic Class	Kinase Inhibitor
Applicant	Novartis Pharmaceuticals
Formulation(s)	Oral
Dosing Regimen	The recommended dose of alpelisib is 300 mg (2x150 mg film-coated tablets) taken orally, (b) (4) food, once daily in combination with fulvestrant 500 mg IM on days 1 and 15 of a 28 day cycle and on day 1 every 28 days thereafter.
Applicant Proposed Indication(s)/Population(s)	Alpelisib (PIQRAY) is indicated for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, HER2-negative, advanced breast cancer with a PIK3CA mutation as detected by an FDA-approved test in combination with fulvestrant after disease progression following an endocrine-based regimen.
Recommendation on Regulatory Action	*Regular Approval*
Recommended Indication(s)/Population(s) (if applicable)	PIQRAY is a kinase inhibitor indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

ADME	absorption, distribution, metabolism, and excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AI	aromatase inhibitor
AKT	protein kinase B
ARA	acid-reducing agent
AUCinf	area under the plasma concentration time curve from time zero to infinity
AUC last	area under the plasma concentration time curve from time zero to last quantifiable concentration
AUC0-24	area under the plasma concentration time curve from time zero to 24 hours
BCRP	breast cancer resistance protein
BCS	Biopharmaceutics Classification System
b.i.d.	twice a day
BIRC	blinded independent review committee
BMD	bone mineral density
BPI-SF	brief pain inventory – short form
CBR	clinical benefit rate
CDK4/6	cyclin-dependent kinase 4/6
CDRH	Center for Devices and Radiological Health
CI	confidence interval
Cmax	peak concentration
Cmin	trough concentration
CNS	central nervous system
COA	clinical outcome assessment
CR	complete response
CRF	case report form
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CV	coefficient of variation
CYP	cytochrome P450
CYP2B6	cytochrome P450 2B6
CYP2C9	cytochrome P450 2C9
CYP3A4	cytochrome P450 3A4
DCR	disease control rate
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DMC	data monitoring committee

DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EC50	50% effectiveness concentration
EoPII	end-of Phase II
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	EuroQol five-dimension five-level questionnaire
ER	estrogen receptor
FAS	full analysis set
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GI	gastro-intestinal
HA	Health Authorities
HbA1c	hemoglobin A1c
HER2	human epidermal growth factor receptor-2
HFHC	high-fat high-calorie
HR	hazard ratio
HR-positive	hormone receptor-positive
IEC	Institutional Ethics Committee
IIT	investigator-initiated trial
i.m.	intramuscular
IRB	Institutional Review Board
IRT	interactive response technology
LFLC	low-fat low-calorie
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
NCI	National Cancer Institute
NDA	new drug application
NE	not estimable
NR	not reached
NSAI	non-steroidal aromatase inhibitor
ORR	overall response rate
OS	overall survival
PBPK	physiologically-based pharmacokinetic modeling
PD	progressive disease
PFS	progression-free survival
PFS2	progression-free survival after next-line of therapy
PgR	progesterone receptor
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

PI3K	phosphatidylinositol-3-kinase
PK	pharmacokinetics
PoC	proof of concept
PPS	per-protocol set
PR	partial response
PRO	patient-reported outcomes
PTEN	phosphatase and tensin homolog
q.d.	once daily
QLQ-C30	quality of life questionnaire – core 30 questions
QoL	quality of life
RDI	relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumors
REMS	Risk Evaluation and Mitigation Strategy
RTK	receptor tyrosine kinase
RTOR	real-time oncology review
SAE	serious adverse event
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology Studies
SCS	Summary of Clinical Safety
SD	stable disease or standard deviation
Tmax	time to reach peak concentration
TTP	time to progression
UGT	UDP-glucuronosyltransferase
UNK	unknown
US	United States
USPI	United States Prescribing Information
VAS	visual analog scale
WOCBP	women of childbearing potential

1 Executive Summary

1.1. Product Introduction

Alpelisib is an oral inhibitor of phosphatidylinositol-3-kinase (PI3K), with inhibitory activity predominantly against PI3K-alpha. It has not been approved for any indication worldwide.

The applicant proposed the following indication for NDA 212526:

PIQRAY is an α-specific class I phosphatidylinositol-3-kinase (PI3K) inhibitor indicated for the treatment of postmenopausal women, and men, with HR-positive, HER2 negative, advanced breast cancer with a PIK3CA mutation as detected by an FDA-approved test in combination with fulvestrant after disease progression following an endocrine-based regimen.

The recommended indication for regular approval is:

PIQRAY is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

The recommended dose for alpelisib is 300 mg (two 150 mg film-coated tablets) taken orally, once daily, with food. When given with alpelisib, the recommended dose of fulvestrant is 500 mg administered intramuscularly on days 1, 15, and 29, and once monthly thereafter.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The basis of the recommendation for regular approval of alpelisib is a favorable benefit-risk profile based upon results from Study C2301 (SOLAR-1), a phase 3, randomized, double-blind, placebo-controlled trial of alpelisib plus fulvestrant versus placebo plus fulvestrant in 572 postmenopausal women, and men, with HR-positive, HER2-negative, advanced or metastatic breast cancer whose disease had progressed or recurred on or after an aromatase inhibitor, with or without a cyclin-dependent kinase 4/6 (CDK 4/6) inhibitor. The trial met its primary endpoint for the PIK3CA-mutant intention-to-treat (ITT) population, with an estimated median PFS by investigator assessment in the alpelisib plus fulvestrant arm of 11.0 months (95% CI: 7.5, 14.5) compared to 5.7 months (95% CI: 3.7, 7.4) in the placebo plus fulvestrant arm (HR 0.65; 95% CI: 0.50, 0.85; p=0.001). Overall survival data were not mature, but no detriment in OS with alpelisib is apparent at this time.

Alpelisib demonstrated acceptable tolerability for the indicated population with a serious and life-threatening disease. The majority of adverse reactions were grade 1-2 in severity, with the exception of hyperglycemia and rash, and successfully managed with dose reductions, temporary treatment discontinuations, supportive care treatments, and/or standard therapy. Severe hypersensitivity, severe cutaneous reactions, hyperglycemia, pneumonitis, diarrhea, and embryo-fetal toxicity are labeled as Warnings and Precautions.

Overall, the benefit-risk profile based upon results from Study C2301 (SOLAR-1) was favorable. This New Drug Application (NDA) represents a new treatment option for postmenopausal women, and men, whose tumors have a PIK3CA mutation. A statistically significant difference was seen for PFS and the toxicity profile of alpelisib added to fulvestrant is acceptable for the indicated population. Male patients were eligible for and treated on SOLAR-1. Male patients with solid tumors were also treated with alpelisib monotherapy during early phase dose-escalation and dose-expansion studies. Treatment options for male patients with breast cancer are a significant area of unmet medical need. PIK3CA mutations are not expected to behave differently in male patients and fulvestrant degrades the estrogen receptor and does not rely on circulating estradiol levels for efficacy. In addition, while only a small number of patients were previously treated with CDK 4/6 inhibitors, fulvestrant monotherapy in metastatic breast cancer progressed on prior AI is an accepted standard of care treatment option for this patient population and an appropriate comparator. Activation of PI3K signaling is one resistance mechanism in patients whose tumors have progressed on CDK 4/6 inhibitors, and therefore using a combination of alpelisib with fulvestrant after progression on CDK 4/6 inhibitor-based regimens is a reasonable approach.

The companion diagnostic test *therascreen*® PIK3CA RGQ PCR Kit, (QIAGEN Manchester, Ltd.) will be used to select patients who have PIK3CA mutations in tumor tissue specimens and/or in circulating tumor DNA (ctDNA) isolated from plasma specimens. If the test is negative for PIK3CA mutations in plasma, patients should undergo testing for PIK3CA mutations in their tumor tissue.

Therefore, the FDA review team recommends granting regular approval of PIQRAY (alpelisib) for the following indication:

PIQRAY is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment by FDA

Alpelisib, an oral inhibitor of phosphatidylinositol-3-kinase (PI3K) with inhibitory activity predominantly against PI3K-alpha, is recommended for regular approval in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

In the United States (US), breast cancer is the most common cancer in women, with more than 260,000 new cases and 40,000 deaths annually. Metastatic breast cancer is categorized into different histopathological subtypes based on expression of ER, PR, and HER2. HR-positive, HER2-negative breast cancer is the most common subtype in both females and males. The majority of people with HR-positive, HER2-negative breast cancer are initially diagnosed and treated at an early stage with a combination of surgery with or without radiation and adjuvant endocrine therapy with or without adjuvant chemotherapy. Breast cancer in male patients is rare, with fewer than 1% of breast cancer diagnosed in male patients. Men with breast cancer tend to present at a higher stage than female patients, at least in part due to the lack of mammographic screening in men.

Approximately one-third of patients with early-stage breast cancer are diagnosed with recurrence, including metastatic, breast cancer. FDA approved therapies for patients with HR-positive, HER2-negative advanced or metastatic breast cancer include hormonal-based (aromatase inhibitor [AI], fulvestrant) therapies in combination with CDK 4/6 inhibitors (abemaciclib, palbociclib, ribociclib), everolimus with exemestane, hormonal monotherapy (AI, fulvestrant, tamoxifen), and chemotherapy (capecitabine, eribulin, ixabepilone, paclitaxel protein-bound, gemcitabine, etc.). Metastatic breast cancer is incurable and has a 5-year survival rate of approximately 25%. Treatment options for all patients, including male patients, remains an area of significant unmet need.

The efficacy and safety of alpelisib plus fulvestrant was demonstrated in 572 postmenopausal women and men with HR-positive, HER2-negative advanced or metastatic breast cancer whose cancer had progressed or recurred on or after an aromatase inhibitor, with or without a cyclin-dependent kinase 4/6 (CDK 4/6) inhibitor in the SOLAR-1 trial. Patients received either alpelisib (300 mg) or placebo orally once daily on a continuous basis, plus fulvestrant (500 mg) administered intramuscularly on Cycle 1 Days 1 and 15,

and then on Day 1 of every 28-day cycle. Patients received treatment until radiographic progression or unacceptable toxicity. Tumor assessments were performed every 8 weeks for the first 18 months and every 12 weeks thereafter.

The trial enrolled two cohorts, a cohort with PIK3CA tumor mutation (n=341) and a cohort without a PIK3CA (n=231) tumor mutation. The major efficacy outcome was investigator-assessed progression-free survival (PFS) in the cohort with a PIK3CA mutation per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Additional efficacy outcome measures were overall response rate (ORR) and overall survival (OS) in the cohort with a PIK3CA mutation. The protocol was amended prior to analysis to change the efficacy analysis for the PIK3CA non-mutant cohort from a primary objective to a secondary, proof-of-concept objective.

The SOLAR-1 trial met its primary endpoint for the PIK3CA-mutant intention-to-treat (ITT) population. The estimated median PFS by investigator assessment in the alpelisib plus fulvestrant arm was 11.0 months (95% CI: 7.5, 14.5) compared to 5.7 months (95% CI: 3.7, 7.4) in the placebo plus fulvestrant arm (HR 0.65; 95% CI: 0.50, 0.85; p=0.001). Results of PFS in the PIK3CA mutant cohort by blinded independent central review (BICR), subgroup analyses, and sensitivity analyses were consistent with the results of the primary endpoint. Overall survival data were not mature. No detriment in OS with alpelisib is apparent at this time.

Alpelisib demonstrated acceptable tolerability for the indicated population with a serious and life-threatening disease. Adverse reactions were common and, except for hyperglycemia and rash, predominantly CTCAE grade 1-2 in severity. The majority of adverse reactions were successfully managed with dose reductions, temporary treatment discontinuations, supportive care treatments, and/or standard therapy. Severe hypersensitivity, severe cutaneous reactions, hyperglycemia, pneumonitis, diarrhea, and embryo-fetal toxicity are labeled as Warnings and Precautions. The most common adverse reactions on the alpelisib plus fulvestrant arm were glucose increased (79%), creatinine increased (67%), diarrhea (58%), rash (52%), lymphocyte count decreased (52%), gamma glutamyl transferase (GGT) increased (52%), nausea (45%), alanine aminotransferase (ALT) increased (44%), lipase increased (42%), and fatigue (42%). Serious adverse reactions occurred in 35% of patients who received alpelisib plus fulvestrant, including hyperglycemia, rash, diarrhea, acute kidney injury, abdominal pain, and anemia. Twenty one percent of patients permanently discontinued alpelisib alone due to adverse reactions and 4.6% permanently discontinued both alpelisib and fulvestrant. Hyperglycemia, rash, diarrhea, and fatigue were the most common adverse reactions leading to treatment discontinuation of alpelisib.

Overall, the benefit-risk profile based upon results from Study C2301 (SOLAR-1) was favorable.
This New Drug Application (NDA) represents a new treatment option for postmenopausal women, and men, whose tumors have a PIK3CA mutation. A statistically significant difference was seen for PFS and the toxicity profile of alpelisib added to fulvestrant is acceptable for the indicated population. Treatment options for male patients with breast cancer is a significant area of unmet medical need. Male patients were eligible for and enrolled on SOLAR-1 and male patients with solid tumors were also treated with alpelisib monotherapy during early phase dose-escalation and dose-expansion studies. PIK3CA mutations are not expected to behave differently in male patients and fulvestrant degrades the estrogen receptor and does not rely on circulating estradiol levels for efficacy. In addition, while only a small number of patients were previously treated with CDK 4/6 inhibitors, fulvestrant monotherapy in metastatic breast cancer which has progressed on prior AI is an accepted standard of care treatment option for this patient population and an appropriate comparator in the US. Activation of PI3K signaling is one resistance mechanism in patients whose tumors have progressed on CDK 4/6 inhibitors, and therefore using a combination of alpelisib with fulvestrant after progression on CDK 4/6 inhibitor-based regimens is a reasonable approach (Vora et al. 2014, Michaloglou et al. 2018).

The companion diagnostic test *therascreen*® PIK3CA RGQ PCR Kit, (QIAGEN Manchester, Ltd.) will be used to select patients who have PIK3CA mutations in tumor tissue specimens and/or in circulating tumor DNA (ctDNA) isolated from plasma specimens. If the test is negative for PIK3CA mutations in plasma, patients should undergo testing for PIK3CA mutations in their tumor tissue.

Alpelisib (Piqray) is recommended for regular approval for the following indication:

PIQRAY is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Breast cancer is the most common cancer in women, with more than 260,000 new cases and 40,000 deaths annually. • Breast cancer in male patients is rare. • Advanced or metastatic breast cancer is incurable.	Advanced or metastatic breast cancer is a serious and life-threatening condition with ongoing unmet medical need in both female and male patients.
Current Treatment Options	• Metastatic breast cancer is not curable, with treatment goals palliative in nature to delay disease progression, prolong survival, and reduce cancer-related symptoms. • FDA approved therapies for patients with HR-positive, HER2-negative advanced or metastatic breast cancer include hormonal-based (aromatase inhibitor [AI], fulvestrant) therapies in combination with CDK 4/6 inhibitors (abemaciclib, palbociclib, ribociclib), everolimus with exemestane, hormonal monotherapy (AI, fulvestrant, tamoxifen), and chemotherapy (capecitabine, eribulin, ixabepilone, paclitaxel protein-bound, gemcitabine, etc.).	All currently available treatment options are palliative. There is an unmet medical need to improve the outcomes of female and male patients with HR-positive, HER2-negative advanced or metastatic breast cancer.
Benefit	• SOLAR-1 enrolled 572 postmenopausal women and men with HR-positive, HER2-negative advanced or metastatic breast cancer whose disease had progressed or recurred on or after an aromatase inhibitor, with or without a CDK 4/6 inhibitor. • In patients with a PIK3CA tumor mutation, the estimated median PFS by investigator assessment in the alpelisib plus fulvestrant arm was 11.0 months (95% CI: 7.5, 14.5) compared to 5.7 months (95% CI: 3.7, 7.4) in the placebo plus fulvestrant arm (HR 0.65; 95% CI: 0.50, 0.85; p=0.001). • The overall response rate (ORR) in patients with a PIK3CA tumor mutation and confirmed response was 36% compared to 16%, in favor of the alpelisib plus fulvestrant arm.	The SOLAR-1 trial met its primary endpoint with a statistically significant and clinically meaningful improvement in PFS. This is also the first drug approved specifically for the treatment of patients with PIK3CA-mutated advanced breast cancer, which represents a new molecular subset in breast cancer. The companion diagnostic test *therascreen*® PIK3CA RGQ PCR Kit, (QIAGEN Manchester, Ltd.) will be used to select patients who have PIK3CA mutations in tumor tissue specimens

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		and/or in circulating tumor DNA (ctDNA) isolated from plasma specimens. If the test is negative for PIK3CA mutations in plasma, patients should undergo testing for PIK3CA mutations in their tumor tissue.
Risk and Risk Management	• Adverse reactions were common and, except for hyperglycemia and rash, predominantly grade 1-2 in severity. • The majority of adverse reactions were successfully managed with dose reductions, temporary treatment discontinuations, supportive care treatments, and/or standard therapy. • Severe hypersensitivity, severe cutaneous reactions, hyperglycemia, pneumonitis, diarrhea, and embryo-fetal toxicity are labeled as Warnings and Precautions. • The most common adverse reactions on the alpelisib plus fulvestrant arm were glucose increased (79%), creatinine increased (67%), diarrhea (58%), rash (52%), lymphocyte count decreased (52%), gamma glutamyl transferase (GGT) increased (52%), nausea (45%), alanine aminotransferase (ALT) increased (44%), lipase increased (42%), and fatigue (42%). • Two patients died while on treatment with alpelisib plus fulvestrant due to causes other than the underlying malignancy, one cardio-respiratory arrest and one second primary malignancy. Neither was suspected to be related to study treatment. • Serious adverse reactions occurred in 35% of patients who received alpelisib plus fulvestrant, including hyperglycemia, rash, diarrhea, acute kidney injury, abdominal pain, and anemia.	The safe use of alpelisib with fulvestrant can be managed through appropriate labeling. No REMS is indicated.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Twenty one percent of patients permanently discontinued alpelisib alone due to adverse reactions, and 4.6% permanently discontinued both alpelisib and fulvestrant. Hyperglycemia, rash, diarrhea, and fatigue were the most frequent adverse reactions leading to discontinuation of alpelisib.	

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

X

Jennifer Gao, MD
Acting Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Breast cancer is the most common cancer diagnosed in women and the second leading cause of cancer-related death (National Breast Cancer Foundation 2018). In 2018, it is estimated that:

- 2,088,849 new breast cancer cases will be diagnosed globally, with 626,679 deaths (Bray et al 2018)
- 266,120 women will be diagnosed with breast cancer in the United States (representing approximately 30% of all cancers in women) and that 40,920 deaths will be recorded (Siegel et al 2018)

In men, breast cancer is a rare condition constituting < 1% of all breast cancer diagnoses (Siegel et al 2018).

Treatment of advanced (locoregionally recurrent or metastatic) breast cancer is palliative in nature as there are no curative treatment options in this setting. The goal is to prolong the progression-free interval, to maintain or improve QoL, and ultimately to improve survival. Metastatic breast cancer represents the most advanced stage of the disease and is associated with a 5-year survival rate of approximately 25% (Cardoso et al 2017).

Breast cancer is a phenotypically diverse disease. Approximately 70% of invasive breast cancers in women > 45 years of age express ER and/or PgR, but not HER2, and are termed HR-positive, HER2-negative (Huang et al 2005). The biology of male breast cancer resembles that of postmenopausal female breast cancer (Anderson et al 2004, Ottini et al 2010).

The PI3K pathway is a central oncogenic pathway that regulates cell proliferation, cell metabolism, growth, survival, and apoptosis. Constitutive activation of PI3K downsignaling is a critical step in mediating the transforming potential of oncogenes and tumor suppressors in many tumor types (Liu et al 2009). PIK3CA mutations are reported in 36% of all breast cancers and in up to 45% of HR-positive, HER2-negative tumors. Constitutive activation of the PI3K pathway has also been linked to resistance for a variety of therapeutic interventions, including chemotherapy, hormonal therapy, and anti-HER2 therapies (McCubrey et al 2006). Activation of the PI3K pathway has been linked to de novo or acquired resistance to endocrine therapy, chemo-, and radiotherapy (Campbell et al 2001, Keegan et al 2018). Recent data from the PALOMA 3 study show acquired PIK3CA and ESR1 Y537S mutations are likely to contribute to endocrine/fulvestrant resistance in subjects with a PIK3CA mutation (Turner et al 2018).

The FDA's Assessment:
The FDA generally agrees with the applicant's assessment with the following comments:

In 2019, approximately 268,600 women will be newly diagnosed with invasive breast cancer in the U.S., and about 41,760 women will die from the disease. In men, breast cancer is rare

with only 2,670 new cases of invasive breast cancer and 500 deaths expected in the U.S in 2019 (American Cancer Society 2019). Though the most common subtype of breast cancer in men is HR-positive and HER2-negative, as it is in postmenopausal women, male breast cancer has not been sufficiently well-characterized to conclude that "the biology of male breast cancer resembles that of postmenopausal female breast cancer" due to the low prevalence of the condition in men and their historical exclusion from breast cancer clinical trials.

There are insufficient data to conclude that patients with PIK3CA-mutated metastatic breast cancer have a worse prognosis than those with PIK3CA-wildtype metastatic breast cancer. Indeed, in the SOLAR-1 trial, the median PFS and ORR in the control arm, reflecting treatment with endocrine therapy alone, were comparable for the PIK3CA-mutated and PIK3CA-wildtype cohorts. In addition, the available data do not indicate that presence of a PIK3CA mutation predicts lesser benefit from the combinations of endocrine therapy plus a CDK 4/6 inhibitor that represent the current standard of care for first- and second-line treatment of patients with HR-positive, HER2-negative advanced or metastatic breast cancer. For example, at the 2019 AACR Annual Meeting, Tolaney and colleagues presented an analysis of PIK3CA mutation status from samples of patients enrolled in the randomized phase 3 MONARCH-2 study (fulvestrant plus abemaciclib/placebo). The addition of abemaciclib to fulvestrant was associated with improved PFS compared to placebo plus fulvestrant, irrespective of PIK3CA mutation status. The HR for PFS was 0.68 (95% CI: 0.42, 1.09) for patients with PIK3CA-wildtype tumors and 0.46 (95% CI: 0.27, 0.78) for patients with PIK3CA-mutated tumors (Tolaney et al 2019).

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Advanced breast cancer is a serious, life-threatening, and incurable condition.

Sequential endocrine therapy with alternative endocrine regimens or combination regimens with targeted agents aimed at multiple pathways represents the preferred treatment for subjects with HR-positive advanced breast cancer. Available endocrine-based therapies for HR-positive, HER2-negative advanced breast cancer are summarized in Table 1.

In contrast to women, male subjects with HR-positive, HER2-negative breast cancer have few approved treatment options. For males, female breast cancer treatment guidelines are followed, relying primarily on the extrapolation of clinical trial data and tumor biology from female subjects to male subjects (Giordano et al 2002, Agrawal et al 2007, Patten et al 2013, Foerster et al 2014).

Still, virtually all subjects progress and eventually die from their disease. De novo and acquired resistance continue to be two of the major limitations. There remains a lack of predictive biomarkers (other than HR status) in this disease. While several efforts to identify biomarker-defined subpopulations receiving greater benefit from targeted agents have been undertaken, so far none of these have been successful.

A medical need therefore exists to develop new targeted therapies paired with predictive biomarkers to allow for the selection of subjects who would benefit most in terms of delaying disease progression.

Table 1: Summary of Current Endocrine Therapy Treatments in HR-positive, HER2-negative Advanced Breast Cancer

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Endocrine Therapy with CDK 4/6 Inhibitors					
Palbociclib (IBRANCE)	Treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with fulvestrant in women with disease progression following endocrine therapy	2015, 2017	125 mg once daily by mouth (taken with food) for 21 days followed by 7 days off treatment	vs. placebo plus fulvestrant (+ goserelin in pre- and peri-menopausal subjects) PFS: 9.5 (95% CI: 9.2, 11.0) vs. 4.6 months (95% CI: 3.5, 5.6) (HR = 0.461; 95% CI: 0.360, 0.591); p < 0.0001) ORR: 24.6% (95% CI: 19.6, 30.2) vs. 10.9% (95% CI: 6.2, 17.3)	Neutropenia and embryo-fetal toxicity
Ribociclib (KISQALI)	In combination with fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine-based therapy or following disease progression on endocrine therapy	2017, 2018	600 mg once daily by mouth (with or without food) for 21 consecutive days followed by 7 days off treatment	vs. placebo plus fulvestrant PFS: 20.5 (95% CI: 18.5, 23.5) vs. 12.8 months (95% CI: 10.9, 16.3) (HR = 0.593; 95% CI: 0.480, 0.732; p < 0.0001) ORR: 40.9% (95% CI: 35.9, 45.8) vs. 28.7% (95% CI: 22.1, 35.3)	QT interval prolongation, increased QT prolongation with concomitant use of tamoxifen, hepatobiliary toxicity, neutropenia, and embryo-fetal toxicity
Abemaciclib (VERZENIO)	- In combination with fulvestrant for the treatment of women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy	2017, 2018	In combination with fulvestrant: 150 mg twice daily by mouth (with or without food)	- vs. placebo plus fulvestrant PFS: 16.4 (95% CI: 14.4, 19.3) vs. 9.3 months (95% CI: 7.4, 12.7) (HR = 0.553; 95% CI: 0.449, 0.681; p < 0.0001)	Diarrhea, neutropenia, hepatotoxicity, venous thrombo-embolism, and embryo-fetal toxicity

	- As monotherapy for the treatment of adult subjects with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting		As monotherapy: 200 mg twice daily by mouth (with or without food)	ORR: 48.1% (95% CI: 42.6, 53.6) vs. 21.3% (95% CI: 15.1, 27.6) - as monotherapy ORR: 19.7% (95% CI: 13.3, 27.5) DoR: 8.6 months (95% CI: 5.8, 10.2)	
Endocrine Therapy with mTOR Inhibitor					
Everolimus (AFINITOR)	Treatment of postmenopausal women with advanced HR-positive, HER2-negative breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole	2012	10 mg once daily by mouth (with or without food)	vs. placebo plus exemestane PFS: 7.8 (95% CI: 6.9, 8.5) vs. 3.2 months (95% CI: 2.8, 4.1) (HR = 0.45; 95% CI: 0.38, 0.54; p < 0.0001) ORR: 12.6% (95% CI: 9.8, 15.9) vs. 1.7% (95% CI: 0.5, 4.2)	Non-infectious pneumonitis, infections, oral ulceration, renal failure, laboratory test alterations, and embryo-fetal toxicity
Aromatase Inhibitors					
Letrozole (FEMARA)	First and second-line treatment of postmenopausal women with HR-positive or unknown advanced breast cancer	1997	2.5 mg once daily by mouth (without regard to meals)	- vs. tamoxifen (first line) TTP: 9.4 vs. 6.0 months (HR = 0.72; 95% CI: 0.62, 0.83; p < 0.0001) OS: 35 vs. 32 months (p = 0.5136) - vs. megestrol acetate (second line) ORR: 23.6% vs. 16.3%	Decreases in BMD, increases in total cholesterol, fatigue, dizziness, somnolence, and embryo-fetal toxicity
Anastrozole (ARIMIDEX)	- First-line treatment of postmenopausal women with HR-positive or HR-unknown locally advanced or metastatic breast cancer	1995	1 mg once daily by mouth (with or without food)	- vs. tamoxifen (first line) TTP: 11.1 vs. 5.6 months (p = 0.006) and 8.2 vs. 8.3 months (p = 0.920)	Ischemic cardio-vascular events (in women with pre-existing ischemic heart disease), decreases in BMD, and increases in total cholesterol

	- Treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy			- vs. megestrol acetate (second line) TTP: 5.7 vs. 5.1 months and 4.4 vs. 3.9 months	
Exemestane (AROMASIN)	Treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy	1999	25 mg once daily by mouth (after a meal)	vs. megestrol acetate ORR: 15.0% vs. 12.4% TTP: 20.3 vs. 16.6 weeks (HR = 0.84)	Reductions in BMD and embryo-fetal toxicity
Selective Estrogen-receptor Down-regulator					
Fulvestrant (FASLODEX)	- Treatment of HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy - Treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy	2002, 2017	500 mg intra-muscular injection on Days 1, 15, 29 and once-monthly thereafter	- vs. anastrozole (in subjects with progression following endocrine therapy) ORR: 20.3% vs. 14.9% - results in combination with palbociclib or abemaciclib are presented in the corresponding sections above	Risk of bleeding, increased exposure in subjects with hepatic impairment, injection site reaction, and embryo-fetal toxicity
Selective Estrogen-receptor Modulator					
Tamoxifen (NOLVADEX)	Treatment of metastatic breast cancer in women and men	1977	20 mg once daily by mouth	- vs. ablation in premenopausal women ORR, TTF, and OS (HR = 1.00; 95% CI: 0.73, 1.37) were similar - male breast cancer ORR: 50%	Uterine malignancies, stroke, pulmonary embolism, and hot flashes

Source: Drugs@FDA

<u>The FDA's Assessment:</u>

The FDA generally agrees with the applicant's summary of available therapy with the following comments:

The current standard of care for first-line treatment of postmenopausal women with HR-positive, HER2 negative metastatic breast cancer in the United States is a combination of endocrine therapy and a CDK 4/6 inhibitor. An important limitation of the NDA is that only 20 patients (6%) on the SOLAR-1 trial had previously been treated with a CDK 4/6 inhibitor. Of these 20 CDK 4/6-pretreated patients, 9 were randomized to the alpelisib arm. As a result, the agency has very limited data with which to assess the efficacy of alpelisib plus fulvestrant in the CDK 4/6 inhibitor-pretreated population of patients likely to receive fulvestrant plus alpelisib in the postmarketing setting.

Furthermore, while there are no drugs specifically approved for treatment of patients with PIK3CA-mutated, HR-positive, HER2-negative breast cancer, PIK3CA mutations are present in approximately 40% of patients with HR-positive, HER2-negative metastatic breast cancer, and therefore these patients have been well-represented in prior randomized trials of endocrine therapy alone and in combination with other kinase inhibitors such as everolimus and CDK 4/6 inhibitors, as well as treated with these agents in routine clinical practice. The available data do not provide compelling evidence that patients with PIK3CA-mutated tumors derive lesser benefit from the current armamentarium of endocrine-based therapy than unselected patients or those with PIK3CA-wildtype tumors.

Other PI3-kinase inhibitors have been tested in randomized clinical trials, though none are FDA-approved. The BELLE-2 trial was a randomized phase 3 trial that compared the PIK3CA inhibitor buparlisib plus fulvestrant versus placebo plus fulvestrant in 1147 patients with HR-positive, HER2-negative breast cancer, of whom 851 had known PI3K status and 372 had PIK pathway alterations. In the ITT population (n=1147), estimated median PFS was 6.9 months in the buparlisib plus fulvestrant arm versus 5.0 months in the control arm (HR 0.78; p < 0.001). In patients with PI3K pathway-activated tumors (n=372), estimated median PFS was 6.8 months in the buparlisib plus fulvestrant arm versus 4.0 months in the control arm (HR 0.76; 95% CI: 0.60, 0.97). (Baselga et al. 2017) Buparlisib is not approved for any indication in the United States. The SANDPIPER trial was a randomized phase 3 trial that compared the PIK3CA inhibitor taselisib plus fulvestrant versus placebo plus fulvestrant in 516 patients with HR-positive, HER2-negative, PIK3CA-mutated advanced breast cancer. In the ITT population, estimated median PFS was 7.4 months in the taselisib plus fulvestrant arm versus 5.4 months in the control arm (HR 0.7; p<0.01). (Baselga et al. 2018) Taselisib is not approved for any indication in the United States.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Alpelisib (BYL719) is not currently registered (or approved) in the US or in any other part of the world.

The FDA's Assessment:
The FDA agrees with the applicant's assessment.

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

Following input from FDA, several key aspects were incorporated into the Phase III study design. These decisions included, but were not limited to: (1) use of a placebo control, (2) assessment of PFS using RECIST 1.1 by BIRC as a supportive analysis of the primary endpoint, (3) demonstration of effectiveness compared to a standard regimen, (4) assessing safety appropriate for a new small molecule in advanced breast cancer, and (5) monitoring of safety and efficacy by an unblinded, independent DMC during the conduct of the study. Table 2 summarizes the key HA interactions.

Table 2: Key FDA Interactions

Type of meeting	Date	Purpose of meeting
Type B End of Phase II (EOPII) Teleconference	14-May-2015	Discuss the design of intended pivotal Phase III study CBYL719C2301 and adequacy of planned registration components
Type C meeting	07-Dec-2015	Discuss several aspects of the clinical pharmacology program including DDI assessment, thorough QT study, and renal impairment study
Type C meeting	16-Oct-2017	Discuss the plan to demonstrate comparability of the drug substance and drug products utilized in the pivotal Phase III study CBYL719C2301 versus the intended for commercial use; the adequacy of the 150 mg film-coated tablets bio-waiver and the drug product registration stability package
Type C meeting	19-Oct-2017	Discuss the adequacy of the planned data analyses and overall presentation of the data generated from CBYL719C2301 and supportive studies, including pooling strategy, content of electronic datasets, and the planned co-review of a companion diagnostic by CDRH.
Type B Pre-NDA meeting	16-Oct-2018	Discuss adequacy of the data from CBYL719C2301 to assess efficacy and safety of alpelisib when supported by CBYL719X2101 and CBYL719X1101 in the proposed indication. Additionally, discuss the contents of the NDA, proposed submission schedule under RTOR, planned safety update, and diagnostic considerations.

<u>The FDA's Assessment:</u>

The FDA agrees with the applicant's summary of the above key regulatory interactions. (b) (4)

(b) (4)

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

4.1. Office of Scientific Investigations (OSI)

The FDA's Assessment:
Inspections by OSI were requested by Division of Oncology Products 1. The objectives of inspections included the following:

- ***Verify efficacy endpoint of PFS as determined by the clinical investigator per RECIST v1.1.***
- ***Verify Overall Survival***
- ***Evaluate identification, documentation, and reporting of adverse events (AEs)***
- ***Assess general compliance with the investigational plan.***

Each site inspected was to be classified into one of the following categories:

- ***NAI = No deviation from regulations.***
- ***VAI = Deviation(s) from regulations.***
- ***OAI = Significant deviations from regulations. Data unreliable.***

A total of five sites from the SOLAR-1 trial were selected by the clinical review team for inspection by OSI. All five sites were classified by OSI as no deviation from regulations/no action indicated (NAI). The sites, rationale for inspection, OSI findings, and OSI classification are described in further detail below.

1. ***Site 4000:***
   Yen-Shen Lu
   No 7 Chung Shan S Road
   Taipei, Taiwan 10002

   Rationale for Inspection: ***This is a non-ICH site that enrolled 10 patients. The treatment effect size in the investigational arm was noted to be an outlier compared to the overall ITT population.***

   OSI Findings: ***The inspection was conducted between March 4-7, 2019. The site screened 17 patients and enrolled 10 patients. A record review was done for all 17 screened patients. At the time of this inspection, nine patients had completed the study. The inspection included review of patient records including eCRFs, and study source documents including, but not limited to, inclusion/exclusion records, randomization, patient visit reports, investigational product accountability, AEs and SAE documentation, and tumor response assessments. The source data was compared to the data listings submitted to the application. While all source documents matched the eCRFs, not all data points were included in the data listings submitted to the application, specifically the site-***

specific data listings provided by the applicant to support clinical site inspections were incomplete. Briefly, the surgical and medical procedures for certain patients were incomplete. For example:

- ***Cataract refractive surgery and tooth extraction for Patient*** (b) (6) ***was not included in the data listings submitted to the application.***
- ***Patient*** (b) (6) ***had documented sequestrectomy over left the posterior maxilla, packed RBC transfusion, tooth extraction, left sequestrectomy maxillectomy Caldwell Luc operation, transfusion of 2 units of RBC, and a maxillectomy that were not included in the data listings submitted to the application.***
- ***Patient*** (b) (6) ***had documented palliative radiotherapy for the T7-L1 spine that was not included in the data listings submitted to the application.***

The applicant appears to have only reported the first surgical and medical procedure for some of the patients treated at this site. An applicant representative present at the site during the inspection promised a written explanation for this observation.

A written response from the applicant dated 03/06/2019 was forwarded from the FDA field investigator to the OSI reviewer and clinical review team. After a complete review of the written response, both OSI and DOP1 agreed that the response was unclear and did not provide an adequate explanation for the observations. DOP1 sent an IR to the applicant on 03/21/2019 requesting that the applicant clarify the information regarding missing surgical and medical procedures, including, but not limited to, whether any of the missing information affects the safety and efficacy of alpelisib + fulvestrant and if so, for which patients. A written response from the applicant, dated 03/22/2019, explained that the structure of the 'Surgical and Medical Procedures' eCRF had incorrect flagging of these records during the programming of four CSR tabular summaries and listings. As a result, 272 records from the ADCM dataset were inadvertently excluded from Table 14.3-2.2 (Surgical and medical procedures by system organ class, preferred term and treatment [Safety Set]) and Listing 16.2.4-1.9 (Surgical and medical procedures [Safety Set]) and were included instead in Table 14.3-2.1 (Concomitant medications prior to or after the start of study drug by ATC class, preferred term and treatment [Safety Set]) and Listing 16.2.4-1.8 (Prior and concomitant medications [Safety Set]) in the CSR. However, the applicant confirmed that the electronic datasets provided to the FDA under NDA 212526 are complete and contain all available records.

A review of the updated listings (Listing 16.2.4-1.8 [Prior and concomitant medications Safety Set] and Listing 16.2.4-1.9 [Surgical and medical procedures Safety Set]) found that the missing procedures noted above for Patients (b) (6) ***were included. The inspectional observations should have no impact on overall study outcomes or have placed patients at undue risk.***

Therefore, the datasets submitted to the application included all procedures as reported; however, the BIMO data listings submitted to the NDA and used to support the

inspections of clinical sites were incomplete for all clinical sites for Study CBYL719C2301 and, as such, the FDA field investigator could not verify that the noted surgical procedures were properly reported in the application datasets.

The inspection revealed no significant deficiencies for this clinical site. The primary efficacy endpoint data, as determined by the clinical investigator, were verifiable with the source records maintained at the site. There was no evidence of under-reporting of AEs.

OSI Classification: No action indicated (NAI).

2. ***Site 2402:***
   Bella Kaufman
   Tel Hashomer Ramat Gan
   Ramat Gan, Israel 5272100

   Rationale for Inspection: This is a non-ICH site that enrolled 12 patients. The death rate was higher than expected in both arms at this site.

   OSI Findings: The inspection was conducted between February 17-19, 2019. The site screened 16 patients and enrolled 12 patients. A record review was done for all 12 patients. At the time of this inspection 10 patients had completed the study and two patients were in follow-up.

   Documents reviewed during the inspection included ethics committee approvals, financial disclosures, training records, monitoring letters, informed consent forms (ICFs), patient records, case report forms, and test article accountability records. All patient records were reviewed in full. Patient source documents, including the primary efficacy endpoint, concomitant medications, adverse events (AEs), serious adverse events (SAEs), and randomization were compared to the data line listings submitted to the application.

   The inspection revealed no significant deficiencies. The primary efficacy endpoint data, as determined by the clinical investigator, were verifiable with the source records maintained at the site. There was no evidence of under-reporting of AEs.

   The inspection did not identify any objectionable conditions or practices that would justify enforcement action by the Office of Compliance.

   OSI Classification: No action indicated (NAI).

3. ***Site 2401:***
   Salomon Stemmer
   39 Jabotinsky St. Davidoff Center POB 85

Petach Tikva, Israel 49100

<u>Rationale for Inspection</u>: This is a non-ICH site that enrolled 7 patients. The number of SAEs was unexpectedly low in both arms for the number of patients enrolled.

<u>OSI Findings</u>: The inspection was conducted between February 24-26, 2019. The site screened 18 patients and enrolled seven patients. A record review was done for all seven enrolled patients. At the time of this inspection two patients were still on study, three patients had completed the study, and two patients were in follow-up.

Documents reviewed during the inspection included ethics committee approvals, financial disclosures, training records, monitoring letters, informed consent forms (ICFs), patient records, case report forms, and test article accountability records. All patient records were reviewed. Patient source documents, including the primary efficacy endpoint, concomitant medications, AEs, SAEs, and randomization were compared to the data line listings submitted to the application.

The inspection revealed no significant deficiencies. However, there were nine AEs that occurred prior to the data cut-off date for analysis, June 12, 2018, but were not entered into the eCRF system until after June 12, 2018. The AEs missing from the data listings submitted to the application are presented below.

Patient #	***Adverse Event***	***Start Date***
(b) (6)	***Dizziness***	(b) (6)
	Weight Loss	
	Face Rash	
(b) (6)	***Migraine***	
	Diarrhea	
	Worsening Hypertension	
(b) (6)	***Right Leg Pain***	
	Weight Loss	
	Alkaline Phosphatase Increase	

A review of the SDTM AE dataset (ae.xpt), the most recent AE dataset submitted to the application, 02/15/2019, found that all AEs listed above are now included in the data sets except for Patient (b) (6) ***and Patient*** (b) (6) ***It should be noted that Patient*** (b) (6) ***had elevated aspartate aminotransferase reported on*** (b) (6) ***and elevated alkaline phosphatase reported on*** (b) (6) ***As of*** (b) (6) ***this site reported a total of 172 AEs for the seven enrolled patients; not including the 2 AEs found to be missing from the datasets. These patients were medically managed for the AEs noted as missing from the datasets. The number of missing AEs was small (9) relative to total number of AEs reported for the***

study (8144) and would not impact study outcomes or overall risk-benefit assessment. Except for the late reporting of 9 AEs, there were no other significant deficiencies at this site. The primary efficacy endpoint data, as determined by the clinical investigator, were verifiable with the source records maintained at the site. There was no evidence of under-reporting of AEs.

The inspection did not identify any objectionable conditions or practices that would justify enforcement action by the Office of Compliance.

OSI Classification: No action indicated (NAI).

4. ***Site 2203:***
   Gabor Rubovszky
   Rath Gyorgy u. 7-9
   Budapest, Hungary H-1122

   Rationale for Inspection: This was a high enrolling site with 14 patients. The number of SAEs reported was unexpectedly low in both arms.

   OSI Findings: The inspection was conducted between March 4-8, 2019. The site screened 25 patients and enrolled 14 patients. A record review was done for all enrolled patients. Study source documents were compared to data listings submitted to the application. All enrolled patient data were verified for primary efficacy endpoint, informed consents, randomization, and investigational product administration and compliance.

   The inspection revealed no significant deficiencies. The primary efficacy endpoint data, as determined by the clinical investigator, were verifiable with the source records maintained at the site. There was no evidence of under-reporting of AEs.

   OSI Classification: No action indicated (NAI).

5. ***Site 5049:***
   Michelle Melisko
   1600 Divisadero Street
   San Francisco, CA 94115 USA

   Rationale for Inspection: This was a US site that enrolled 5 patients and is more likely to be representative of the US population than the other sites selected for inspection. There were no SAEs reported in either arm.

   OSI Findings: The inspection was conducted between February 20-22, 2019. The site screened 16 patients and enrolled four patients, plus one patient who was transferred from another site. A record review was done for all 5 patients treated at this site. At the

time of this inspection, all five patients had completed the study. The FDA field investigator assessed study documents maintained by the site, including applicant and IRB correspondences, monitoring visits and site staff training during the site initiation visit, signed informed consent forms for all patients and drug accountability records. Patient source data were compared to the data listings submitted to the application; including inclusion/exclusion records, randomization, patient visit reports, AE and SAE documentation, tumor response assessments and general protocol compliance. No discrepancies were noted.

The inspection revealed no significant deficiencies. The primary and secondary efficacy endpoint data, as determined by the clinical investigator, were verifiable with the source records maintained at the site. There was no evidence of under-reporting of AEs. The inspection did not identify any objectionable conditions or practices that would justify enforcement action by the Office of Compliance.

OSI Classification: No action indicated (NAI).

4.2. Product Quality

The FDA's Assessment:

Assay stability, physical stability, dosing accuracy, palatability, microbial limits, leachables, dissolution, and other attributes were reviewed, and the Product Quality review team recommends approval. Refer to the 3/20/2019 review of NDA 212526 by Dr. Anamitro Banerjee for further details.

4.3. Clinical Microbiology

The FDA's Assessment:

Not applicable.

4.4. Devices and Companion Diagnostic Issues

The FDA's Assessment:

Refer to the CDRH review by Drs. Francisca Reyes-Turcu, Deb Chatterjee, Soma Ghosh, and Reena Philip for full details.

The applicant partnered with Qiagen to submit a PMA of the therascreen PIK3CA RGQ PCR Kit (P190004) for the qualitative detection of defined mutations in the phosphatidylinositol 3-kinase catalytic subunit alpha (PIK3CA) gene (Exon 7: C420R; Exon 9: E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R; and Exon 20: H1047L, H1047R, H1047Y) from

circulating tumor DNA (ctDNA) isolated from K_2EDTA plasma from breast cancer patients, and Exon 7: C420R; Exon 9: E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R; and Exon 20: H1047L, H1047R, H1047Y mutations from formalin-fixed, paraffin-embedded (FFPE) breast tumor tissue for treatment with alpelisib. Patients whose FFPE tissue or plasma sample produce a positive therascreen PIK3CA RGQ PCR Kit test result for the presence of one or more PIK3CA mutations are eligible for treatment with alpelisib. Patients whose plasma sample produces a negative result using this test should be reflexed to testing for the presence of PIK3CA mutations with FFPE tumor tissue. The positive percent agreement (PPA) of the plasma test for 11 mutations compared to tissue test was 179/328 (54.6%) in the concordance analysis. This represents only slightly more than half of the tissue positive samples, which causes concern. The low PPA may be in part attributed to variables such as low tumor shedding. The negative percent agreement (NPA) was 97.2% (209/215), which is reasonable. However, the PPA of the tissue test compared to the plasma test, raises concern, which has necessitated reflex testing language. Note that 5 (H1047Y, Q546R, Q546E, E545D, and E545A) of the 11 mutants are not detected by PIK3CA kit using plasma from clinical samples.

There were 341 patients enrolled by tumor tissue in the cohort with a PIK3CA mutation and 231 enrolled in the cohort without a PIK3CA mutation. Of the 341 patients in the cohort with a PIK3CA mutation, 336 (99%) patients had one or more PIK3CA mutations confirmed in tumor tissue using the FDA-approved therascreen® PIK3CA RGQ PCR Kit. Out of the 336 patients with PIK3CA mutations confirmed in tumor tissue, 19 patients had no plasma specimen available for testing with the FDA-approved therascreen® PIK3CA RGQ PCR Kit. Of the remaining 317 patients with PIK3CA mutations confirmed in tumor tissue, 177 patients (56%) had PIK3CA mutations identified in plasma specimen, and 140 patients (44%) did not have PIK3CA mutations identified in plasma specimen. Clinical efficacy of alpelisib in combination with fulvestrant for the PIK3CA Kit-positive population (HR = 0.64, 95% CI: 0.48, 0.85) was similar to the clinical efficacy in the SOLAR-1 PIK3CA mutant cohort (HR = 0.65; 95% CI: 0.50, 0.85).

The data support the reasonable assurance of safety and effectiveness of the device when used in accordance with the indications for use. The use of this device to aid clinicians in identifying advanced breast cancer patients who may be eligible for treatment with alpelisib based on a PIK3CA mutation detected result is expected to provide a benefit in progression-free survival of approximately five months. There is some uncertainty to this assessment based primarily on analytical performance factors of the device. Accordingly, post-market commitments with respect to the following analytical studies will be required: precision (repeatability and reproducibility), certain interference studies (adipose tissue), PIK3CA Kit reagent stability.

In summary, considering all factors including conditions of approval (postmarket actions), the benefits of the use of QIAGEN therascreen® PIK3CA RGQ PCR Kit in patients with breast carcinoma are judged to outweigh the risks.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The FDA's Assessment:

PIQRAY (alpelisib, BYL719, NVP-BYL719) is a kinase inhibitor with inhibitory activity predominantly against the α-isoform of class I phosphatidylinositol-3-kinase (PI3K). Gain-of-function mutations in the gene encoding the catalytic α-subunit of PI3K (PIK3CA) leads to activation of PI3Kα and downstream signaling, cellular transformation, and tumorigenesis. In this NDA, the applicant submitted study reports and literature for nonclinical pharmacology, pharmacokinetics, and toxicology studies to support the approval of PIQRAY in combination with fulvestrant for the treatment of advanced HR-positive, HER2-negative, PIK3CA-mutated advanced breast cancer.

In pharmacology studies, alpelisib demonstrated higher activity against the α-isoform of PI3K compared to β, δ, and γ isoforms. Alpelisib inhibited phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (p110α) kinase activity with IC50 values in the nanomolar range in in vitro biochemical kinase assays and cell-based assays. Alpelisib showed similar activities against mutant p110α (H1047R, E545K) compared to wild type (WT) p110α in biochemical kinase assays; however, in cell-based assays it had higher kinase inhibitory activity in PIK3CA-mutated cell lines compared to WT cell lines. Cell viability assays showed that a higher percentage of PIK3CA-mutant cancer cell lines were sensitive to alpelisib treatment compared with PIK3CA-wildtype cell lines tested. In vitro, luminal estrogen receptor (ER)-positive or HER2 amplified sub-types of human breast cancer cell lines were more sensitive to alpelisib than other subtypes of breast cancer; overall, sensitivity to alpelisib was observed in ER+/HER2-, HER2+/ER- or HER2+/ER+ cell lines though the proposed indication is for HR-positive, HER2-negative, advanced breast cancer. In vivo, single agent alpelisib showed anti-tumor activity in mouse xenograft models of breast cancer, including the ER-positive breast cancer models with PIK3CA mutations, and the observed anti-tumor activity correlated with inhibition of PI3K/Akt pathway. Inhibition of PI3K in breast cancer cell lines using alpelisib was shown to induce an increase in ER expression and activity. The combination of alpelisib and fulvestrant demonstrated an increase in anti-tumor activity in vivo in ER-positive breast cancer models with PIK3CA mutations compared to fulvestrant or alpelisib alone. In addition, alpelisib in combination with fulvestrant was effective in mouse xenograft models of ER-positive breast cancer cell lines with acquired resistance to everolimus (mTORC1) treatment or CDK4/6 inhibitor treatment. Overall, the available in vitro and in vivo pharmacology data provided a scientific basis and mechanism of action of using alpelisib in combination with fulvestrant in HR-positive, HER2-negative advanced breast cancer with a PIK3CA mutation. The approved Established Pharmacologic Class (EPC) of "kinase inhibitor" is applicable to alpelisib based on its pharmacologic activity.

Secondary pharmacology studies indicate the potential inhibitory function of alpelisib on

adenosine receptors, in particular Ad3 receptor. As Ad3 has been implicated in inhibiting inflammation (Jacobson et al 2018; Pnina Fishman et al 2012), inhibition of this receptor may result in pro-inflammatory responses. Alpelisib was also shown to cause hyperglycemia and insulin insensitivity in animals, in secondary pharmacology studies. A single oral administration of alpelisib induced a dose-independent increase in systolic and diastolic blood pressure in dogs at all doses tested (5, 15, 30 mg/kg) in the conducted safety pharmacology study. Alpelisib had no adverse effects on ECG, respiration, or neurological behavior in animals.

Nonclinical ADME studies indicated distribution of radioactivity to hair and eyes of pigmented rats, thus alpelisib and/or its metabolites can bind melanin. This can explain findings of skin toxicities in animals and patients, as well as ocular toxicities in animals. The main metabolic pathway was amide hydrolysis, forming metabolite M4 (BZG791) in mouse, rat, dog and human hepatocytes. Alpelisib was the primary component in plasma, and BZG791 is a primary metabolite (26.7% of total circulating drug related material) in human. BZG791 is an inactive metabolite and is not genotoxic. There was adequate exposure to BZG791 in animal studies. The systemic exposure of BZG791 (about 4% of total circulating drug related material) in male rats at 30 mg/kg in the 4-week toxicology study was a little over the human exposure to BZG791 at the recommended dose. No separate safety assessment is needed for metabolite BZG791 considering the proposed indication and the available nonclinical data with BZG791.

Daily oral administration of alpelisib was assessed in repeat-dose toxicity studies for up to 3 months in rats and dogs, consistent with the clinical route of administration and intended dosing schedule. The pivotal repeat-dose toxicology studies were conducted in compliance with Good Laboratory Practice regulations (21 CFR part 58). Administration of alpelisib to rats and dogs resulted in adverse effects in the GI tract, hemolymphoid system, skin, metabolic, and reproductive system. The effects in the GI tract and skin included inflammatory responses, and epithelial or epidermal atrophic changes. The effects in the hemolymphoid system included inflammation and/or suppressive effects in the bone marrow, spleen, thymus, or lymph nodes. The changes in the reproductive system involved the male and female reproductive organs and associated tissues including vaginal epithelial atrophy and atypical estrous cycle phases with uterine atrophy in female rats and decreased prostate weight and glandular atrophy in male dogs. Administration of alpelisib to rats and dogs increased blood insulin and glucose levels, which correlated with histopathologic changes in the pancreas (vacuolation or hyperplasia of endocrine cells). The other changes related to alpelisib included atrophy in mammary gland and lacrimal glands in rats; odontoblast degeneration with dentin thinning and pulpa necrosis; thickening and decreased metaphyseal trabecular bone density in rats; and ocular toxicities including cornea vacuole/cornea vesicle in rats and increased mitotic figures in the cornea in dogs. Most alpelisib-induced toxicities were dose-dependent and generally reversible after a 4- or 8-week treatment-free recovery period. The toxicity profile in animals was similar to that in patients treated with PIQRAY. The most observed toxicologically relevant changes were associated with the pharmacologic

activity of alpelisib.

Alpelisib did not induce mutations in the bacterial reverse mutation (Ames) assays and was not genotoxic in either the in vitro micronucleus and chromosome aberration tests or the in vivo rat micronucleus assay at 20 mg/kg, the top dose tested (1.7x human exposure based on AUC).

No fertility and early embryonic development studies have been conducted or are warranted to support the proposed indication. In repeated-dose toxicity studies in rats and dogs with alpelisib, histopathological changes observed in reproductive organs suggest that alpelisib has the potential to impair male or female fertility. Adverse findings in animals included vaginal atrophy and estrous cycle variations in rats at ≥ 6 mg/kg following 13 weeks of treatment with an AUC of 18700 hr*mg/mL (0.6x human exposure based on AUC at the recommended dose), and prostate atrophy and testicular hypocellularity in dogs at 15 mg/kg following 4 weeks of treatment with an AUC of 85700 hr*mg/mL (2.6x human exposure based on AUC at the recommended dose).

In embryo-fetal toxicity studies, administration of alpelisib at doses of 3, 10, and 30 mg/kg/day to pregnant rats from GD 6 to 17 resulted in maternal body weight loss at 30 mg/kg/day and a dose-related decrease in body weight gain at 3 and 10 mg/kg/day. Females administered 30 mg/kg/day (HD) had no viable fetuses at scheduled necropsy due to increased post-implantation losses. The maternal systemic exposure at 30 mg/kg is about 3x the human exposure (AUC) at the recommended dose of 300 mg/day. Reduced fetal weight and increased numbers of litters with fetal malformations (bent scapula and thickened or bent long bones) and fetal variations including enlarged brain ventricle at 10 mg/kg (MD), with an AUC of 26,600 ng.h/mL, about 0.8x human exposure (AUC) at the recommended dose of 300 mg/day. In a non-GLP study in rabbits, alpelisib was orally administered at dose levels of 3, 15 and 25 (or 30) mg/kg/day from GD 7 to 20. Maternal body weight loss associated with reduced food intake was observed at 30 or 25 mg/kg/day. Increased embryo-fetal deaths and malformations (acaudia and/or short tail and misshapen head) were observed at ≥ 15 mg/kg/day. The systemic exposure (AUC) to alpelisib in rabbits at 15 mg/kg was 170,000 ng·h/mL, about 5x human exposure (AUC) at the recommended dose of 300 mg/day. The human AUC used to calculate animal to human exposure margins was 33200 ng·h/mL at the recommended dose of 300 mg/day.

Based on findings in animals and mechanism of action, alpelisib can cause fetal harm when administered to a pregnant woman. In general, reproductive toxicology studies are not warranted when the patient population consist of postmenopausal women. However, since the data on embryofetal toxicity is available, the pharmacology/toxicology team recommends adding this information in the product label. Females of reproductive potential and male patients with female partners of reproductive potential should use effective contraception during treatment with alpelisib and for one week after the last dose, which covers a period of at least 5 half-lives for alpelisib ($T_{1/2}$ = 8 to 9 h). The applicant

recommended that male patients use condoms and effective contraception due to potential exposure of a female partner of reproductive potential to alpelisib. Because of the potential for serious adverse reactions in a breastfed child, lactating women should not breastfeed during treatment with PIQRAY and for one week after the last dose. PIQRAY is indicated in combination with fulvestrant. Therefore, the alpelisib prescribing information includes a reference to the fulvestrant prescribing information for pregnancy, contraception, infertility, and lactation information.

No carcinogenicity studies were conducted or warranted to support this NDA, as the proposed indication was for advanced cancer.

The nonclinical data submitted in this NDA are adequate to support approval for the oral daily use of alpelisib for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

There are no referenced NDAs, BLAs, or DMFs related to nonclinical pharmacology or toxicology for alpelisib.

5.3. Pharmacology

The Applicant's Position:

Alpelisib (BYL719) potently inhibits both wild type and mutated forms of p110α ≥ 50x compared to inhibition of the β, δ, and γ isoforms of PI3K. In vitro, alpelisib showed selectivity towards cell lines harboring a PIK3CA mutation (Huang et al 2012). In vivo, alpelisib treatment showed dose and time-dependent inhibition of the PI3K/Akt pathway and dose-dependent tumor growth inhibition in relevant tumor xenograft models, including models of breast cancer. In in vivo studies in estrogen receptor positive (ER+) breast cancer xenograft models, combination of alpelisib and fulvestrant demonstrated increased anti-tumor activity compared to fulvestrant alone (Bosch et al 2015). Combination of alpelisib with fulvestrant was also shown to be effective in ER+ breast cancer cell line xenografts progressing on everolimus (mTORC1) treatment or cyclin-dependent kinase (CDK)4/6 inhibitor treatment (O'Brien et al 2017).

Primary pharmacology:
In biochemical assays, alpelisib inhibited p110α (IC50 = 4.6 nM) much more potently than the p110δ (IC50 = 290 nM) and γ-isoforms (IC50 = 250 nM) with weak activity against p110β (IC50 = 1156 nM) (Fritsch et al 2014). Alpelisib was equipotent against the most common somatic mutations of p110α (H1047R, E545K) compared to wild type p110α. The compound lacked activity against the class III family member Vps34, the related class IV Phosphatidylinositol 3-kinase-related kinases (PIKKs) protein kinases mTOR, deoxyribonucleic acid-dependent protein kinase (DNA-PK) and ataxia-teleangiectasia mutated and Rad3-related (ATR) and was significantly less potent against the distinct lipid kinase PIK4β. The kinase

selectivity profile of alpelisib was further examined in an in vitro kinase assay panel. The IC50 or dissociation constant (Kd) values of alpelisib for all the kinases tested (excluding class I PI3K and PI4Kβ) were at least 50-fold higher when compared to PI3Kα.

In vivo data in TSC1 null mice suggested that alpelisib does not inhibit mTORC1. Similarly, alpelisib does not appear to interfere with the PIKKs involved in DNA-damage repair processes.

Alpelisib was also profiled across a panel of 474 cancer cell lines (Barretina et al 2012). Alpelisib showed markedly selective efficacy in PIK3CA mutated cell lines when compared to wild-type cell lines, and when compared to pan-PI3K inhibitors (Fritsch et al 2014).

Alpelisib was tested in a separate panel of 41 human breast cancer cell lines. Luminal ER+ or HER2 amplified sub-types were more sensitive to alpelisib than other subtypes of breast cancer, with the 16 most sensitive cell lines being ER+/HER2-, HER2+/ER- or HER2+/ER+. Eight of the 16 most sensitive cell lines harbored PIK3CA mutations (O'Brien et al 2014).

In vivo, alpelisib showed time-dependent inhibition of the PI3K/Akt pathway (p110α-mechanistic model and p110α-mutant xenograft models) in nude mice and rats. In Rat1-myr-p110a tumor-bearing nude mice, alpelisib induced significant dose dependent anti-tumor effect which correlated with inhibition of Akt phosphorylation (Fritsch et al 2014). In the in vivo BT-474 luminal B breast tumor bearing mice model which harbors a K111N mutation in PIK3CA and an ERBB2 amplification, a single dose of alpelisib inhibited Akt phosphorylation at 70% up to 6 hours. These data were confirmed when alpelisib was administered to mice bearing a diverse range of breast cancer tumor xenografts, including the ER-positive breast cancer mouse models with PIK3CA mutations as well as additional breast cancer patient-derived xenograft (PDX) models (Fritsch et al 2014). The in vivo activity of alpelisib was further investigated in models of ER+ and HER2+ breast cancer. All tested models displayed tumor control with single agent treatment (O'Brien et al 2014).

The combination of alpelisib and fulvestrant was demonstrated in vivo in ER positive breast cancer models with PIK3CA mutations. The combination of alpelisib and fulvestrant demonstrated an increased anti-tumor activity compared to fulvestrant alone in two xenograft models derived from cell lines MCF-7 and KPL1 (Bosch et al 2015). In the MCF-7 derived xenografts, the combination of alpelisib and fulvestrant led to a marked tumor regression.

Combination of alpelisib with fulvestrant was also shown to be effective in ER+ breast cancer cell line xenografts progressing on everolimus (mTORC1) treatment or CDK4/6 inhibitor treatment. In the MCF7 PIK3CA mutated model with acquired resistance to everolimus, the combination of alpelisib and fulvestrant induced increased inhibition of tumor progression relative to either single agent. Mice with tumors (EFM19 PIK3CA mutated) progressing on palbociclib plus fulvestrant showed significant regressions in engrafted tumors when switched to alpelisib plus fulvestrant. Similarly, ER+ breast cancer cell line xenografts (HCC1500 PIK3CA WT) progressing on ribociclib plus fulvestrant showed a significant reduction in the rate of tumor progression when switched to alpelisib plus fulvestrant. Finally, ER+ breast cancer cell

line xenografts (KPL1 PIK3CA mutated) that show de novo resistance to ribociclib were found to be significantly more sensitive to alpelisib plus fulvestrant (O'Brien et al 2017).

Taken together, these pre-clinical in vivo data support the development of alpelisib in combination with fulvestrant in ER+ breast cancer in tumors with a PIK3CA mutation, with or without prior mTOR or CDK4/6 inhibitor treatments.

The FDA's Assessment:

The applicant uses terminology such as "potent", "markedly selective", and "marked" to describe results of pharmacology studies; such terms should be avoided as they are vague, subjective, and promotional.

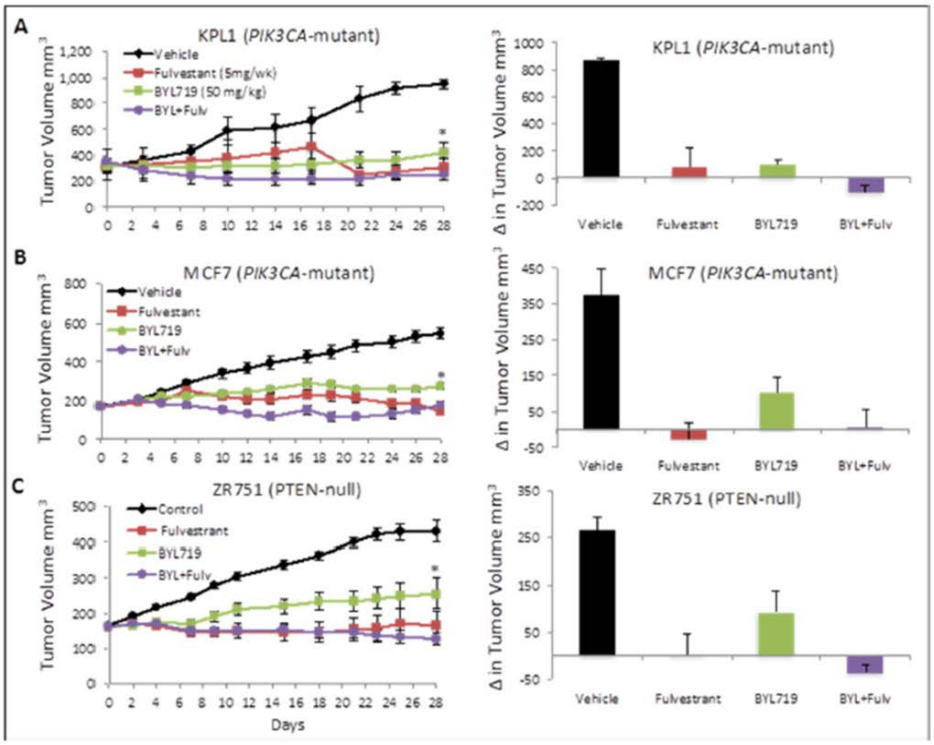
In vitro kinase activity: the FDA agrees with the study results summarized by the applicant and have additional study results presented in the following paragraphs.

In vitro biochemical activity assays (Study RD-2009-00368) were conducted using recombinant PI3Kα, PI3Kβ, PI3Kγ, PI3Kδ, Vps34, PI4Kβ, and the kinase activities were determined by a luminescence assay based on ATP consumption. The IC50 values of alpelisib for PI3K subtypes (α, β, δ, and γ), Vps34 and PI4Kβ were 0.01 µM, 1.16 µM, 0.06 µM, 0.56 µM, >10µM and 0.58 µM, respectively. These data indicate that the inhibitory effect of alpelisib on PI3Kα isoform was 6-fold higher compared to its effect on isoform δ and greater than 50-fold on other isoforms based on IC50s. In a cell based in vitro assay with Rat1-myr-p110 cells, NVP-BYL719 (alpelisib) inhibited p110α activity with IC50 values of 74 nM. IC50 values against p110β and p110δ isoforms were 2.2 µM and 1.2 µM, respectively (Study RD-2011-00523).

In vitro anti-cancer activity: There were insufficient data to support the Applicant's statement of markedly selective efficacy of alpelisib in PIK3CA-mutated cell lines compared to wildtype cell lines. Cell viability assays were conducted with alpelisib on 474 cancer cell lines. Sixty-five percent of PIK3CA mutant cell lines tested were sensitive to alpelisib treatment with IC50 values below 3 µM, while 23% of PIK3CA WT cells lines tested were sensitive to alpelisib treatment (Fritsch et al 2014).

In vivo anti-tumor activity: Another study (Study RD-2017-00437) showed that the combination of BYL719 and fulvestrant had similar anti-tumor activity compared with the treatment using 50 mg/kg daily dose of BYL719 alone or 5 mg once per week dose of fulvestrant alone (see the figure below, copied from the applicant's submission). Note that higher doses were used in this study and better anti-tumor activities were shown in the single agent treatment.

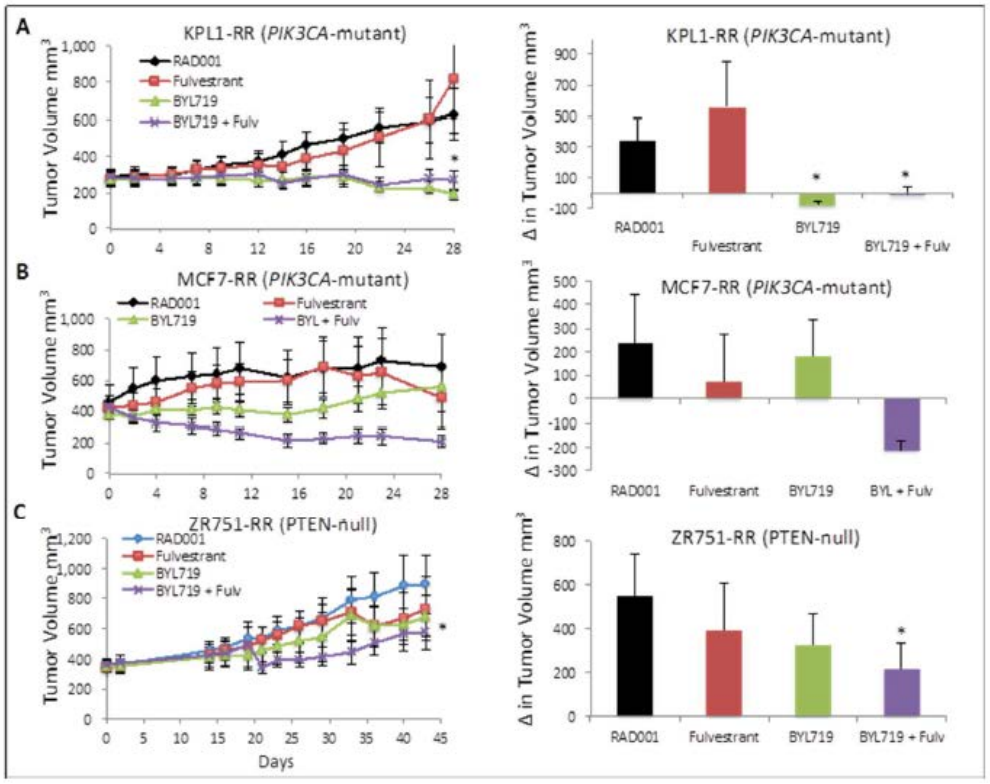
BYL719 in vivo efficacy in ER+ breast cancer



[Excerpted from Applicant's submission]

The FDA agrees that the combination of BYL719 and fulvestrant reduced tumor progression relative to either single agent in the MCF7 PIK3CA mutated and PTEN-null ZR751 xenograft models with acquired resistance to everolimus (Study RD-2017-00437). The FDA notes that single agent treatment with BYL719 or the combination treatment with BYL719 and fulvestrant showed similar inhibition of tumor progression in the KPL1 PIK3CA mutant xenograft model of acquired resistance to everolimus. The study results are shown in the figure below (copied from the applicant's submission).

BYL719 in vivo efficacy in everolimus (RAD001) resistant ER+ breast cancer.



[Excerpted from the applicant's submission]

The FDA agrees with the applicant's provided summary of anti-tumor activity of alpelisib and fulvestrant in xenograft models of CDK 4/6 inhibitor-resistant, ER+ breast cancer.

Secondary pharmacology:

Alpelisib was assessed for its off-target activity by binding assays on 143 GPCRs, transporters, ion channels, nuclear receptors and enzymes. Activities of > 50% inhibition at 10 µM were found only on the adenosine receptor Ad3 (IC50 = 2.25 µM, Ki = 2.15 µM, n = 2) and slightly weaker on the adenosine Ad1 receptor (IC50 = 15 µM, Ki = 13 µM) and phosphodiesterase PDE4d (IC50 = 13 µM), At maximum recommended therapeutic dose levels of 300 mg/day, a mean Cmax of 2900 ng/mL is achieved. As the protein-unbound fraction in humans is 10.8%, an unbound mean Cmax of 313 ng/mL is obtained at that dose, which provides a sufficient safety margin versus those off-targets identified in vitro. In addition to those off-targets screened, secondary pharmacodynamic effects were observed known to be associated with the pharmacological activity of alpelisib as a PI3K inhibitor. As such, as a result of inhibition of the insulin signaling pathway, insulin insensitivity was consistently observed across species, with the induced hyperglycemia partially compensated by hyperinsulinemia, and generally reversible upon treatment cessation. Clinically, hyperglycemia can be effectively managed by

pharmacological intervention. Further, inhibition of VEGF signaling and neovascularization have been observed with PI3K inhibitors (Graupera and Potente 2013).

The FDA's Assessment:

The FDA agrees with the off-target activity assay results of alpelisib on adenosine Ad3 receptor, adenosine Ad1 receptor, and PDE4d and the effects of alpelisib on glucose homeostasis. Maximum recommended therapeutic dose levels of 300 mg/day results in a total Cmax of 2480 ng/mL (approximately 5.6 µM). While there is about 3-fold safety margin using data from unbound alpelisib at the 300 mg/day dose (unbound Cmax of 313 ng/mL, ≈ 0.7µM) for binding to adenosine receptor Ad3 (IC50 = 2.25 µM) , there is no margin of safety using the total Cmax value. In addition, alpelisib may possibly have an effect on serotonin 5HT2A receptors as activities of >50% inhibition of 5HT2A receptors at 10 µM (IC50 = 6.7 µM) were found with drug batch NX-1, though the results were not confirmed with drug batch NX-2 in a repeated experiment.

To test whether BYL719 is less immunosuppressive than pan-class I PI3K inhibitors, the effects of BYL719 on anti-IgD-induced B cell activation and T cell-dependent antibody responses were assessed in Balb/c mice. B cell activation was determined by measuring CD86 expression, following stimulation with anti-IgD antibodies, and T cell-dependent antibody responses were measured following immunization with DNP-KLH (Study RD-2009-00527). A single oral administration of the pan-PI3K inhibitor NVP-CAA224 prevented B cell activation and reduced IgG and IgM serum levels in a dose-dependent manner. A single dose of 12.5 or 25 mg/kg BYL719 inhibited anti-IgD induced upregulation of CD86 by 29 and 47%, respectively. The clinical relevance of a 47% inhibition of B cell activation by BYL719 is unknown. Daily dosing with 12.5 or 25 mg/kg BYL719 for 7 days did not affect the IgG response to immunization with DNP-KLH but IgM levels were reduced by ~70% at 25 mg/kg.

An in vivo pharmacology study (Study RD-2010-00184) showed that NVP-BYL719 had dose-dependent inhibitory effects on the growth of vascularized tissue induced by human VEGF or bFGF.

Safety pharmacology

The Applicant's Position:

Nervous and respiratory systems function
In rats, functional observations and measurements conducted as part of the Functional Observational Battery (FOB) did not reveal any relevant changes in males at a single dose of 80 mg/kg, compared to controls, and no biologically relevant changes were observed upon respiratory measurements using plethysmography.

Cardiovascular function
In vitro: In a single-concentration hERG channel patch clamp screening test using HEK293 cells stably transfected with the channel, no significant inhibition was seen at 10 µM (4.4 µg/mL). In a GLP test using the same cell type, BYL719 inhibited hERG current with an IC50 of 9.4 µM (4.2 µg/mL).

In vivo: In electrocardiographic readouts using standard surface recorded ECGs in dogs, within 2- and 4- and 13-week repeated dose studies and a single rising dose study up to 180 mg/kg there were no treatment-related ECG effects.

In a single-dose invasive telemetry study in dogs, dose-independent, minimal to slight and transient increases in systolic and diastolic blood pressure with a compensatory slight decrease in heart rate was seen, in the absence of any electrophysiological abnormality.

In summary, the data indicate the absence of a relevant electrophysiological risk, but treatment with BYL719 was associated with slight, transient arterial blood pressure increase in dogs.

The FDA's Assessment:

The FDA agrees that no adverse effects on ECG, respiration, or neurological behavior were observed in the conducted safety pharmacology studies. There is however a potential for drug-related increased blood pressure. The applicant submitted data from a GLP-compliant single-dose telemetry study in dogs. Four healthy telemetered male dogs received a single dose of the vehicle or test item formulation at doses of 5, 15, and 30 mg/kg with a treatment-free period between each dosage of at least 6 days. The electrocardiogram, arterial blood pressure and core body temperature were recorded for 2 minutes every 15 minutes, beginning about 1 hour before administration and ending about 21 hours post-dose. BYL719 treatment was associated with a dose-independent increase in systolic and diastolic blood pressure of approximately 10% (≤ 10 mm Hg) starting 1-hour post dose and ending 8 hours post dose. This finding corresponded with a dose-independent decrease of approximately 10% (≤ 10 beats per minutes) in heart rate starting 1-hour post dose and ending 20 hours post dose. The changes in heart rate were secondary to the increase in arterial blood pressure. These findings suggest that BYL719 could have some effects on blood pressure; however, the changes were transient and mild and no changes on heart rate were observed in the repeat dose toxicity studies in dogs (4-week and 13 week).

5.4. ADME/PK

Absorption *Absorption, distribution, metabolism and excretion in rats after oral (15 mg/kg) and intravenous (3.4 and 5 mg/kg) administration of [^{14}C]BYL719: DMPK R0900368*
Alpelisib was rapidly absorbed after p.o. dosing, with a Tmax of 0.5h for both alpelisib and total radioactivity. Absorption was estimated to be 62.5%. Bioavailability was

calculated to be 57.3%, indicating a negligible first pass effect. The systemic half-life of alpelisib was short, at 1.5h.
Distribution *Absorption, distribution, metabolism and excretion in rats after oral (15 mg/kg) and intravenous (3.4 and 5 mg/kg) administration of [^{14}C]BYL719: DMPK R0900368* *QWBA and metabolism in male rats after single oral (15 mg/kg) and intravenous (5 mg/kg) administration of [^{14}C]BYL719: DMPK R1100487*
After both i.v. and p.o. administration to albino rats, ^{14}C-alpelisib-derived radioactivity distributed rapidly throughout the body with highest tissue concentrations in liver (and bile), kidney, and harderian gland. Tmax in most tissues was achieved at 15 minutes and 1 hour post dose after i.v. and p.o. administration, respectively. The ^{14}C-alpelisib-derived radioactivity observed in the intestinal walls indicate active secretion into the lumen of the GI tract, which is in line with the excretion data observed in bile duct-cannulated rats. The distribution in partially pigmented rats (DMPK R1100487) was similar to the albino rats, with the exception that higher levels of radioactivity were detected in melanin containing structures (eye choroid, hair follicle and skin). However radioactivity levels in these structures declined with time, suggesting that ^{14}C-alpelisib-derived radioactivity undergoes specific but reversible binding to melanin. No evidence for brain penetration of alpelisib related material was observed.
Metabolism *In vitro biotransformation of [14C]BYL719: Species comparison using hepatocytes of rat, dog and human: DMPK R0900574*
In hepatocytes from all species, the most important metabolic pathway (based on radiopeak abundance in the metabolic profile) was amide hydrolysis, forming metabolite BZG791. Other phase I metabolites observed were formed by C hydroxylation (M2, M3 and M5) and a combination of C-hydroxylation and dehydrogenation (M6). Metabolites M2 and M3 were observed in rat and human hepatocytes, whereas M5 and M6 were only observed in rat. Only one phase II conjugate was observed, in rat hepatocytes only, which was a combination of oxygenation and glucuronidation (M1). With the exception of metabolites M5 and M6, all metabolites identified in vitro in hepatocytes were subsequently detected in vivo in either rat, dog or human.
Excretion *Absorption, distribution, metabolism and excretion in rats after oral (15 mg/kg) and intravenous (3.4 and 5 mg/kg) administration of [^{14}C]BYL719: DMPK R0900368*
The predominant route of excretion in rat was fecal, with 75.8 and 12.3% of the dose found in feces and urine, respectively, after i.v. dosing. Results after p.o. dosing were similar (83.7 and 15.0% of the dose in feces and urine, respectively). Alpelisib in feces and urine after p.o. dosing amounted to 21.4 and 0.61% of the dose, respectively. In BDC rats (after i.v. dosing) 38.3% of dose was eliminated in bile up to 48 hours post dose, with alpelisib amounting to 8.66% of dose in bile. Furthermore

alpelisib amounted to 10.9% of the dose in feces of BDC rats, indicating direct intestinal secretion of alpelisib.
TK data from general toxicology studies *4-week and 13-week repeat dose toxicology studies in rats; Study numbers 0970325 and 1070415*
Plasma exposure to alpelisib in rats increased roughly dose-proportionally with oral doses up to 30 mg/kg/day. Exposures following single and multiple dosing were less than 3 fold different, and no clear gender difference was observed in terms of AUC (area under the curve) or Cmax.
TK data from reproductive toxicology studies *Oral (gavage) study of embryo-fetal development in the rat; Study number 1770537: Embryo-fetal development dose range finding study in rabbit; study number 1770536.*
In pregnant rats and rabbits, exposure to alpelisib increased approximately dose proportionally. Alpelisib passed the placental barrier in rats and rabbits, but fetal plasma concentrations were low (rat approximately 10-fold lower; rabbit approximately 70-fold lower) compared to maternal plasma. In rat, the alpelisib maternal plasma AUC0-24h at the NOAEL (3.0 mg/kg/day) and MTD (30/mg/kg/day) was 3540 and 97500 ng•h/mL, respectively. In rabbit, the alpelisib maternal plasma AUC0-24h at the NOAEL (3.0 mg/kg/day) and MTD (25/mg/kg/day) was 26400 and 293000 ng•h/mL, respectively.

<u>The FDA's Assessment</u>:

The FDA agrees with the results of ADME studies and the PK parameters summarized by the applicant. Additional study results are summarized in the table below.

Type of Study	Major Findings
<u>Absorption</u>	
Dogs Absorption, pharmacokinetics, metabolism, and excretion of BYL719 in male dogs after oral (5 mg/kg) administration of [^{14}C]BYL719 (#DMPK R1300123) Pharmacokinetics in dogs of the PI3K alpha inhibitor NVP-BYL719 after intravenous and oral administration (#RD-2009-00575)	T_{max} was reached 2 h after oral administration of 5 mg/kg BY719 and the T1/2 was 6.2 h for the parent drug and 13 h for total radioactivity (parent and metabolites). Absolute oral bioavailability was high.
Distribution	
Rats	Tissue distribution was extensive after either oral or IV route of administration and included distribution to hair and eyes of pigmented LE rats. Thus BYL719 (or its metabolites) can bind melanin. While the t_{last}

In vitro blood distribution and plasma protein binding of [^{14}C]BYL719 including stability in blood and plasma of mouse, rat, dog, and human (#DMPK R0900535)	of BYL719 was 8 hours in most of tissues, traces of BYL719 were still present in the hair and eyes of LE rats after 7 days. This observation is consistent with the histological findings of skin toxicities (e.g. scab, ulceration, and inflammation; Study 1670271) and ocular findings (e.g. corneal epithelial atrophy and corneal mitosis; Study 970212, Study 970324) in the repeat dose toxicity studies. • The mean fraction in plasma (fp) compared to blood: Human: 54%; rat: 54%; mouse: 58%; dog: 59% • The mean unbound protein fractions (fu) in plasma: Mouse: 8.8%, rat: 9.4%, dog: 10.8%, human:10.8%
Metabolism	
Rats Absorption, distribution, metabolism, and excretion in rats after oral (15 mg/kg) and intravenous (3.4 and 5 mg/kg) administration of [^{14}C]BYL719 (DMPK R0900368) *Dog* [^{14}C] BYL719: Ex vivo Metabolite Profiling in the Dog Following Single Oral administration (DMPK R1300327)	male rats (5 mg/kg) parent compound (alpelisib): 65.5% M2: 3.1% M3: 5.1% BZG791(M4): 4.0% male dogs (5 mg/kg) parent compound (alpelisib): 77.1% BZG791 (M4): 4.61% M1: 1.35% M10: 0.91%
Note: *In vivo metabolism in human* Parent compound (alpelisib): 67.9%, BZG791 (M4): 26.7% BZG791 showed low or no activity on the p110α, p110β and p110δ isoforms in contrast to alpelisib based on the conducted in vitro biochemical assays and cell-based assay. BZG791 was not genotoxic in in vitro assays (Ames and micronucleus test with cultured human peripheral blood lymphocytes).	
Excretion	
No additional comments to the Applicant's summary	
TK data from general toxicology studies A 13-week repeated dose study in rats (Study 1070415) 2, 6, 20 mg/kg/day	<u>TK for the parent compound (alpelisib)</u> > dose proportional ↑ from 2 mg/kg to 6 mg/kg < dose proportional ↑ from 6 mg/kg to 20 mg/kg Exposure in females> Exposure in males On Day 75 AUC: 2360-41900 ng*hr/mL (male)

A 13-week repeated dose study in dogs (Study 1070416) 0.2, 1, 5 mg/kg/day	4250-60300 ng*hr/mL (female) $C_{max:}$ 436-5070 ng/mL (male) 725-6740 ng/mL (female) $T_{1/2}$: not defined T_{max}: 0.5-1 hours Accumulation (1.3 – 2-fold) C_{max} dose proportional ↑ AUC > dose proportional ↑ On Day 72 AUC: 442-15100 ng*hr/mL C_{max}: 95-1860 ng/mL No gender differences No accumulation $T_{1/2}$: not defined T_{max}: 0.5-1 hours

LE: Long Evans; TK: toxickinetics

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:

Alpelisib is a PI3K inhibitor intended for the treatment of advanced cancers. Therefore, the toxicology program was designed in accordance with ICH S9 guidance, as well as with all other relevant ICH guidances on safety, with a few lines of investigation exceeding those requirements. All principal toxicology studies were conducted in accordance with GLP and currently accepted guidelines.

Alpelisib was tested in a single rising-dose study in dogs and repeated-dose studies in rats and dogs of 2 (non-GLP, dose-range finding), 4 and 13 weeks (GLP) of treatment duration. Generally, due to the higher dose levels used, the findings in the 4-week studies were of higher severity than in the 13-week studies, why the 4-week studies are described in detail below and the results of the 13-week studies summarized.

4-week oral (gavage) toxicity study in rats with a 4-week recovery period/ Study 0970325:

Key Study Findings

- Doses of 80 and 60 mg/kg/day not tolerated due to weight loss necessitating premature sacrifices.
- Treatment-related effects on hemo- and lymphopoiesis, disturbances in glucose and lipid metabolism, changes in endocrine pancreas and estrus cycle, and

morphological alterations in bones, teeth and tissues with an epithelial or glandular structure, mostly at 30 mg/kg/day.

- All changes fully or partially reversible after 4 weeks of treatment-free recovery.

Conducting laboratory and location: Novartis, Basel, Switzerland
GLP compliance: Yes

Methods
Dose and frequency of dosing: 10, 30, 80-->60 (day 6)-->30 (day 8) mg/kg/day, daily dosing
Route of administration: oral gavage
Formulation/Vehicle: (b) (4)
Species/Strain: HanRcc: Wist rats
Number/Sex/Group: 10m, 10f (recovery: 5m, 5f (vehicle and high dose only))
Age: about 10 weeks at start of treatment
Satellite groups/ unique design: none
Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No mortality but early sacrifice of 2m and 4f at 80 mg/kg/day due to body weight loss (intestinal and bone marrow toxicity was considered to be the cause of the effect).
Clinical Signs	Piloerection at 80 mg/kg/day, persisting after dose reduction to 60 mg/kg/day on day 6. Partially closed eyes or discharges from eyes at 80 mg/kg/day. Signs disappeared after dose reduction to 30 mg/kg/day on day 8. No clinical signs at mid and low dose.
Body Weights	At 80 mg/kg/day marked reduction in food intake with associated body weight loss and necessitated early sacrifice of 2 males and 4 females. Based on the weight loss in the remaining animals the dose was reduced to 60 mg/kg/day as of day 6 and to 30 mg/kg/day as of day 8. At 30 mg/kg/day decrease in overall food intake associated with lack of body weight gain. At 10 mg/kg/day a slight decrease in body weight gain in both sexes and a slight decrease in food intake in f only.
Hematology	Decrease in reticulocytes, hemoglobin, hematocrit, red blood cell counts and associated alterations in red blood cell indices, decrease in white blood cell counts and associated alterations in the white blood cell differential in males at 30 mg/kg/day and in f at ≥10 mg/kg/day.
Clinical Chemistry	Disturbance in glucose metabolism (insulin, glucose, fructosamine) at 30 mg/kg/day in m and at ≥10 mg/kg/day in f, disturbance in lipid metabolism (triglycerides, cholesterol) (possible liver effect) at 30 mg/kg/day in m and f.
Urinalysis	No relevant treatment-related changes.
Gross Pathology	Small spleen in m and f at 30 mg/kg/day, small thymus in individual f at 30 mg/kg/day, small prostate in Individual m at >10 mg/kg/day, discolored incisors in several m or f at 30 mg/kg/day.

	After the recovery period, broken and pale incisors were observed in one f but with no corresponding microscopic finding.
Organ Weights	Decreased in spleen, thymus, uterus, pituitary, adrenal glands (f only) at >10 mg/kg/day, prostate, liver, kidneys, testes, ovaries at 30 mg/kg/day.
Histopathology	Generally dose-dependent changes at >10 mg/kg/day in the bone marrow (hypocellularity with congestion/hemorrhage), spleen (decreased hemopoiesis and lymphoid depletion), thymus (lymphoid depletion), lymph nodes (lymphoid depletion and reduced germinal center development), endocrine pancreas (morphological changes in the islets of Langerhans), prostate (decreased secretion). Mainly at 30 mg/kg/day changes in the vagina (diffuse epithelial atrophy and atypical estrous cycle phase with uterine atrophy) and pituitary gland (decreased acidophilia in the pars distalis and increased FSH/LH (follicle stimulating hormone/luteinizing hormone) content), in the femoral/tibial (knee joint) and sternal growth plate (thickening and decreased metaphyseal trabecular bone density), in incisors (mainly odontoblast degeneration with dentin thinning and pulpa necrosis), in tongue, esophagus, larynx and forestomach (diffuse epithelial atrophy), in skin and mammary area (epidermal atrophy in females and diffuse mammary gland atrophy) and in lacrimal glands (diffuse acinar atrophy). All findings fully or partially reversible within 4 weeks recovery time.
Other evaluations	None.

LD: low dose; MD: mid dose; HD: high dose; m: male(s); f: female(s)

13-Week Oral (Gavage) toxicity study in the rat followed by a 8 week treatment-free period and including micronucleus assay/ Study 1070415

Daily oral treatment of male and female Wistar rats at dose levels of 2, 6 or 20 mg/kg/day for 13 weeks was generally well tolerated with only minor clinical signs (pale teeth) in high-dose females and decreased body weight gain at 6 and 20 mg/kg/day. Reversible major clinical pathology changes included decreased lymphocyte count, and increased insulin and glucose levels. Mostly minimal to slight treatment-related microscopic findings at 6 or 20 mg/kg/day in the haemolymphoreticular tissues, pancreas, pituitary gland and incisor teeth of both sexes, along with male kidney, female skin and minor variation in estrous cycle in uterus were generally reversible or show a trend towards reversibility. Furthermore, alpelisib did not induce an increase in micronuclei in peripheral blood reticulocytes sampled after 4 weeks of treatment.

4-week oral (gavage) toxicity study in dogs with a 4-week recovery period/ Study 0970324:

Key Study Findings

- Body weight loss started from the lowest dose of 2 mg/kg/day.

- Test item-related changes in insulin and glucose levels indicative of altered glucose metabolism at ≥ 2 mg/kg/day, and morphologically mainly atrophic changes in the epithelium of the oral mucosa, tongue, esophagus, larynx or skin partly at all dose levels as well as in the mucosa of the gastrointestinal tract and in the lymphoid system at the highest dose of 15 mg/kg/day.
- All changes fully or partially reversible after 4 weeks of treatment-free recovery.

Conducting laboratory and location: Novartis, Basel, Switzerland
GLP compliance: Yes

Methods
Dose and frequency of dosing: 2, 5, 15 mg/kg/day, daily dosing
Route of administration: oral gavage
Formulation/Vehicle: (b) (4)
Species/Strain: Beagle dogs
Number/Sex/Group: 3m, 3f (recovery: 2m, 2f (vehicle and high dose only))
Age: 11-12 months at start of treatment
Satellite groups/ unique design: none
Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No treatment-related mortality occurred, but one recovery animal was terminated moribund at the beginning of the recovery phase (day 31). Moribundity was assigned to an acute/ subacute intestinal invagination.
Clinical Signs	Focal atrophic mucosa changes in the mouth, reddened gingiva, and mouth odor at 15 mg/kg/day. One male at 15 mg/kg/day showed also focal atrophic mucosa changes and mucosal reddening on the penis.
Body Weights	Body weight development moderately reduced at 2 and 5 mg/kg/day and severely at 15 mg/kg/day at the end of the treatment period, with correlating food consumption changes.
Ophthalmoscopy	No relevant treatment-related changes.
ECG	No relevant treatment-related changes.
Hematology	Increase in white blood cell counts, fibrinogen, globulin, platelets at 15 mg/kg/day indicative of inflammatory processes.
Clinical Chemistry	Decrease in glucose and insulin concentrations starting from 2 mg/kg/day in m and 5 mg/kg/day in f indicative of disturbances of glucose metabolism.
Urinalysis	No relevant treatment-related changes.
Gross Pathology	Effects in thymus (small size), digestive tract and oral cavity (white foci in the esophagus and red discoloration in the cardiac area (i.e transition esophagus/ stomach) of the stomach, reddish foci/discoloration in the oral mucosa (erosion/ ulceration)). One m at 5 mg/kg/day showed a single reddish focus in the oral mucosa correlating to erosion/ ulceration.

Organ Weights	Thymus: moderate decrease in both sexes at 15 mg/kg/day; Prostate: slight to marked dose-dependent decrease at ≥ 5 mg/kg/day.
Histopathology	At ≥ 2 mg/kg/day (m) or 15 mg/kg/day (f) degenerative/ inflammatory changes in the epithelium of the oral mucosa, tongue or esophagus consisting mainly of erosion/ ulceration, diffuse epithelial atrophy, epithelial/ submucosal neutrophilic or mixed cell inflammation and/or single cell necrosis. In bone marrow hypercellularity characterized by an increased myeloid/erythroid ratio. At ≥ 5 mg/kg/day diffuse epithelial atrophy in the epidermis and/or hair follicles in the skin. At 15 mg/kg/day lesions in the larynx (epithelial atrophy), thymus and gut-associated lymphoid tissue (lymphoid depletion), mesenteric and/or retropharyngeal lymph nodes (lymphoid depletion, decreased germinal center development and/or neutrophilic infiltration, edema, inflammatory cell infiltration and/or histiocytosis), stomach (erosion/necrosis in the pyloric area, mixed cell inflammation), small and large intestine (mucosal basophilia, edema and/or granulocytic inflammation), endocrine pancreas (atrophy of the islet cells, cyptoplasmic inclusions) and prostate (glandular atrophy), In the eye increased mitotic figures in the corneal epithelium with highest mean severity at 2 mg/kg/day (m), gradually decreasing to background values at 15 mg/kg/day; no ophthalmologic findings. All findings fully or partially reversible within 4 weeks recovery time.
Other evaluations	None.

LD: low dose; MD: mid dose; HD: high dose; m: male(s); f: female(s)

13-week oral administration toxicity study in the dog followed by a 4-week treatment-free period/ Study 1070416

Daily treatment of male and female beagle dogs with 0.2, 1.0, 5.0 mg/kg/day was generally well tolerated with no mortality or toxicologically significant test article-related clinical or post-dosing observations, or adverse effects on the ECG or at ophthalmoscopic examination. Reduced body weight gain mainly at 5 mg/kg/day was associated with a reduced food intake in males of this group. Clinical pathology findings indicative of interference with the glucose and insulin homeostasis at all doses and minor post-mortem findings in tongue and lymphatic system of individual high-dose animals suggest a relationship to the pharmacological activity of the test article. All findings were fully or partially reversed after a 4-week treatment-free recovery period (in the mesenteric lymph nodes, minimal lymphoid depletion was seen in two males and one female after recovery).

The FDA's Assessment:

The 4-week rat and dog toxicology studies were reviewed by the FDA under IND (b) (4) ***the original IND submitted with BLY719. In general, we agree with the results presented by the applicant. Additional noteworthy findings are listed below.***

4-week rat study (Study #0970325):

- ***Increased glucose, insulin, and cholesterol, and reduced triglycerides. Some effects started at LD but effects were most evident at HD. Changes in pancreatic islet cells in all dose groups and decreased zymogen granules at HD.***
- ***Adverse effects on teeth, joints and bones: growth plate thickening of knee joint and decreased trabeculae bone density; degeneration and dentin thinning of incisors. Effects were seen at MD and HD.***
- ***Uterine atrophy (starting at LD); decreased secretion of seminal vesicle (HD) and that of prostate (starting at LD). Mammary gland atrophy at MD and HD (male and female)***
- ***Eyes (cornea vacuole, females, MD and HD).***

4-week dog study (Study #0970324):

- ***Mortality: 1 Female dog at 15 mg/kg/day (HD) was euthanized on day 31 due to moribund condition. The cause of death was acute intestinal intussusception at the ileocolonic junction. Although no mortalities occurred during the 30-day treatment period, two of the high dose females were unable to be dosed on day 30 due to severe body weight loss and poor health.***
- ***Clinical Chemistry: There was a significant dose-dependent increase in insulin levels in MD (5 mg/kg) animals (↑41% in males, 62% in females) and HD (15 mg/kg) animals (↑62% in males, 139% in females). This increase was accompanied by variable glucose levels and increased triglyceride and cholesterol values.***
- ***Organ Weights: A decrease in pituitary gland (~35%), spleen (~30%), and thymic weights (~30%) was observed in HD animals. There was also dose-dependent decrease in ovary (up to ~35%), uterus (up to ~50%), and prostate weights (up to ~40%). These changes were reversible or trending towards reversible in recovery animals.***
- ***Histological Findings: uterine atrophy at HD.***

The FDA agrees with the applicant's provided summary for the 13-week toxicology studies in rats and dogs. See below details on study methods and results for the rat study. Findings in the dog study were comparable to effects previously reported in 4-week studies in rats and dogs and 13-week study in rats and not captured below.

Study title/ number: BYL719: 13-Week Oral (Gavage) Administration Toxicity Study in the Rat Followed by a 8-Week Treatment-Free Period and Including Micronucleus Assay/ Study#1070415

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 2, 6 or 20 mg/kg/day, once daily for 13 weeks

Route of administration: Oral gavage

Formulation/Vehicle: [redacted] (b) (4)
Species/Strain: Rat: Crl:WI(Han)
Number/Sex/Group: 20/sex/group (main), 10/sex/group (recovery, control and HD)
Age: 8 weeks old
Satellite groups/ unique design: TK, 8/group (4 control)
Deviation from study protocol affecting interpretation of results: No

Observations and Results:

<table>
<tr><td>Parameters</td><td>Major findings</td></tr>
<tr><td>Mortality</td><td>None</td></tr>
<tr><td>Clinical Signs</td><td>14/30 female animals dosed at 20 mg/kg/day had pale teeth at the end of the 13-week dosing phase. This observation continued through the first 4 weeks of the treatment-free phase.</td></tr>
<tr><td>Body Weights</td><td>↓ body weight gain, dose-dependent, males and females, at ≥ 6 mg/kg
Reversed at the end of recovery period
<table>
<tr><td colspan="7">Changes compared to the control (%) at the end-of-dosing</td></tr>
<tr><td>Sex</td><td colspan="3">male</td><td colspan="3">female</td></tr>
<tr><td>Dose (mg/kg)</td><td>2</td><td>6</td><td>20</td><td>2</td><td>6</td><td>20</td></tr>
<tr><td>body weight</td><td></td><td>-5</td><td>-18</td><td></td><td>-6</td><td>-12</td></tr>
<tr><td>body weight gain</td><td></td><td>-18**</td><td>-49***</td><td></td><td>-19**</td><td>-45***</td></tr>
</table>
** P<=0.01, *** P<=0.001</td></tr>
<tr><td>Food Consumption</td><td>↓up to 16% in male animals, ↓up to 11% in female animals (in Week 13-14)</td></tr>
<tr><td>Ophthalmoscopy</td><td>unremarkable</td></tr>
<tr><td>Hematology</td><td><u>Week 13 (compared to the control)</u>
-↓red cell mass (HD, erythrocytes, hemoglobin; ↓4-7%)
-↓WBC (MD & HD, ↓15-42% in males, ↓21-28% in females)
-↓neutrophil (HD, ↓22% in males)
-↓lymphocyte (MD & HD, ↓29-48% in males, ↓24-35% in females)
-↓eosinophil (HD, ↓50% in males, ↓25% in females)
-↓basophil (HD, ↓100% in males)
-↓LUC (HD, ↓50% in males; MD & HD, ↓50% in females)
-↑platelets (HD, ↑9% in males, 15% in females)</td></tr>
<tr><td>Clinical Chemistry</td><td>-↓triglyceride concentration (dose dependent, ↓59% in males, ↓54% in females at HD compared to the controls)
-↑glucose and insulin (dose dependent, more than 10x increase at HD, generally was reversed by 24 hours post-dose)</td></tr>
<tr><td>Urinalysis</td><td>unremarkable</td></tr>
<tr><td>Gross Pathology</td><td>Pale incisor teeth were recorded in five females at 20 mg/kg/day, and there was also a minor reduction in the incidence of uterine distension in females at 20 mg/kg/day.</td></tr>
<tr><td>Organ Weights</td><td>Main: Change compared to control values (%) in rats
<table>
<tr><td></td><td colspan="4">Absolute change</td><td colspan="4">Relative change (to BW*)</td></tr>
<tr><td>Dose (mg/kg)</td><td colspan="2">6</td><td colspan="2">20</td><td colspan="2">6</td><td colspan="2">20</td></tr>
<tr><td>Sex</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td></tr>
<tr><td>Spleen</td><td>-12</td><td>-2</td><td>-19</td><td>-21</td><td>-11</td><td></td><td>-18</td><td>-21</td></tr>
<tr><td>Thymus</td><td>-5</td><td>-9</td><td>-14</td><td>-15</td><td>-6</td><td>-11</td><td>-16</td><td>-23</td></tr>
<tr><td>Pituitary</td><td>-11</td><td>-21</td><td>-22</td><td>-36</td><td>5</td><td>-18</td><td></td><td>-30</td></tr>
<tr><td>Kidney</td><td>-8</td><td>-4</td><td>-16</td><td>-5</td><td>-6</td><td></td><td>-8</td><td></td></tr>
<tr><td>Prostate</td><td>-8</td><td>-</td><td>-30</td><td>-</td><td>-5</td><td>-</td><td>-25</td><td>-</td></tr>
<tr><td>Epididymis</td><td>-4</td><td>-</td><td>-19</td><td>-</td><td></td><td>-</td><td>-5</td><td>-</td></tr>
</table></td></tr>
</table>

Blank: unremarkable; "-": not applicable; *BW, Body Weight

Recovery: unremarkable

Histopathology
Adequate battery: Yes

Sex		Male				Female			
Dose (mg/kg)		0	2	6	20	0	2	6	20
		Main							
Number of animals		20	20	20	19	20	20	20	20
Thymus									
lymphoid depletion	-Grade 1		1	3	4	1	2	2	6
	-Grade 2				1				
Mesenteric lymph node									
lymphoid depletion	-Grade 1	2	1	2	6	1		3	6
	-Grade 2			1	3				4
sinus histiocytosis	-Grade 1	2	4	6	10	3		11	10
	-Grade 2			3	1				6
	-Grade 3			1	1				
Mandibular lymph node									
lymphoid depletion	-Grade 1	1	1	2	4			2	2
	-Grade 2				2				3
sinus histiocytosis	-Grade 1	1	1	1	5	1	2	3	5
	-Grade 2			1		1			2
GALT/Peyers Patch									
lymphoid depletion	-Grade 1		1	1	6			3	4
	-Grade 2	1		3	9			1	6
Spleen									
pigment	-Grade 1	1		6	5	6	6	8	4
	-Grade 2				3		2	2	8
	-Grade 3								7
Femur+Marrow									
marrow fat	-Grade 1	5	4	2		12	8	7	1
	-Grade 2	12	14	13	2	6	5	10	4
	-Grade 3	1	2	5	17		1	2	15
Sternum+Marrow									
marrow fat	-Grade 1	4	5	8	3	10	9	8	1
	-Grade 2			1	3	3	2	6	6
	-Grade 3				13	3	2	5	13
Pancreas									
islet cell hyperplasia	-Grade 1	1	1	7	7			3	4
	-Grade 2				6				7
Pituitary									
decreased eosinophilia									
	-Grade 1				7			2	9
Tooth									
reduced/irregular dentin									
	-Grade 1				5				8
Kidney									
hyaline droplets	-Grade 1	13	16	16	13				
	-Grade 2	6	4	3	1				
	-Grade 3	1	0						
Skin/subcutis									
adnexal atrophy	-Grade 1							3	7
Uterus									

	Pro-oestrus	-	-	-	-	4	4	5	3
	Oestrus	-	-	-	-	6	7	5	2
	Metoestrus	-	-	-	-	5	6	4	8
	Dioestrus	-	-	-	-	5	3	6	7
	Recovery								
	Unremarkable								
	1 = minimal, 2 = slight, 3 = moderate, Blank=no related findings								
Additional assessment: Micronucleus assay	No drug-related finding								

5.5.2. Genetic Toxicology

Alpelisib was not genotoxic in an in vitro genotoxicity package consisting of a 2-strain mini-screen Ames and a TK6 micronucleus screen, ICH S2 guidance-compliant GLP tests for Salmonella reverse mutations in five strains, and chromosome aberrations in primary human lymphocytes, and an in vivo micronucleus test in peripheral blood reticulocytes obtained in week 4 of the 13-week rat toxicity study.

The FDA's Assessment:
The FDA agrees with the study results described above.

5.5.3. Carcinogenicity

No carcinogenicity studies have been conducted with alpelisib.

The FDA's Assessment:
The FDA agrees that no carcinogenicity studies are required for the proposed indication.

5.5.4. Reproductive and Developmental Toxicology

No studies to investigate fertility and early embryonal development have been conducted. In repeated-dose toxicity studies in rats and dogs, histopathologically discernable effects in germinal organs of both genders were observed; therefore, impairment of fertility and other reproductive functions after alpelisib treatment cannot be excluded.

Embryo-Fetal Development

The Applicant's Position:

In both rats and rabbits, alpelisib treatment induced fetal developmental abnormalities and death. In rats, the fetal effects were observed at dose levels that were associated with maternal toxicity such as reduced body weight gain and food intake, whereas in rabbits embryofetal effects occurred at dose levels below overtly maternally toxic ones. Thus, a relevant embryo/feto toxic

risk cannot be excluded so that appropriate measures should be implemented to avoid the risk to the developing fetus, in conjunction with applicable risk-benefit considerations.

Oral (Gavage) Study of Embryo-Fetal Development in the Rat/ Study 1770537

Key Study Findings

- Maternal body weight loss or stagnation of body weight gain and embryonal death at 30 mg/kg/day (high dose)
- Reduced maternal body weight gain, reduced fetal weight and increased malformations at 10 mg/kg/day (mid dose); no maternal or fetal effects at 3 mg/kg/day (low dose; NOAEL)
- Animal-to-human AUC ratio for fetal effects for recommended human dose of 300 mg/day versus 30 mg/kg/day (mid dose) in this study: 0.87 (Ratio for low dose (10 mg/kg/day; NOAEL) = 0.12)

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods
Dose and frequency of dosing: 3, 10, 30 mg/kg/day daily
Route of administration: oral gavage
Formulation/Vehicle: (b) (4)
Species/Strain: Crl: WI(Han) rats
Number/Sex/Group: 5f
Satellite groups: 4f for TK, 3f for plasma glucose levels
Study design: Administration on gestation days (GD) 6 to 17 (main groups) or GD 7 to 18 (toxicokinetic groups)
Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	**Major findings**
Mortality	None
Clinical Signs	Red discharge around the urogenital area or from the vulva between GD 14 to 21, which was associated with loss of viable embryos at 30 mg/kg/day
Body Weights	Maternal body weight loss or stagnation in body weight gain at 30 mg/kg/day and a dose-related reduced body weight gain at 3 and 10 mg/kg/day (minimal and thus not considered adverse at 3 mg/kg/day)

Necropsy findings Cesarean Section Data	LD: No macroscopic findings MD: No macroscopic findings HD: No macroscopic findings
Necropsy findings Offspring	LD: No effects (NOAEL) MD: Reduced mean fetal weight; increased numbers of litters with fetal malformations and variations (mostly bent scapula and long bones) HD: No viable fetuses due to increased pre- and post-implantation losses

LD: low dose; MD: mid dose; HD: high dose

Oral (Gavage) Combined Preliminary/ Dose Range-Finding Study of Embryo-Fetal Development in the Rabbit/ Study 1770536

Key Study Findings

- Maternal body weight loss with reduced food intake at 25 or 30 mg/kg/day, transient at 15 mg/kg/day.
- Increased numbers of fetuses with malformations starting at mid dose (15 mg/kg/day), with total fetal loss in majority of animals at high dose (25/30 mg/kg/day).
- Animal-to-human AUC ratio for fetal effects for recommended human dose of 300 mg/day versus 15 mg/kg/day (mid dose) in this study: 5.54 (Ratio for low dose (10 mg/kg/day; NOAEL) = 0.86)

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

Methods
Dose and frequency of dosing: 3, 15, 30 mg/kg/day daily (Phase I) or 3, 15, 25 mg/kg/day (Phase II)
Route of administration: oral gavage
Formulation/Vehicle: (b) (4)
Species/Strain: New Zealand White: Hra:(NZW)SPF rabbits
Number/Sex/Group: 3f (6f for high dose group in Phase II)
Satellite groups: 3f
Study design: Administration on gestation days (GD) 7 to 20 for main study animals or GD 7 to 21 for toxicokinetic (TK) animals
Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	**Major findings**

Mortality	No mortality but one animal prematurely sacrificed at 30 mg/kg/day on GD 23 and another one at 25 mg/kg/day on GD 20 following abortion of fetuses.
Clinical Signs	Brown staining around the urogenital area between GD 15 and 20 in the animal prematurely sacrificed on GD 20 at 25 mg/kg/day.
Body Weights	Maternal body weight loss with reduced food intake at 25 or 30 mg/kg/day. Transient slight body weight loss at 15 mg/kg/day with subsequent recovery, in the absence food intake effects.
Necropsy findings Cesarean Section Data	LD: No macroscopic findings MD: No macroscopic findings HD: No macroscopic findings
Necropsy findings Offspring	LD: No effects (NOAEL) MD: Increased number of fetuses and litters with malformations (mainly tail or head). HD: Reduced mean fetal weight. No viable fetuses in both surviving animals at 30 mg/kg/day and 2/5 animals at 25 mg/kg/day. Reduced number of live fetuses with increased post-implantation loss in remaining animals at 25 mg/kg/day. Increased number of fetuses and litters with malformations.

LD: low dose; MD: mid dose; HD: high dose

The FDA's Assessment:

The FDA agrees with the summary of study results described above. Additional study results are included in the table below.

Rat

Parameters	**Major findings**
Body Weights	Dose-related body weight loss or lower body weight gain was recorded for all groups administered BYL719 3 mg/kg: unremarkable 10 mg/kg: body weight gain (GD6-18): ↓24% compared to control (statistically significant); BW (mean): ↓5% on G17, ↓7% on G21 compared to control 30 mg/kg: BW loss of 8.7 g (GD 6-9) and 3.3 g (GD 12-15); BW (mean): ↓22% on GD17, ↓32% on GD21 compared to control
Necropsy findings Offspring	3 mg/kg: unremarkable 10 mg/kg: ↓ mean fetal weight, 22% lower than the control; ↑ in the number of litters with fetal malformations/variations

The majority of the malformations were associated with bent scapula and thickened or bent long bones.
30 mg/kg: no live fetuses, statistically significant increased pre-implantation and post-implantation losses

Fetal Malformations			
Malformations (historical control; % litters affected)	Malformation % in Each Litter (Number of Litters)		
	0	3 mg/kg	10 mg/kg
Aortic arch interrupted, carotid artery malpositioned (0 - 4.35)	0	0	5(1)
Rib branched (0)	0	0	5(1)
Sacral centrum fused (0)	0	0	5(1)
Humerus thick (0), Scapula bent (0-5.0)	0	0	21(4)
Radius bent (0)	0	0	16(3)
Ulna bent (0)	0	0	5(1)
Femur bent (0)	0	0	5(1)
Clavicle misshapen (0)	0	0	5(1)
Total litters with malformations	0	0	6
Fetal Variations (selected findings)			
Variations (historical control; % litters affected)	Variations % in Each Litter (Number of Litters)		
	0	3 mg/kg	10 mg/kg
Brain ventricle dilated (0)			63***(12)
Sternebra incomplete ossification (0-25)		22*(4)	37**(7)
Statistically significant: *** = P < 0.001; ** = P < 0.01; * = P < 0.05.			

Toxicokinetics

Mean (n = 2) toxicokinetic parameters for BYL719 - Gestation Day 17

Dose level mg/kg	C_{max} (ng/mL)	Dose Normalized C_{max}	AUC_{0-24h} ng.h/mL	Dose Normalized AUC_{0-24}
3	647	216	3540	1180
10	2950	295	26600	2660
30	20200	10200	97500	3250

Rabbit (nonGLP)

- ***Fetal malformations included acaudia, short tail, and misshapen head at 15 and 25 mg/kg doses; facial cleft and retina fold at 25 mg/kg; anophthalmia at 15 mg/kg; thyroid absent at 15 and 25 mg/kg doses***
- ***No live fetuses at 30 mg/kg dose***
- ***Reduced maternal weight of up to 7% at 25 mg/kg on GD20 and GD29.***
- ***Mean TK parameters on GD 20 are listed below:***

Dose level mg/kg	C_{max} (ng/mL)	Dose Normalized C_{max}	AUC_{0-24h} ng.h/mL	Dose Normalized AUC_{0-24}
3	3230	1080	26400	8800
15	20400	1360	170000	11300
25	32900	1320	293000	11700

Animal-to-human AUC ratio:
Rats

- ***AUC at 10 mg/kg (26600 ng.h/mL) was approximately 0.8 times the exposure in humans at the recommended dose of 300 mg/kg (33224 ng.h/mL)***

Rabbits

- ***AUC at 15 mg/kg (170000 ng.h/mL) was approximately 5 times the exposure in humans at the recommended dose of 300 mg/kg (33224 ng.h/mL)***

Other Toxicology Studies

Local Tolerance

The Applicant's Position:

Alpelisib was tested for contact sensitizing potential in a murine local lymph node assay (LLNA TIER I), after application on the dorsum of both ears once a day on 3 consecutive days. In a second study, primary skin irritation and corrosion was tested in rabbits applying the test item to the skin of one flank covered by a patch for 4 hours.

There was no evidence for sensitization, irritation or corrosion in these studies.

The FDA's Assessment:

The FDA agrees with the conclusion.

Phototoxicity Studies

The Applicant's Position:

In a non-GLP and a GLP 3T3 NRU uptake in vitro study, the phototoxic potential of alpelisib was assessed according to guideline ICH S10. In both studies, it was concluded that alpelisib is devoid of a phototoxic potential.

The FDA's Assessment:

The FDA agrees with the conclusion.

Insulin/glucose/insulin Tolerance Test

The Applicant's Position:

Alpelisib was tested in a non-GLP insulin and glucose tolerance study in mice in order to determine if inhibition of insulin receptor function and altered regulation of glucose metabolism occurred in vivo.

In this study, alpelisib-related insulin insensitivity/resistance was seen after single and repeated dosing (day 15 of treatment). In the absence of clinical signs of toxicity, histopathologically these effects correlated with minimal pancreatic cytoplasmic changes of the Langerhans islet cells, which is considered to be an adaptive response to the insulin demand induced by alpelisib.

The FDA's Assessment:

The FDA agrees with the conclusion.

4-week oral investigative skin toxicity study in Brown Norway rats

The Applicant's Position:

Alpelisib is associated with frequent skin related adverse effects in humans, a finding that was not clearly demonstrated in the standard nonclinical toxicology studies. Therefore, alpelisib was tested in an exploratory study with the purpose to investigate the toxicological effects on the skin when administered orally to female Brown Norway (BN) rats for 4 weeks, a rat strain that has been used to investigate drug-induced skin reactions and shown a higher sensitivity than standard rat strains.

Alpelisib induced clinically apparent skin lesions in practically all treated rats starting after 3 – 4 weeks of daily treatment with 50 mg/kg/day, which were not previously observed in albino Wistar-Han rats. Histologically, these macroscopic findings correlated with large areas of ulcerations and crust formation, and included discolored skin, flakey skin, crusty skin, localized hair loss, scabs, scratches, abrasions, wounds, red ears and/or swellings, and continued until necropsy.

The macroscopic and histological changes (epidermal hyperplasia and hyperkeratosis, ulceration with fibrinous exudate, bacterial colonies, infiltration of neutrophilic granulocytes, and lack of anagen hair follicles, and increased CD163+ and CD8+ T and non-T cells as well as NK cells and CD68+ macrophages, signs of CD4+ and CD8+ T as well as B cell activation in skin-draining lymph nodes,CD68+ macrophages, and mononuclear cell infiltration into dermis) correlated with increases in skin inflammatory gene signatures, with peripheral lymph node immunophenotyping changes, and with serum cytokine/chemokine/growth factor changes (fractalkine, leptin, and others).

<u>The FDA's Assessment:</u>

The FDA agrees with the conclusion.

X	X
Wei Chen Primary Reviewer	Tiffany Ricks Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

Alpelisib is a small molecule inhibitor of phosphatidylinositol-3-kinase (PI3K) with inhibitory activity predominantly against PI3Kα. The applicant is seeking approval of alpelisib for the treatment of postmenopausal women, and men, with HR-positive, HER2-negative, advanced breast cancer with a PIK3CA mutation as detected by an FDA-approved test in combination with fulvestrant after disease progression following an endocrine-based regimen. The proposed alpelisib dosing regimen is 300 mg orally once daily (QD) with food.

The clinical pharmacology review focused on the dose selection, organ dysfunction, drug-drug interactions, QT/QTc prolongation, food effect, as well as the impact of acid reducing agents.

Recommendations: The Office of Clinical Pharmacology has reviewed the information submitted in NDA 212526. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below in Table 3. Post-marketing commitments and requirements are detailed in Table 4.

Table 3: Key FDA Clinical Pharmacology Review Issues

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	The primary evidence of effectiveness comes from the pivotal phase 3 Study CBYL719C2301 (SOLAR-1). The proposed dosing regimen is supported by the a statistically significant PFS improvement of alpelisib in combination with fulvestrant compared to the fulvestrant group (median 11.1 months vs. 3.7 months) in patients with HR-positive, HER2-negative, catalytic subunit alphaPIK3CA-mutated, advanced or metastatic breast cancer.
General dosing instructions	The proposed alpelisib dosing regimen of 300 mg taken orally once daily with food, is acceptable for approval: • This dosing regimen demonstrated a statistically significant PFS improvement compared to the fulvestrant group (11.1 months vs. 3.7 months) in SOLAR-1. • The proposed starting alpelisib dose of 300 mg QD is high, with 75% dose adjustment (dose reduction and/or interruption) and 25% discontinuation due to AEs such as hyperglycemia, diarrhea and rash. • Stable doses in individual patients were reached in the first two treatment cycles by dose interruptions or reductions, as demonstrated by the median time to the first dose reduction of 1.81 (95% CI: 1.41, 2.79) months in the overall patient population in SOLAR-1. During the remainder of the treatment period, around 40%, 30% and 30% of patients received daily doses of alpelisib at 300 mg, 250 mg, and 200 mg, respectively.

Review Issue	Recommendations and Comments
	• Administration with food is acceptable, as both high-fat high-calorie meal and low-fat low-calorie meal boost alpelisib systemic exposure by 75% compared to fasting condition.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• No dose adjustment is recommended for patients with mild, moderate and severe hepatic impairment (Child-Pugh A, B and C). • No dose adjustment is recommended for patients with mild and moderate renal impairment (CLcr 30 to <90 mL/min). • The effect of severe renal impairment (CLcr < 30 mL/min) on alpelisib PK is unknown. • PopPK analyses did not identify clinically important covariates influencing alpelisib PK.
Drug-drug interactions	Labeling language: • CYP3A4 inducers: Avoid coadministration of alpelisib with a strong CYP3A4 inducer. • BCRP inhibitors: Avoid the use of BCRP inhibitors in patients treated with alpelisib. If unable to use alternative drugs, closely monitor for increased adverse reactions. • CYP2C9 substrates: Closely monitor when alpelisib is coadministered with CYP2C9 substrates where decreases in the plasma concentration of these drugs may reduce activity. • Acid reducing agents (ARAs): Alpelisib can be co-administered with acid reducing agents given that alpelisib should be taken with food, as alpelisib systemic exposure decreased by 21% with ranitidine in the presence of low-fat low-calorie meal. Food exhibited a more pronounced effect on the solubility of alpelisib than the effect of gastric pH value. PMC studies: • A drug-drug interaction study with a strong CYP3A4 inducer • A cocktail drug-drug interaction study with sensitive substrates of CYP2B6, CYP3A4 and CYP2C-family enzymes (CYP2C9, CYP2C19 and / or CYP2C8)
Labeling	Overall, the proposed labeling recommendations are acceptable upon the applicant's agreement to the FDA revisions to the label. Clinical pharmacology labeling recommendations are detailed in Section 11.

Table 4: Clinical Pharmacology Post-Marketing Requirements and Commitments

PMR or PMC	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
PMC	Determination of an appropriate alpelisib dose for patients with concomitant use of a strong CYP3A4 inducer.	Alpelisib is metabolized by CYP3A4. Strong CYP3A4 inducers may decrease alpelisib systemic exposures and require dose adjustment. In clinical trials, alpelisib exhibited a trend of decrease in exposure with coadministration of CYP3A4 inducer encorafenib. However, the effect of CYP3A4 inducer encorafenib on PK of alpelisib is inconclusive due to the small patient number.	Conduct a clinical trial to evaluate the effect of repeated doses of a strong CYP3A4 inducer on the PK of alpelisib
PMC	Dose adjustment in patients with comedications of CYP substrates whose PK may be affected by alpelisib.	Based on in vitro studies, alpelisib is a strong time-dependent inhibitor of CYP3A4, and an inducer of CYP3A4, CYP2B6 and CYP2C9 at clinically relevant plasma concentrations. The drug-drug interaction potential of alpelisib on CYP2C8 and CYP2C19 have not been evaluated in humans. Alpelisib may increase or decrease exposures of concomitant sensitive substrates or substrates with a narrow therapeutic index of the above CYP enzymes.	Conduct a clinical trial to evaluate the effect of repeat doses of alpelisib on the single dose PK of sensitive substrates of CYP2B6, CYP3A4 and CYP2C-family enzymes (CYP2C9, CYP2C19 and / or CYP2C8) to assess the magnitude of exposure change for sensitive substrates of the above CYP enzymes

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

The clinical pharmacology of alpelisib has been well characterized. The data included in the dossier encompasses the pharmacokinetic properties following single dose and multiple-doses of alpelisib in healthy subjects and subjects with cancer, as well as population PK analyses of single agent and combination studies included in the dossier. The results from both in vitro human biomaterial studies and in vivo clinical pharmacology studies (mass balance, food effect and acid reducing DDI, hepatic impairment and CYP3A4 perpetrator DDI) conducted in healthy subjects and subjects with cancer were integrated to describe the ADME properties of alpelisib in humans and assess intrinsic and extrinsic factors which may affect the PK of alpelisib. In

addition, the outcomes of the exposure-efficacy and exposure-safety analyses conducted in early and late (confirmatory) studies for alpelisib, which were used for the Phase III dose selection and justification in cancer subjects, support the use of the recommended dose of 300 mg alpelisib, administered orally, once daily, on a continuous schedule.

The FDA's Assessment:

The FDA generally agrees with the applicant's assessment on Pharmacology and Clinical Pharmacokinetics. However, the FDA does not agree with the applicant's evaluations on the DDI potential. See details in the sections below.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's Position:

Selection of the alpelisib 300 mg daily continuous dosing schedule was based on the results of the first in-human study, CBYL719X2101, where alpelisib was administered both as a single agent and in combination with fulvestrant.

In Study CBYL719X2101, 134 adult subjects with advanced solid malignancies whose tumors had an alteration (mutation or amplification) of the PIK3CA gene were treated until the 22-Mar-2017 data cut-off date. These subjects received treatment with increasing doses of oral alpelisib (30 mg to 450 mg orally q.d. or 120 mg to 200 mg orally b.i.d.) and the MTD for alpelisib monotherapy was determined to be 400 mg. Eighty-seven subjects with heavily pretreated HR-positive, HER2-negative metastatic breast cancer were treated with alpelisib (300 mg, 350 mg, or 400 mg q.d.) in combination with fulvestrant (500 mg i.m. administered on Days 1 and 15 of the first cycle and Day 1 of subsequent cycles). The MTD for alpelisib in combination with fulvestrant was declared at 400 mg. The recommended dose for expansion (further development) was determined to be 300 mg as a result of its acceptable safety profile, lower risk for hyperglycemia or rash compared with 400 mg, adequate exposure, and preliminary evidence of clinical activity.

Fulvestrant was administered in accordance with its well-established dosing regimen: 500 mg i.m. on Days 1 and 15 of Cycle 1 and Day 1 of subsequent treatment cycles.

The clinical results of Study CBYL719C2301 as well as the accompanying exposure-response analysis are in further support of the 300 mg dose in the target indication.

The FDA's Assessment:

Based on the results of the SOLAR-1 trial, the alpelisib 300 mg QD dosage is acceptable for approval, given a statistically significant improvement in PFS compared to the placebo group (11.1 months vs. 3.7 months) in patients whose tumors had an alteration (i.e. mutation or amplification) of the PIK3CA gene (Figure 7). However, the starting dose of 300 mg QD is high, with 75% of participants requiring dose adjustment (dose reduction and/or interruption) and 25% discontinuing due to treatment-related AEs such as hyperglycemia, diarrhea, and rash.

Selection of the alpelisib 300 mg QD dosing schedule was based on the results of the first-in-human study BYL719X2101. Based on the applicant's assessment, similar levels of pharmacodynamic and clinical activity were observed among the dose levels explored (300, 350, and 400 mg QD) of alpelisib plus fulvestrant (500 mg) combination (Table 5). Compared to higher dose levels of 350 or 400 mg QD, lower incidences in AE leading to dose reduction and/or interruption, and study drug discontinuation (Table 6) was observed at the dose level of 300 mg QD. However, the observed lower incidence of AEs (33% dose adjustments and 0% treatment discontinuation) was misleading, possibly due to small subject number (N=9), as high dose reduction/interruption of 75% and treatment discontinuation of 25% were observed in Phase 3 Study CBYL719C2301 with alpelisib 284 treated patients.

Stable doses in individual patients were reached quickly in the first two treatment cycles by dose reductions, as demonstrated by the median time to the first dose reduction of 1.81 (95% CI: 1.41, 2.79) months in the overall patient population (Figure 1) in SOLAR-1. The dosing vs. time data (Figure 2) also suggested that alpelisib dose stabilized within the first 2 months of the treatment. During the remainder of the treatment period, around 40%, 30% and 30% of patients received daily doses of alpelisib at 300 mg, 250 mg, and 200 mg, respectively.

Exposure-response (E-R) analyses on safety conducted by both the applicant and FDA showed that greater alpelisib exposure was associated with an increase in the risk of hyperglycemia adverse events (of grade ≥ 2 and grade ≥ 3), suggesting alpelisib dose couldn't go above 300 mg QD. E-R analysis of efficacy conducted by FDA showed a trend for greater efficacy with increasing exposure, suggesting that lower dose may compromise the efficacy. The dose levels lower than 300 mg QD have not been tested. A non-inferiority trial at a lower dose (e.g. 250 mg QD or lower) would be difficult to conduct, given the large sample size required and the availability of other treatment options (i.e. CDK 4/6 inhibitors) for this patient population.

Table 5: Best overall response of alpelisib plus fulvestrant combination therapy in Study BYL719X2101

	Alpelisib 300 mg plus fulvestrant N=9 n (%)	Alpelisib 350 mg plus fulvestrant N=8 n (%)	Alpelisib 400 mg plus fulvestrant N=32 n (%)	All subjects N=49 n (%)
Best overall response				
Complete response (CR)	0	0	0	0
Partial response (PR)	3 (33.3)	3 (37.5)	8 (25.0)	14 (28.6)
Stable disease (SD)	6 (66.7)	5 (62.5)	14 (43 8)	25 (51.0)
Progressive disease (PD)	0	0	6 (18.8) [1]	6 (12.2)
Unknown	0	0	4 (12.5)	4 (8.2)
Overall response rate (ORR) (CR or PR)	3 (33.3)	3 (37.5)	8 (25.0)	14 (28.6)
95% CI for ORR	(7.5, 70.1)	(8.5, 75.5)	(11.5, 43.4)	(16.6, 43.3)
Disease control rate (DCR) (CR or PR or SD)	9 (100)	8 (100)	22 (68 8)	39 (79.6)
95% CI for DCR	(66.4, 100.0)	(63.1, 100.0)	(50.0, 83.9)	(65.7, 89.8)
Clinical benefit rate (CBR) (CR or PR or SD > 24 weeks)	4 (44.4)	7 (87.5)	11 (34.4)	22 (44.9)
95% CI for CBR	(13.7, 78.8)	(47.3, 99.7)	(18.6, 53.2)	(30.7, 59.8)

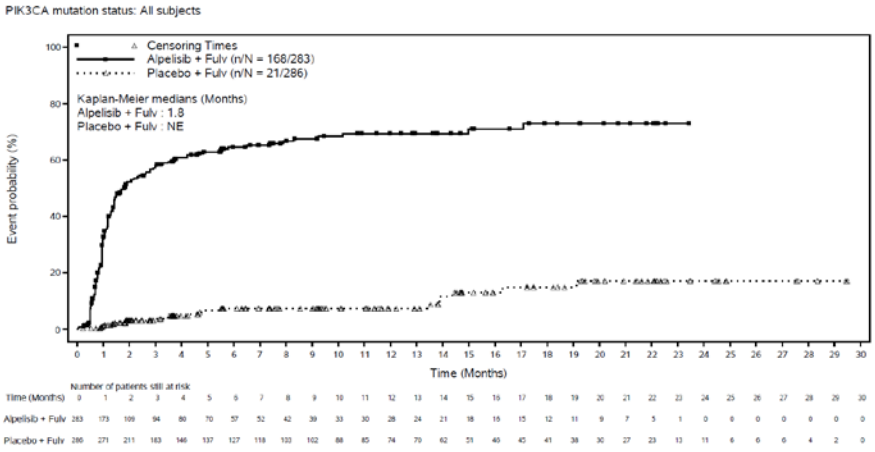
Source: Table 3-14 of Applicant's Summary of Clinical Efficacy

Table 6: Adverse events leading to dose reduction and/or interruption and study drug discontinuation by alpelisib plus fulvestrant in Study BYL719X2101 and SOLAR-1

Study	Alpelisib Dose	Patient number	Dose reduction and/or interruption	Study Drug discontinuation
BYL719X2101	300 mg QD	9	33.3%	0%
	350 mg QD	8	87.5%	0%
	400 mg QD	70	71.4%	12.9%
CBYL719C2301	300 mg QD	284	75%	25%

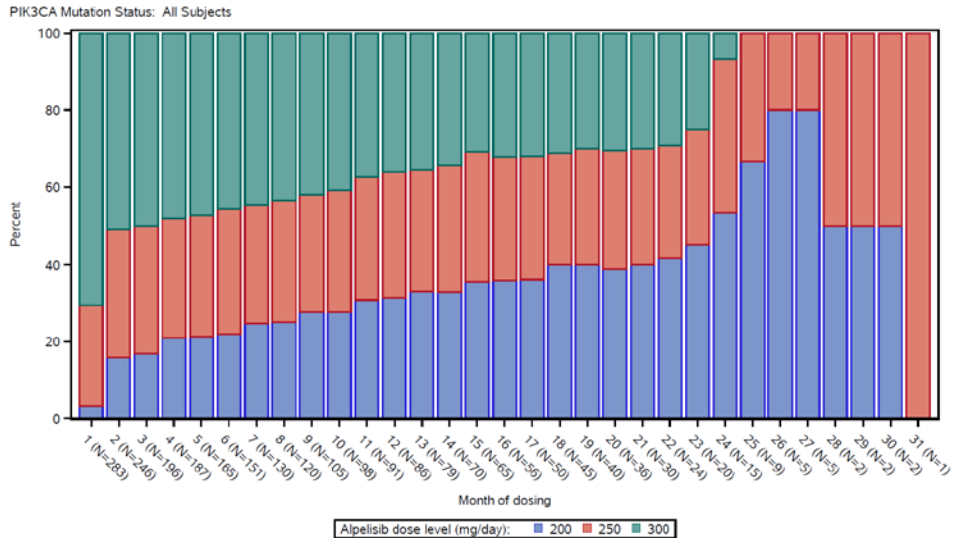
Source: Tables 1-7, 2-15 and 2-16 of Applicant's Summary of Clinical Safety

Figure 1: Kaplan-Meier plot of time to first alpelisib/placebo dose reduction by treatment in SOLAR-1



Source: Figure 6-1.1 of Applicant's Summary of Clinical Safety

Figure 2: Stacked Column plot of alpelisib dose level by treatment month/cycle in SOLAR-1



Source: Figure 1-1 of Applicant's response to FDA IR conveyed on January 31, 2019.

6.2.2.2. Therapeutic Individualization

The Applicant's Position:

No therapeutic individualization is needed in the proposed indication based on demographic factors (body weight, age, gender), DDIs that may affect alpelisib pharmacokinetics, or in special populations (hepatic or renal impairment). For more information, see Section 6.3.2.

The FDA's Assessment:

The FDA agrees with the applicant's position that no therapeutic individualization is needed based on demographic factors (body weight, age, sex), in patients with mild, moderate, or severe hepatic impairment (based on Child-Pugh classification), in patients with mild or moderate renal impairment, or in patients who take acid reducing agents.

However, the FDA does not agree with the applicant's position regarding the DDI potential. See additional FDA comments in Section 6.3.2.4.

6.2.2.3. Outstanding Issues

The Applicant's Position:

None

The FDA's Assessment:

Two PMC clinical pharmacology studies are described in Table 4:

- ***Conduct a clinical trial to evaluate the effect of repeat doses of a strong CYP3A4 inducer on pharmacokinetics of alpelisib to assess the magnitude of decreased alpelisib exposure and to determine appropriate dosing recommendations. Design and conduct the trial in accordance with the FDA Guidance for Industry; "Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications."***

- ***Conduct a clinical trial to evaluate the effect of repeat doses of alpelisib on the single dose pharmacokinetics of sensitive probe substrates to assess the magnitude of exposure change for sensitive substrates of CYP2B6, CYP3A4 and CYP2C-family enzymes (CYP2C9, CYP2C19 and / or CYP2C8) and to determine appropriate dosing recommendations. Design and conduct the trial in accordance with the FDA Guidance for Industry; "Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications."***

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

An overview of the ADME properties, clinical pharmacokinetics, and DDI potential of alpelisib is provided below.

Absorption: Alpelisib is classified as a BCS Class II compound (low solubility, high permeability). Under fed conditions absorption is virtually complete (> 99%) independent of dose across the tested dose range (30-450 mg) based on absorption biopharmaceutics modelling. Bioavailability in vivo under fasted conditions is limited by solubility, resulting in a fraction absorbed of 68.7% after a 300 mg and 50-60% for a 400 mg single dose in healthy subjects.

Distribution: The apparent volume of distribution was 114 L (49% CV) based on Phase III population PK analysis, suggesting wide distribution into tissues compared to total body water. The fraction of alpelisib bound to plasma proteins in vitro was moderate (89.2%) and independent of plasma concentrations. Alpelisib was equally distributed between plasma and red blood cells. Evidence suggests that alpelisib and BZG791 are not able to cross the blood-brain-barrier in humans.

Metabolism: Alpelisib's primary metabolism pathway in vivo is amide hydrolysis to BZG791, which is the major circulating metabolite in plasma. BZG791 is pharmacologically inactive and does not contribute to clinical activity. Formation of BZG791 is governed by multiple, ubiquitously expressed, high-capacity enzymes (esterases, amidases, and choline esterase) that

are unlikely to become subject to drug-drug-interactions. Metabolism of alpelisib is therefore largely non-hepatic which was further confirmed by the results from the hepatic impairment study that showed no significant increase in alpelisib exposure with severe hepatic impairment (Child-Pugh class C). The overall contribution of liver-mediated metabolism (CYP-mediated Phase I and Phase II metabolism together) was low, contributing to ≤ 15% of the elimination.

Excretion: Alpelisib and its metabolites are almost exclusively excreted in the feces (81.0%) after oral administration, most likely through hepatobiliary export and/or intestinal secretion of either unchanged parent or metabolized to BZG791. Excretion in the urine is minor (13.5%), with only a fraction of the dose being excreted as unchanged alpelisib (2%).

Clinical Pharmacokinetics: Alpelisib was quickly absorbed following single dose and repeated daily administration with a median Tmax of 2-4 hours independent of dose and time in most cancer subjects. Cmax and AUC0-24 increased in an approximately dose proportional manner after daily oral dosing of alpelisib in the fed state. Alpelisib terminal half-life was short (~9 hours) based on population analysis. After repeated daily administration, alpelisib only minimally accumulates in plasma (between 1.3- and 1.5-fold) with steady state reached by day 3. Single-agent PK under fed conditions showed moderate inter-subject variability (~20-40%) in subjects with cancer. Intra-subject variability was high (CV% ≥ 30%) in cancer subjects across the dose range between 30 mg and 450 mg. PK in subjects with cancer was consistent between studies.

The primary metabolite BZG791 had similar PK characteristics as the parent drug with concentration time course of the metabolite being parallel to that of the parent (formation-rate limited metabolite). Following single dose and repeated daily administration of alpelisib, median Tmax across studies (and food conditions) was approximately 4 hours. The apparent elimination half-life was similar to the parent drug, indicating that accumulation of the metabolite is limited. In the systemic circulation, the relative abundance of BZG791 was usually between 20% and 30% of alpelisib.

In vitro victim DDI risk: Alpelisib is a substrate of BCRP. Alpelisib is metabolized by CYP3A4 in vitro but the in vivo relevance was found to be minor in the human mass balance study (fm, CYP3A4 ~0.12). The clinical relevance of these interactions are described in Section 6.3.2.4.

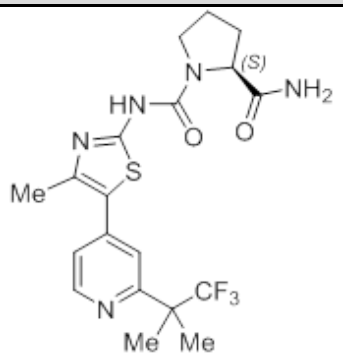
In vitro perpetrator DDI risk: The DDI potential of alpelisib and its primary metabolite BZG791 was assessed in vitro with all common metabolic enzymes and transporters**.** Alpelisib may only induce the metabolic clearance of co-medications metabolized by CYP2B6, CYP2C9, and CYP3A, and may inhibit the metabolic clearance of co-medications metabolized by CYP3A4/5 (strong time-dependent inhibition). The clinical relevance of these interactions are described in Section 6.3.2.4. BZG791 will not cause any metabolic or transporter-mediated DDIs with concomitant medications based on its systemic exposure and low free fraction.

<u>The FDA's Assessment:</u>

The FDA generally agrees with the applicant's position on general pharmacology and pharmacokinetic characteristics. However, the FDA does not agree with the applicant's PBPK model prediction in fraction of absorption under fasted or fed condition. The FDA also does not agree with the applicant's position on alpelisib's low potential to inhibit p-gp based on a static DDI risk assessment.

The general overview of alpelisib ADME and clinical PK information as assessed by the FDA are presented in Table 7:

Table 7: Highlights of Clinical Pharmacology for Alpelisib

Physiochemical properties	
Chemical structure and molecular weight	 Chemical Structure of alpelisib Molecular weight: 441.47 g/mol LogD: 2.8 in an n-octanol/pH 6.8 buffer system (Source: Tables 1-1 and 1-2 of Applicant's Summary of Biopharmaceutics studies)

<table>
<tr><td>Aqueous solubility</td><td>Alpelisib has two experimentally determined dissociation constants with pKa values of 3.3 and 9.4
<table>
<tr><th>Solvent</th><th>Solubility (mg/mL)</th></tr>
<tr><td>Water</td><td>0.02 mg/mL</td></tr>
<tr><td>pH 1.0 (HCl 0.1N)</td><td>3.64 mg/mL</td></tr>
<tr><td>SGF (pH 1.1)</td><td>1.43 mg/mL</td></tr>
<tr><td>Buffer pH 2.0 (citrate)</td><td>0.37 mg/mL</td></tr>
<tr><td>Buffer pH 3.0 (citrate)</td><td>0.08 mg/mL</td></tr>
<tr><td>Buffer pH 4.0 (acetate)</td><td>0.03 mg/mL</td></tr>
<tr><td>Buffer pH 5.0 (acetate)</td><td>0.02 mg/mL</td></tr>
<tr><td>FeSSIF (pH 5.0)</td><td>0.32 mg/mL</td></tr>
<tr><td>Buffer pH 6.8 (phosphate)</td><td>0.02 mg/mL</td></tr>
<tr><td>FaSSIF (pH 6.5)</td><td>0.04 mg/mL</td></tr>
</table>
Source: Tables 1-2 and 1-3 of Applicant’s Summary of Biopharmaceutics</td></tr>
<tr><td colspan="2">Pharmacology</td></tr>
<tr><td>Mechanism of Action</td><td>Alpelisib is an alpha-specific inhibitor of phosphatidylinositol-3-kinase (PI3K). Gain-of-function mutations in the gene encoding the catalytic α-subunit of PI3K (PIK3CA) lead to activation of PI3Kα and growth-factor independent activation of Akt-signaling, cellular transformation and the generation of tumors in in vitro and in vivo models.</td></tr>
<tr><td>Active Moieties</td><td>Alpelisib</td></tr>
<tr><td>QT/QTc Prolongation</td><td>The effect of alpelisib was evaluated in Study BYL719X2101. The dose groups with the largest sample sizes (400 mg QD with or without fulvestrant) were used to characterize the effects on QTc interval. These treatment groups cover the therapeutic exposures when dosing with the proposed clinical dose, 300 mg QD. There was no placebo or positive control in the study.

An analysis of clinical ECG data demonstrates the absence of large effect (i.e. >20 ms) on QTcF prolongation at the recommended 300 mg dose with or without fulvestrant.
<table>
<tr><th>ECG parameter</th><th>Dose Regimen</th><th>Time</th><th>ΔQTcF (ms)</th><th>90% CI (ms)</th></tr>
<tr><td>QTc</td><td>Alpelisib 400 mg QD</td><td>C1D8- 8 hrs post-dose</td><td>12.4</td><td>(7.4, 17.4)</td></tr>
<tr><td>QTC</td><td>Alpelisib 400 mg QD + Fulvestrant</td><td>C1D8- 2 hrs post-dose</td><td>8.4</td><td>(4.8, 11.9)</td></tr>
</table>
Source: Table 1 of FDA QT-IRT review.</td></tr>
<tr><td colspan="2">General Information</td></tr>
</table>

<table>
<tr><td>Bioanalysis</td><td>In the pivotal study CBYL719C2301, alpelisib and its major metabolite, BZG791, were measured using validated LC-MS/MS methods. A summary of the method validation reports is included as an appendix.</td></tr>
<tr><td>Healthy Volunteers vs. Patients</td><td>Lower exposure was observed for alpelisib in healthy subjects compared to subjects with cancer, though data for comparison under the same PK conditions were limited and confounded by other factors. On the other hand, alpelisib PK in patients with cancer were consistent between studies.</td></tr>
<tr><td>Drug exposure at steady state following the therapeutic dosing regimen</td><td>In adult patients who received alpelisib 300 mg once daily in Study CBYL719C2301, popPK approach derived mean steady-state alpelisib (CV%) for Cmax was 2480 (23%) ng/mL and $AUC_{0\text{-}24hr}$ was 33224 (21%) ng*h/mL.</td></tr>
<tr><td>Minimal effective dose or exposure</td><td>Not determined. Dose levels lower than 300 mg were not tested.</td></tr>
<tr><td>Maximal tolerated dose or exposure</td><td>In Study BYL719X2101, the established MTD of alpelisib single-agent treatment in patients with advanced solid malignancies was 400 mg QD.</td></tr>
<tr><td>Dose Proportionality</td><td>Alpelisib showed dose-proportional increase in both C_{max} and AUC across the dose range of 30 to 450 mg following a single dose and multiple doses. Oral plasma clearance values of alpelisib (CL/F) were similar following a single dose and at steady state, suggesting that alpelisib exhibits linear PK in humans. See 18.3 OCP Appendices for detail.
<table>
<tr><th>Estimated slopes (90% CI)</th><th>Single Dose</th><th>Multiple Doses</th></tr>
<tr><td>Cmax</td><td>0.93 (0.79, 1.07)</td><td>0.97 (0.88, 1.07)</td></tr>
<tr><td>AUC</td><td>1.01 (0.90, 1.12)</td><td>1.00 (0.91, 1.09)</td></tr>
</table>
Source: Section 3.1.8 of the Applicant’s Summary of Clinical Pharmacology</td></tr>
<tr><td>Accumulation</td><td>The mean accumulation ratios (R_{acc}) following alpelisib 90 to 450 mg QD were between 1.3- and 1.5-fold</td></tr>
<tr><td>Variability</td><td>Following alpelisib 300 to 400 mg QD + fulvestrant combination treatments, the inter-subject variability (CV%) of steady state alpelisib AUC_{tau} and C_{max} was 23% and 30%, respectively.</td></tr>
<tr><td colspan="2">Absorption</td></tr>
<tr><td>Bioavailability</td><td>The absolute bioavailability of alpelisib is unknown.</td></tr>
<tr><td>T_{max}</td><td>The median time to reach peak plasma concentration (Tmax) ranged between 2.0 to 4.0 hours.</td></tr>
</table>

<table>
<tr><td>Food effect (Fed/fasted)</td><td>In Study BYL719A2103, both high-fat high-calorie meal (HFHC, 985 calories with 58.1 g of fat) and low-fat low-calorie meal (LFLC, 334 calories with 8.7 g of fat) showed a positive food effect on absorption of alpelisib in healthy subjects. No significant difference was found for AUC_{inf} between LFLC and HFLC with a GMR of 0.978 (90%CI: 0.876, 1.09).
<table>
<tr><th></th><th>R_AUC_{0-inf} (GMR, 90% CI)</th><th>R_C_{max} (GMR, 90% CI)</th><th>T_{max} (hours) (range)</th></tr>
<tr><td>Fasted</td><td>N/A</td><td>N/A</td><td>2.0 (1.0 – 2.5)</td></tr>
<tr><td>HFHC</td><td>1.73 (1.55-1.93)</td><td>1.84 (1.56-2.17)</td><td>3.0 (1.0 – 4.1)</td></tr>
<tr><td>LFLC</td><td>1.77 (1.58-1.97)</td><td>2.45 (2.08-2.89)</td><td>2.5 (1.0 – 4.0)</td></tr>
</table>
Source: Table 2-1 of Applicant’s Summary of Clinical Pharmacology</td></tr>
<tr><td>Acid-reducing agent effect (Ranitidine)</td><td>In Study BYL719A2103, coadministration of the H_2 receptor antagonist ranitidine in combination with a single 300 mg oral dose of alpelisib decreased the absorption and overall exposure of alpelisib. In the presence of a low-fat low-calorie meal, AUC was decreased on average by 21% and Cmax by 36% with ranitidine. Under the fasted state, AUC was decreased on average by 30% and Cmax by 51% with ranitidine.
<table>
<tr><th></th><th>R_AUC_{0-inf} (GMR, 90% CI)</th><th>R_C_{max} (GMR, 90% CI)</th><th>T_{max} (hours) (range)</th></tr>
<tr><td>Fasted</td><td>0.70 (0.62-0.78)</td><td>0.49 (0.42-0.58)</td><td>2.0 (1.5 – 4.1)</td></tr>
<tr><td>LFLC</td><td>0.79 (0.71-0.88)</td><td>0.64 (0.54-0.75)</td><td>2.5 (1.5 – 4.0)</td></tr>
</table>
Source: Table 2-1 of Applicant’s Summary of Clinical Pharmacology

Alpelisib can be coadministered with acid reducing agents, since alpelisib should be taken with food. Food exhibited a more pronounced effect on the solubility of alpelisib than the effect of gastric pH value.</td></tr>
<tr><td colspan="2">Distribution</td></tr>
<tr><td>Volume of distribution</td><td>The popPK approach derived mean (%CV) apparent volume of distribution of alpelisib at steady-state is 114 L (46%).</td></tr>
<tr><td>Plasma protein binding</td><td>In vitro, protein binding of alpelisib is 89% and is independent of concentration.</td></tr>
<tr><td>Blood to plasma ratio</td><td>The mean blood-to-plasma ratio was 1.03 for alpelisib.</td></tr>
<tr><td colspan="2">Elimination</td></tr>
<tr><td>Half-life</td><td>The popPK approach derived terminal half-life of alpelisib is 8 to 9 hours.</td></tr>
<tr><td>Clearance</td><td>The popPK approach derived mean (%CV) clearance of alpelisib is 9.2 L/hr (21%) under fed conditions.</td></tr>
<tr><td colspan="2">Metabolism</td></tr>
</table>

Primary metabolic pathway(s)	• In vitro, alpelisib is primarily metabolized by chemical and enzymatic hydrolysis to form its metabolite BZG791 and to a lesser extent by CYP3A4. • In vivo, the relative abundance of BZG791 in the systemic circulation is between 20% and 30% of alpelisib. BZG791 exhibits similar PK characteristics as the parent drug with concentration time course of the metabolite being parallel to that of the parent (formation-rate limited metabolite). • In vitro, alpelisib is a substrate of BCRP.
Inhibitor/Inducer	• In vitro, alpelisib is a strong time-dependent inhibitor of CYP3A4. Alpelisib was also identified to be a strong inducer of CYP3A4. • In vitro, alpelisib induces mRNA and activity of CYP2B6 and CYP2C9. • In vitro, alpelisib inhibits P-gp at clinically relevant concentration ranges. • In vitro, alpelisib showed low potential to inhibit SULT, BSEP, OATP1B1, OATP1B3, OCT1, OAT3, MATE1, and MATE2K at clinically relevant concentrations. Alpelisib didn't show modulatory effect on other drug metabolizing enzymes or transposers. • In vitro, BZG791 showed low potential to induce CYP2B6 and CYP2C9. BZG791 showed low potential to inhibit CYP2C8, OCT1, OATP1B1, OATP1B3, BCRP, BSEP, OAT1, OAT3, MATE1 and BCRP. BZG791 didn't show modulatory effect on other drug metabolizing enzymes or transposers.
Excretion	
Primary excretion pathways (% dose) ±SD	Following a single oral dose of 400 mg radiolabeled alpelisib under fasted condition, 81% of the administered dose was recovered in feces (36% unchanged, 32% BZG791) and 14% (2% unchanged, 7.1% BZG791) in urine. CYP3A4-mediated metabolites (12%) and glucuronides amounted to approximately 15% of the dose.

6.3.2. Clinical Pharmacology Questions

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

The Applicant's Position:

Yes. Results from the Phase III exposure-efficacy (PFS) analyses show that a higher median exposure or dose intensity of alpelisib leads to a greater treatment benefit in subjects with PIK3CA mutation in combination with fulvestrant, supporting the use of 300 mg. Adverse events, such as rash or hyperglycemia, can be managed through dose interruptions and dose reductions to 250 mg and to 200 mg (if toxicities cannot be managed by interruptions and clinical intervention alone). Hence, alpelisib has a positive benefit-risk ratio at a 300 mg daily dose regimen.

The FDA's Assessment:

The FDA generally agrees with applicant's position. See the FDA's assessment in Section 6.2.2.1 for more details.

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

The Applicant's Position:

Yes. The proposed dose of 300 mg daily is effective and generally well tolerated with no dosing difference based on gender. No new safety signals were identified in Study CBYL719C2301; AEs were effectively managed with concomitant medications, and dose interruption and/or reduction as needed. Safety data from Study CBYL719C2301 were consistent with the alpelisib mechanism of action and results from previous studies. Adverse events were transient and reversible upon alpelisib treatment discontinuation. Details of AEs are provided in Section 8.2.

The FDA's Assessment:

The proposed dose of alpelisib 300 mg QD is approvable from a clinical pharmacology perspective. Although the alpelisib 300 mg QD dose is high (75% of participants in SOLAR-1 required dose reduction/interruption), dose levels lower than 300 mg QD have not been adequately evaluated in the clinical trials. A non-inferiority trial at a lower dose (e.g. 250 mg QD) would be challenging given the large sample size required and the availability of other treatment options (i.e. CDK 4/6 inhibitors) for this patient population. See FDA's assessment in Section 6.2.2.1 for more details.

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

The Applicant's Position:

No. Based on the assessment of intrinsic factors, no dose adjustment or change in regimen is required based on demographics or in special populations (i.e. hepatic and renal impairment).

Demographic Factors

Based on population analyses from Phase I and Phase III data, there was no clinically meaningful difference in alpelisib PK across ethnicities (i.e. Japanese vs non-Japanese, Asian vs. Non-Asian) that warrant dose adjustments. Data for some ethnic groups were limited. Therefore, based on PK data, no dose adjustment of alpelisib is recommended for any ethnicity or race.

Special Populations

Hepatic impairment: No dose adjustment is necessary in subjects with mild, moderate, or severe hepatic impairment based on both the results of the hepatic impairment Study CBYL719A2105 in subjects with moderate and severe hepatic impairment (based on Child-Pugh classification) and population PK analyses of data collected from studies in cancer subjects with varying degrees of impairment based on NCI criteria.

Renal impairment: No dose adjustment is necessary in subjects with mild or moderate renal impairment based upon the understanding of the fractional elimination pathway (i.e. negligible renal excretion and limited liver mediated metabolism) and further supported by the results of population PK analyses (Phase I and III analysis). Caution should be used in subjects with severe renal impairment, as no dedicated study in subjects with severe renal impairment was conducted with alpelisib and since there is no experience with fulvestrant in this population.

The FDA's Assessment:

The FDA generally agrees. In the labeling, the FDA stated that the effect of severe renal impairment (CLcr < 30 mL/min) on alpelisib PK is unknown.

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

The Applicant's Position:

The clinically relevant food-drug and drug-drug interactions with concomitant medications are described in further detail below with their respective recommendation for management.

Effect of food
Alpelisib absorption is affected by food. Safety, efficacy, and PK (including dose-proportionality) of alpelisib have been established in the fed state in cancer subjects from studies included in the dossier. In healthy volunteers after a single 300 mg oral dose of alpelisib, compared to the fasted state, a high-fat, high-calorie (HFHC) meal increased AUCinf by 73% and Cmax by 84%, and a LFLC meal increased AUCinf by 77% and Cmax by 145%. No significant difference was found for AUCinf between LFLC and HFHC showing that neither fat content nor overall caloric intake has an impact on absorption. The increase in gastrointestinal solubility by bile, secreted in response to food intake, is considered the cause of the food effect. Therefore, alpelisib should be taken immediately after food, at approximately the same time each day.

Co-administration of alpelisib with BCRP inhibitors
Alpelisib is a substrate of the efflux transporter BCRP. Based on an integrated risk assessment of the available in vitro data, absorption of alpelisib is unlikely to be affected by BCRP inhibition due to saturation of the transporter in the intestine. However, due to the involvement of BCRP in the hepatobiliary export and intestinal secretion of alpelisib and in the absence of clinical data, caution is advised when co-administering alpelisib with a clinically proven BCRP inhibitor, as inhibition of BCRP in the liver and in the intestine during the elimination phase could potentially lead to an increase in systemic exposure of alpelisib.

Effect of alpelisib on CYP3A4 substrates
In vitro studies showed that alpelisib is a strong time-dependent inhibitor of CYP3A4. Alpelisib was also identified to be a strong inducer of CYP3A4. Due to the complex nature of concurrent

and opposing time-dependent inhibition and induction of CYP3A4, the magnitude of the effect was investigated by both a clinical DDI study and supporting PBPK simulations. Based on the results of both the in silico PBPK predictions and clinical results in Study BYL719Z2102, no dose adjustment is recommended when co-administering alpelisib with sensitive CYP3A4 substrates such as everolimus and midazolam, as the time-dependent inhibition of CYP3A4 was largely offset by a comparably strong CY3A4 induction effect, resulting in a net in vivo DDI potential of alpelisib as a weak perpetrator that is not clinically relevant.

Caution is recommended, however, with drugs, which are auto-inhibitors, or auto-inducers of CYP3A4 and which have narrow therapeutic windows. Systemic exposure of such drugs may be decreased or increased when co-administered with alpelisib depending on the drug's own auto-inhibition or auto-induction potential, based on PBPK modelling.

Effect of alpelisib on CYP2C9 and CYP2B6

CYP2C9: (b) (4) In the absence of clinical data, however, caution is recommended when alpelisib is co-administered with drugs that are sensitive CYP2C9 substrates and have a narrow therapeutic window, such as warfarin.

CYP2B6: In the absence of clinical data, use of sensitive CYP2B6 substrates or CYP2B6 substrates with a narrow therapeutic window should be cautioned, as alpelisib may reduce the clinical activity of such drugs based on static mechanistic assessment.

The FDA's Assessment:

The FDA generally agrees with the applicant's position on the food effect, BCRP inhibitors, as well as some drug metabolizing enzymes and transporters. However, the FDA does not agree with applicant's position on the effect of alpelisib on substrates of CYP3A4, CYP2C9 and CYP2B6, as described below (see Section 18.3 OCP Appendices for detail):

Effect of alpelisib on PK of CYP3A4 substrates

The FDA concluded that the applicant should conduct a PMC clinical trial to evaluate the effect of repeat doses of alpelisib on the single dose pharmacokinetics of sensitive substrates of CYP3A4 to assess the magnitude of exposure change for sensitive CYP3A4 substrates and to determine appropriate dosing recommendations, based on the following rationales:

- ***In vitro, alpelisib is a strong time-dependent inhibitor (TDI) with a KI of 5.6 µM (5.2 µM unbound) and a kinact of 0.011 (min^{-1}). Alpelisib was also identified as a strong inducer of CYP3A4 in a hepatocyte induction assay (EC_{50} = 1.7 µM, E_{max} = 0.83 relative to rifampicin as control). Alpelisib is also a weak inhibitor of P-gp.***

- ***In vivo, the effect of alpelisib on the steady-state PK of everolimus (a substrate for both CYP3A4 and P-gp) was small and considered not clinically meaningful (Table 8). However, FDA's assessment suggested that this clinical DDI study cannot differentiate the modulatory effect of alpelisib on CYP3A4 and P-gp. Therefore, the effect of alpelisib on CYP3A4 cannot be determined by this DDI study with everolimus.***

Table 8: Effect of alpelisib on everolimus PK parameters

		$AUC_{tau}R$* (90% CI)	**$C_{max}R$* (90% CI)**
Everolimus	Cycle 1 day 15 (N = 17)	1.04 (0.93, 1.18)	1.12 (0.97, 1.29)
	Cycle 2 day 1 (N = 14)	0.88 (0.78, 1.01)	1.11 (0.95, 1.29)

* compared to the baseline data from Cycle 1 day 7
Source: Table 2-4 of the Applicant's Summary of Clinical Pharmacology

- ***The FDA does not agree with the Applicant's PBPK model predictions of the effect of alpelisib on CYP3A4 substrates, including CYP3A4 auto-inducers and auto-inhibitors, because there are multiple gaps existing in the model validation.***
- ***The FDA recommends a cocktail DDI study to evaluate the effect of alpelisib on CYP3A4 together with CYP2B6 and CYP2C-family enzymes (CYP2C9, CYP2C19 and/or CYP2C8) using the sensitive index substrates to fulfill PMC #3 (See Section 13).***

Effect of CYP3A4 inhibitors and inducers on PK of alpelisib

The FDA concluded that the applicant should conduct a clinical trial to evaluate the effect of repeat doses of a strong CYP3A4 inducer on pharmacokinetics of alpelisib to assess the magnitude of decreased alpelisib exposure and to determine appropriate dosing recommendations, based on the following rationales:

- ***Due to the minor contribution of CYP3A4 to the alpelisib systemic clearance (fm~ 0.12), the effect of strong CYP3A4 inhibitors on alpelisib PK is expected to be low. The reviewers conclude that a low DDI risk is expected for alpelisib as victim with a strong CYP3A inhibitor.***
- ***However, the FDA does not agree with the applicant's PBPK model predictions of the effects of rifampicin (a CYP3A auto-inducer) on alpelisib PK due to uncertainties. In addition, based on the literature reported clinical PK study of alpelisib with a CYP3A inducer encorafenib, alpelisib (200 mg) exposure was reduced by up to 45% with coadministration of 300 mg encorafenib (van Geel et al 2017). However, due to the small number of patients included in the data analysis (n=2 to 4), the DDI of alpelisib as victim with CYP3A inducer in inconclusive. Before the availability of PMC DDI study, the labeling recommends that coadministration of alpelisib with a strong CYP3A4 inducer be avoided.***

Effect of alpelisib on CYP2C9, CYP2B6, CYP2C8 and CYP2C19

The FDA concluded that the applicant should conduct a clinical trial to evaluate the effect of

repeat doses of alpelisib on the single dose pharmacokinetics of sensitive substrates of CYP2B6 and CYP2C-family enzymes (CYP2C9, CYP2C19 and / or CYP2C8), to assess the magnitude of exposure change for sensitive substrates of the above CYP enzymes, and to determine appropriate dosing recommendations, based on the following rationales:

- ***In vitro, alpelisib induces mRNA and activity of CYP2B6 and CYP2C9.***
- ***The FDA does not agree with the applicant's PBPK model predictions of the effects of alpelisib on PK of warfarin (a CYP2C9 substrate) due to the uncertainty associated with alpelisib's in vivo CYP2C9 induction effect. In the labeling, it is recommended that patients be closely monitored when alpelisib is coadministered with CYP2C9 substrates where decreases in the plasma concentration of these drugs may reduce activity.***
- ***The FDA does not agree with the applicant's static mechanistic assessments and PBPK model prediction of the effects of alpelisib on PK of bupropion (a CYP2B6 substrate) due to the uncertainty associated with alpelisib's in vivo CYP2B6 induction effect.***
- ***The effect of alpelisib on CYP2C8 and CYP2C19 had not been evaluated by the applicant at time of the NDA submission.***
- ***The FDA recommends a cocktail DDI study to evaluate the effect of alpelisib on CYP2B6 and CYP2C-family enzymes (CYP2C9, CYP2C19 and / or CYP2C8) together with CYP3A4 using the sensitive index substrates to fulfill PMC #3 (See Section 13).***

<u>Effects of alpelisib and active metabolite BZG791 on other drug metabolizing enzymes and transporters</u>

The FDA agrees with the applicant's assessment. The applicant used static DDI risk assessment with experimentally determined in vitro Ki values for alpelisib and major metabolite BZG791. Alpelisib displayed potential for P-gp inhibition based high luminal concentration in the intestine. Alpelisib and BZG791 showed low potential to inhibit BCRP, MRP2, BSEP, OATP1B1, OATP1B3, OCT1, OAT1, OAT3, OCT2, MATE1, and MATE2K at clinically relevant concentrations (Table 46 and Table 47). In vitro assays also suggested that alpelisib and BZG791 didn't show signal in modulating other drug metabolizing enzymes and transporters.

<u>Co-administration of alpelisib with acid reducing agents</u>

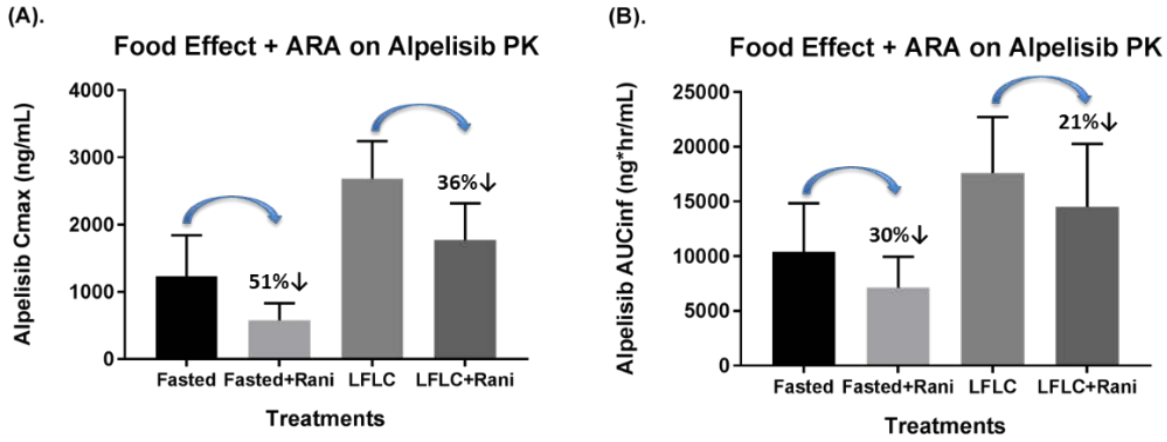
It is noteworthy that, in the SOLAR-1 trial, about 46% of patients took at least one dose of an acid reducing agent (ARAs), including proton pump inhibitors (PPIs), H_2 receptor antagonists, and antacids, and at least 21% of patients took ARAs consistently throughout treatment.

In Study BYL719A2103, the applicant evaluated the effect of co-administered H_2 receptor antagonist ranitidine on a single 300 mg oral dose of alpelisib either under fasted state or under fed state following a low-fat, low-calorie meal. However, whether the study results can be generalized to all ARAs is a question, given the fact that PPI are considered to represent

the worst-case scenario in the in vivo evaluation of pH effect because they generally have a more sustained suppression effect on gastric acid (Zhang et al 2014).

The study results of BYL719A2103 trial reported that AUC_{inf} was decreased by 21% and C_{max} by 36% with ranitidine compared to the fed state following a LFLC meal without co-administration of ranitidine; in the absence of food, the effect was more pronounced with a 30% decrease in AUC_{inf} and 51% decrease in C_{max} with ranitidine compared to the fasted state without co-administration of ranitidine (Figure 3). Of note, alpelisib absorption is enhanced by food and a LFLC meal increased AUC_{inf} by 77% and C_{max} by 145% compared to fasted state.

Figure 3: Effect of ranitidine on alpelisib Cmax (A) and AUC_{inf} (B) under fasted condition a fed condition following a low-fat, low-calorie (LFLC) meal



Source: Table 2-1 of Applicant's Summary of Clinical Pharmacology

The applicant's in vitro evaluations showed that alpelisib exhibits pH-dependent solubility (Table 9). The decrease in alpelisib solubility reached a plateau at 0.02 mg/mL when pH ≥ 5.0. The solubility of alpelisib in fed state simulated intestinal fluid (FeSSIF) increased substantially to 0.32 mg/mL, suggesting that solubility of alpelisib would have a significant increase under fed condition.

Table 9: Solubility of alpelisib

Solvent	Solubility (mg/mL)
Water	0.02 mg/mL
pH 1.0 (HCl 0.1N)	3.64 mg/mL
SGF[1] (pH 1.1)	1.43 mg/mL
Buffer pH 2.0 (citrate)	0.37 mg/mL
Buffer pH 3.0 (citrate)	0.08 mg/mL
Buffer pH 4.0 (acetate)	0.03 mg/mL
Buffer pH 5.0 (acetate)	0.02 mg/mL
FeSSIF[2] (pH 5.0)	0.32 mg/mL
Buffer pH 6.8 (phosphate)	0.02 mg/mL
FaSSIF[3] (pH 6.5)	0.04 mg/mL

[1] SGF: Simulated gastric fluid (pH ~1.1), prepared according to European Pharmacopeia 5.17.1
[2] FeSSIF: Fed state simulated intestinal fluid
[3] FaSSIF: Fasted state simulated intestinal fluid

Source: Table 1-3 of Applicant's Summary of Biopharmaceutics

Based upon published literature, food itself could increase the gastric pH from about 1.1 to 4.8, and ranitidine 300 mg with food could increase the gastric pH to about 6.5 (Kakuda et al 2006). Based on alpelisib in vitro solubility data (Table 9), if only pH change is taken into consideration, food alone would cause a significant decrease of solubility of alpelisib from about 1.5 mg/mL to a plateau of 0.02 mg/mL, and further increases in pH by use of an ARA would not further decrease solubility of alpelisib. In Study BYL719A2103, the fed state led to an approximately 75% increase in alpelisib systemic exposure compared to the fasted state; and in the presence of a LFLC meal, AUC_{inf} was decreased by 21% with ranitidine. These observations all indicate that food exhibits a more pronounced effect on the solubility of alpelisib than the effect of gastric pH value. This could be attributed to slowed gastric emptying, increased hepatic blood flow, prolonged gastrointestinal (GI) transit times relative to the fasted state, and stimulation of bile secretion (Farha et al 2019; Schmidt et al 2002).

Based on the above information, labeling recommendations are that alpelisib may be co-administered with acid reducing agents, given that alpelisib should be taken with food.

X

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7 Sources of Clinical Data

7.1. Table of Clinical Studies

The Applicant's Position:
All studies pertinent to the evaluation of efficacy and safety are summarized in Table 10.

Table 10: Listings of Clinical Trials Relevant to this NDA

Trial Identity NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of subjects enrolled	Study Population	No. of Centers and Countries
BYL719C2301 SOLAR-1) NCT02437318	Randomized, double-blind, placebo-controlled, international multicenter Phase III study	Alpelisib 300 mg once daily in 28-day cycle Fulvestrant i.m. on Days 1 and 15 of Cycle 1 and on Day 1 (± 3 days) of every cycle thereafter	**Primary:** PFS by Investigator assessment for PIK3CA mutant cohort **Key Secondary**: OS **Other secondary**: PFS by Investigator assessment for PIK3CA non-mutant cohort, ORR, CBR, ECOG performance status, change in global health status/QOL, characterization of PK of fulvestrant and alpelisib. Association between PIK3CA mutation status as measured in ctDNA at baseline with PFS	PIK3CA mutant cohort: median duration of exposure to treatment was 8.3 mo for the alpelisib plus fulvestrant arm and 5.5 mo for the placebo arm. Median duration of exposure to alpelisib was 5.5 mo.	572 PIK3CA mutant: 341 PIK3CA non-mutant: 231	Postmenopausal women and men with HR-positive, HER2-negative advanced breast cancer whose disease progressed on or after AI treatment	275 centers across 33 countries.
BYL719X2101 NCT01219699	Phase 1A, multicenter, open label dose escalation study	Alpelisib once daily: Alpelisib twice daily: 120, 150, 200 mg	**Primary:** MTD of alpelisib as single agent and in combination with fulvestrant **Secondary:** ORR, DCR, PK profile of alpelisib.	Median duration of exposure to: Combination study treatment - 7.4, 8.8, and 3.7 mo for alpelisib 300 mg, 350 mg, and 400 mg arms. Alpelisib - 7.2, 8.8, and 3.2 mo,	134	Adult subjects with advanced solid malignancies, whose tumors have an alteration of the PIK3CA gene.	11 centers across 5 countries

Trial Identity NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of subjects enrolled	Study Population	No. of Centers and Countries
				respectively Single agent alpelisib across all dose levels - 2.7 mo			
Studies to Support Safety							
BYL719X1101 NCT01387321	Phase 1, open-label, multicenter study in Japanese subjects	Alpelisib p.o. once daily: escalation part: 90, 180, 270, 350, 400 mg expansion part: 350 mg	**Primary**: MTD of BYL719 as single agent in subjects with advanced solid malignancies. **Secondary**: Safety and tolerability of BYL719, PK profile of BYL719 after single and multiple administrations, and ORR.	Median duration of exposure to alpelisib single agent across all dose levels: 2.3 mo	33 (including 4 subjects with breast cancer)	Adult subjects with advanced solid malignancies and documented genetic alteration of the PIK3CA gene	4 centers in 1 country
Other Studies (Clinical Pharmacology Studies)							
BYL719A2103	Single-center, open-label, randomized, five period, ten sequence crossover study	Single dose-300 mg, fasted and fed	**Primary:** Cmax, Tmax and AUCinf of alpelisib. Other PK parameters such as **Secondary**: Other PK parameters such as AUC0-t, AUClast, Cl/F, Vz/F, T1/2, derived PK parameters of ranitidine, and safety data.	Subjects received a single dose of 300 mg of alpelisib during each of the 5 periods	21	Healthy volunteers	1 center in in 1 country
BYL719X1101 NCT01387321	Details described above						
BYL719X2107	Single-center, open-label study	Single, oral dose of 400 mg ^{14}C-alpelisib (two gelatin	**Primary**: Recovery of ^{14}C-alpelisib, metabolite ID, metabolite % of dose excreted. Cmax, Tmax, T1/2 and AUC for alpelisib and its metabolite.	Subjects received a single dose of 400 mg of alpelisib	4	Healthy volunteers	1 center in one country

Trial Identity NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of subjects enrolled	Study Population	No. of Centers and Countries
		capsules)	**Secondary**: Safety				
BYL719A2105	Phase 1, open-label, single-dose, multicenter, parallel group study	Single, oral 300 mg dose of alpelisib for all groups	**Primary**: Cmax, AUClast, AUC inf **Secondary**: PK parameter after a single oral dose; Tmax, Cmax, AUC0-t, AUClast, AUCinf, CL/F, Vz/F and T1/2. Safety	Subjects received a single dose of 300 mg of alpelisib	23	Healthy volunteers and subjects with moderate and severe hepatic impairment	4 centers in one country
BYL719Z2102 NCT NCT02077933	Phase Ib dose-finding study		**Primary**: Incidence of DLT **Secondary**: Safety, PK parameters	Median duration of exposure: 82 days across all dose levels of doublet combination (alpelisib plus everolimus) and 123 days for triplet combination (alpelisib plus everolimus plus exemestane).	79	Subjects with advanced solid tumors	21 centers across 9 countries

<u>The FDA's Assessment:</u>

The FDA agrees with the applicant's table of studies of alpelisib. Study CBYL719C2301 (SOLAR-1) formed the basis for evaluation of the efficacy and safety of alpelisib in the indicated population.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The Applicant's Position:

The efficacy evaluation for this submission is based primarily on all efficacy data available at the time of the final PFS analysis in the subject population with a PIK3CA mutation from the registration Phase III Study CBYL719C2301. Data from the dose-expansion phase of Study CBYL719X2101 are used to support the efficacy evaluation.

The FDA's Assessment:

FDA agrees with the applicant's position.

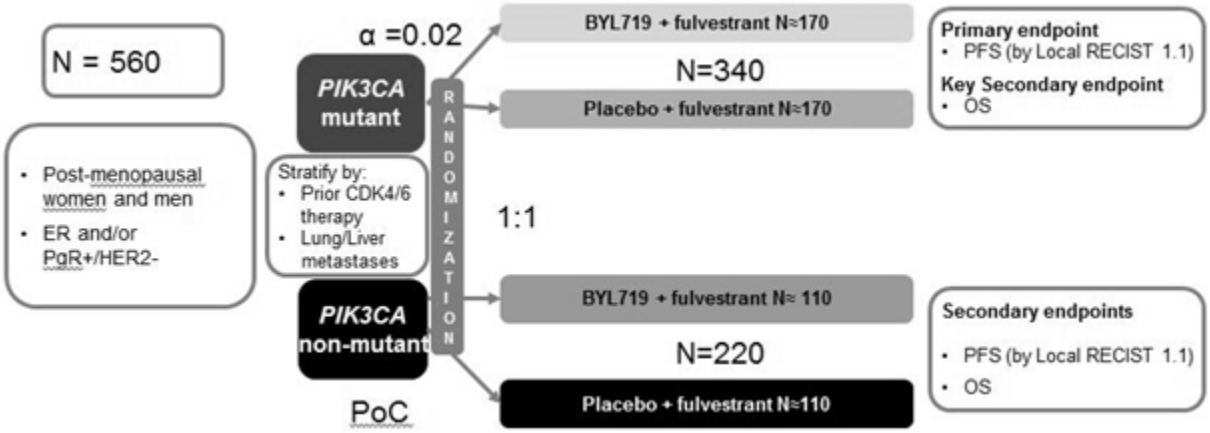
8.1.1. Study CBYL719C2301 (SOLAR-1 study)

The Applicant's Position:

Trial Design
Basic study design

This is a randomized, double-blind, placebo-controlled, international, multicenter Phase III study to determine the efficacy and safety of treatment with alpelisib plus fulvestrant versus placebo plus fulvestrant in men and postmenopausal women and men with HR-positive, HER2-negative advanced breast cancer which progressed on or after AI treatment (Figure 4). This represents the gold standard required by Health Authorities for demonstrating efficacy and safety of therapeutic agents. Subjects with identified PIK3CA mutational status as determined by a Novartis designated laboratory were enrolled; subjects and investigators are blinded to tumor mutational status and study treatment.

Figure 4: Study Design – Study CBYL719C2301



Trial location
275 sites across 33 countries in North and Latin America, Europe, and Asia enrolled a total of 572 subjects (341 mutant, 231 non-mutant).

Choice of control group
Fulvestrant 500 mg monotherapy is a standard therapy for subjects with HR-positive, HER2-negative breast cancer with disease progression following anti-estrogen therapy and who require a well-tolerated alternative therapy (Ciruelos et al 2014).

Diagnostic criteria
Subjects with identified PIK3CA mutational status as determined by a Novartis designated laboratory were enrolled. Refer to study design section above.

Key inclusion/exclusion criteria
Enrollment was open to men and postmenopausal women with locally confirmed HR-positive, HER2-negative advanced breast cancer, who had relapsed or progressed on/after prior treatment with an aromatase inhibitor in either the (neo)adjuvant or advanced disease setting, were eligible for further endocrine therapy, and had adequate tumor tissue for central analysis of *PIK3CA* mutational status. For postmenopausal women, previous ovarian radiation or treatment with a luteinizing hormone-releasing hormone agonist for induction of ovarian suppression was prohibited. Prior chemotherapy in the advanced setting or prior therapy with fulvestrant, or any PI3K, Akt, or mTOR inhibitor was prohibited.

Subjects had either measurable disease (≥1 measurable lesion per RECIST v1.1 or ≥1 predominantly lytic bone lesion, Eastern Cooperative Oncology Group performance status ≤1, and adequate organ and bone marrow function. Subjects were excluded if they had inflammatory breast cancer, uncontrolled central nervous system metastases, concurrent malignancy or malignancy within 3 years of randomization (except adequately treated basal/squamous cell carcinoma, non-melanomatous skin cancer, or curatively resected cervical cancer), type 1 or uncontrolled type 2 diabetes (fasting plasma glucose >140 mg/dL [7.7 mmol/L] or glycosylated hemoglobin >6.4%), or currently documented pneumonitis.

Primary resistance was defined as relapse within 24 months on adjuvant endocrine therapy or progression within 6 months on endocrine therapy for advanced disease. Secondary resistance was defined as relapse after ≥24 months on adjuvant endocrine therapy, relapse within 12 months of ending adjuvant endocrine therapy, or progression after ≥6 months on endocrine therapy for advanced disease. Subjects who relapsed ≥12 months after completion of adjuvant endocrine therapy with no treatment for advanced disease were defined as endocrine sensitive.

Dose selection
Selection of the alpelisib 300 mg daily continuous dosing schedule was based on the results of the first in-human study CBYL719X2101 where alpelisib was administered both as a single agent and in combination with fulvestrant. Details are provided in Section 6.2.2.1.

Study treatments, treatment assignment, and blinding
IRT was used to assign subjects centrally to one of the two cohorts (PIK3CA mutant and non-mutant). The system was also used to randomize subjects in a 1:1 ratio based on a fixed block size randomization scheme to receive either:

- Alpelisib 300 mg orally continuously q.d. + fulvestrant 500 mg i.m. on Days 1 and 15 of Cycle 1 and on Day 1 ± 3 days of each of the subsequent cycles where a cycle was 28 days
  or
- Placebo orally continuously q.d. + fulvestrant 500 mg i.m. on Days 1 and 15 of Cycle 1 and on Day 1 ± 3 days of the subsequent cycles where a cycle was 28 days

Within each cohort, randomization was stratified by: (1) the presence of lung and/or liver metastases (yes vs. no), given their well-recognized prognostic value in this treatment setting, and (2) previous treatment with any CDK4/6 inhibitor (yes vs. no), acknowledging the potential change in treatment landscape at the time this study was initiated.

Crossover from placebo plus fulvestrant to alpelisib plus fulvestrant was not permitted in this study. Subjects, investigators, and local radiologists remained blinded to the identity of the assigned cohort and treatment.

The same IRT system was also used to dispense study medication.

Differences in the frequency of certain AEs and laboratory tests may have resulted in partial unblinding to treatment, and thus may have led to bias affecting the investigator assessment of tumor response, although this may have been further minimized due to subjects and investigators also being blinded to tumor mutational status. Robustness of the primary PFS analysis was confirmed by the analysis per audit-based BIRC assessment which is reassuring as this central assessment was blinded to treatment assignment and other clinical data.

Dose modification, dose discontinuation
For AEs suspected to be related to alpelisib, management guidance and dose modifications were provided in the protocol. A maximum of two dose reductions (to 250 mg and to 200 mg) was allowed, after which the subject was to be discontinued from treatment with alpelisib/placebo. Dose reduction was based on the worst preceding toxicity and clinical judgment of the treating physician based on subject's individual benefit/risk assessment. No dose modification was permitted for fulvestrant. Please refer to section "Dose/Dose response" for additional details.

Administrative structure
Trial oversight was managed by:

- A Study Steering Committee, consisting of selected investigators and Sponsor representatives, ensuring management of the study in accordance with the protocol.
- An external, independent DMC, comprising four oncologists and one biostatistician, was responsible for reviewing the safety and efficacy results in each cohort, overseeing the safety data accruing in the trial at regular intervals of approximately 6 months. An

independent statistical group external to Novartis, and not involved in the conduct of the study, prepared semi-blinded data statistical reports for the DMC.

The primary endpoint, PFS per Investigator assessment in the PIK3CA mutant cohort, was further assessed by BIRC. Imaging data used for local tumor assessment was transmitted to a designated CRO for centralized analysis, quality control, as well as further processing and data reconciliation.

Procedures and schedule
Imaging (CT and/or MRI) for response evaluation was performed at screening within 4 weeks before randomization, every 8 weeks for the first 18 months, then every 12 weeks until disease progression/withdrawal for any other reason. Vital signs, and hematological and biochemical laboratory tests, were performed at screening, every 2 weeks for the first 8 weeks, then every 4 weeks; AEs (per NCI CTCAE v4.03) were recorded continuously until 30 days after the last dose of study treatment. For details on Concurrent medications, treatment compliance and rescue medications please refer to section "Treatment compliance, concomitant medications, and rescue medication use".

Subject completion, discontinuation, or withdrawal
Subjects were to be treated until disease progression, unacceptable toxicity, withdrawal of consent, loss to follow-up, death, or discontinuation from the study treatment due to any other reason. The SAP specifies the handling of data for subjects who discontinued for any reason. Subjects who withdrew from the study were not replaced, regardless of reason for withdrawal. If a subject did not discontinue study treatment due to documented disease progression, death, lost to follow-up, or withdrawal of consent for efficacy follow-up, tumor and PRO assessments as well as overall survival assessments continued to be performed.

Study Endpoints
The study endpoints PFS, OS, and ORR are all accepted and well-recognized for oncology trials (FDA Guidance for Industry 2007). PFS is less affected by bias introduced by subsequent therapies than OS and may therefore provide a more biologically relevant measure of the effect of treatment on the disease process. As a supportive analysis to the primary endpoint of PFS by investigator assessment, tumor assessments were also reviewed by a BIRC, using an audit-based approach based on a random selection of approximately 50% of subjects from the PIK3CA mutant cohort.

Statistical Analysis Plan and Amendments
The SAP was agreed upon and finalized prior to the conduct of any efficacy analysis and unblinding of the database.

Efficacy analysis
The primary analysis of PFS was based on the local radiological assessment. The FAS comprised all subjects who were randomized to study treatment. According to the intent to treat principle, subjects were analyzed according to the cohort, treatment, and strata they were assigned to during the randomization procedure. The FAS was the main population for analyses of subject

disposition, demographics, baseline characteristics, and efficacy analyses. Subjects who did not provide main study informed consent were excluded from the FAS.

Rules for the handling of missing data were specified in the SAP to ensure overall data integrity. Sensitivity analyses (for handling missing tumor assessments) and supportive analyses (including a Per-Protocol set (PPS) analysis and central tumor assessment by a BIRC) were performed to assess the overall robustness of the primary efficacy results. Subgroup analyses based on important demographic and prognostic factors to explore the intrinsic consistency of any treatment effect in the overall population of subjects with PIK3CA mutant tumors were prespecified in the SAP.

The primary efficacy analysis was the comparison of the distribution of PFS between the two treatment groups using a stratified log-rank test at a one-sided 2.0% level of significance in the PIK3CA mutant cohort. A group sequential design using a Haybittle-Peto boundary was used to address multiplicity and control the overall type-I error rate. A maximum of three analyses was planned; a futility interim analysis after observing approximately 97 PFS events (corresponding to a 40% information fraction), an interim efficacy analysis after approximately 185 PFS events (76% information fraction), and a final PFS analysis after approximately 243 events.

The key secondary efficacy endpoint was the comparison of the distribution of OS between the two treatment groups in the PIK3CA mutant cohort. A hierarchical testing strategy was used to control the overall type-I error rate, where OS was to be statistically evaluated and interpreted only if PFS was statistically significant. The distribution of OS between the two treatment arms was compared using a stratified log-rank test and a 3-look group sequential design using an O'Brien-Fleming alpha spending function at a one-sided 2.0% level of significance.

PFS in the PIK3CA non-mutant cohort was analyzed as a secondary endpoint and the treatment effect in this cohort was considered to be clinically relevant if the estimated HR ≤ 0.60 and the posterior probability (true HR < 1) ≥ 90%. If both criteria were met then the comparison of PFS between the two treatment arms in this cohort using a stratified log-rank test at a one-sided 0.5% level of significance was to be made. OS analyses were to be performed only if PFS in this cohort met the PoC criteria and was statistically significant.

The statistical plan was amended four times during the study to reflect changes in protocol design (see Section “Protocol Amendments”). Key changes included the following:

Amendment 3 (27-Nov-2017)

1. Added new analysis to present ORR and CBR in the subset of subjects with measurable disease at baseline.

2. A subgroup analysis for the primary endpoint of PFS, in subjects with primary or secondary endocrine resistance vs. endocrine sensitivity was added.

Amendment 4 (03-Jul-2018)

A subgroup analysis for the primary endpoint of PFS, by (i) PIK3CA somatic mutation and (ii) PIK3CA somatic mutation exon location was added.

The Cochran-Mantel Haenszel chi-square test (strata based on the randomization stratification factor) was used to compare the two treatment groups with respect to the ORR and CBR. An analysis of time to definitive deterioration of the ECOG PS and time to 10% deterioration in the global health status/QOL scale and secondary PRO variables of interest were performed using Kaplan-Meier methodology.

Change from baseline in all subscales obtained from EORTC QLQ-C30, the VAS of EQ-5D-5L and BPI-SF were analyzed using a linear mixed effect model.

Safety analysis
All safety analyses were based on the safety population which consisted of all subjects who received at least one dose of the study treatment. Subject data were analyzed according to the treatment actually received. Separate AE summaries were presented by system organ class, preferred term, and maximum CTC grade. All AEs, grade 3-4 AEs, treatment-related AEs, SAEs, AEs leading to discontinuation, AEs requiring dose adjustment or interruption, AESIs, and the number (%) of subjects with worst post-baseline laboratory data, clinically notable vital sign abnormalities, and notable ECG abnormalities were summarized by treatment group. Safety summary tables included "on-treatment" events/assessments, i.e. those collected on or after the first date of study treatment and collected no later than 30 days after the date of last study treatment administration.

PK analysis
The PK Analysis Set (PAS) consisted of all subjects who received at least one dose of study treatment and had at least one post-treatment concentration measurement. PK concentrations were summarized using descriptive statistics.

Exposure-efficacy and exposure-safety relationships were modeled using Cox regression models.

Protocol Amendments
The study protocol and the SAP accordingly were amended four times during the study. None of the implemented changes impacted the integrity of the trial or the interpretation of the results. Key features of each amendment included:

Amendment 1 (09-Mar-2016) changed the efficacy analysis for the PIK3CA non-mutant cohort from a primary objective to a secondary, proof-of-concept objective. Consequently, the primary and key secondary objectives of the study focused on the comparison of PFS and OS between treatment groups for subjects in the PIK3CA mutant cohort. Considering that the analysis of the PIK3CA non-mutant cohort was updated to be conducted independently of the primary analysis in the PIK3CA mutant cohort, an alpha of 0.5% was assigned to the non-mutant cohort comparison, while an alpha of 2% was assigned to the mutant cohort comparison to control the overall type I error.

Additional relevant changes were related to safety and included an update on study entry criteria for subjects with hyperglycemia and updated monitoring and management guidance for hyperglycemia and skin events.

Amendment 2 (30-Aug-2016) made further modifications to the inclusion/exclusion criteria and trial design (i.e. updates to futility criteria, change in BIRC assessment from full read to audit-based approach, and the addition of PFS2 as an exploratory endpoint).

Amendment 3 (14-Dec-2016) modified the interim PFS analysis efficacy stopping boundary for the primary endpoint to a more stringent Haybittle-Peto boundary.

Amendment 4 (22-Nov-2017) provided further clarity on guidance for management of skin and subcutaneous reactions.

The FDA's Assessment:

The FDA agrees with the applicant's summary of the protocol and amendments for the SOLAR-1 trial.

The FDA notes that the one-sided 0.025 alpha is split between the PIK3CA-mutated and PIK3CA-wildtype cohorts into 0.02 and 0.005, respectively. In Figure 6, the alpha of 0.005 for the PIK3CA-wildtype cohort is not depicted.

The portions of the Assessment Aid completed by the applicant report the one-sided level of significance and p-values. The FDA reports all p-values at the two-sided level of significance. To get the equivalent two-sided value, the estimate should be multiplied by two.

Study CBYL719C2301 (SOLAR-1) was designed to have approximately 84% power to detect a hazard ratio of 0.60 (median PFS 11.7 months versus 7 months) in the PIK3CA-mutated cohort with a two-sided type I error of 4%. The primary PFS analysis was planned to be performed when approximately 243 events had occurred. The first and second interim PFS analyses were timed to occur at 97 and 185 PFS events. Based on the meeting minutes from the data monitoring committee (DMC), the boundary conditions were not crossed at either of the interim analyses of PFS. The OS analyses had 72% power to detect a HR of 0.67 with 178 deaths to occur at 54 months from the date of first randomized patient. There were two planned interim analyses for OS, the first timed to coincide with the final analysis of PFS and the second to occur after 151 deaths had been observed (85% information fraction). A hierarchical testing strategy was employed in which PFS was tested first at the two-sided 0.04 level in the PIK3CA-mutated cohort, followed by the key secondary endpoint of OS in the PIK3CA-mutated cohort. OS was to be tested if statistical significance was reached for PFS. No multiplicity adjustments were made for other secondary endpoints.

In the PIK3CA-wildtype cohort, a two-sided alpha of 0.1 was allocated for testing the proof-of-concept (POC) hypothesis. With 102 PFS events in approximately 18 months, the HR of 0.60 would translate into an increase of the median PFS to 12.3 months from 7.4 months in the control arm if the POC endpoint were met.

8.1.2. Study Results

The Applicant's Position:

Compliance with Good Clinical Practices
The study was conducted in full conformance with the ethical principles of GCP and the Declaration of Helsinki. Written informed consent was obtained from each subject or legally acceptable representative of the subject, before conducting any study-specific procedures. The study protocol and all amendments were reviewed by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB).

Informed consent was obtained in writing from each subject or legally acceptable representative of the subject, before conducting any study-specific procedures. The study was described by the Investigator or designee, who answered any questions, and written information was also provided. The study included an optional biomarker component which required a separate consent if the subject agreed to participate.

Financial Disclosure
Details of financial disclosure are presented in Section 0.

Subject Disposition
A total of 572 subjects were enrolled in this study: 341 in the PIK3CA mutant cohort (169 in the alpelisib plus fulvestrant arm and 172 in the placebo plus fulvestrant arm) and 231 in the PIK3CA non-mutant cohort (115 in the alpelisib plus fulvestrant arm and 116 in the placebo plus fulvestrant arm). Primary efficacy analysis is based on all 341 subjects of the PIK3CA mutant cohort (ITT population). One subject in the PIK3CA mutant cohort, who was randomized to the placebo plus fulvestrant arm, did not receive study treatment as she did not meet the inclusion criteria. This subject was included in the ITT population, but not in the Safety Set (Table 11).

Table 11: Subject Disposition – Study CBYL719C2301 (FAS)

	PIK3CA mutant cohort			PIK3CA non-mutant cohort		
	Alpelisib plus fulvestrant	**Placebo plus fulvestrant**	**All subjects**	**Alpelisib plus fulvestrant**	**Placebo plus fulvestrant**	**All subjects**
	N = 169	**N = 172**	**N = 341**	**N = 115**	**N = 116**	**N = 231**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Subjects randomized						
Treated	169 (100)	171(99.4)	340 (99.7)	115 (100)	116 (100)	231 (100)
Untreated	0	1 (0.6)	1 (0.3)	0	0	0
Subjects treated						
Treatment ongoing[1]	42 (24.9)	32 (18.6)	74 (21.7)	13 (11.3)	14 (12.1)	27 (11.7)
End of treatment	127 (75.1)	139 (80.8)	266 (78.0)	102 (88.7)	102 (87.9)	204 (88.3)
Reason for not being treated						
Protocol deviation	0	1 (0.6)	1 (0.3)	0	0	0

	PIK3CA mutant cohort			PIK3CA non-mutant cohort		
	Alpelisib plus fulvestrant	Placebo plus fulvestrant	All subjects	Alpelisib plus fulvestrant	Placebo plus fulvestrant	All subjects
	N = 169	N = 172	N = 341	N = 115	N = 116	N = 231
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Primary reason for end of treatment						
Progressive disease	93 (55.0)	117 (68.0)	210 (61.6)	80 (69.6)	91 (78.4)	171 (74.0)
Subject/guardian decision	16 (9.5)	6 (3.5)	22 (6.5)	6 (5.2)	4 (3.4)	10 (4.3)
Physician decision	6 (3.6)	6 (3.5)	12 (3.5)	5 (4.3)	4 (3.4)	9 (3.9)
Adverse event	5 (3.0)	3 (1.7)	8 (2.3)	9 (7.8)	0	9 (3.9)
Death	3 (1.8)	4 (2.3)	7 (2.1)	1 (0.9)	0	1 (0.4)
Protocol deviation	4 (2.4)	3 (1.7)	7 (2.1)	1 (0.9)	3 (2.6)	4 (1.7)
[1] Subjects ongoing at the time of the data cut-off date						

Protocol Violations/Deviations

In the PIK3CA mutant cohort, 52.5% subjects had protocol deviations with no appreciable imbalance in the types of protocol deviations evident across the two treatment arms. The most commonly reported deviations were due to not meeting the study inclusion criteria (30.8%) (the majority of which were related to medical history of prior endocrine therapy, 9.1%) and the use of prohibited medication while on study (17.3%).

Not all protocol deviations were considered to have an impact on efficacy; the PPS, as defined per pre-specified criteria in the statistical analysis plan, excluded 14.4% of FAS subjects in the PIK3CA mutant cohort.

The FDA's Assessment:

Details of the protocol deviations in SOLAR-1 are shown in the applicant's table 10-4 from the CSR below. While the number of protocol deviations is of concern, these were generally well-balanced, with deviations reported in approximately half of the participants in each arm of the PIK3CA-mutated population. A common cause of protocol violations was use of prohibited medications. The medications used were prohibited due to concern for increased toxicity (and, in particular, a potential increase in risk of QT prolongation). Protocol violations were reported in 21% of the alpelisib plus fulvestrant arm versus 14% of the control arm, which would bias towards a greater number of adverse reactions in the alpelisib arm. QT prolongation was rare in SOLAR-1 and did not differ between arms.

The FDA agrees with the applicant's assessment that the overall pattern and nature of protocol deviations would not alter the conclusion of a net favorable benefit-risk relationship for use of alpelisib in the indicated population. In total, 14% of patients in the PIK3CA-mutant cohort had protocol deviations that resulted in their exclusion from the per protocol set, used for sensitivity analysis. The PFS results in the PIK3CA-mutant per protocol set are presented in the results below.

Table 10-4 Protocol deviations by deviation category (in greater than 5 percent of subjects in either treatment arm) (FAS, PIK3CA mutant cohort)

Category	Alpelisib + fulvestrant N=169 n (%)	Placebo + fulvestrant N=172 n (%)	All subjects N=341 n (%)
Any protocol deviation	**92 (54.4)**	**87 (50.6)**	**179 (52.5)**
Any inclusion criteria deviation	**50 (29.6)**	**55 (32.0)**	**105 (30.8)**
Pat. relapsed on/or within 12 months from completion of (neo)adj. endocrine therapy (ET) and subsequently progressed after 1 line of ET or progressed on more than 1 line of ET for metastatic disease.	16 (9.5)	15 (8.7)	31 (9.1)
No ECG triplicate at Screening.	13 (7.7)	13 (7.6)	26 (7.6)
Baseline laboratory results criteria (creatinine clearance) missing.	5 (3.0)	11 (6.4)	16 (4.7)
Baseline laboratory results criteria (fasting serum amylase) missing.	6 (3.6)	10 (5.8)	16 (4.7)
Prohibited concomitant medication	**35 (20.7)**	**24 (14.0)**	**59 (17.3)**
Other deviation	**13 (7.7)**	**15 (8.7)**	**28 (8.2)**
Patient has not provided consent for the optional biopsy sample collected.	4 (2.4)	9 (5.2)	13 (3.8)
Any exclusion criteria deviation	**11 (6.5)**	**16 (9.3)**	**27 (7.9)**
Subject not withdrawn as per protocol	**13 (7.7)**	**9 (5.2)**	**22 (6.5)**
Study treatment discontinued but patient not withdrawn from treatment phase	9 (5.3)	8 (4.7)	17 (5.0)

Source Table 14.1-1.7a

Source: Applicant's CSR

The Applicant's Position:

Demographic and Baseline Characteristics

Treatment arms were generally well balanced and represented the intended subject population with respect to demographic and baseline characteristics, ECOG performance status, tumor burden, and prior antineoplastic therapy, thereby providing reassurance with regard to the interpretation of the treatment comparison and validity of the efficacy conclusions (Table 12, Table 13).

Table 12: Demographic Characteristics – Study CBYL719C2301 (FAS)

	PIK3CA mutant cohort			PIK3CA non-mutant cohort		
	Alpelisib plus fulvestrant	Placebo plus fulvestrant	All subjects	Alpelisib plus fulvestrant	Placebo plus fulvestrant	All subjects
Demographic variable	**N = 169**	**N = 172**	**N = 341**	**N = 115**	**N = 116**	**N = 231**
Age (years)						
N	169	172	341	115	116	231

	PIK3CA mutant cohort			PIK3CA non-mutant cohort		
	Alpelisib plus fulvestrant	**Placebo plus fulvestrant**	**All subjects**	**Alpelisib plus fulvestrant**	**Placebo plus fulvestrant**	**All subjects**
Demographic variable	**N = 169**	**N = 172**	**N = 341**	**N = 115**	**N = 116**	**N = 231**
Mean (SD)	62.7 (10.22)	64.0 (9.99)	63.3 (10.11)	62.5 (9.01)	62.3 (10.61)	62.4 (9.83)
Median (range)	63.0 (25–87)	64.0 (38–92)	63.0 (25–92)	62.0 (39–82)	63.0 (32–88)	62.0 (32–88)
Age category (years) – n (%)						
18 to < 65	95 (56.2)	89 (51.7)	184 (54.0)	72 (62.6)	65 (56.0)	137 (59.3)
65 to < 85	73 (43.2)	80 (46.5)	153 (44.9)	43 (37.4)	50 (43.1)	93 (40.3)
≥ 85	1 (0.6)	3 (1.7)	4 (1.2)	0	1 (0.9)	1 (0.4)
Sex – n (%)						
Female	168 (99.4)	172 (100)	340 (99.7)	115 (100)	116 (100)	231 (100)
Male	1 (0.6)	0	1 (0.3)	0	0	0
Race – n (%)						
White	117 (69.2)	109 (63.4)	226 (66.3)	82 (71.3)	69 (59.5)	151 (65.4)
Asian	34 (20.1)	40 (23.3)	74 (21.7)	25 (21.7)	26 (22.4)	51 (22.1)
Black or African American	1 (0.6)	3 (1.7)	4 (1.2)	1 (0.9)	3 (2.6)	4 (1.7)
American Indian or Alaska native	1 (0.6)	2 (1.2)	3 (0.9)	0	2 (1.7)	2 (0.9)
Other	8 (4.7)	10 (5.8)	18 (5.3)	1 (0.9)	7 (6.0)	8 (3.5)
Unknown	8 (4.7)	8 (4.7)	16 (4.7)	6 (5.2)	9 (7.8)	15 (6.5)
Ethnicity – n (%)						
Other	66 (39.1)	65 (37.8)	131 (38.4)	39 (33.9)	44 (37.9)	83 (35.9)
East Asian	27 (16.0)	34 (19.8)	61 (17.9)	23 (20.0)	22 (19.0)	45 (19.5)
Hispanic or Latino	21 (12.4)	27 (15.7)	48 (14.1)	19 (16.5)	14 (12.1)	33 (14.3)
Not reported	24 (14.2)	19 (11.0)	43 (12.6)	16 (13.9)	17 (14.7)	33 (14.3)
Unknown	15 (8.9)	13 (7.6)	28 (8.2)	12 (10.4)	10 (8.6)	22 (9.5)
Russian	5 (3.0)	6 (3.5)	11 (3.2)	4 (3.5)	5 (4.3)	9 (3.9)
South Asian	3 (1.8)	3 (1.7)	6 (1.8)	0	3 (2.6)	3 (1.3)
West Asian	4 (2.4)	2 (1.2)	6 (1.8)	1 (0.9)	1 (0.9)	2 (0.9)
Southeast Asian	2 (1.2)	2 (1.2)	4 (1.2)	1 (0.9)	0	1 (0.4)
Mixed ethnicity	2 (1.2)	1 (0.6)	3 (0.9)	39 (33.9)	44 (37.9)	83 (35.9)
ECOG performance status – n (%)						
0	112 (66.3)	113 (65.7)	225 (66.0)	84 (73.0)	79 (68.1)	163 (70.6)
1	56 (33.1)	58 (33.7)	114 (33.4)	30 (26.1)	37 (31.9)	67 (29.0)
Missing	1 (0.6)	1 (0.6)	2 (0.6)	1 (0.9)	0	1 (0.4)

Table 13: Baseline Characteristics – Study CBYL719C2301 (FAS)

	PIK3CA mutant cohort			PIK3CA non-mutant cohort		
	Alpelisib plus fulvestrant	Placebo plus fulvestrant	All subjects	Alpelisib plus fulvestrant	Placebo plus fulvestrant	All subjects
	N = 169	N = 172	N = 341	N = 115	N = 116	N = 231
Sites of metastases — no. (%)[1]						
Breast	1 (0.6)	3 (1.7)	4 (1.2)	5 (4.3)	4 (3.4)	9 (3.9)
Bone						
Any	131 (77.5)	121 (70.3)	252 (73.9)	79 (68.7)	89 (76.7)	168 (72.7)
Only	42 (24.9)	35 (20.3)	77 (22.6)	26 (22.6)	23 (19.8)	49 (21.2)
Visceral						
Any	93 (55.0)	100 (58.1)	193 (56.6)	66 (57.4)	74 (63.8)	140 (60.6)
Liver	49 (29.0)	54 (31.4)	103 (30.2)	41 (35.7)	36 (31.0)	77 (33.3)
Lung	57 (33.7)	68 (39.5)	125 (36.7)	37 (32.2)	55 (47.4)	92 (39.8)
Number of metastatic sites — no. (%)						
0	0	1 (0.6)	1 (0.3)	0	0	0
1	63 (37.3)	52 (30.2)	115 (33.7)	44 (38.3)	33 (28.4)	77 (33.3)
2	58 (34.3)	60 (34.9)	118 (34.6)	35 (30.4)	38 (32.8)	73 (31.6)
≥3	48 (28.4)	59 (34.3)	107 (31.4)	36 (31.3)	45 (38.8)	81 (35.1)
Prior treatment — no. (%)[2]						
Any CDK4/6 inhibitor	9 (5.3)	11 (6.4)	20 (5.9)	7 (6.1)	8 (6.9)	15 (6.5)
Tamoxifen	59 (34.9)	62 (36.0)	121 (35.5)	37 (32.2)	50 (43.1)	87 (37.7)
Chemotherapy[3]	101 (59.8)	107 (62.2)	208 (61.0)	78 (67.8)	72 (62.1)	150 (64.9)
Neoadjuvant	25 (14.8)	29 (16.9)	54 (15.8)	20 (17.4)	23 (19.8)	43 (18.6)
Adjuvant	78 (46.2)	86 (50.0)	164 (48.1)	64 (55.7)	58 (50.0)	122 (52.8)
Line of treatment in advanced disease — no. (%)[4]						
First line	88 (52.1)	89 (51.7)	177 (51.9)	72 (62.6)	61 (52.6)	133 (57.6)
Second line	79 (46.7)	82 (47.7)	161 (47.2)	44 (38.3)	52 (44.9)	96 (41.6)
Endocrine status — no. (%)¶						
Primary resistance	23 (13.6)	22 (12.8)	45 (13.2)	31 (27.0)	26 (22.4)	57 (24.7)
Secondary resistance	120 (71.0)	127 (73.8)	247 (72.4)	66 (57.4)	65 (56.0)	131 (56.7)
Sensitive	20 (11.8)	19 (11.0)	39 (11.4)	16 (13.9)	20 (17.2)	36 (15.6)

[1] One subject in the placebo group had locally advanced disease with no metastases
[2] All subjects previously received treatment with an aromatase inhibitor
[3](Neo)adjuvant disease only. Subjects may have received chemotherapy in both the neo-adjuvant and adjuvant settings. One subject in the placebo group received chemotherapy for advanced disease (protocol deviation).
[4]Three subjects, two from the alpelisib group and one from the placebo group, were excluded due to protocol deviations

The FDA's Assessment:

The FDA agrees with the data presented in the baseline demographic table 13 and notes that only 53 patients were enrolled from U.S. sites, which is likely to have contributed to the underrepresentation of racial minorities in the SOLAR-1 trial. The following is the distribution of the patients by country, region and mutation status.

Table 14: Patient Enrollment by Country, Region and PIK3CA Mutation Status

	PIK3CA mutant cohort			PIK3CA non-mutant cohort		
Country	**Alpelisib plus fulvestrant N=169 n(%)**	**Placebo plus fulvestrant N=172 n(%)**	**All Patients N=341 n(%)**	**Alpelisib plus fulvestrant N=115 n(%)**	**Placebo plus fulvestrant N=116 n(%)**	**All Patients N=231 n(%)**
Argentina	4 (2)	4 (2)	8 (2)	1 (1)	1 (1)	2 (1)
Australia	3 (2)	1 (1)	4 (1)	2 (2)	1 (1)	3 (1)
Austria	1 (1)	2 (1)	3 (1)	2 (2)	1 (1)	3 (1)
Belgium	10 (6)	5 (3)	15 (4)	3 (3)	3 (3)	6 (3)
Brazil	4 (2)	3 (2)	7 (2)	0 (0)	0 (0)	0 (0)
Bulgaria	4 (2)	7 (4)	11 (3)	2 (2)	1 (1)	3 (1)
Canada	4 (2)	3 (2)	7 (2)	2 (2)	4 (3)	6 (3)
Chile	2 (1)	3 (2)	5 (1)	1 (1)	5 (4)	6 (3)
Czech Republic	2 (1)	2 (1)	4 (1)	0 (0)	2 (2)	2 (1)
France	16 (9)	17 (10)	33 (10)	11 (10)	10 (9)	21 (9)
Germany	10 (6)	4 (2)	14 (4)	10 (9)	11 (9)	21 (9)
Greece	0 (0)	2 (1)	2 (1)	1 (1)	1 (1)	2 (1)
Hong Kong	1 (1)	0 (0)	1 (0)	1 (1)	0 (0)	1 (0)
Hungary	7 (4)	9 (5)	16 (5)	6 (5)	5 (4)	11 (5)
India	4 (2)	1 (1)	5 (1)	1 (1)	0 (0)	1 (0)
Israel	11 (7)	3 (2)	14 (4)	7 (6)	9 (8)	16 (7)
Italy	6 (4)	10 (6)	16 (5)	7 (6)	5 (4)	12 (5)
Japan	17 (10)	19 (11)	36 (11)	15 (13)	17 (15)	32 (14)
Korea, Republic of	6 (4)	13 (8)	19 (6)	2 (2)	4 (3)	6 (3)
Lebanon	4 (2)	2 (1)	6 (2)	2 (2)	0 (0)	2 (1)
Mexico	2 (1)	2 (1)	4 (1)	0 (0)	0 (0)	0 (0)
Netherlands	3 (2)	1 (1)	4 (1)	1 (1)	0 (0)	1 (0)
Peru	2 (1)	5 (3)	7 (2)	1 (1)	3 (3)	4 (2)
Romania	4 (2)	4 (2)	8 (2)	0 (0)	1 (1)	1 (0)
Russian Federation	3 (2)	5 (3)	8 (2)	3 (3)	1 (1)	4 (2)
Spain	13 (8)	17 (10)	30 (9)	21 (18)	14 (12)	35 (15)
Sweden	2 (1)	1 (1)	3 (1)	0 (0)	3 (3)	3 (1)

	PIK3CA mutant cohort			PIK3CA non-mutant cohort		
Country	**Alpelisib plus fulvestrant N=169 n(%)**	**Placebo plus fulvestrant N=172 n(%)**	**All Patients N=341 n(%)**	**Alpelisib plus fulvestrant N=115 n(%)**	**Placebo plus fulvestrant N=116 n(%)**	**All Patients N=231 n(%)**
Taiwan, Province of China	3 (2)	3 (2)	6 (2)	5 (4)	2 (2)	7 (3)
Thailand	1 (1)	2 (1)	3 (1)	0 (0)	3 (3)	3 (1)
United Kingdom	5 (3)	1 (1)	6 (2)	0 (0)	0 (0)	0 (0)
United States	15 (9)	21 (12)	36 (11)	8 (7)	9 (8)	17 (7)
Region						
Asia	32 (19)	38 (22)	70 (21)	24 (21)	26 (22)	50 (22)
Europe	86 (51)	87 (51)	173 (51)	67 (58)	58 (50)	125 (54)
Latin America	14 (8)	17 (10)	31 (9)	3 (3)	9 (8)	12 (5)
North America	19 (11)	24 (14)	43 (13)	10 (9)	13 (11)	23 (10)
Other	18 (11)	6 (3)	24 (7)	11 (10)	10 (9)	21 (9)

Source: ADSL.XPT, FDA reviewer generated

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment compliance
No formal treatment compliance measurement for alpelisib/placebo was performed. Compliance was assessed by Investigators examining the records of drug administration and the numbers of boxes as well as the tablets dispensed, received, and returned for alpelisib and placebo.

Concomitant medications
Overall, the proportion of subjects who required concomitant medication was similar in both treatment groups and within both cohorts. Protocol deviations due to the use of prohibited concomitant medications were reported in 17.3% of subjects. The majority of these prohibited concomitant medications did not have any impact on efficacy but were prohibited as a safety precaution.

Rescue medication
Not applicable.

The FDA's Assessment:

The FDA agrees that concomitant medications were similar in both treatment arms at baseline and between PIK3CA-mutated and PIK3CA-wildtype cohorts. The FDA generally agrees with the applicant's assessment of treatment adherence.

The FDA reviewed the concomitant medications used most frequently in the alpelisib + fulvestrant arm versus the placebo + fulvestrant arm for AEs, irrespective of PIK3CA tumor mutation status. Anti-diabetic medications were initiated in 163/187 (87%) patients who developed at least 1 event of hyperglycemia in the alpelisib + fulvestrant group vs. 10/30 (33%) in the placebo + fulvestrant group. Metformin was the most commonly used anti-diabetic medication used in the study to manage hyperglycemia.

Anti-rash medications were initiated in 134/153 (88%) patients who developed at least 1 event of rash in the alpelisib + fulvestrant group vs. 14/24 (58%) in the placebo + fulvestrant group. The most frequently used anti-rash medications were prednisone, dexamethasone, prednisolone, fexofenadine, hydrocortisone, desloratadine, hydroxyzine, and loratadine.

Anti-diarrheal agents were initiated in 104/164 (63%) patients who developed at least 1 event of diarrhea in the alpelisib + fulvestrant group vs. 17/45 (38%) in the placebo + fulvestrant group. The most frequently used anti-diarrheal medications were loperamide and prednisone.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The Applicant's Position:

Progression-free Survival

Alpelisib in combination with fulvestrant demonstrated superiority over fulvestrant alone for the primary endpoint of PFS per investigator assessment using RECIST v1.1 in the PIK3CA mutant cohort; the prespecified Haybittle-Peto efficacy boundary (one-sided p-value ≤ 0.0199) was crossed at this final planned analysis. As of the 12-Jun-2018 data cut-off date for this PFS analysis, 232 PFS events were reported and the median study follow-up (defined as the duration between randomization and the data cut-off date) in the PIK3CA mutant cohort was 20.0 months.

An estimated 35% risk reduction in disease progression or death was observed in favor of the alpelisib plus fulvestrant arm relative to the placebo plus fulvestrant arm (HR = 0.65; 95% CI: 0.50, 0.85; p = 0.00065 based on a one-sided stratified log-rank test). Median PFS was prolonged by a clinically meaningful 5.3 months, from 5.7 months in the placebo plus fulvestrant arm to 11.0 months in the alpelisib plus fulvestrant arm (Table 15).

Table 15: PFS Analyses per Investigator Assessment – Study CBYL719C2301 (FAS, PIK3CA Mutant Cohort)

	Alpelisib plus fulvestrant	Placebo plus fulvestrant
Progression-free survival [a]	**N = 169**	**N = 172**
Number of PFS events – n (%)	103 (60.9)	129 (75.0)
Progression	99 (58.6)	120 (69.8)
Death	4 (2.4)	9 (5.2)
Number censored – n (%)	66 (39.1)	43 (25.0)
Median PFS (95% CI) [b] – months	11.0 (7.49, 14.52)	5.7 (3.65, 7.36)
Hazard ratio (95% CI) [c]	0.65 (0.50, 0.85)	
p-value	0.00065	

The Kaplan-Meier PFS curves diverged after approximately 8 weeks, corresponding to the time of the first post-baseline tumor assessment, with the progression-free probability remaining higher during the follow-up for the alpelisib plus fulvestrant arm than for the placebo plus fulvestrant arm, indicating an early and sustained advantage for alpelisib plus fulvestrant therapy (The Applicant's Position:

Figure 6). A total of 46.3% of subjects (95% CI: 38.1, 54.0) receiving alpelisib plus fulvestrant were estimated to be progression-free at 12 months compared with 32.9% (95% CI: 25.8, 40.2) in the fulvestrant control arm, indicating that a larger proportion of subjects derived longer benefit relative to the placebo plus fulvestrant control.

The FDA's Assessment:

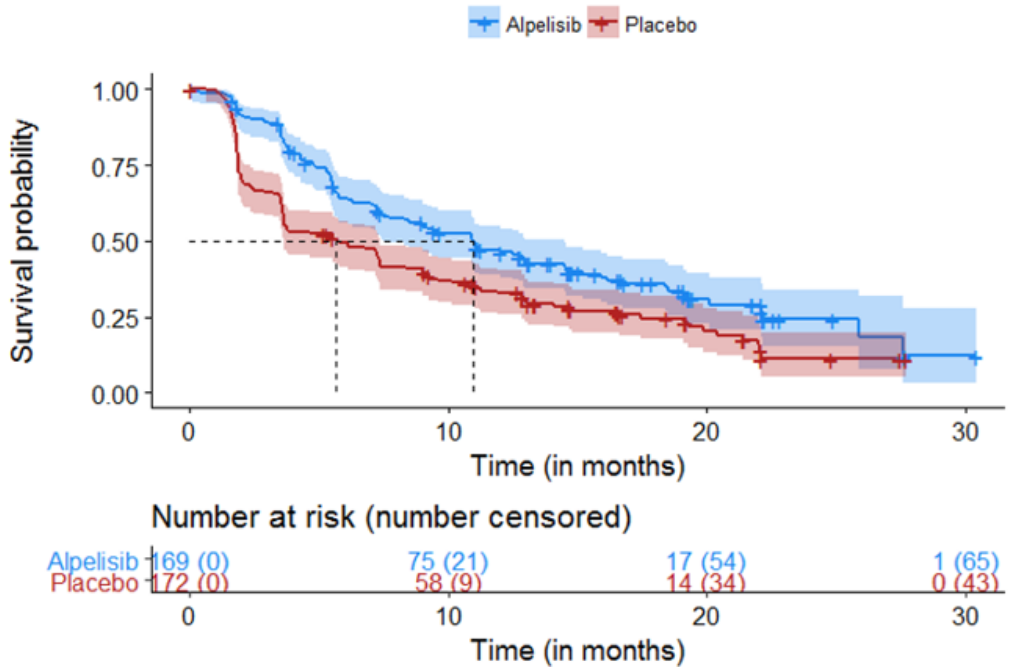
The FDA agrees with the applicant's results presented in Table 15 and notes that the p-value presented is one-sided. The corresponding two-sided p-value is 0.0013.

The missing description for the superscripts in Table 15 correspond to the following:
a: Both Log-rank test and Cox PH model were stratified by Prior CDK4/6 inhibitor usage and presence of lung/liver metastases.
b: Median (time to event) and its 95% CI were generated by KM estimation.
c: Hazard Ratio of alpelisib plus fulvestrant versus placebo plus fulvestrant (placebo plus fulvestrant is the control).

The FDA agrees with the applicant's KM curve but notes that the PFS comparison at the 12 month time point is arbitrary and was not pre-specified. The difference in the PFS rates is lower at other timepoints. No conclusions should be drawn, nor any efficacy claims made, based upon differences in PFS at the 12 month time point.

The KM plot with the 95% CI are provided in Figure 5 below.

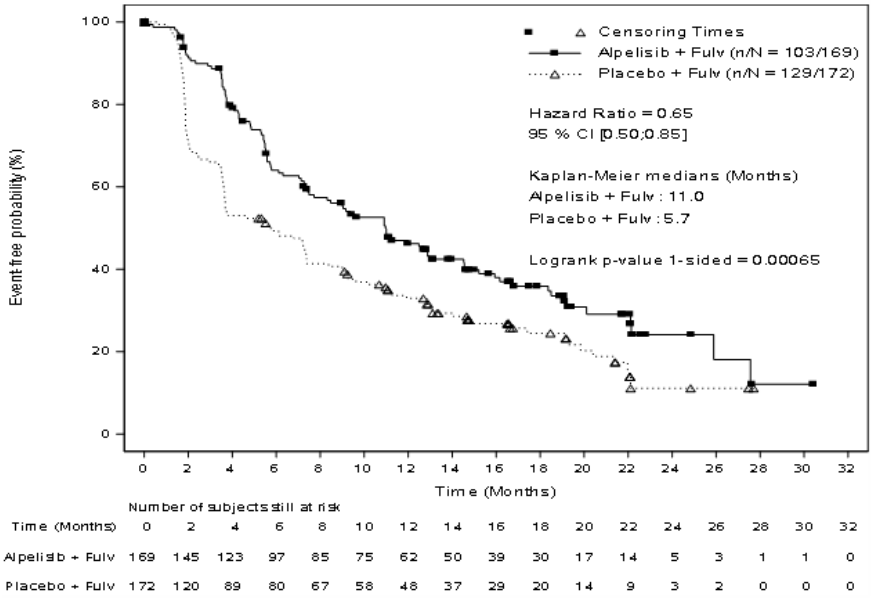
Figure 5: Kaplan-Meier Plot of Progression Free Survival in the PIK3CA-Mutated Cohort



Source: FDA reviewer generated using the adrecist.xpt dataset

The Applicant's Position:

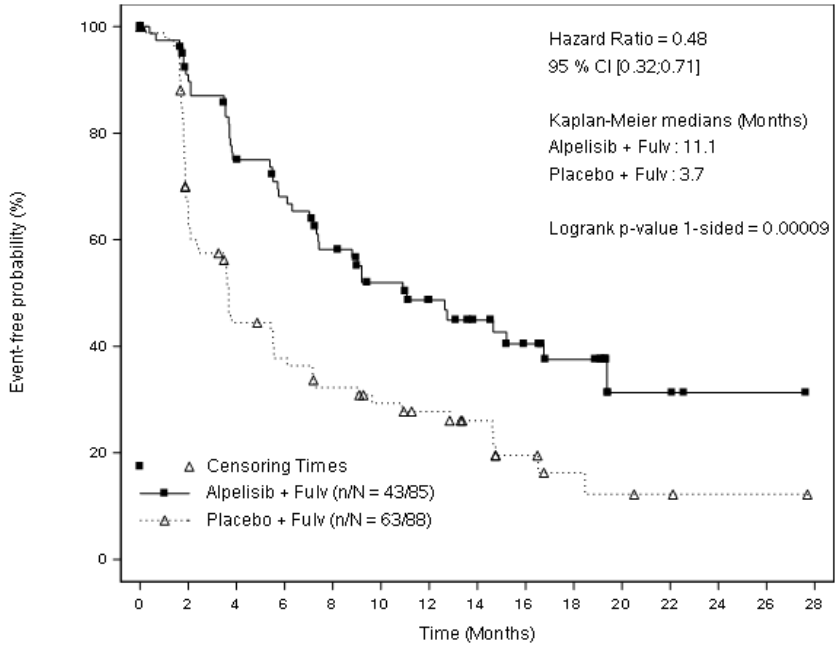
Figure 6: Kaplan-Meier Plot of PFS per Investigator Assessment – Study CBYL719C2301 (FAS, PIK3CA Mutant Cohort)



Supportive analyses - PFS per BIRC assessment

Robustness of the primary analysis was confirmed by the PFS analysis per audit-based BIRC assessment. Based on a randomly selected (approximate) 50% sample of randomized subjects in the PIK3CA mutant cohort (n = 173) included in the BIRC review, an estimated 52% risk reduction in disease progression or death was observed in favor of the alpelisib plus fulvestrant arm (HR = 0.48; 95% CI: 0.32, 0.71). The prolongation in median PFS was 7.4 months (from 3.7 months for the placebo plus fulvestrant arm to 11.1 months for the alpelisib plus fulvestrant arm) (Figure 7).

Figure 7: Kaplan-Meier Plot of PFS per BIRC Assessment - Study CBYL719C2301 (FAS, PIK3CA Mutant Cohort)



<u>The FDA's Assessment:</u>

The FDA notes that the point estimates from the audit sample overestimated the actual treatment effect. The PFS estimates from the audit sample are to be used as supportive evidence of the primary analysis of PFS. The 50% audit sample size had approximately 80-90% power to demonstrate that the hazard ratio from the BIRC assessment was < 1.0, so the applicant's BIRC audit strategy appears reasonable.

According to the SAP, two additional methods were used to summarize the data from the BIRC assessment to determine whether a 100% BIRC review would be conducted, the NCI and the PhRMA methods.

The following thresholds based on the NCI and PhRMA methods were used to define the trigger for a full BIRC review: If the upper-bound of the one-sided 95% confidence interval for BIRC-based log-hazard ratio exceeds zero (i.e. HR>1) based on the NCI method, and/or if ≥ 15% differential discordance (treatment-control) is observed in early discrepancy rate (EDR) or late discrepancy rate (LDR) based on the PhRMA method (a negative observed differential discordance for the EDR or a positive differential discordance for the LDR).

The results from the NCI method yielded an auxiliary variable estimator of 0.57 (95%CI: 0.40, 0.82). Since the upper bound of the 95% CI of the auxiliary variable estimator was less than 1.0, a full BICR review was not triggered.

In addition, the results from the PhRMA yielded a discordance difference in the EDR of 11.1% and -9.5% in the LDR, both rates less than 15%, thereby a full BICR review was not triggered.

The Applicant's Position:

Sensitivity analyses
Multiple preplanned sensitivity analyses (including a PPS analysis, an 'actual event analysis' (date of progression was accepted even after ≥ 2 missing tumor assessments), a 'backdating' approach (date of next scheduled assessment was used as PFS event date whenever it occurred after missing tumor assessment), and a 'censoring subjects after new antineoplastic therapy' approach) demonstrated that the observed benefit for PFS was robust, with estimated HRs ranging from 0.64 to 0.66.

The FDA's Assessment:

The FDA disagrees that the range of the estimated HRs is 0.64-0.66 in the sensitivity analyses of PFS in the PIK3CA-mutated cohort. The correct values are 0.64-0.73. The PFS analysis in the PPS, i.e. excluding the 14% of patients with protocol violations listed in Table 10-4, yielded an estimated HR of 0.73 (95% CI: 0.55, 0.96).

The Applicant's Position:

Subgroup analyses
Homogeneity and consistency of the PFS treatment effect was evident across major demographic and prognostic subgroups with hazard ratios favoring treatment with alpelisib

plus fulvestrant. For some subgroups, e.g. for subjects ≥ 75 years of age and those enrolled from Latin America, the numbers of PFS events and numbers of subjects were limited.

Alpelisib in combination with fulvestrant demonstrated substantial improvement in PFS over fulvestrant alone in subgroups that are considered of particular interest in the current treatment landscape (endocrine-resistant population (both primary and secondary), population with visceral metastases, subjects with prior use of CDK4/6 inhibitor, and subjects undergoing second-line therapy) (The Applicant's Position:

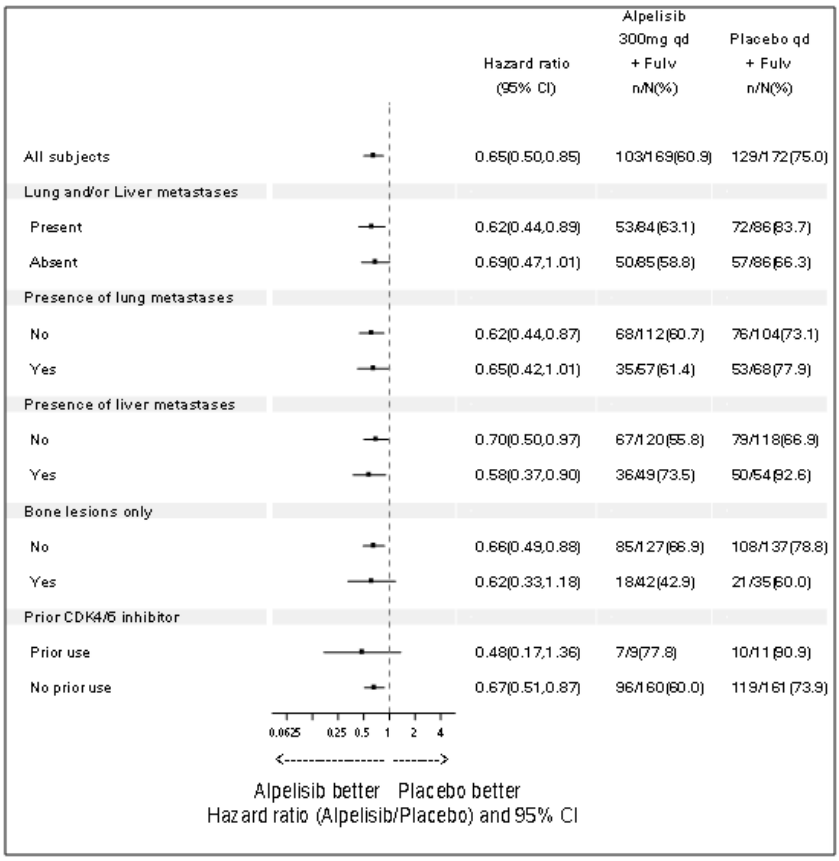
Figure 8).

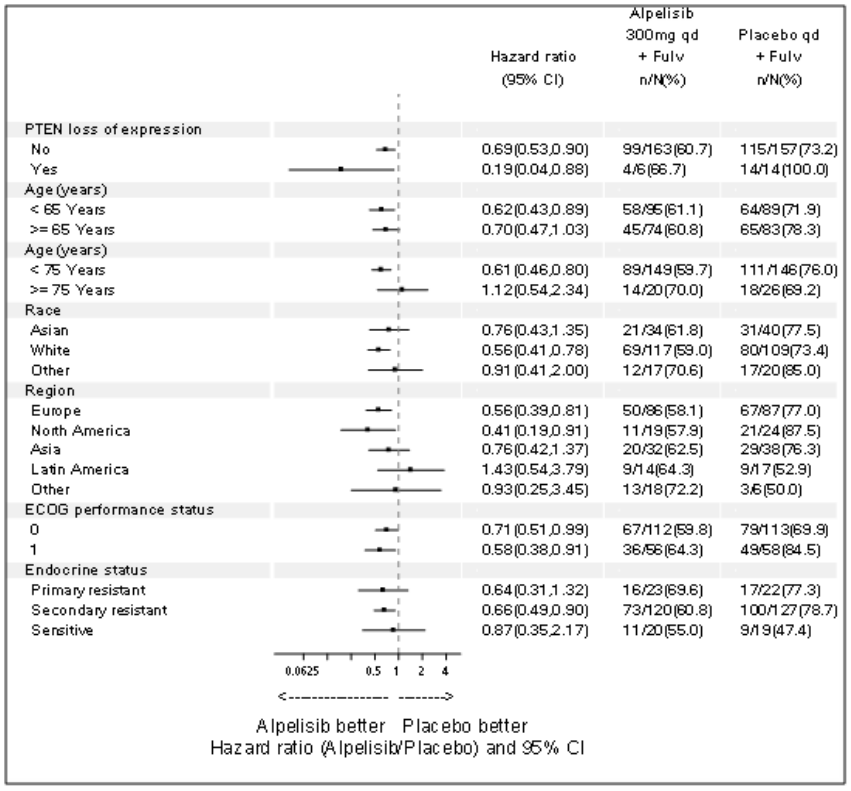
The FDA's Assessment:

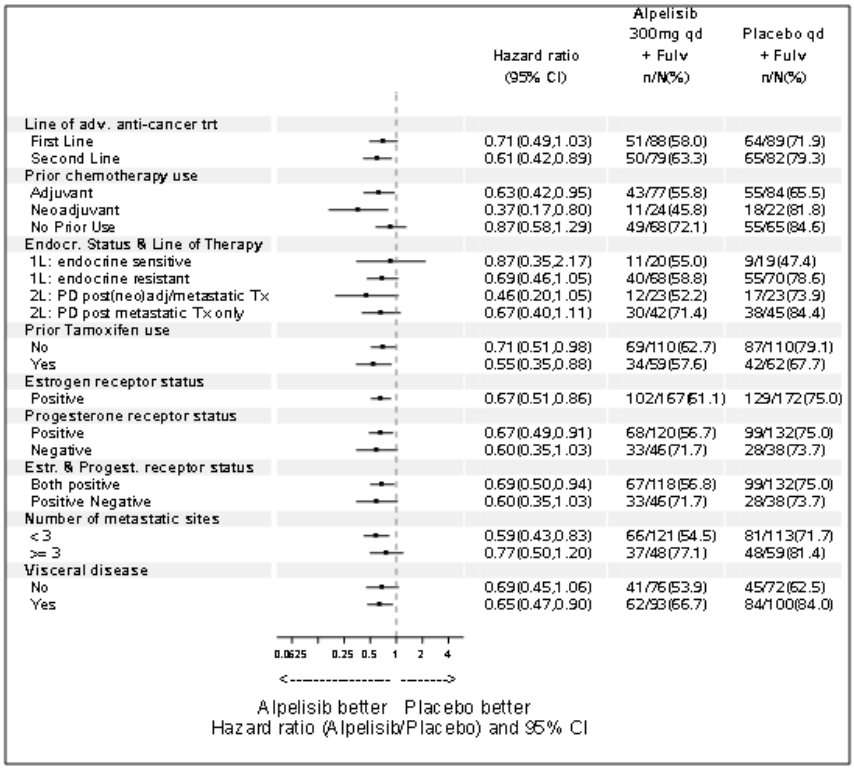
The FDA agrees with the point estimates of the applicant's subgroup analyses, but disagrees with the promotional nature of the applicant's language, i.e., "substantial improvement" and "in the current treatment landscape." This language is misleading and implies that alpelisib has demonstrated superior efficacy to the full landscape of currently available therapy in patients with endocrine-resistant cancer, visceral metastases, prior use of a CDK 4/6 inhibitor, or second-line use, which is not true. The HRs in the subgroup analyses are comparable to those in the PIK3CA mutant ITT population for the comparison of alpelisib plus fulvestrant versus placebo plus fulvestrant. There are no comparative data to support that alpelisib plus fulvestrant has superior efficacy to other approved combinations of endocrine therapy plus kinase or CDK 4/6 inhibitors. No alpha has been allocated to the subgroup analyses, and therefore all results should be considered exploratory. Importantly, the analysis of PFS for patients with prior CDK 4/6 inhibitor is based upon only 20 patients, 9 of whom were randomized to alpelisib. The confidence interval for the PFS hazard ratio is accordingly wide and crosses 1 [HR 0.48 (95% CI: 0.17, 1.36)].

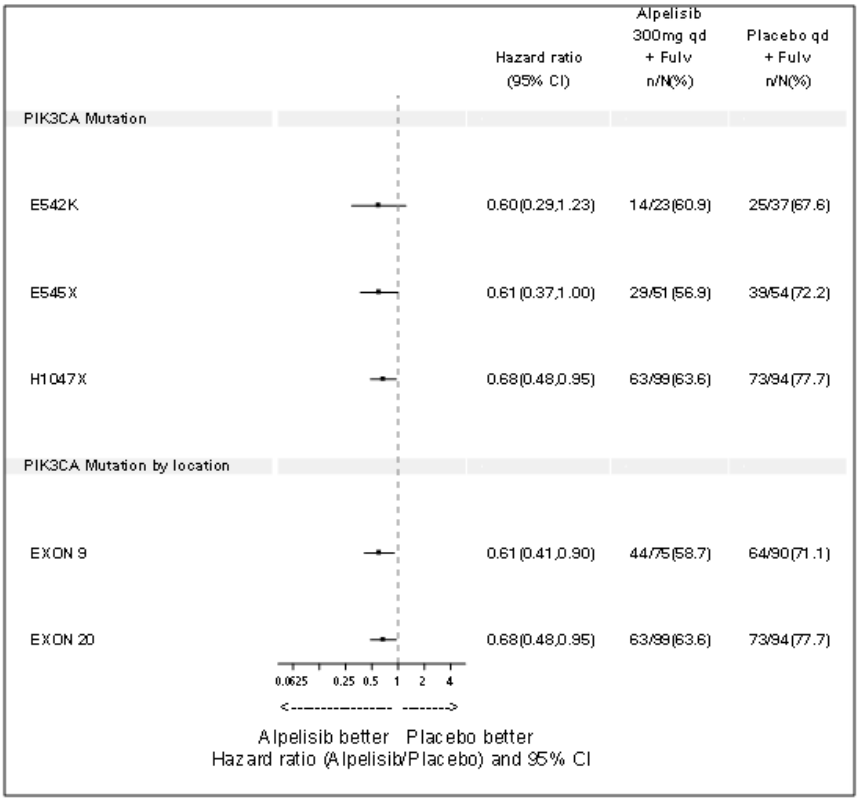
The Applicant's Position:

Figure 8: Forest Plot for PFS per Investigator Assessment in Different Subgroups - Study CBYL719C2301 (FAS, PIK3CA Mutant Cohort)




Alpelisib 300mg qd + Fulv n/N(%)
Placebo qd + Fulv n/N(%)
Hazard ratio (95% CI)
PTEN loss of expression
No 0.69(0.53,0.90) 99/163(60.7) 115/157(73.2)
Yes 0.19(0.04,0.88) 4/6(66.7) 14/14(100.0)
Age (years)
< 65 Years 0.62(0.43,0.89) 58/95(61.1) 64/89(71.9)
>= 65 Years 0.70(0.47,1.03) 45/74(60.8) 65/83(78.3)
Age (years)
< 75 Years 0.61(0.46,0.80) 89/149(59.7) 111/146(76.0)
>= 75 Years 1.12(0.54,2.34) 14/20(70.0) 18/26(69.2)
Race
Asian 0.76(0.43,1.35) 21/34(61.8) 31/40(77.5)
White 0.56(0.41,0.78) 69/117(59.0) 80/109(73.4)
Other 0.91(0.41,2.00) 12/17(70.6) 17/20(85.0)
Region
Europe 0.56(0.39,0.81) 50/86(58.1) 67/87(77.0)
North America 0.41(0.19,0.91) 11/19(57.9) 21/24(87.5)
Asia 0.76(0.42,1.37) 20/32(62.5) 29/38(76.3)
Latin America 1.43(0.54,3.79) 9/14(64.3) 9/17(52.9)
Other 0.93(0.25,3.45) 13/18(72.2) 3/6(50.0)
ECOG performance status
0 0.71(0.51,0.99) 67/112(59.8) 79/113(69.9)
1 0.58(0.38,0.91) 36/56(64.3) 49/58(84.5)
Endocrine status
Primary resistant 0.64(0.31,1.32) 16/23(69.6) 17/22(77.3)
Secondary resistant 0.66(0.49,0.90) 73/120(60.8) 100/127(78.7)
Sensitive 0.87(0.35,2.17) 11/20(55.0) 9/19(47.4)
0.0625 0.5 1 2 4
Alpelisib better Placebo better
Hazard ratio (Alpelisib/Placebo) and 95% CI


Alpelisib 300mg qd + Fulv n/N(%)
Placebo qd + Fulv n/N(%)
Hazard ratio (95% CI)
Line of adv. anti-cancer trt
First Line 0.71(0.49,1.03) 51/88(58.0) 64/89(71.9)
Second Line 0.61(0.42,0.89) 50/79(63.3) 65/82(79.3)
Prior chemotherapy use
Adjuvant 0.63(0.42,0.95) 43/77(55.8) 55/84(65.5)
Neoadjuvant 0.37(0.17,0.80) 11/24(45.8) 18/22(81.8)
No Prior Use 0.87(0.58,1.29) 49/68(72.1) 55/65(84.6)
Endocr. Status & Line of Therapy
1L: endocrine sensitive 0.87(0.35,2.17) 11/20(55.0) 9/19(47.4)
1L: endocrine resistant 0.69(0.46,1.05) 40/68(58.8) 55/70(78.6)
2L: PD post(neo)adj/metastatic Tx 0.46(0.20,1.05) 12/23(52.2) 17/23(73.9)
2L: PD post metastatic Tx only 0.67(0.40,1.11) 30/42(71.4) 38/45(84.4)
Prior Tamoxifen use
No 0.71(0.51,0.98) 69/110(62.7) 87/110(79.1)
Yes 0.55(0.35,0.88) 34/59(57.6) 42/62(67.7)
Estrogen receptor status
Positive 0.67(0.51,0.86) 102/167(61.1) 129/172(75.0)
Progesterone receptor status
Positive 0.67(0.49,0.91) 68/120(56.7) 99/132(75.0)
Negative 0.60(0.35,1.03) 33/46(71.7) 28/38(73.7)
Estr. & Progest. receptor status
Both positive 0.69(0.50,0.94) 67/118(56.8) 99/132(75.0)
Positive Negative 0.60(0.35,1.03) 33/46(71.7) 28/38(73.7)
Number of metastatic sites
< 3 0.59(0.43,0.83) 66/121(54.5) 81/113(71.7)
>= 3 0.77(0.50,1.20) 37/48(77.1) 48/59(81.4)
Visceral disease
No 0.69(0.45,1.06) 41/76(53.9) 45/72(62.5)
Yes 0.65(0.47,0.90) 62/93(66.7) 84/100(84.0)
0.0625 0.25 0.5 1 2 4
Alpelisib better Placebo better
Hazard ratio (Alpelisib/Placebo) and 95% CI



Data Quality and Integrity
No data integrity concerns were reported following completion of site inspections.

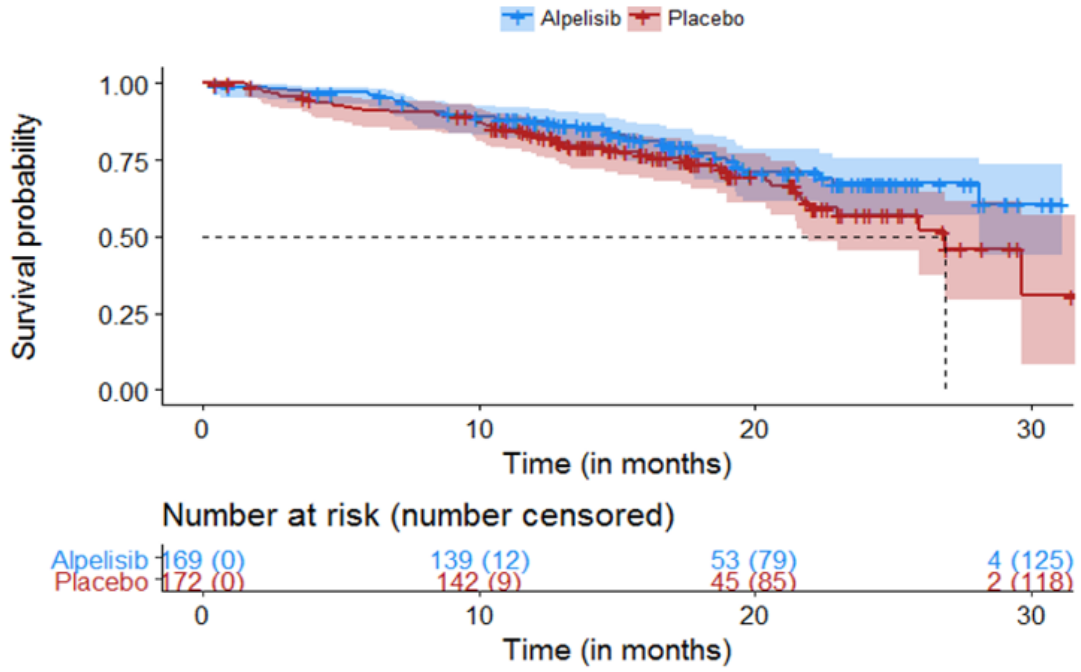
Efficacy Results – Secondary and other relevant endpoints
Results of secondary and exploratory outcome measures for the PIK3CA mutant cohort were in general supportive of the observed benefit in PFS.

Key secondary efficacy variable - OS in subjects with PIK3CA mutant tumors
As of the 12-Jun-2018 data cut-off date, OS data at this first interim analysis were immature with 92 deaths reported (40 (23.7%) in the alpelisib plus fulvestrant arm and 52 (30.2%) in the placebo plus fulvestrant arm), corresponding to a 51.7% information fraction (of the targeted 178 events for the final OS analysis). The pre-specified interim O'Brien-Fleming stopping boundary (one-sided $p \leq 0.00121$) was not crossed (HR = 0.73; 95% CI: 0.48, 1.10; p = 0.06). The median OS was not yet reached for the alpelisib plus fulvestrant arm (95% CI: 28.1, NE) and was 26.9 months (95% CI: 21.9, NE) for the fulvestrant control arm.

The FDA's Assessment:

The FDA agrees that the OS data at the first interim analysis of OS are immature. No detriment in OS with alpelisib is apparent at this time. The final report of OS is expected in 08/2022 per Postmarketing Commitment (PMC) #1. The KM plot for the OS analysis with the 95% CI is presented in Figure 9 below.

Figure 9: Kaplan-Meier Plot for Overall Survival in the PIK3CA Mutant Cohort



Source: FDA reviewer generated using the adrecist.xpt dataset

The Applicant's Position:

Other secondary efficacy variables

Overall response rate and clinical benefit rate
Treatment with the combination of alpelisib plus fulvestrant was associated with marked improvements in ORR and CBR relative to placebo plus fulvestrant for subjects with PIK3CA mutant tumors for both the FAS and for subjects with measurable disease at baseline.

In subjects with measurable disease at baseline, ORR was 35.7% (95% CI: 27.4, 44.7) vs. 16.2% (95% CI: 10.4, 23.5) (p = 0.0002); and CBR was 57.1% (95% CI: 48.0, 65.9) vs. 44.1% (95% CI: 35.6, 52.9) (p = 0.02) in the alpelisib plus fulvestrant arm relative to the placebo plus fulvestrant arm (Table 16).

Table 16: Best Overall Response per Investigator Assessment – Study CBYL719C2301 (FAS)

	PIK3CA mutant tumors		PIK3CA non-mutant tumors	
	Alpelisib plus fulvestrant	Placebo plus fulvestrant	Alpelisib plus fulvestrant	Placebo plus fulvestrant
	N = 169	N = 172	N = 115	N = 116
	n (%)	n (%)	n (%)	n (%)
Best overall response				

	PIK3CA mutant tumors		PIK3CA non-mutant tumors	
	Alpelisib plus fulvestrant	**Placebo plus fulvestrant**	**Alpelisib plus fulvestrant**	**Placebo plus fulvestrant**
	N = 169	**N = 172**	**N = 115**	**N = 116**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Complete response (CR)	1 (0.6)	2 (1.2)	1 (0.9)	0
Partial response (PR)	44 (26.0)	20 (11.6)	14 (12.2)	12 (10.3)
Stable disease (SD)	58 (34.3)	63 (36.6)	57 (49.6)	52 (44.8)
Non-CR/non-PD	38 (22.5)	25 (14.5)	19 (16.5)	19 (16.4)
Progressive disease (PD)	16 (9.5)	53 (30.8)	19 (16.5)	26 (22.4)
Unknown (UNK)	12 (7.1)	9 (5.2)	5 (4.3)	7 (6.0)
Overall response rate (ORR: CR + PR)	45 (26.6)	22 (12.8)	15 (13.5)	12 (10.3)
95% confidence interval	20.1, 34.0	8.2, 18.7	7.5, 20.6	5.5, 17.4
P-value	0.0006		0.27	
Clinical benefit rate (CBR: CR + PR +SD + non-CR/non-PD ≥ 24 weeks)	104 (61.5)	78 (45.3)	45 (39.1)	36(31.0)
95% confidence interval	53.8, 68.9	37.8, 53.1	30.2, 48.7	22.8, 40.3
P-value	0.002		0.10	
Subjects with measurable disease	**126 (74.6)**	**136 (79.1)**	**91 (79.1)**	**94 (81.0)**
Best overall response				
Complete response (CR)	1 (0.8)	2 (1.5)	1 (1.1)	0
Partial response (PR)	44 (34.9)	20 (14.7)	14 (15.4)	12 (12.8)
Stable disease (SD)	58 (46.0)	63 (46.3)	57 (62.6)	52 (55.3)
Progressive disease (PD)	13 (10.3)	45 (33.1)	15 (16.5)	24 (25.5)
Unknown (UNK)	10 (7.9)	6 (4.4)	4 (4.4)	6 (6.4)
Overall response rate (ORR: CR + PR)	45 (35.7)	22 (16.2)	15 (16.5)	12 (12.8)
95% confidence interval	27.4, 44.7	10.4, 23.5	9.5, 25.7	18.9, 37.8
P-value	0.0002		0.25	
Clinical benefit rate (CBR: CR + PR + SD + non-CR/non-PD ≥ 24 weeks)	72 (57.1)	60 (44.1)	37 (40.7)	26 (27.7)
95% confidence interval	48.0, 65.9	35.6, 52.9	30.5, 51.5	18.9, 37.8
P-value	0.02		0.03	
No multiplicity adjustment for the testing of ORR and CBR was made, thus the p-values mentioned here are nominal p-values.				

The FDA's Assessment:

The applicant's analysis of ORR and CBR are exploratory, as no alpha was allocated to these endpoints. All p-values are nominal, and no efficacy claims should be made based upon differences in ORR or CBR.

The FDA agrees with the applicant's point estimates of ORR. The FDA does not concur with the interpretation of the results in the paragraph directly above Table 16. Specifically, the FDA disagrees with the promotional language referring to "marked improvements" in ORR and CBR. The FDA does not accept the use of CBR as a regulatory endpoint, and CBR was only 13% higher in the alpelisib arm (57% versus 44%). While the ORR in patients with measurable disease was approximately doubled in the alpelisib plus fulvestrant arm relative to the control arm, the absolute ORR was modest in both arms, and complete responses were rare and did not differ between arms. The alpelisib plus fulvestrant arm reported one CR and 44 PRs, while the placebo plus fulvestrant arm reported two CRs and 20 PRs. In the duration of response (DoR) analysis, 22 (56%) responders on alpelisib plus fulvestrant and 9 (41%) responders on the control arm had experienced disease progression as of the data cutoff date. Although responses were more common with alpelisib plus fulvestrant, the reported median DoR was shorter in the alpelisib plus fulvestrant arm (12.6 months [95% CI: 8.5, 18.5] versus 14.8 months [95% CI: 10.1, NE]).

The FDA also disagrees with the applicant's assertion elsewhere in this review that PIK3CA mutations are associated with a poorer outcome. In the SOLAR-1 trial, participants randomized to the control arm (fulvestrant plus placebo) with PIK3CA-wildtype tumors had an estimated median PFS of 5.6 months (95% CI: 3.9, 9.1) compared with 5.7 months (95% CI: 3.7, 7.4) for participants with PIK3CA-mutated tumors. Similarly, the ORR in the fulvestrant plus placebo arm was 10.3% (95% CI: 5.5, 17.4) for patients with PIK3CA-wildtype tumors compared with 12.8% (95% CI: 8.2, 18.7) in those with PIK3CA-mutated tumors. These data suggest similar outcomes for patients with PIK3CA-mutated and PIK3CA-wildtype HR-positive, HER2-negative breast cancer treated with fulvestrant monotherapy.

PFS in subjects with PIK3CA non-mutant cohort

Proof-of-concept (PoC) criteria for PFS per investigator assessment (i.e. observed HR ≤ 0.60 and posterior probability that the true HR < 1 was ≥ 90%) were not met in the non-mutant PIK3CA cohort indicating a lack of clinical efficacy in this population (estimated HR = 0.85; 95% CI: 0.58, 1.25; 79.4% posterior probability for true HR < 1). Median PFS was 7.4 months (95% CI: 5.4, 9.3) and 5.6 months (95% CI: 3.9, 9.1), respectively, in the alpelisib plus fulvestrant and placebo plus fulvestrant treatment arms.

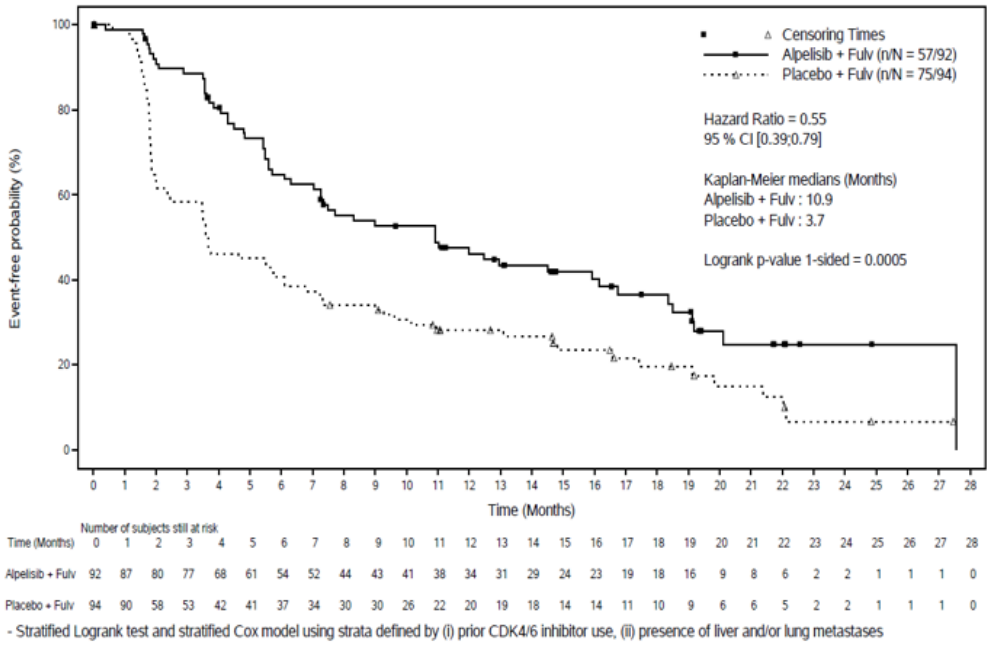
Assessment of PFS, as determined by ctDNA

Of all 572 randomized subjects, 186 subjects were identified as PIK3CA mutant by ctDNA in plasma at baseline ('plasma mutant'), 363 were identified as PIK3CA non-mutant by ctDNA in plasma at baseline ('plasma non-mutant'), and in 23 subjects, mutation status could not be determined in plasma at baseline.

PFS in the subset of subjects harboring PIK3CA mutations as determined by ctDNA demonstrated consistency with the primary results (where mutation status was detected by a tumor sample). This confirmed the robustness of the primary PFS endpoint and the clinical utility of the ctDNA test in selecting a PIK3CA mutant subject population.

In the plasma mutant group, a clinically meaningful 45% risk reduction in disease progression or death was observed in the alpelisib plus fulvestrant treatment arm (HR = 0.55; 95% CI: 0.39, 0.79), with a 7.2-month prolongation in median PFS from 3.7 months in the placebo plus fulvestrant arm to 10.9 months in the alpelisib plus fulvestrant arm (Figure 10).

Figure 10: Kaplan-Meier Plot of PFS per Investigator Assessment by ctDNA – Study CBYL719C2301 (FAS, PIK3CA Mutant Cohort)



Tumor response in subjects with PIK3CA mutant status measured using ctDNA

Results of BOR in subjects harboring PIK3CA mutations as determined using ctDNA in plasma were similar to the BOR rates observed in all subjects with PIK3CA mutations using tissue.

In the PIK3CA mutant cohort, the ORR in the subset of subjects for whom mutation status was measured using ctDNA in plasma was 28.3% (95% CI: 19.4, 38.6) in the alpelisib plus fulvestrant arm compared to 9.6% (95% CI: 4.5, 17.4) in the placebo plus fulvestrant arm (p = 0.0004). The observed CBRs in the alpelisib plus fulvestrant arm and placebo plus fulvestrant arm were 64.1% (95% CI: 53.5, 73.9) and 36.2% (95% CI: 26.5, 46.7), respectively (p = 0.0001).

The FDA's Assessment:

The applicant's analysis of PFS as determined by ctDNA is exploratory as no alpha was allocated for this endpoint. All p-values in the text and Figure 10 are nominal, and no efficacy claims should be made based upon these reported differences in PFS. See also CDRH review by Drs. Francisca Reyes Turca, Deb Chatterjee, and Soma Ghosh.

The Applicant's Position:

Dose/Dose Response
Results from the Phase III exposure-efficacy analyses show that maintaining a high exposure or dose intensity is associated with greater treatment benefit in cancer subjects with a PIK3CA mutation in combination with fulvestrant, supporting the use of the 300 mg dose. Adverse events, such as rash or hyperglycemia, can be managed through dose interruptions and dose reductions to 250 mg and to 200 mg (if toxicities cannot be managed by interruptions and clinical intervention alone).

Persistence of Effect
No long-term efficacy data with the exception of those presented in the preceding sections are available at the time of this application.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Patient-reported outcomes
The changes in global health status/QoL were not clinically meaningful based on the previously established criteria for the EORTC QLQ-C30 instrument, and no differences were observed between the two treatment arms in the time to deterioration (≥ 10%) of global health status/QoL domain score of the EORTC QLQ-C30 questionnaire (PIK3CA mutant cohort: HR = 1.03; 95% CI: 0.72, 1.48).

Analyses of secondary PRO variables of interest (EORTC subscales) generally showed no clinically meaningful differences between the alpelisib plus fulvestrant and placebo plus fulvestrant arms, although there were some exceptions:

- In the alpelisib plus fulvestrant arm, there was a slight delay in worsening of pain (based on the BPI-SF pain severity index and worst pain item), and the EQ-5D-5L index score was maintained.
- There was a trend for deterioration of social functioning scale in the subjects treated with alpelisib plus fulvestrant while it was maintained in the subjects treated with placebo plus fulvestrant.

Analyses of time to 10% deterioration in EORTC physical functioning, social functioning, and emotional functioning scores did not suggest any meaningful differences between the alpelisib plus fulvestrant vs. placebo plus fulvestrant arms.

The FDA's Assessment:

The applicant's position on the PRO data presented above was reviewed. The FDA disagrees with the applicant's conclusions regarding COA (PRO) endpoints.

The PRO analyses with composite scores were not controlled for multiple comparisons, and therefore all of these analyses are considered exploratory.

The definition of a delay to worsening in pain was not clearly defined. When investigating pain deterioration, the impact of the use of analgesic medication, as well as whether the deterioration in pain occurred at one time point or was observed at two or more consecutive time points, needs to be assessed. As this analysis was not defined sufficiently either a priori or even as an exploratory analysis, FDA disagrees with the applicant's conclusion.

The FDA does not concur with the applicant's use of the phrase "meaningful difference" in describing results of the PRO analyses. The 10 point or 10% decrease is based on work in which the interpretability of the anchor used to derive this threshold was questioned by the authors (Osoba et al 1998).

The analysis of COA endpoints was not adequately powered to support a non-inferiority conclusion (i.e. a finding of no difference between the two arms). It is not possible to exclude a detrimental effect of alpelisib on global health status or quality of life for patients enrolled in the SOLAR-1 trial.

The Applicant's Position:

Additional Analyses Conducted on the Individual Trial

Additional PRO analyses were requested in an information request and are summarized below.

Text to be added should such analyses be requested.

The FDA's Assessment:

The FDA review of the submitted patient-reported outcome data revealed reasonable data quality with a completion rate >95% at baseline and > 84% for assessments on both arms during the first 12 months of therapy regardless of treatment arm. The FDA obtained and analyzed additional information from the applicant regarding descriptive PRO data for healthcare utilization, physical function assessments, and change in response for selected symptoms that were frequently reported in SOLAR-1 (e.g., hyperglycemia, diarrhea, nausea, vomiting). The following comments concern the individual domains considered important to the patients.

Pain

Analysis of pain is considered exploratory without pre-specification of a hypothesis testing plan and control of Type I error. The definition of a delay to worsening in pain was not clearly stated. When investigating pain deterioration, there are 2 important considerations;

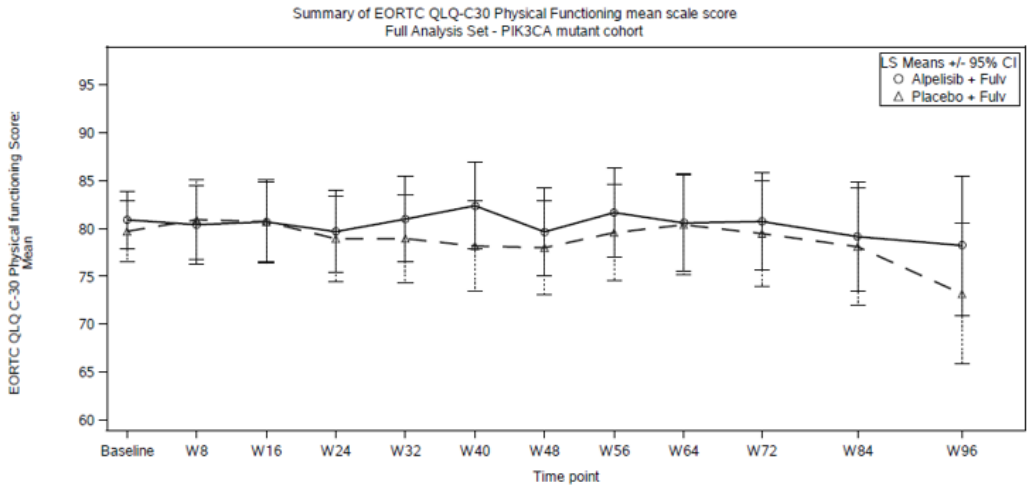
1. ***How did the use of analgesic medications impact pain and;***

2. ***Was deterioration persistent (i.e., was there deterioration at consecutive time points).***

Neither of these points were incorporated into the applicant's conclusions. Descriptive statistics, such as mean changes in worst reported pain, suggest that pain on average was not largely different between the two arms.

Functioning

Physical and role functioning are considered to be core outcomes at the agency and they were adequately captured in this trial. Assessing descriptive distributions of the items measuring these concepts, for patients who remained on therapy, patient responses to both physical and role functioning items were not indicative of large decrements, suggesting that the additional toxicity of alpelisib did not appear to cause large limitations in ability to carry out daily activities or hobbies/leisure activities as captured. However it is noted that there is a more rapid drop in the number of patients in the placebo + fulvestrant arm.

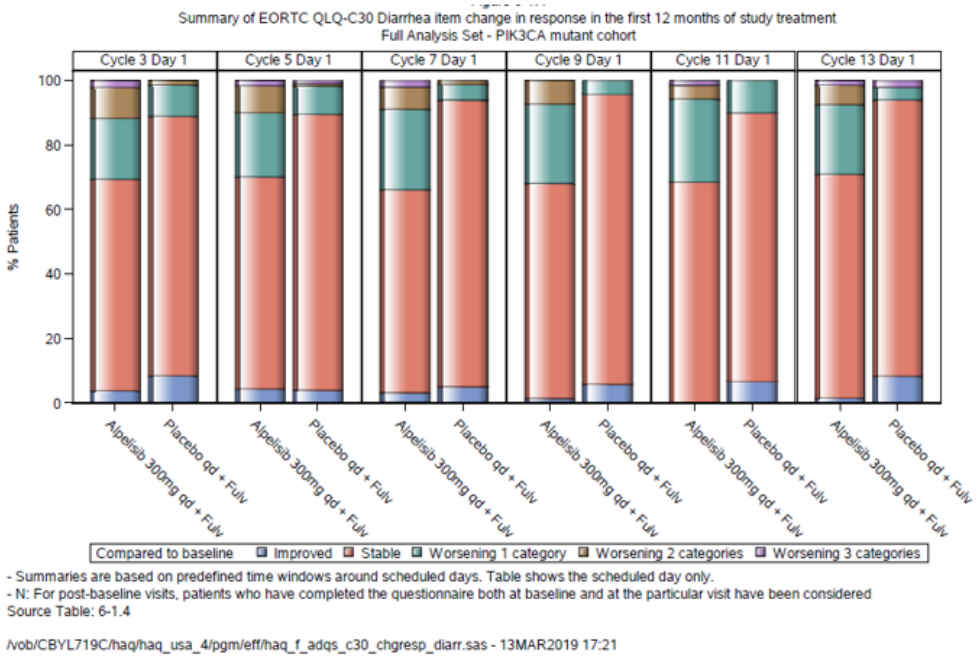


Source: Applicant Patient Reported Outcomes Information Request

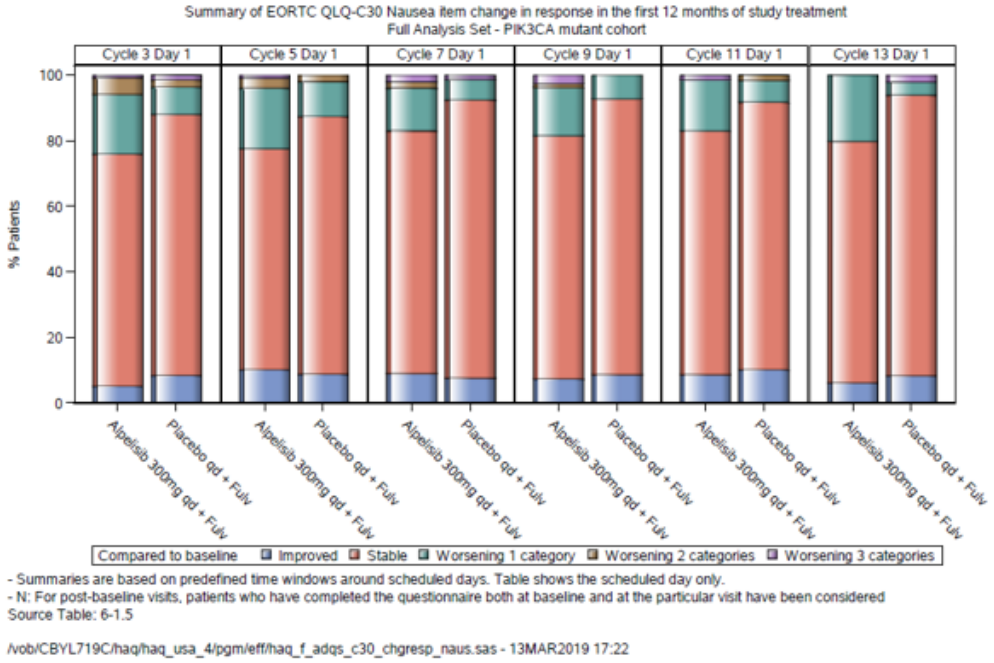
Social and emotional functioning are important concepts to patients, however they are distal

to the drug effect and capture information unrelated to the mechanism of action of the therapy which is under review in this assessment. As a result, this information is generally not included in the agency's benefit:risk assessment.

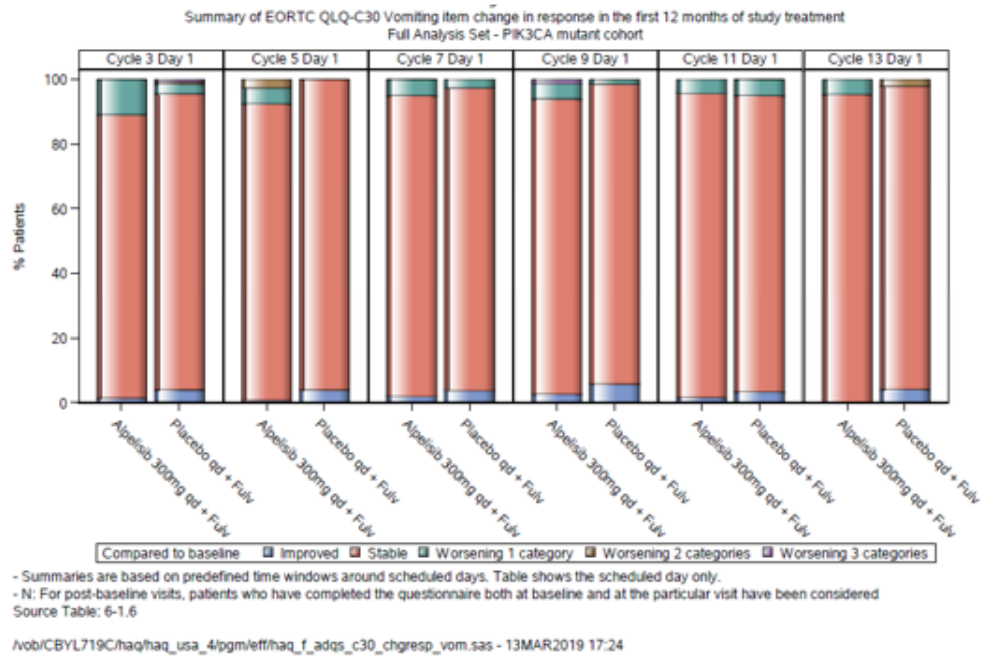
Looking at the descriptive distributions of patients reporting key gastrointestinal adverse events that were captured using PRO measures, we see a similar pattern to that reflected in the adverse reaction table, i.e., that more patients in the alpelisib arm reported worsening diarrhea, nausea and vomiting. In analyzing the patterns of these side effects over time, there is generally a stable incidence of these adverse events for patients who remained on therapy through cycle 13, with the exception of vomiting, which had the highest incidence at the first follow-up visit and less vomiting reported in subsequent cycles.



Source: Applicant Patient Reported Outcomes Information Request



Source: Applicant Patient Reported Outcomes Information Request



Source: Applicant Patient Reported Outcomes Information Request

The overall review of the PRO results did not identify a large decrement in symptoms or function that would materially alter the overall favorable risk-benefit determination.

8.1.3. Supportive study for efficacy - Study CBYL719X2101

The Applicant's Position:

Overview of study design – Study CBYL719X2101
This was a Phase IA, open-label, dose-escalation study of oral alpelisib in adult subjects with advanced solid malignancies, whose tumors mostly have an alteration (mutation or amplification) of the PIK3CA gene. The study consisted of a dose escalation part and a dose expansion part. Dose-escalation was started with oral daily BYL719 at a starting dose of 30 mg. The length of each treatment cycle was 28 days. All subjects were treated until they met the criteria for study discontinuation (e.g. disease progression, unacceptable toxicity, patient withdrawal, investigator's discretion).

The FDA's Assessment:

The FDA concurs with the applicant's description of the study design.

8.1.4. Efficacy results – Study CBYL719X2101

The Applicant's Position:

Results from the Phase I/II dose expansion part of Study CBYL719X2101 provide further supportive evidence of the antitumor activity of the alpelisib plus fulvestrant drug combination in the proposed indication.

Eighty-seven postmenopausal women with ER-positive locally advanced or metastatic breast cancer (median age 58 years; range: 37 to 79) who had disease progression during or following anti-estrogen therapy or whose disease had relapsed following adjuvant anti-estrogen therapy were treated in the dose-expansion part of this study with alpelisib and fulvestrant. Alpelisib was dosed at 300 mg (n = 9), 350 mg (n = 8), and at the MTD of 400 mg (n = 70).

All 87 subjects were heavily pretreated, with a median of 5.0 prior antineoplastic regimens (range: 1 to 16). Of the 87 subjects, 86 (98.9%) had undergone prior surgery. Sixty-six subjects (75.9%) received prior chemotherapy in the advanced or metastatic setting, and 65 subjects (74.7%) received prior radiotherapy. Prior anti-estrogen therapy was received by 53 subjects (60.9%) in the metastatic setting.

Among the 87 subjects, 52 subjects with ER-positive breast cancer harbored an alteration of the PIK3CA gene (mutation or amplification) and 33 subjects had PIK3CA wild-type ER-positive breast cancer based on central laboratory testing; for 2 subjects, the PIK3CA mutation status was unknown as it could not be determined by the central laboratory.

Overall response rate and clinical benefit rate
Of the 49 evaluable subjects with ER-positive, HER2-negative breast cancer with PIK3CA mutation, 14 subjects achieved a PR; the ORR was 28.6% (95% CI: 16.6, 43.3). The DCR in was 79.6% (95% CI: 65.7, 89.8) and the CBR was 44.9% (95% CI: 30.7, 59.8).

Progression-free survival per investigator assessment
The PFS analysis demonstrated that the alpelisib plus fulvestrant combination was associated with prolonged PFS among the 49 subjects with PIK3CA mutant tumors (median PFS: 9.1 months (95% CI: 7, 15)) relative to the 32 evaluable subjects with PIK3CA wild-type tumors (where the median PFS was 4.7 months (95% CI: 2, 6).

The FDA's Assessment:

The FDA concurs with the data presented by the applicant but cautions that the efficacy data in patients with heavily pretreated metastatic HR-positive, HER2-negative breast cancer at the 300 mg dosage schedule are very limited. Most patients in the metastatic breast cancer expansion cohorts were treated at higher doses (350-400 mg) that were associated with greater toxicity and are not recommended for use in the postmarketing setting. Only 9 patients in total in the metastatic breast cancer expansion cohorts were treated at the 300 mg dose studied in the SOLAR-1 trial. No conclusions can therefore be drawn, and no claims should be made, regarding the efficacy of alpelisib plus fulvestrant in more heavily pre-treated patients treated at the alpelisib 300 mg QD dose for which approval is being granted.

Integrated Review of Effectiveness

The FDA's Assessment:

The SOLAR-1 trial was a well-designed, well-conducted, randomized, controlled trial and met its primary endpoint. The addition of alpelisib to fulvestrant resulted in a clinically meaningful and statistically significant improvement in PFS in the ITT population of patients with HR-positive, HER2-negative, PIK3CA-mutated advanced or metastatic breast cancer following progression on or after endocrine therapy, as compared to placebo plus fulvestrant. Analyses of secondary endpoints, including PFS by BICR and ORR, were supportive of results of the primary endpoint.

Per the SAP, PFS by investigator assessment in the PIK3CA-mutated cohort was the primary endpoint, and OS in the PIK3CA-mutated cohort was the key secondary endpoint to be tested in a hierarchical fashion followed by other secondary endpoints. Given that the null hypothesis was rejected for the PFS endpoint (i.e. the primary endpoint was met), all alpha allocation remained to test OS at the first interim analysis of OS. The first interim OS analysis was not statistically significant, and hence there is no alpha allocation remaining for testing additional secondary endpoint hypotheses. The OS data remain immature, and final OS results will be provided to the FDA by the applicant as a postmarketing commitment. There is no evidence of a detrimental effect of alpelisib on OS. Statistical significance has not been demonstrated for any endpoint other than the primary endpoint of investigator-assessed PFS.

As a result, p-values reported for all other secondary efficacy endpoints, such as ORR, are nominal p-values, and no efficacy claims should be made based upon other endpoints.

The FDA does not concur with the interpretation of the results of other exploratory endpoints (e.g., above Table 16). Specifically, the FDA disagrees with the promotional language regarding "marked improvements" in ORR and CBR. While the ORR in patients with measurable disease was approximately doubled in the alpelisib plus fulvestrant arm relative to the control arm, the ORR was modest in both arms, and complete responses were rare and did not differ between arms. The alpelisib plus fulvestrant arm reported one CR and 44 PRs, while the placebo plus fulvestrant arm reported two CRs and 20 PRs. In the duration of response analysis, 22 (56%) responders on alpelisib plus fulvestrant and 9 (41%) responders on the control arm had experienced disease progression as of the data cutoff date. Although responses were more common with alpelisib plus fulvestrant, the median duration of response was shorter in the alpelisib plus fulvestrant arm (12.6 months [95% CI: 8.5, 18.5] versus 14.8 months [95% CI: 10.1, NE]).

The FDA concurs with the point estimates from exploratory subgroup analyses of efficacy represented in the applicant's forest plot above (e.g. patients with visceral metastases, endocrine resistance, prior CDK 4/6 inhibitor use, etc.), but disagrees with the applicant's promotional language that alpelisib has demonstrated "substantial improvement in PFS" in patient "subgroups that are considered of particular interest in the current treatment landscape." This language implies that alpelisib has demonstrated superior efficacy to the landscape of other available therapy in patients with endocrine-resistant cancer, visceral metastases, prior use of a CDK 4/6 inhibitor, or second-line use, which is not true. The HRs in the subgroup analyses are comparable to those in the ITT population for the comparison of alpelisib plus fulvestrant versus placebo plus fulvestrant; however, there are no comparative efficacy data to support that alpelisib plus fulvestrant has superior efficacy to other approved combinations of endocrine therapy plus kinase or CDK 4/6 inhibitors. No alpha has been allocated to these subgroup analyses, and therefore all results should be considered exploratory.

The current standard of care for first-line treatment of postmenopausal women with HR-positive, HER2-negative metastatic breast cancer in the United States is a combination of endocrine therapy and a CDK 4/6 inhibitor, irrespective of PIK3CA mutation status. Only 6% of patients on the SOLAR-1 trial had previously received an aromatase inhibitor plus CDK 4/6 inhibitor combination. No patients had previously received fulvestrant plus a CDK 4/6 inhibitor. While cross-trial comparisons are discouraged, multiple CDK 4/6 inhibitor trials have reported hazard ratios and absolute improvements in median PFS over endocrine therapy alone that are similar to those reported in the SOLAR-1 trial, as shown in Table 2.

The applicant noted that some patients with metastatic disease previously treated with a CDK 4/6 inhibitor had been enrolled in SOLAR-1, and that the PFS results favored the alpelisib arm (HR = 0.48; 95% CI: 0.17, 1.36). This observation was based on a very small sample size of 20 patients, of whom only 9 were treated with fulvestrant plus alpelisib, with correspondingly wide confidence intervals. No conclusions should be drawn regarding the efficacy of alpelisib

plus fulvestrant in the CDK 4/6 inhibitor-pretreated population.

To maintain consistency and with the common understanding of the customary p=0.05 boundary for statistical significance, the agency reports p-values at the two-sided level of significance. The portions of the Assessment Aid completed by the applicant report the one-sided level of significance and p-values. To get the equivalent two-sided value, the p-values in the applicant's portion of the document should be multiplied by two. Examples of this issue are detailed in the review.

The applicant's position on the PRO data presented above was reviewed. The FDA disagrees with the applicant's conclusions regarding COA (PRO) endpoints. The PRO analyses with composite scores were not controlled for multiple comparisons, and these analyses are considered exploratory. Also, FDA does not concur with the applicant's use of the phrase "meaningful difference" in describing results of the PRO analyses. The analysis of COA endpoints was not adequately powered to support a non-inferiority conclusion (i.e. a finding of no difference between the two arms). It is not possible to exclude a detrimental effect of alpelisib on global health status or quality of life for patients enrolled in the SOLAR-1 trial.

8.1.5. Assessment of Efficacy Across Trials

The Applicant's Position:

Data from the ongoing Phase I/II study (Study CBYL719X2101) provide further supportive evidence of the efficacy of the combination of alpelisib plus fulvestrant in a more heavily pretreated population of subjects with PIK3CA altered advanced breast cancer. Details of the efficacy results are provided in section 8.1.2.

Additional Efficacy Considerations

No additional efficacy data are considered other than the data described in section 8.1.2.

The FDA's Assessment:

The SOLAR-1 trial was used to assess the efficacy of alpelisib for approval. The data from the phase 1/2I Study CBYL719X2101 included only nine patients treated at the approved dose and schedule. Data to support the efficacy of alpelisib plus fulvestrant in more heavily pretreated population of patients with HR-positive, HER2-negative, PIK3CA-mutated advanced breast cancer are very limited. No conclusions should be drawn regarding the efficacy of the alpelisib plus fulvestrant combination in the heavily pre-treated patients.

8.1.6. Integrated Assessment of Effectiveness

The Applicant's Position:

Compelling evidence of the efficacy of alpelisib in combination with fulvestrant was demonstrated in the PIK3CA mutant cohort.

- Alpelisib in combination with fulvestrant demonstrated superiority over fulvestrant alone for the primary endpoint of PFS per investigator assessment using RECIST 1.1.
    - An estimated 35% risk reduction in disease progression or death was observed in favor of the alpelisib plus fulvestrant arm (HR = 0.65; 95% CI: 0.50, 0.85); this result was statistically significant, crossing the Haybittle-Peto boundary at the final PFS analysis (one-sided p = 0.00065 based on a stratified log-rank test).
    - Median PFS was prolonged by 5.3 months, from 5.7 months (95% CI: 3.7, 7.4) in the placebo plus fulvestrant arm to 11.0 months (95% CI: 7.5, 14.5) in the alpelisib plus fulvestrant arm. The magnitude of this benefit is considered to be clinically meaningful for this population.
- Blinded independent review and multiple preplanned sensitivity analyses demonstrated the robustness of the observed PFS benefit.
- Subgroup analyses demonstrated a homogeneous and generally consistent treatment effect across important prognostic and disease characteristics, thus indicating that the observed benefit in favor of the alpelisib plus fulvestrant arm is applicable to the entire subject population.
- OS data in the PIK3CA mutant cohort were not mature at this first interim analysis.
- 92 deaths were reported: 40 (23.7%) in the alpelisib plus fulvestrant arm and 52 (30.2%) in the placebo plus fulvestrant arm. The pre-specified O'Brien-Fleming stopping boundary of $p \leq 0.00121$ was not crossed (HR = 0.73; 95% CI: 0.48, 1.10; p = 0.06). Median OS was not yet reached for the alpelisib plus fulvestrant arm (95% CI: 28.1, NE) and was 26.9 months (95% CI: 21.9, NE) for the fulvestrant control arm.
- Treatment with alpelisib plus fulvestrant was associated with marked improvements in ORR and CBR relative to placebo plus fulvestrant in subjects with measurable disease at baseline.
    - ORR (based on RECIST 1.1) of 35.7% (95% CI: 27.4, 44.7) was observed in subjects receiving treatment with alpelisib plus fulvestrant compared to 16.2% (95% CI: 10.4, 23.5) in subjects receiving treatment with placebo plus fulvestrant (p = 0.0002).
    - The observed CBR in the alpelisib plus fulvestrant and placebo plus fulvestrant arms were 57.1% (95% CI: 48.0, 65.9) and 44.1% (95% CI: 35.6, 52.9; p = 0.02).

Proof-of-concept criteria for PFS per investigator assessment were not met in the non-mutant PIK3CA cohort, indicating a lack of clinical activity in this population (estimated HR = 0.85; 95% CI: 0.58, 1.25; 79.4% posterior probability for true HR < 1).

Data from the ongoing Phase I/II study (Study CBYL719X2101) provide further supportive evidence of the efficacy of the combination of alpelisib plus fulvestrant in a more heavily pretreated population of subjects with PIK3CA-altered advanced breast cancer.

In conclusion, the combination of alpelisib plus fulvestrant at the recommended dose offers a valuable new treatment option for subjects with HR-positive, HER2-negative advanced breast cancer harboring a PIK3CA mutation, as determined using either tumor or plasma specimens, with disease progression following an endocrine-based regimen.

The FDA's Assessment:

The FDA concurs with the applicant that the combination of alpelisib plus fulvestrant yields a net favorable benefit-risk profile compared to placebo plus fulvestrant based upon results of SOLAR-1, a multinational, randomized, placebo-controlled trial. The SOLAR-1 trial met its primary endpoint in the intended use population of patients with HR-positive, HER2-negative PIK3CA-mutated advanced or metastatic breast cancer. The estimated median PFS by investigator assessment in the ITT population for the alpelisib plus fulvestrant arm was 11.0 months (95% CI: 7.5, 14.5) compared to 5.7 months (95% CI: 3.7, 7.4) in the placebo plus fulvestrant arm (HR 0.65; 95% CI: 0.50, 0.85; p=0.001). Results of several exploratory analyses, including PFS in the PIK3CA-mutated cohort by blinded independent central review (BICR), subgroup analyses, additional efficacy endpoints, and sensitivity analyses were generally consistent with the results of the primary endpoint. The pre-specified O'Brien-Fleming stopping boundary for OS was not crossed at the first interim analysis of OS, and thus no alpha remains for further assessment of OS. The final OS analysis will be reported by the applicant as a PMC.

The FDA disagrees with the applicant's use of promotional language such as "marked improvements" in efficacy and notes that the magnitude of benefit observed from addition of alpelisib to fulvestrant is similar to that observed for several approved CDK 4/6 inhibitors in combination with endocrine therapy in an overlapping patient population. In addition, the incremental improvements in ORR and CBR with addition of alpelisib to fulvestrant are supportive of the primary endpoint but modest in absolute terms, as noted earlier in the review, and because no alpha has been allocated to these additional efficacy analyses, they should be considered exploratory. Finally, only 6% of patients in the SOLAR-1 trial had previously received an aromatase inhibitor plus CDK 4/6 inhibitor combination, which represents the current standard of care for first-line treatment of postmenopausal women with HR-receptor positive, HER2-negative metastatic breast cancer in the United States, and thus no conclusions may be drawn regarding the efficacy of alpelisib plus fulvestrant in the CDK 4/6 inhibitor-pretreated population that will be treated in the postmarketing setting. However, activation of PI3K signaling is a known mechanism of resistance in patients whose tumors have progressed on CDK 4/6 inhibitors, and therefore a strategy of combining endocrine therapy plus a PI3K inhibitor after progression on CDK 4/6 inhibitor-based regimens is a rational approach (Vora et al. 2014, Michaloglou et al. 2018).

The available data do not provide compelling evidence that patients whose tumors have PIK3CA mutations derive lesser benefit from the combinations of endocrine therapy plus CDK inhibitor that represent the current U.S. standard of care in the indicated patient population.

Superior efficacy was not demonstrated for the combination of alpelisib plus fulvestrant compared to placebo plus fulvestrant in the PIK3CA-wildtype cohort, and therefore use of alpelisib plus fulvestrant should be limited to the PIK3CA-mutated population, as reflected in the indication for which approval is recommended.

8.2. Review of Safety

The Applicant's Position:

This safety evaluation is based on data from 825 subjects treated in three clinical studies. The primary focus is on data from 571 subjects treated with at least one dose of study drug in the randomized, double-blind, placebo-controlled Phase III Study CBYL719C2301 in subjects with HR-positive, HER2-negative advanced breast cancer, with 284 subjects in the alpelisib 300 mg plus fulvestrant group (169 subjects in the PIK3CA mutant cohort and 115 subjects in the PIK3CA non-mutant cohort) and 287 subjects in the placebo plus fulvestrant group (171 subjects in the PIK3CA mutant cohort and 116 subjects in the PIK3CA non-mutant cohort).

The presence or absence of PIK3CA mutations was not expected to affect the occurrence of AEs. The incidence of AEs, SAEs, and AESIs was generally consistent between the PIK3CA mutant and non-mutant cohorts and therefore safety data from both cohorts were combined to present the safety profile of alpelisib from a larger number of subjects.

In addition, 167 subjects were exposed to single-agent alpelisib and 87 subjects were exposed to alpelisib in combination with fulvestrant in the dose-finding Studies CBYL719X2101 and CBYL719X1101. The safety data from the two dose-finding studies did not reveal any additional findings that would affect the safety profile of alpelisib in combination with fulvestrant in the advanced breast cancer setting.

Data from these studies allow for an informed assessment of the safety profile of the alpelisib plus fulvestrant combination and an evaluation of the overall benefit-risk in subjects with HR-positive, HER2-negative, advanced breast cancer with PIK3CA mutation. This safety population is also considered appropriate for the detection and characterization of common AEs and to provide guidance on toxicity management.

The FDA's Assessment:

For this NDA, the applicant submitted safety data from SOLAR-1, a phase 3 randomized, double-blind, placebo-controlled trial in patients with HR-positive, HER2-negative advanced breast cancer. Data were combined from the PIK3CA-mutated and PIK3CA-wildtype cohorts by the applicant for the overall safety analysis. The applicant also provided datasets for the two dose-finding studies CBYL719X2101 (single agent alpelisib) and CBYL719X1101 (alpelisib + fulvestrant). These were not pooled with the data from SOLAR-1 by the applicant for safety analysis.

The FDA's independent safety analysis for this NDA is based on 571 safety-evaluable patients who received at least 1 dose of study treatment and who had at least one post-baseline safety assessment in the SOLAR-1 trial, irrespective of PIK3CA mutation status. The FDA also conducted an additional safety analysis in the PIK3CA-mutated cohort (169 subjects in the alpelisib + fulvestrant arm and 171 subjects in the placebo + fulvestrant arm) and agrees that the AEs, SAEs and AESIs were generally consistent between the PIK3CA-mutated and overall

safety population. The FDA agrees that the data from the two dose-finding studies were generally consistent with the safety findings from the SOLAR-1 trial.

The FDA reviewed the 90-day safety datasets submitted by the applicant and did not identify any new safety signals not already discussed in this review.

8.2.1. Safety Review Approach

The Applicant's Position:

The data presented here is a comprehensive analysis of safety data relevant to the use of alpelisib in combination with fulvestrant in the treatment of postmenopausal women and men with HR-positive, HER2-negative advanced breast cancer.

Based on the mechanism of action, the main expected toxicities of alpelisib were hyperglycemia and skin toxicities, mainly rash. Clinical experience with alpelisib administered as a single agent, in combination with fulvestrant, and in combination with other agents, confirm that these events are some of the most frequent toxicities observed with alpelisib, as well as GI toxicities (mainly diarrhea, but also nausea and vomiting). In addition, pneumonitis is a class effect with PI3K/mTOR inhibition.

The FDA's Assessment:

The FDA agrees with the applicant's assessment.

8.2.2. Review of the Safety Database

Overall Exposure

The Applicant's Position:

The Safety evaluation included all subjects who received at least one dose of study treatment. Safety data were not pooled across studies (Study CBYL719C2301, Study CBYL719X2101, and Study CBYL719X1101) due to the different study populations, wide range of alpelisib dose levels (30 mg to 450 mg/day), administration schedules (once and twice-daily dosing), and regimens (single agent and combination with fulvestrant) used in the studies.

Extent of exposure
Exposure to study treatment in Study CBYL719C2301 was considered appropriate to allow for an adequate assessment of safety in subjects who were representative of the intended target population. Exposure to the alpelisib plus fulvestrant combination was 2847.3 months and 2530.4 subject-months to placebo plus fulvestrant.

The median duration of exposure to study treatment was longer in the alpelisib plus fulvestrant group (8.2 months) compared to the placebo plus fulvestrant treatment group (5.6 months) (Table 17).

Table 17: Duration of Exposure to Study Drug – Study CBYL719C2301 (Safety set)

	Alpelisib 300 mg plus fulvestrant			Placebo plus fulvestrant		
	N=284			N=287		
	Alpelisib	**Fulvestrant**	**Overall**	**Placebo**	**Fulvestrant**	**Overall**
No. of subjects - n (%)	283 (99.6)	284 (100.0)	284 (100.0)	286 (99.7)	287 (100.0)	287 (100.0)
Duration of exposure (months)						
Mean (SD)	8.0 (7.43)	10.0 (7.34)	10.0 (7.34)	8.4 (7.61)	8.8 (7.65)	8.8 (7.64)
Median	5.5	8.2	8.2	5.6	5.6	5.6
Min-Max	0.0* - 30.8	0.4 - 30.8	0.4 - 30.8	0.0* - 30.1	0.5 - 30.1	0.5 - 30.1
Duration of exposure categories – n (%)						
At least 1 month	246 (86.6)	269 (94.7)	269 (94.7)	274 (95.5)	276 (96.2)	278 (96.9)
At least 3 months	187 (65.8)	231 (81.3)	231 (81.3)	189 (65.9)	191 (66.6)	192 (66.9)
At least 6 months	130 (45.8)	168 (59.2)	168 (59.2)	138 (48.1)	141 (49.1)	141 (49.1)
At least 12 months	79 (27.8)	101 (35.6)	101 (35.6)	78 (27.2)	83 (28.9)	83 (28.9)
At least 18 months	40 (14.1)	52 (18.3)	52 (18.3)	45 (15.7)	48 (16.7)	48 (16.7)

Overall: Corresponds to duration of study treatment.

* One subject in the alpelisib plus fulvestrant group and one subject in the placebo plus fulvestrant group received no alpelisib/placebo

The FDA's Assessment:

The FDA agrees with the exposure data the applicant presented.

Relevant characteristics of the safety population:

The Applicant's Position:

The eligibility criteria in the pivotal Phase III Study CBYL719C2301 were clinically relevant for the target population of subjects who would receive alpelisib combination therapy following regulatory approval in the proposed indication. The study was open to enroll postmenopausal women and men with HR-positive, HER2-negative advanced breast cancer whose disease had progressed on or after AI-based treatment reflecting a predominantly endocrine-resistant population.

Demographic characteristics were well balanced between the two treatment groups (alpelisib plus fulvestrant versus placebo plus fulvestrant), thereby providing reassurance with regard to the interpretation of the treatment comparison and the validity of the safety conclusions. Overall, the baseline characteristics were representative of the broad population of subjects with HR-positive, HER2-negative, recurrent or metastatic breast cancer (Table 12 and Table 13).

The FDA's Assessment:

The FDA agrees that the demographic characteristics between the two treatment groups were generally well balanced based on independent review.

However, the FDA disagrees in part with the applicant's assessment that "the baseline characteristics were representative of the broad population of subjects with HR-positive, HER2-negative, recurrent or metastatic breast cancer." The SOLAR-1 safety population differed notably in terms of prior therapy from the population that will receive alpelisib post-approval. In the United States, the current standard of care for first-line treatment of metastatic breast cancer is a CDK 4/6 inhibitor in combination with hormonal therapy. Although patients who previously received a CDK 4/6 inhibitor with hormonal therapy were eligible for the SOLAR-1 trial, the study population included only 20 patients who had previously received a CDK 4/6 inhibitor, of whom 9 were randomized to receive alpelisib. However, activation of PI3K signaling is a known mechanism of resistance in patients whose tumors have progressed on CDK 4/6 inhibitors, and therefore a strategy of combining endocrine therapy plus a PI3K inhibitor after progression on CDK 4/6 inhibitor-based regimens is a rational approach (Vora et al. 2014, Michaloglou et al. 2018).

Treatment options for male patients with breast cancer are a significant area of unmet medical need. PIK3CA mutations are not expected to behave differently in male patients and fulvestrant degrades the estrogen receptor and does not rely on circulating estradiol levels for efficacy. Male patients were eligible for and enrolled on SOLAR-1. In addition, 36 male patients with various solid tumors were treated with alpelisib monotherapy in Study X2101 during early phase dose-escalation (across different dose levels) and dose-expansion studies.

Adequacy of the safety database:

The Applicant's Position:

The evaluation of safety is based on data from the registration study (Study CBYL719C2301) and Phase I dose-finding studies (Studies CBYL719X2101 and CBYL719X1101). Further details are provided in Section 8.2. This population allows for an informed assessment of the safety profile of alpelisib plus fulvestrant and a judgment of the overall benefit-risk in subjects with HR-positive, HER2-negative advanced breast cancer.

The FDA's Assessment:

The FDA's independent safety analysis for this NDA is based on 571 safety-evaluable patients who received at least 1 dose of study drug and who had at least one post-baseline safety assessment in the SOLAR-1 trial, irrespective of PIK3CA mutation status.

The applicant also provided datasets for the two dose-finding studies CBYL719X2101 (single agent alpelisib) and CBYL719X1101 (alpelisib + fulvestrant). These were not pooled with the data from SOLAR-1 by the applicant or FDA for safety analysis due to differences in study

population, dose levels, and regimen differences between the studies. The FDA agrees that the safety data from the two dose-finding studies was generally consistent with the safety findings from the SOLAR-1 trial and did not reveal any new safety signals. The 90-day safety data also did not reveal any new safety signals based on FDA review.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets and individual case narratives; these were sufficiently complete to allow for a thorough review of safety. Furthermore, no data integrity concerns were reported following completion of site inspections; data in the CRFs and adverse event databases were consistent.

The FDA's Assessment:

Based upon the agency's review and the findings of inspections by OSI, the FDA agrees with the applicant's assessment regarding the quality and integrity of the submitted datasets. Refer to Section 4.1 in this document for further details on inspections.

Categorization of Adverse Event

The Applicant's Position:

The safety of study treatment was evaluated on the basis of the:

- Frequency, type, severity, and causal relationship of AEs to study treatment.
- AEs and laboratory parameters were graded using NCI CTCAE Version 4.03 in Study CBYL719C2301 and Study CBYL719X2101, and Version 4.0 in Study CBYL719X1101
- Frequency of deaths, SAEs, and other clinically significant AEs (including AEs leading to discontinuation and AEs requiring dose interruption and/or reduction)
- Frequency and type of AEs in key demographic subgroups (age, race, and region) and by baseline disease characteristics (including PIK3CA mutation status in tissue)
- Changes in laboratory variables, with particular attention to grade 3/4 abnormalities

Adverse events were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 for Study CBYL719C2301, Version 18.1 for Study CBYL719X1101, and Version 17.1 for Study CBYL719X2101. Adverse events of special interest (AESI) are described in Section 8.2.4.

The FDA's Assessment:

The FDA agrees with the applicant's assessment.

Routine Clinical Tests

The Applicant's Position:

Data from all sources (central and local laboratories) were combined. The summaries included all laboratory assessments collected no later than 30 days after study treatment discontinuation.

The clinical monitoring of subject safety was considered adequate for the expected toxicities associated with combination therapy with alpelisib and fulvestrant. Subjects were questioned about AEs at each clinic visit. In addition, AEs could also be detected when reported by the subjects during or between visits or through physical examination, laboratory test results, or other assessments. Further to the standard safety evaluations outlined above, AE categories expected to be associated with alpelisib were also analyzed. These AESIs were selected based on the mechanism of action of alpelisib as well as nonclinical and early clinical observations.

The FDA's Assessment:

The FDA agrees with the applicant's assessment.

Safety Results

Deaths

The Applicant's Position:

A review of the deaths in Studies CBYL719C2301, CBYL719X2101, and CBYL719X1101 did not identify any pattern as most subjects who died had underlying contributing comorbidities and complications associated with their disease. Most deaths were due to disease progression (Table 18).

Table 18: Overview of Deaths – Studies CBYL719C2301, CBYL719X2101, and CBYL719X1101 (Safety set)

	Study CBYL719C2301		Study CBYL719X2101	Study CBYL719X2101	Study CBYL719X1101
	Alpelisib plus fulvestrant	Placebo plus fulvestrant	Alpelisib plus fulvestrant	Alpelisib	Alpelisib
	N = 284	N = 287	N = 87	N = 134	N = 33
Category	n (%)	n (%)	n (%)	n (%)	n (%)
All deaths	78 (27.5)	91 (31.7)	7 (8.0)	15 (11.1)	3 (9.0)
Death within 28/30 days of treatment discontinuation [a]	7 (2.5)	12 (4.2)	5 (5.7)	13 (9.7)	3 (9.0)
Progressive disease	5 (1.8)	8 (2.8)	4 (4.6)	12 (9.0)	2 (6.0)
Adverse events	2 (0.7)	4 (1.4)	1 (1.1)	1 (0.7)	1 (3.0)
Cardio-respiratory arrest	1 (0.4)	0	0	0	0

	Study CBYL719C2301		Study CBYL719X2101	Study CBYL719X2101	Study CBYL719X1101
	Alpelisib plus fulvestrant	Placebo plus fulvestrant	Alpelisib plus fulvestrant	Alpelisib	Alpelisib
	N = 284	N = 287	N = 87	N = 134	N = 33
Category	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Second primary malignancy	1 (0.4)	1 (0.3)	0	0	0
Death	0	1 (0.3)	1 (1.1)	0	0
GI haemorrhage	0	1 (0.3)	0	0	0
Pneumonia	0	1 (0.3)	0	0	0
Septic shock	0	1 (0.3)	0	0	0
Tumor embolism	0	0	0	0	1 (3.0)
Hypoxia	0	0	0	1 (0.7)	0

Of the 825 subjects in the safety population across the three studies, 40 subjects (4.8%) died while 'on-treatment' (i.e. while receiving study treatment or within 28/30 days of study treatment discontinuation). Thirty-one of these 40 'on-treatment' deaths were attributed to the underlying malignancy while the remaining 9 were secondary to other causes that were not classified as disease progression.

As of the 12-Jun-2018 data cut-off in Study CBYL719C2301, 19 'on-treatment' deaths were reported (7 (2.5%) in the alpelisib plus fulvestrant group vs. 12 (4.2%) in the placebo plus fulvestrant group). Review of these cases did not identify any pattern. Thirteen of these 19 'on-treatment' deaths were attributed to progression of the underlying disease while the remaining 6 deaths were secondary to other causes that were not classified as disease progression: 2 deaths in the alpelisib plus fulvestrant group were due to cardio-respiratory arrest and a second primary malignancy, and the 4 deaths in the placebo plus fulvestrant group were due to gastrointestinal hemorrhage, pneumonia, septic shock, and unknown cause, respectively. None of these deaths was considered to be related to study treatment by the Investigator or Novartis.

Five 'on-treatment' deaths were reported during the conduct of Study CBYL719X2101; 4 were attributed to the underlying disease and 1 was due to an unknown cause (but followed disease progression). All deaths occurred in the alpelisib 400 mg plus fulvestrant dose group. A further 16 subjects (treated with single-agent alpelisib) died 'on-treatment' in Studies CBYL719X2101 (12 were due to disease progression, and 1 death was attributed to hypoxia due to underlying disease) and CBYL719X1101 (2 attributed to disease progression and 1 due to tumor embolism). None of the 'on-treatment' deaths due to AEs were suspected to be related to study treatment by the investigator.

The FDA's Assessment:

The FDA's independent analysis of deaths in the SOLAR-1 (Study CBYL719C2301) trial is generally consistent with the data the applicant presented. All-cause death occurred in 78/284 (27%) of patients in the alpelisib + fulvestrant arm and in 91/287 (32%) of patients in the placebo + fulvestrant arm. The majority of deaths in both treatment arms were due to disease progression. The FDA reviewed all the narratives provided by the applicant.

Below is a summary of the narratives for the 2 deaths reported on the alpelisib + fulvestrant arm that occurred within 30 days of the last dose of study treatment in SOLAR-1:

1. ***Patient ID*** (b) (6) ***: Tumor was PIK3CA-mutated. The 76-year-old female received last dose of alpelisib on Day 442. On Day 443, she experienced a fall and suffered a hip fracture. Study treatment was discontinued. She experienced a cardiac arrest and died the same day. The fall and hip fracture are confounding factors for death.***

2. ***Patient ID*** (b) (6) ***: Tumor was PIK3CA-wildtype. The 82-year-old female developed abdominal pain on Day 88 and was eventually diagnosed with a second primary malignancy of the peritoneal region. She had been on a reduced dose of alpelisib 250 mg due to prior episode of rash on Day 13. Fulvestrant was discontinued on Day 85 and alpelisib on Day 112 (the narrative was not clear on why she continued study medications after the diagnosis of second primary malignancy). She died 27 days after receiving last dose of study drug. The FDA agrees that alpelisib was likely not related to development of the second primary malignancy and no other patient developed second primary malignancies on SOLAR-1.***

Four deaths resulting from AEs were reported on the placebo + fulvestrant arm in the SOLAR-1 trial that occurred within 30 days of treatment:

1. ***Patient ID*** (b) (6) ***: Tumor was PIK3CA-mutated. The 84-year-old female at study entry had metastatic involvement that included lung, pleural effusion and liver. She presented with dyspnea, edema in both lower extremities and tachycardia. She was found to have atrial fibrillation and cardiac failure (both grade 2). Placebo was stopped however no action was taken with fulvestrant. On day 50, she developed pneumonia. Pneumonia worsened and on day 64, she died. The FDA agrees that death likely related to worsening acute issues (pneumonia and underlying baseline metastatic disease).***

2. ***Patient ID*** (b) (6) ***: Tumor was PIK3CA-mutated. The 79-year old female experienced gastrointestinal hemorrhage on day 616. Placebo was stopped (last dose on day 615), and no action was taken with fulvestrant (last dose day 589). On day 620 gastroscopy revealed bulbar ulcer. Despite supportive care and transfusions, her condition deteriorated, and death occurred on day 620. The FDA agrees that study***

treatment was likely not related to GI hemorrhage given fulvestrant was given 27 days prior to adverse event.

3. ***Patient ID*** (b) (6)***: Tumor was PIK3CA-mutated. The 71-year-old female at study entry had metastatic involvement of the lung. On day 341, the participant was diagnosed with pulmonary tuberculosis (TB). Placebo was held on day 347, and the participant was initiated on anti-TB treatment. Last day of fulvestrant was on day 311. She developed elevated bilirubin (grade 3) and grade 1 AST on day 355. On day 362 she developed altered mental status and septic shock and died on the same day. Autopsy was not performed. The FDA agrees that study treatment was likely not related given timing of events and anti-TB medication may have contributed to elevated liver enzymes.***

4. ***Patient ID*** (b) (6)***: Tumor was PIK3CA-mutated. The 51-year-old female had poorly differentiated metastatic breast cancer that was widely metastatic to bone, liver, lung, posterior mediastinal and retroperitoneal lymph nodes, omentum, ascites and parotid gland. On day 38, CT scan revealed progression in liver, lymph nodes and new malignant pericardial effusion. Study treatment was permanently discontinued due to progression (last placebo day 38, last fulvestrant day 29). She died due to unknown reasons on day 51 while sleeping. The FDA agrees that study treatment was likely not related as the participant experienced progression including a new cardiac effusion that potentially contributed to death. No additional details were provided to the FDA regarding her death.***

One death resulting from an adverse event was reported in study CBYL719X1101:

1. ***Patient ID*** (b) (6)***: The 66-year-old male entered the dose escalation phase of the study with undifferentiated advanced unresectable gastric cancer. Seven days prior to starting study medication, he was diagnosed with grade 2 tumor embolism. No treatment was reported for this. On day 18, while he was on 400 mg alpelisib daily as monotherapy, abdominal ultrasound revealed progression of disease in liver and liver abscess and he was diagnosed with grade 3 hepatic infection. This was reported as secondary to tumor necrosis due to antitumor effect from study medication. Alpelisib was held and abscess drained along with antibiotics administered. On day 42, alpelisib was restarted at 400 mg daily. On day 87 dose was reduced to 270 mg daily due to grade 3 palmar-plantar erythrodyesthesia. On day 98, he was noted with second episode of hepatic abscess. Alpelisib was held on the same day. The participant was hospitalized and treated with supportive care. On day 108 alpelisib was restarted at 270 mg. The participant died on day 160 reportedly due to tumor embolism. The FDA believes that study treatment potentially contributed to episodes of hepatic abscess; however, the contribution of study drug to death is not clear given reported progression of disease, and presence of tumor embolism prior to start of study treatment. This participant received 400 mg daily of alpelisib for a portion of their treatment which is higher than the dose for which the applicant is currently seeking an***

indication in this NDA (300 mg daily).

Two deaths resulting from an adverse event were reported in study CBYL719X2101, one in the alpelisib monotherapy group and one in the alpelisib + fulvestrant group:

1. ***Patient ID*** (b) (6)***: 70-year-old female with PIK3CA-mutated metastatic adenocarcinoma of the lung. She was in the dose escalation phase at dose of 300 mg alpelisib monotherapy daily. On day 44, she had worsening cough and developed grade 3 hypoxia. A CT scan revealed progression of disease, and alpelisib was permanently discontinued (last dose was on day 42). On day 48, she died due to hypoxia. The FDA agrees that cause of death was likely due to progression of disease.***

2. ***Patient ID*** (b) (6)***: 62-year-old female with PIK3CA-mutated metastatic breast cancer assigned to alpelisib 400 mg daily + fulvestrant 500 mg once every 4 weeks. At baseline, she reportedly had elevations in liver enzymes. On day 22, she developed grade 3 hyperbilirubinemia. No treatment was reported. On day 22, a CT scan revealed disease progression. Study treatment was permanently discontinued due to progression. Last dose of fulvestrant was on day 15 and alpelisib on day 22. On day 31, she died due to an unknown reason. The FDA agrees death was likely due to disease progression.***

Serious Adverse Events

The Applicant's Position:

Serious AEs in Study CBYL719C2301 were reported more frequently in the alpelisib plus fulvestrant group relative to the placebo plus fulvestrant group (34.9% vs. 16.7%). Except for hyperglycemia (9.9%) which was the most frequent SAE in the alpelisib plus fulvestrant group; the incidence of SAEs was low for both groups. Other SAEs reported in the alpelisib plus fulvestrant group in at least 2% of subjects included diarrhea (2.8%) and abdominal pain (2.1%) (Table 19).

Table 19: Serious Adverse Events (At Least 1.5% in Either Treatment Group) – Study CBYL719C2301 (Safety set)

	Alpelisib plus fulvestrant		Placebo plus fulvestrant	
	N=284		N=287	
	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Hyperglycaemia	28 (9.9)	26 (9.2)	0	0
Diarrhoea	8 (2.8)	4 (1.4)	0	0
Abdominal pain	6 (2.1)	4 (1.4)	2 (0.7)	1 (0.3)
Acute kidney injury	5 (1.8)	3 (1.1)	1 (0.3)	1 (0.3)
Anaemia	5 (1.8)	3 (1.1)	0	0
Nausea	5 (1.8)	4 (1.4)	2 (0.7)	1 (0.3)

	Alpelisib plus fulvestrant		Placebo plus fulvestrant	
	N=284		N=287	
	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Osteonecrosis of jaw	5 (1.8)	4 (1.4)	1 (0.3)	1 (0.3)
Rash	5 (1.8)	4 (1.4)	0	0
Vomiting	5 (1.8)	2 (0.7)	3 (1.0)	1 (0.3)

The FDA's Assessment:

The FDA generally agrees with the data presented above by the applicant. The FDA also conducted an independent review of SAEs. Serious adverse events occurred in 99 (35%) of patients in the alpelisib + fulvestrant arm and 47 (16%) of patients in the placebo + fulvestrant arm, which included both PIK3CA-mutated and PIK3CA-wildtype cohorts. The incidence of all-grade rash for alpelisib + fulvestrant is 3.5% when all types of rash experienced in the study using preferred terms are combined (i.e., rash, rash generalized, rash macular, rash maculo-papular, and rash pruritic).

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

Treatment discontinuations (of one or both study drugs) as a result of AEs in Study CBYL719C2301 were reported in 25.0% of subjects in the alpelisib plus fulvestrant group and 4.5% of subjects in the placebo plus fulvestrant group. The most commonly reported AEs leading to treatment discontinuation of alpelisib (± fulvestrant) (with an incidence ≥ 2%) were hyperglycemia (6.3%), rash (3.2%), diarrhea (2.8%), and fatigue (2.1%) (Table 20).

Table 20: Adverse Events Leading to Discontinuation (At Least 1.5% in Either Treatment Group) – Study CBYL719C2301 (Safety set)

	Alpelisib plus fulvestrant		Placebo plus fulvestrant	
	N=284		N=287	
	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Hyperglycaemia	18 (6.3)	12 (4.2)	0	0
Rash	9 (3.2)	3 (1.1)	0	0
Diarrhoea	8 (2.8)	1 (0.4)	0	0
Fatigue	6 (2.1)	3 (1.1)	0	0
Nausea	5 (1.8)	1 (0.4)	0	0

The FDA's Assessment:

The FDA agrees with the data presented above for adverse events leading to treatment discontinuations.

The FDA conducted an independent review of the adverse events leading to discontinuation. Updated datasets for ADAE were obtained from the applicant to further analyze discontinuations of alpelisib only versus of fulvestrant only in both study arms. In the alpelisib + fulvestrant arm, 4.6% of patients permanently discontinued both alpelisib and fulvestrant, and 21% discontinued alpelisib alone. This information was included in the alpelisib USPI.

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

Adverse events requiring dose interruption and/or reduction in Study CBYL719C2301 were more frequent in the alpelisib plus fulvestrant group (78.5% of subjects vs. 22.6% in the placebo plus fulvestrant group). The most commonly occurring AEs necessitating adjustment or interruption (with an incidence ≥ 5%) with the alpelisib plus fulvestrant combination were hyperglycemia (38.4%), diarrhea (13.7%), and skin-related events (rash (12.7%) and rash maculo-papular (10.2%)) (Table 21)

Table 21: Adverse Events Leading to Dose Adjustments and/or Interruptions (At Least 1.5% in Either Treatment Group) - Study CBYL719C2301 (Safety set)

	Alpelisib plus fulvestrant		Placebo plus fulvestrant	
	N=284		N=287	
	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Hyperglycaemia	109 (38.4)	89 (31.3)	2 (0.7)	0
Diarrhoea	39 (13.7)	16 (5.6)	4 (1.4)	1 (0.3)
Rash	36 (12.7)	26 (9.2)	1 (0.3)	1 (0.3)
Rash maculo-papular	29 (10.2)	25 (8.8)	1 (0.3)	1 (0.3)
Stomatitis	19 (6.7)	6 (2.1)	0	0
Mucosal inflammation	14 (4.9)	4 (1.4)	0	0
Nausea	13 (4.6)	4 (1.4)	3 (1.0)	0
Lipase increased	11 (3.9)	10 (3.5)	6 (2.1)	5 (1.7)
Pyrexia	11 (3.9)	2 (0.7)	2 (0.7)	1 (0.3)
Fatigue	10 (3.5)	4 (1.4)	2 (0.7)	0
Pruritus	10 (3.5)	1 (0.4)	0	0
Vomiting	10 (3.5)	1 (0.4)	6 (2.1)	1 (0.3)
Asthenia	9 (3.2)	3 (1.1)	4 (1.4)	0
Decreased appetite	9 (3.2)	1 (0.4)	2 (0.7)	0
Alanine aminotransferase increased	8 (2.8)	6 (2.1)	7 (2.4)	2 (0.7)

	Alpelisib plus fulvestrant		Placebo plus fulvestrant	
	N=284		N=287	
	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Hypokalaemia	8 (2.8)	6 (2.1)	0	0
Blood creatinine increased	7 (2.5)	4 (1.4)	0	0
Hyponatraemia	6 (2.1)	6 (2.1)	1 (0.3)	1 (0.3)
Acute kidney injury	5 (1.8)	2 (0.7)	1 (0.3)	1 (0.3)
Aspartate aminotransferase increased	5 (1.8)	3 (1.1)	5 (1.7)	1 (0.3)
Dysgeusia	5 (1.8)	0	2 (0.7)	0
Weight decreased	5 (1.8)	2 (0.7)	1 (0.3)	0

The FDA's Assessment:

The FDA independently analyzed dose interruption and dose reductions separately in the SOLAR-1 trial. The FDA agrees generally with the data the applicant presented above.

Patients in the alpelisib + fulvestrant arm required dose reductions much more frequently compared to those in the placebo + fulvestrant arm. Dose reductions occurred in 156/284 (55%) of patients receiving alpelisib + fulvestrant versus 13/287 (4.5%) receiving placebo + fulvestrant. Eighty (28%) of the patients on alpelisib + fulvestrant required dose reductions due to hyperglycemia versus 2 (0.7%) of the patients on placebo + fulvestrant. Sixteen (6%) of the patients were dose reduced for diarrhea on alpelisib + fulvestrant versus 1 (0.3%) patient on placebo + fulvestrant.

Dose interruptions were also much more common for patients on the alpelisib + fulvestrant arm when compared to the placebo + fulvestrant arm. Dose interruptions occurred in 188/284 (66%) on alpelisib + fulvestrant compared to 61/287 (21%) on placebo + fulvestrant. Interruptions due to hyperglycemia occurred in 73 (26%) of patients versus 0 patients. respectively. Diarrhea led to dose interruption in 31 (11%) of patients on alpelisib + fulvestrant versus 3 (1%) of those on placebo + fulvestrant.

Significant Adverse Events

The Applicant's Position:

The significant AEs reported are described in other sections of this document.

The FDA's Assessment:

Refer to the FDA assessment of "Serious Adverse Events" above and "Adverse Events and Adverse Reactions" below.

Adverse Events and Adverse Reactions

The Applicant's Position:

Most Frequent AEs by Preferred Term

Hyperglycemia (reported in 63.7% of subjects in the alpelisib plus fulvestrant group vs. 9.8% of subjects in the placebo plus fulvestrant group), diarrhea (57.7% vs. 15.7%), nausea (44.7% vs. 22.3%), decreased appetite (35.6% vs. 10.5%), rash (35.6% vs. 5.9%), vomiting (27.1% vs. 9.8%), weight decreased (26.8% vs. 2.1%), stomatitis (24.6% vs. 6.3%), fatigue (24.3% vs. 17.1%), and asthenia (20.4% vs. 12.9%) were the most common AEs reported with alpelisib plus fulvestrant therapy in Study CBYL719C2301, each occurring in ≥ 20% of subjects (Table 22). These events are consistent with the mechanism of action and known safety profile of alpelisib, and are manageable and reversible in the clinical setting. The AE profile in the placebo plus fulvestrant group was consistent with the fulvestrant labeling information (for the 500 mg dose) in subjects with HR-positive advanced breast cancer.

Severity of AEs: AEs that were grade 3 (64.4% vs. 30.3%) or grade 4 (11.6% vs. 5.2%) in severity were more frequent in the alpelisib plus fulvestrant group (Table 22). The imbalance was mainly driven by hyperglycemia (grade 3: 32.7% vs. 0.3%; grade 4: 3.9% vs. 0.3%).

Table 22: Adverse Events (At Least 10% All Grades in Either Treatment Group) by Preferred Term and Maximum Grade – Study BYL719C2301 (Safety set)

	Alpelisib 300 mg plus fulvestrant		Placebo plus fulvestrant	
	N=284		N=287	
	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Total	282 (99.3)	216 (76.1)	264 (92.0)	102 (35.5)
Hyperglycaemia	181 (63.7)	104 (36.6)	28 (9.8)	2 (0.7)
Diarrhoea	164 (57.7)	19 (6.7)	45 (15.7)	1 (0.3)
Nausea	127 (44.7)	7 (2.5)	64 (22.3)	1 (0.3)
Decreased appetite	101 (35.6)	2 (0.7)	30 (10.5)	1 (0.3)
Rash	101 (35.6)	28 (9.9)	17 (5.9)	1 (0.3)
Vomiting	77 (27.1)	2 (0.7)	28 (9.8)	1 (0.3)
Weight decreased	76 (26.8)	11 (3.9)	6 (2.1)	0
Stomatitis	70 (24.6)	7 (2.5)	18 (6.3)	0
Fatigue	69 (24.3)	10 (3.5)	49 (17.1)	3 (1.0)
Asthenia	58 (20.4)	5 (1.8)	37 (12.9)	0
Alopecia	56 (19.7)	0	7 (2.4)	0
Mucosal inflammation	52 (18.3)	6 (2.1)	3 (1.0)	0
Pruritus	51 (18.0)	2 (0.7)	16 (5.6)	0
Headache	50 (17.6)	2 (0.7)	38 (13.2)	0
Dysgeusia	47 (16.5)	0	10 (3.5)	0

	Alpelisib 300 mg plus fulvestrant		Placebo plus fulvestrant	
	N=284		N=287	
	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Dry skin	42 (14.8)	0	10 (3.5)	0
Oedema peripheral	41 (14.4)	0	13 (4.5)	0
Pyrexia	41 (14.4)	2 (0.7)	14 (4.9)	1 (0.3)
Rash maculo-papular	40 (14.1)	25 (8.8)	5 (1.7)	1 (0.3)
Back pain	39 (13.7)	5 (1.8)	37 (12.9)	4 (1.4)
Abdominal pain	33 (11.6)	4 (1.4)	20 (7.0)	3 (1.0)
Arthralgia	32 (11.3)	1 (0.4)	47 (16.4)	3 (1.0)
Dyspepsia	32 (11.3)	0	16 (5.6)	0
Blood creatinine increased	29 (10.2)	5 (1.8)	4 (1.4)	0
Urinary tract infection	29 (10.2)	2 (0.7)	15 (5.2)	3 (1.0)
Dyspnoea	24 (8.5)	1 (0.4)	30 (10.5)	6 (2.1)
Constipation	22 (7.7)	0	36 (12.5)	1 (0.3)

Adverse Drug Reactions

Novartis clinical and safety databases were included in the screening for ADR candidates. Study CBYL719C2301 was used to determine the frequency of ADRs; the Phase I studies were used for ADR screening purposes. The safety database was used as an internal control against the clinical database. AEs which would not have met the ADR screening selection strategy criteria (e.g. ADR candidates with a very low occurrence rate, or single cases) were taken into consideration and added as an ADR if deemed medically relevant and suspected to be treatment related.

Most ADRs in association with the alpelisib plus fulvestrant combination treatment were predominantly grade 1 or grade 2 in intensity, and the majority of these events are consistent with the mechanism of action and known safety profile of alpelisib and are easily managed in the clinical setting with concomitant medication, non-drug therapies, or dietary intervention. Grade 3 or 4 ADRs were infrequent, with the exception of hyperglycemia and rash (Table 23).

Table 23: Percentage of Subjects with Adverse Drug Reactions – Study CBYL719C2301 (Safety set)

	Alpelisib plus fulvestrant			Placebo plus fulvestrant		
	N = 284			N = 287		
Adverse reactions	**All grades %**	**Grade 3 %**	**Grade 4 %**	**All grades %**	**Grade 3 %**	**Grade 4 %**
Blood and lymphatic system disorders						
Anemia	10	4	0	5	1	0
Gastrointestinal disorders						

	Alpelisib plus fulvestrant			Placebo plus fulvestrant		
	N = 284			N = 287		
Diarrhea	58	7	0	16	<1	0
Nausea	45	2	0	22	<1	0
Stomatitis[1]	30	2	0	6	0	0
Vomiting	27	<1	0	10	<1	0
Abdominal pain	17	1	0	11	1	0
Dyspepsia	11	0	0	6	0	0
General disorders and administration site conditions						
Fatigue[2]	42	5	0	29	1	0
Mucosal inflammation	19	2	0	1	0	0
Edema peripheral	15	0	0	5	<1	0
Pyrexia	14	<1	<1	5	<1	0
Mucosal dryness[3]	12	<1	0	4	0	0
Infections and infestations						
Urinary tract infection[4]	10	<1	0	5	1	0
Investigations						
Weight decreased	27	4	0	2	0	0
Blood creatinine increased	10	2	0	1	0	0
Metabolism and nutrition disorders						
Hyperglycemia	65	33	4	10	<1	<1
Decreased appetite	36	<1	0	10	<1	0
Nervous system disorders						
Dysgeusia[5]	18	<1	0	3	0	0
Headache	18	<1	0	13	0	0
Skin and subcutaneous tissue disorders						
Rash[6]	52	20	0	7	<1	0
Alopecia	20	0	0	2	0	0
Pruritus	18	<1	0	6	0	0
Dry skin[7]	18	<1	0	4	0	0

Grading according to CTCAE Version 4.03
[1] Stomatitis: including stomatitis, aphthous ulcer and mouth ulceration
[2] Fatigue: including fatigue, asthenia
[3] Mucosal dryness: including dry mouth, mucosal dryness, vulvovaginal dryness
[4] Urinary tract infection: including UTI and single case of urosepsis
[5] Dysgeusia : including dysgeusia, ageusia, hypogeusia

	Alpelisib plus fulvestrant	Placebo plus fulvestrant
	N = 284	N = 287
[6] Rash: including rash, rash maculo-papular, rash macular, rash generalized, rash papular, rash pruritic [7] Dry skin: including dry skin, skin fissures, xerosis, xeroderma		

The FDA's Assessment:

The FDA agrees with the data the applicant presented above for the most common AEs, as well as the data presented in Table 22. Of note, in FDA's independent review of SOLAR-1, when all AEs of rash were combined using preferred terms (i.e., rash, rash generalized, rash macular, rash maculo-papular, rash popular, rash pruritic, and rash pustular) and compared between the alpelisib + fulvestrant arm versus the control arm, the incidence of all grade rash was 52% versus 7%, and the incidence of grade 3 was 20% versus 0.3%, respectively. No grade ≥ 4 AEs of rash were reported in either arm.

The FDA agrees with the data presented in Table 23 which organizes the most common adverse reactions by body system and combines PT terms for many of the AEs listed in the table. Table 23 lists adverse reactions reported in ≥ 20% of participants in the SOLAR-1 trial in decreasing order by PT.

Laboratory Findings

The Applicant's Position:

The hematological abnormalities were predominantly grade 1 or 2 in both treatment groups, and the incidence of these abnormalities was generally similar, except for decreased lymphocyte count (+11.4%) and decreased hemoglobin (+12.6%) which were more frequent in the alpelisib plus fulvestrant group relative to the placebo plus fulvestrant group.

The clinical chemistry abnormalities were predominantly grade 1 or 2 in both treatment groups, except for a higher incidence of grade 3 increased glucose in the alpelisib plus fulvestrant group compared to the placebo plus fulvestrant group. Increased glucose abnormalities were expected and can be attributed to the on-target effect of PI3K inhibition given the role of the PI3K pathway in glucose homeostasis, and these abnormalities are also observed commonly with other PI3K inhibitors (Table 24).

Table 24: Laboratory Abnormalities – Study CBYL719C2301 (Safety set)

	Alpelisib plus fulvestrant N=284			Placebo plus fulvestrant N= 287		
Laboratory Abnormality	**All grades %**	**Grade 3 %**	**Grade 4 %**	**All grades %**	**Grade 3 %**	**Grade 4 %**
Hematological parameters						
Lymphocytes (hypo)	52	7	1	40	5	0
Hemoglobin (hypo)	42	4	0	29	1	0
Activated partial thromboplastin time (hyper)	21	<1	0	16	<1	0
Platelets (hypo)	14	<1	<1	6	0	0
Biochemical parameters						
Glucose (hyper)	79	33	5	34	<1	<1
Creatinine (hyper)	67	3	0	25	<1	0
Gamma glutamyl transferase (hyper)	52	10	1	44	8	2
Alanine aminotransferase (hyper)	44	3	<1	34	2	0
Lipase, pancreatic (hyper)	42	6	1	25	5	1
Calcium corrected(hypo)	27	2	<1	20	<1	1
Glucose (hypo)	26	0	<1	14	0	0
Potassium (hypo)	14	5	1	3	<1	0
Albumin (hypo)	14	0	0	8	0	0
Magnesium (hypo)	11	<1	0	4	0	0

The FDA's Assessment:

The FDA generally agrees with the data presented in Table 25 with a few changes based on independent review:

- ***Grade 4 platelet decrease (hypo) is <1% not 0% in the placebo + fulvestrant arm.***
- ***Grade 3 albumin decrease (hypo) is <1% not 0% in the alpelisib + fulvestrant arm.***

Vital Signs

The Applicant's Position:

With the exception of weight, no major differences between the treatment groups were observed. The number of subjects with a decrease in weight ≥ 10% from baseline was higher in the alpelisib plus fulvestrant group (42.2% vs. 9.3% in the placebo plus fulvestrant group). Weight decreased (any grade) was reported as an AE in 26.8% vs. 2.1% of subjects (alpelisib vs.

placebo). In the alpelisib plus fulvestrant group, the median BMI was 26.4 kg/m^2 therefore the impact of weight loss is not considered to be critical.

The FDA's Assessment:

The FDA agrees with applicant's assessment.

Electrocardiograms (ECGs)

The Applicant's Position:

No evidence of an increased risk of QT prolongation was observed with alpelisib in combination with fulvestrant. In the alpelisib plus fulvestrant group, new QTcF values >500 ms were observed in two subjects (0.7%), vs one subject (0.4%) in the placebo plus fulvestrant group. New QTcF values >480 ms and ≤500 ms were observed in 2.6% vs 1.8% of subjects (alpelisib vs placebo). These values were single occurrences and not reported as AEs for most subjects.

QT

No dedicated QT studies were conducted for alpelisib. Preclinical studies indicate a minimal risk of an electrophysiological effect with alpelisib. Based on a comprehensive analysis of clinical ECG and PK data derived from Study CBYL719X2101, no clinically relevant impact on ECG parameters or systolic/diastolic blood pressure was expected for the combination of alpelisib 300 mg/day with fulvestrant.

The FDA's Assessment:

The FDA agrees with the applicant's assessment.

Immunogenicity

The Applicant's Position:

Not applicable as this was not assessed nor expected.

The FDA's Assessment:

The FDA agrees with the applicant's assessment.

8.2.4. Analysis of Submission-Specific Safety Issues

The Applicant's Position:

AESIs are groupings of AEs that were selected during clinical development based on medical significance, the mechanism of action of alpelisib coupled with biological plausibility, as well as nonclinical observations. The AESI selected for alpelisib are hyperglycemia, hypersensitivity and

anaphylactic reactions, severe cutaneous reaction, rash, GI toxicity (nausea, vomiting, diarrhea), pancreatitis, and pneumonitis.

Hyperglycemia
Hyperglycemia is a reversible, on-target effect of PI3K inhibition. Hyperglycemia events were therefore more frequently reported in subjects in the alpelisib plus fulvestrant group than in the placebo plus fulvestrant group (65.8% vs. 10.5%). Alpelisib-induced hyperglycemia events occur early on (median time to grade ≥2 elevation was 15 days in Study CBYL719C2301). Grade 3 hyperglycemia-related events are also common (33.5%) while grade 4 events are infrequent (4.6%).

Severe complications of hyperglycemia, such as ketoacidosis, were reported rarely (two cases occurred both of which resolved).

Although hyperglycemia-related events are one of the most common side effects associated with alpelisib, these events are manageable with appropriate oral antidiabetic therapy and/or alpelisib dose adjustment/interruption, if needed.

Among the 187 subjects with hyperglycemia AESI in the alpelisib plus fulvestrant group, at least one of the events was managed with medication in 86.6% (162/187) (most commonly metformin; 87.1% (142/163 subjects), with dose interruption in 40.6% (76/187), and dose adjustment in 43.9% (82/187) of subjects.

Among the 160 subjects with a grade ≥2 FPG value, the median time to resolution was 10 days (range: 8 to 13 days), and among the 110 subjects with a grade ≥3 FPG value, the median time to resolution of the grade ≥3 increase was 8 days (range: 7 to 8 days)Overall, 94.1% (176/187) of subjects had at least one hyperglycemia AESI that had improved or resolved at the time of the data cut-off and only 6.7% of subjects permanently discontinued treatment with alpelisib due to hyperglycemia events.

Hypersensitivity (including anaphylactic reaction)
Hypersensitivity events were reported in 16.5% of subjects in the alpelisib plus fulvestrant group. The events were mostly hypersensitivity (3.5%) and face edema (2.8%). Most of these cases were grade 1 or 2, and were effectively managed with concomitant medication, and/or treatment interruption. Among the subjects with a hypersensitivity event, 83.0% (39/47) had at least one hypersensitivity event that resolved by the time of data cut-off. There were no grade 4 events. There were no cases of anaphylactic reactions in Study CBYL719C2301. One case of anaphylactic reaction (grade 3) occurred in Study CBYL719X2101 in a subject receiving alpelisib 400 mg plus fulvestrant (treatment was discontinued and the subject recovered).

Severe cutaneous reactions
In Study CBYL719C2301, severe cutaneous reactions were reported in 4 subjects in the alpelisib plus fulvestrant group, including erythema multiforme (EM) in 3 subjects and Stevens-Johnson syndrome (SJS) in 1 subject. The Investigator reported that findings characteristic of SJS, such as necrosis or blistering, were not observed; however, the possibility of SJS could not be ruled out

since symptoms could have been masked by the early administration of steroids. All four cases were reported from sites in Japan; all were considered related to study treatment and all resolved without sequelae.

No severe cutaneous reaction AESI were identified among subjects receiving combination treatment in Studies CBYL719X2101 or CBYL719X1101.

Rash
Alpelisib combination treatment is associated with a higher incidence of rash compared to fulvestrant alone (53.9% vs. 8.4%). Most cases, however, were of low grade (1 or 2); grade 3 events were reported in 20.1% of subjects and no grade 4 events were reported. The onset is typically within the first few weeks of treatment start (median time to first onset of grade ≥ 2 rash was 12 days). The majority of cases are effectively managed with topical/systemic medications or alpelisib dose modifications as indicated.

Among the 153 subjects with a rash AESI, at least one of the events was managed with topical/systemic medication in 83.0% (127/153), with alpelisib dose interruption in 40.5% (62/153), and with dose reduction in 17.0% (26/153) of subjects. 92.2% (141/153) had at least one rash AESI that resolved.

GI toxicity
Gastrointestinal events (nausea, vomiting, diarrhea) were reported more frequently in the alpelisib plus fulvestrant group than the placebo plus fulvestrant group (75.4% vs. 34.8%). Most cases, however, were of low grade (1 or 2); grade 3 events were reported in 8.8% vs. 1.0% of subjects and no grade 4 events were reported. The majority of cases were effectively managed with concomitant medication or dose adjustments/interruption. Among the 214 subjects with a GI toxicity AE, 94.9% (203/214) had a GI toxicity event that resolved.

Diarrhea was reported in 57.7% in the alpelisib plus fulvestrant group, with events being predominantly grade 1 (32.7%) or grade 2 (18.3%); 6.7% of subjects had grade 3 diarrhea and no grade 4 diarrhea was reported. SAEs were reported in 2.8% of subjects, and 2.8% of subjects discontinued due to diarrhea (one of them due to a grade 3 event).

Severe complications of diarrhea were rare. In two cases, diarrhea and associated dehydration may have contributed to the development of acute kidney injury (reported as SAEs). The incidence of grade 3 creatinine increases, and of grade 4 low potassium and low sodium values, was higher in subjects who had diarrhea compared to the overall population based on shift table analysis of electrolytes and renal parameters (baseline vs worst post-baseline after the event) for subjects with diarrhea reported as an AE.

The majority of cases of GI toxicity were effectively managed with appropriate interventions (with concomitant medication or dose adjustments/interruption) and resolved.

Pancreatitis
One case of acute pancreatitis was observed in Study CBYL719C2301 in the alpelisib plus fulvestrant group. Elevated lipase values (laboratory data) were more frequent in the alpelisib plus fulvestrant group (41.9%) vs. the placebo plus fulvestrant group (25.4%), primarily due to more grade 1 and grade 2 elevations occurring on alpelisib. No difference between the treatment groups was observed for grade 3 or 4 lipase elevations based on laboratory data.

Pneumonitis
Low-grade pneumonitis (including related terms) was diagnosed clinically in 5 subjects (1.8%) in the alpelisib combination group: pneumonitis in 4 subjects and interstitial lung disease in 1 subject. Study treatment was discontinued prior to the pneumonitis event (due to disease progression) in one of these subjects. The remaining four cases were suspected to be related to study treatment, and treatment was discontinued; in three cases the event resolved and no further information was available for the fourth case of ongoing grade 1 pneumonitis. None of these events had a fatal outcome.

The FDA's Assessment:

The FDA generally agrees with the applicant's assessment of adverse events of special interest based upon the agency's independent review of the data.

Given the high incidence of diarrhea in the alpelisib + fulvestrant arm as noted above in the applicant's assessment, FDA has included diarrhea in the Warnings and Precautions section of the USPI. Among the 164 patients with diarrhea in the alpelisib + fulvestrant arm, dose interruption occurred in 18.9% (31/164), and dose modification was required in 9.8% (16/164). Serious adverse events and discontinuations due to diarrhea were each reported in 2.8% (8/284) of participants who received alpelisib + fulvestrant versus 0% each for participants in the placebo + fulvestrant arm.

Osteonecrosis of the jaw (ONJ) was reported in 4.2% of patients (12/284) in the PIQRAY + fulvestrant arm compared to 1.4% of patients (4/287) in the placebo arm. All patients experiencing ONJ had received prior or concomitant treatment with a bisphosphonate or RANK-ligand inhibitor, for which ONJ is a known adverse drug reaction, based on FDA's review of data submitted by the applicant in response to information requests.

8.2.5. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:
Patient-reported outcomes have been discussed above in Section 8.1.2.

The FDA's Assessment:

Refer to the FDA's assessment of COA/PRO in Section 8.1.2.

8.2.6. Safety Analyses by Demographic Subgroups

The Applicant's Position:

Subgroup analyses were conducted to identify potential safety issues restricted to particular subpopulations; these typically demonstrated a pattern of events consistent with that reported for the overall study populations.

Age

In the alpelisib plus fulvestrant group, there was a trend towards an increase in the incidence of all grade GI toxicity AESI (primarily nausea), and grade 3-4 hyperglycemia AESI, with age ≥ 75 years. No clear trend was seen for rash AESI with age. Hypersensitivity and anaphylactic reaction AESI were less frequent among subjects ≥ 75 years of age than the younger subgroups.

Race

In the alpelisib plus fulvestrant group, the incidences of GI toxicities and hyperglycemia were similar regardless of race. However, rash AESI and hypersensitivity and anaphylactic reaction AESI events were more common in Asian subjects compared to other races. Of note, severe cutaneous reactions were reported in 4 subjects in the alpelisib plus fulvestrant group, including erythema multiforme (EM) in 3 subjects and Stevens-Johnson syndrome in 1 subject, and all four cases were reported from sites in Japan.

The FDA's Assessment:

The FDA generally agrees with the applicant's assessment above. The agency also conducted an independent review by subgroups of sex, age, and race. Of 284 patients who received alpelisib + fulvestrant in the SOLAR-1 trial, 117 were ≥ 65 years of age and 34 were ≥75 years of age. In participants treated with alpelisib + fulvestrant, there was a higher incidence of Grade 3-4 hyperglycemia in those ≥ 65 years of age (44%) compared to those < 65 years of age (32%). This information was included in the USPI for alpelisib. FDA agrees there an increase in grade 3-4 hyperglycemia in the alpelisib + fulvestrant arm in those ≥ 75 years of age compared with patients < 75 years of age (53% versus 34%, respectively); however, given the small number of patients ≥ 75 years of age, the agency did not believe that any significant safety conclusions could be drawn.

The FDA agrees that the incidences of GI toxicities and hyperglycemia were similar regardless of race. Erythema multiforme was seen in 3 patients (2 patients with grade 3) and Stevens-Johnson syndrome in 1 patient (grade 3), all of whom were Asian patients enrolled at Japanese sites. All cases were reported to have resolved with supportive medications. There was also a higher overall incidence of all-grade and grade 3-4 maculo-papular rash in Asian patients compared to other races represented in the SOLAR-1 trial.

The tables below summarize the FDA's analysis of all-grade and grade 3-4 hyperglycemia by sex, race and age. However, given the small numbers in some of these subgroups (e.g., 1 male

patient in the trial), these results should be considered exploratory.

Table 25: FDA Subgroup Analysis of All grade (1-5) Hyperglycemia (safety population regardless of mutation status)

Demographic Characteristic	*PRIQAY plus fulvestrant N=284 N (%)*	*Placebo plus fulvestrant N=287 N (%)*
Sex		
Men	***0 (0)***	***0 (0)***
Women	***181 (64)***	***28 (9.8)***
Race		
White	***126 (63.3)***	***18 (10.2)***
Asian	***39 (66.1)***	***6 (9.1)***
Other**	***16 (61.5)***	***4 (9.1)***
Age Group		
< 65 years	***104 (62.3)***	***15 (9.8)***
≥ 65 years	***78 (66.7)***	***13 (9.7)***

*****Other includes Black or African American, American Indian or Alaska Native, Other, Unknown***

Table 26: FDA Subgroup Analysis of Grade 3-4 Hyperglycemia (safety population regardless of mutation status)

Demographic Characteristic	*PRIQAY plus fulvestrant N=284 N (%)*	*Placebo plus fulvestrant N=287 N (%)*
Sex		
Men	***0 (0)***	***0 (0)***
Women	***104 (36.7)***	***2 (0.7)***
Race		
White	***74 (37.2)***	***1 (0.6)***
Asian	***19 (32.2)***	***0 (0)***
Other**	***11 (42.3)***	***1 (2.3)***
Age Group		
< 65 years	***53 (31.7)***	***1 (0.7)***
≥ 65 years	***52 (44.5)***	***1 (0.7)***

*****Other includes Black or African American, American Indian or Alaska Native, Other, Unknown***

8.2.7. Specific Safety Studies/Clinical Trials

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable, no specific safety studies were submitted for the FDA to review.

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

Carcinogenicity studies have not been conducted with alpelisib.

The FDA's Assessment:

The FDA agrees that carcinogenicity studies have not been conducted.

Human Reproduction and Pregnancy

The Applicant's Position:

There were no reported pregnancies or lactation events reported in the alpelisib clinical development program. Of relevance, for WOCBP, pregnancy status should be verified prior to treatment with alpelisib. For sexually active WOCBP, effective contraception methods (i.e. results in < 1% pregnancy rate) should be used when using alpelisib during treatment and for (b) (4) after stopping treatment with alpelisib. It is recommended that women should not breastfeed during treatment and for (b) (4) after the last dose of alpelisib.

Male subjects with sexual partners who are pregnant, possibly pregnant, or who could become pregnant should use condoms during sexual intercourse while taking alpelisib and for (b) (4) after stopping treatment with alpelisib.

The FDA's Assessment:

The FDA agrees that there were no reported pregnancy or lactation events in the alpelisib development program. The FDA disagrees with the recommendation (b) (4) of contraception after the last dose of alpelisib. Per the alpelisib USPI, females and males of reproductive potential should use effective contraception for 1 week after stopping alpelisib. Given that alpelisib will be indicated for use in combination with fulvestrant, the recommended duration of contraception after the last dose of fulvestrant + alpelisib should be 1 year, for consistency with the USPI for fulvestrant.

With regard to breastfeeding, the FDA agrees that women should not breastfeed while taking alpelisib. Women should wait at least 1 week after the last dose of alpelisib prior to breastfeeding, (b) (4)

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

There is limited experience of overdose with alpelisib in clinical studies. In these clinical studies, alpelisib was administered at doses up to 450 mg once daily. In cases where accidental over dosage of alpelisib was reported, the AEs associated with the overdose were consistent with the known safety profile of alpelisib and included hyperglycemia, nausea, asthenia, and rash. No antidote is known for alpelisib. General symptomatic and supportive measures should be initiated in all cases of overdose, as necessary. Subjects should be followed until full recovery or confirmed stabilization of the events.

In clinical studies with alpelisib, subjects were followed for 28/30 days or longer after discontinuation of alpelisib, and no withdrawal or rebound effects were observed. No formal studies have been conducted to assess withdrawal and rebound effects from alpelisib treatment as a single agent or in combination with fulvestrant.

The FDA's Assessment:

The FDA reviewed the 3 cases of accidental overdose reported in the alpelisib development program. No deaths were reported as a result of these overdoses.

Case 1: Occurred in study CBYL719A2201 (alpelisib + letrozole). The participant reportedly ingested 6 tablets of 200mg alpelisib instead of 6 tablets of 50mg alpelisib. This overdose of 1200mg occurred daily for 6 days. The participant experienced grade 4 hyperglycemia and grade 2 dehydration as a result of the overdose, which resolved with supportive care.

Case 2: Occurred in study CMEK162X2109 (alpelisib + MEK162). The participant reportedly mixed up bottles of medication and ingested 800mg of alpelisib for a day, then 600mg of alpelisib twice a day for the following 5 days. The participant also took binimetinib (MEK162)

15mg for 5 days. The participant experienced grade 3 mucositis, grade 1 rash, and grade 2 xerophthalmia. All the AEs were reported as non-serious and resolved with supportive care. The xerophthalmia was potentially related to the binimetinib.

Case 3: Occurred in study CLEE011X2108 (alpelisib + ribociclib + fulvestrant). Due to a dispensing error, the participant was given 3 tablets of 200mg of alpelisib instead of ribociclib. No AEs were reported as a result of the overdose.

The FDA believes the above cases were isolated and, with the planned commercial packaging, which includes blister packs, accidental overdoses are unlikely to occur.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Not applicable (alpelisib is not currently registered (or approved) in the US or in any other part of the world).

The FDA's Assessment:

Not applicable.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Toxicities appear to have been adequately represented in CBYL719C2301 study. Potential safety concerns beyond the risks conveyed in the proposed labeling are not expected. Routine pharmacovigilance will be conducted to monitor for unexpected adverse events.

The FDA's Assessment:

The FDA will continue to monitor any post-marketing reports and safety reports that are submitted after approval. However, the FDA generally agrees that the safety of alpelisib + fulvestrant was adequately characterized in the SOLAR-1 study.

8.2.10. Integrated Assessment of Safety

The Applicant's Position:

Treatment with alpelisib in combination with fulvestrant is characterized by a predictable and manageable safety profile in subjects with HR-positive, HER2-negative advanced breast cancer. The safety profile in Study CBYL719C2301 was consistent with the mechanism of action of alpelisib and prior clinical experience. Adverse events reported were typically manageable with

appropriate intervention (standard medical care and/or alpelisib dose reduction or treatment interruption), and were reversible upon treatment discontinuation.

Overall, safety was well characterized in the intended target population. In Study CBYL719C2301, higher proportions of subjects reported AEs (99.3% vs. 92.0%), grade 3/4 AEs (76.1% vs. 35.5%), SAEs (34.9% vs. 16.7%), AEs leading to treatment discontinuation (25.0% vs. 4.5%), and AEs leading to dose adjustment/interruption (78.5% vs. 22.6%), in the alpelisib plus fulvestrant group relative to the fulvestrant control, which is consistent with the increase in toxicity that could be expected when adding a targeted agent to endocrine 'backbone therapy'.

Hyperglycemia
Hyperglycemia is a reversible, on-target effect of PI3K inhibition. In Study CBYL719C2301, hyperglycemia AESI occurred in 65.8% vs. 10.5% of subjects (alpelisib plus fulvestrant vs. fulvestrant control); these events were maximum grade 3 in 33.5% vs. 0.3%, and grade 4 in 4.6% vs. 0.3%. Severe complications of hyperglycemia, such as diabetic ketoacidosis, were reported uncommonly (with 2 cases in Study CBYL719C2301, both of which resolved).

Alpelisib-induced hyperglycemia develops early (median time to grade ≥ 2 elevation of 15 days in subjects reporting a grade ≥ 2 event), allowing for the early identification and initiation of appropriate clinical management (i.e. oral antidiabetic medication (primarily metformin) and alpelisib dose interruption and/or reduction, as needed). Based on an analysis of fasting plasma glucose, the median duration of grade ≥ 2 hyperglycemia was 10 days, and of grade 3 hyperglycemia 8 days, indicating that with appropriate intervention, hyperglycemia is manageable. Treatment discontinuation due to hyperglycemia occurred in 6.7% of subjects treated with alpelisib plus fulvestrant. Alpelisib-induced hyperglycemia is reversible upon discontinuation of alpelisib treatment. No sustained induction of diabetic metabolism was observed.

Like other PI3K inhibitors, skin-related events and GI toxicities were also frequent with alpelisib; these events are generally manageable and are predictable based upon the mechanism of action of alpelisib.

Rash
Skin toxicity was observed in the form of maculopapular and generalized rashes accompanied on occasion by pruritus and dry skin. Rash AESI occurred in 53.9% vs. 8.4% of subjects (alpelisib plus fulvestrant vs. fulvestrant control), and 20.1% vs. 0.3% had a grade 3 event (no grade 4 rashes were reported). Rash was more common when alpelisib was administered in combination with fulvestrant than as a single agent. It is important to note that fulvestrant itself carries a risk of rash and an increased incidence can therefore be expected with the alpelisib plus fulvestrant combination.

Onset is typically within the first 2 weeks of treatment (with a median time to onset of grade ≥ 2 rash of 12 days in subjects with a grade ≥ 2 rash event). Rash was effectively managed with concomitant usage of oral antihistamines and/or topical/oral corticosteroids, and alpelisib

dosing modifications, as needed. A trend towards a lower incidence of rash, with less severe events, was observed among the 30% of subjects who received prophylactic antihistamines. Treatment discontinuation due to rash AESI was reported in 4.2% of subjects in the alpelisib plus fulvestrant group.

GI toxicity (nausea, vomiting, and diarrhea)
GI toxicity occurred in 75.4% vs. 34.8% of subjects (alpelisib plus fulvestrant vs. fulvestrant control). Most of these events were grade 1 or grade 2, with 8.8% vs. 1.0% of subjects with grade 3 events; no grade 4 events were reported. Most of these AEs were manageable with appropriate intervention (concomitant medication in the majority of cases and alpelisib dosing modifications, as needed). Grade 3 diarrhea occurred in 6.7% of subjects in the alpelisib plus fulvestrant group, with a median time to improvement to grade ≤ 2 of 18 days. Diarrhea led to the discontinuation of study drug in 2.8% of subjects.

Pneumonitis, hypersensitivity, and severe cutaneous reactions were considered as important identified risks in addition to hyperglycemia.

A clinical diagnosis of pneumonitis was made in 5 subjects in the alpelisib combination group. These events were typically associated with multiple confounding factors including respiratory failure, asthma, and lung metastases. Pneumonitis with alpelisib was limited in extent, and was reversible upon discontinuation of therapy.

Hypersensitivity events were reported in 16.5% of subjects treated with alpelisib plus fulvestrant in Study CBYL719C2301 (most frequently hypersensitivity (3.5%) and face edema (2.8%)). The majority of cases were grade 1 or grade 2, and were effectively managed with appropriate treatment; events resolved in 13.7% of subjects. No cases of anaphylactic reaction were reported in Study CBYL719C2301.

Severe cutaneous reactions were reported in 4 subjects in the alpelisib plus fulvestrant group in Study CBYL719C2301 (all enrolled at sites in Japan), including erythema multiforme in 3 subjects and Stevens-Johnson syndrome in 1 subject. The characteristic findings of Stevens-Johnson syndrome (i.e. necrosis and blistering) were not observed in this case; however, the possibility could not be excluded that symptoms were masked by early administration of corticosteroids. All 4 subjects recovered from these events without sequelae. Labelling has reflected these increased risks so that healthcare providers and subjects are aware of the signs and symptoms of these events and the importance of promptly addressing them to mitigate potential harm.

'On-treatment' deaths, not attributed to disease progression, were reported in 2 subjects (0.7%) in the alpelisib plus fulvestrant group in Study CBYL719C2301; SAEs were more frequent in the alpelisib plus fulvestrant group (34.9%) than the fulvestrant control (16.7%) as were AEs leading to treatment discontinuation (25.0% vs. 4.5%).

Trends toward numerical increases in the incidence of GI toxicity and hyperglycemia AESI were observed in subjects aged > 75 years. Rash AESI and hypersensitivity and anaphylactic reaction AESI were more common in Asian subjects.

In conclusion, alpelisib plus fulvestrant is characterized by a manageable safety profile in postmenopausal women and men with HR-positive, HER2-negative advanced breast cancer. The AE profile is characterized by predictable, primarily low-grade events. These events are generally reversible (through the use of standard medical care and/or alpelisib dose reduction or treatment interruption) and non-cumulative. No unknown or unexpected safety signals were observed in the pivotal Study CBYL719C2301 relative to earlier nonclinical and clinical findings; safety data from Study CBYL719C2301 were consistent with the mechanism of action and results from previous alpelisib studies.

The FDA's Assessment:

Overall, the FDA agrees that the SOLAR-1 study adequately characterized the safety profile of alpelisib in combination with fulvestrant.

A high number of dose modifications and discontinuations were reported in the SOLAR-1 trial. Dose interruptions occurred in 188/284 (66%) of those in the alpelisib + fulvestrant arm versus 61/287 (21%) in the placebo + fulvestrant arm. Dose reductions due to adverse events occurred in 156/284 (55%) versus 13/287 (4.5%), respectively. Discontinuations were reported in 71/284 (25%) versus 13/287 (4.5%), respectively. The most frequent adverse reactions resulting in discontinuation of alpelisib were hyperglycemia, rash, diarrhea, and fatigue. While many of the AEs were manageable with supportive care and medications, the high percentage of dose modifications and discontinuations suggest that the alpelisib dose of 300 mg daily is too high for most patients and contributes to overall toxicity (refer to FDA assessment in section 6.2.2.1 for further details regarding dose selection). With appropriate management of AEs and dose modifications/discontinuations per the USPI, the overall safety profile of alpelisib is acceptable.

Although the safety data for both the PIK3CA-mutated and wildtype cohorts were pooled for analysis in this trial by the applicant; the FDA's independent analysis of the data from the PIK3CA-mutated cohort did not reveal any additional safety signals.

Alpelisib demonstrated acceptable tolerability for the indicated population with a serious and life-threatening disease. Adverse reactions were common and, except for hyperglycemia and rash, predominantly grade 1-2 in severity. The most common adverse reactions observed in the alpelisib arm were hyperglycemia (65%), diarrhea (58%), and rash (52%). Hypersensitivity reactions, severe cutaneous reactions, hyperglycemia, pneumonitis, diarrhea, and embryo-fetal toxicity are labeled as Warnings and Precautions. Additional common adverse reactions with alpelisib included nausea and vomiting, stomatitis, fatigue, decreased appetite, weight loss, alopecia, pruritus, and dry skin.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

The FDA did not identify any major statistical concerns in the design, conduct, or analyses of the SOLAR-1 clinical trial. The SOLAR-1 trial met its primary objective of PFS per investigator assessment, the results appeared consistent across sensitivity analyses, and no apparent outliers were observed in subgroup analyses.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The clinical and statistical reviewers agree with regular approval for this NDA for the reasons stated in the FDA's assessments above.

X X

Laura Fernandes
Statistical Reviewer

Shenghui Tang
Statistical Team Leader

X X

Tatiana Prowell (Efficacy)
Preeti Narayan (Safety and PRO)
Clinical Reviewers

Jennifer Gao
Acting Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

No advisory committee discussion or consultations external to the FDA were deemed necessary for this NDA.

10 Pediatrics

The Applicant's Position:

Not applicable

The FDA's Assessment:

Not applicable

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant's Position:

The final USPI for Piqray reflects several changes from the version originally submitted by the Applicant.

The FDA's Assessment:

The FDA's labeling revisions to the applicant's proposed labeling are included in the table below.

Summary of Significant Labeling Changes		
Section	**Applicant's Proposed Labeling**	***FDA's Labeling Revisions***
Highlights	Adverse reactions (ARs), (b) (4) were included in the list of most common ARs	***FDA revised the proposed labeling as follows:*** - ***Revised the established pharmacologic class (EPC) from*** (b) (4) ***to "kinase inhibitor"*** - ***Added "or metastatic" to the Indications and Usage statement*** - ***Added "severe" to cutaneous reaction Warning and Precaution (W&P).*** - ***Added "including ketoacidosis" and a statement to inform prescribers that the safety of PIQRAY has not been established in diabetic patients (to the Hyperglycemia W&P).*** - ***Revised the common ARs statement to add weight decreased and alopecia ARs; and to add common laboratory abnormalities.*** - ***Revised the Drug Interactions section to add CYP3A4 inducers, remove*** (b) (4) ***information, and to remove and revise*** (b) (4)

		(b) (4) ***statements.***
1 Indications and Usage	Included established pharmacologic class in indication	***FDA removed the EPC from this section (not required) and added "or metastatic" to the indications statement.***
2 Dosage and Administration	(b) (4) dose modification and management tables: Dose reduction guidelines and dose modification and management for hyperglycemia, rash, and other toxicities, respectively. Did not include CTCAE grades for each category in table for dose modification and management for hyperglycemia (b) (4) (b) (4)	***2.2 Dosage and Administration*** ***FDA removed*** (b) (4) ***statements and reformatted to remove redundancy and improve the order of information delivery.*** ***2.3 Dose Modifications for Adverse Reactions*** ***FDA added the table 4 for dose modification and management of diarrhea; and agreed to the proposed labeling and dose modification tables with other minor revisions.*** ***FDA removed*** (b) (4)
5 Warnings and Precautions, 17 Patient Counseling Information, Highlights	(b) (4)	***FDA agreed to the Warnings and Precautions (W&Ps) for hypersensitivity (5.1), severe cutaneous reactions (5.2), and pneumonitis (5.4) with minor edits.*** ***FDA added an Embryo-Fetal Toxicity (5.6) W&P to adequately describe the risks of fetal harm associated with PIQRAY to pregnant women, females of reproductive potential, and male patients with female partners of reproductive potential.***
5.3 Hyperglycemia	Information was provided in a different order	***FDA revised the W&P for hyperglycemia (5.3) to reorganize and increase the prominence of severe hyperglycemia (including ketoacidosis), add incidence and management information for antidiabetic medications, and made minor revisions for clarity and by grouping similar concepts and information.***
6 Adverse Reactions	Additional text on ARs was	***FDA revised the study***

	included above and below the table representing ARs. Included laboratory-abnormalities in the table representing ARs. Separated Grade 3 and 4 events in different columns in both tables representing ARs and laboratory abnormalities. Laboratory abnormalities table included units and source designations	***characteristics and text results for safety as follows:*** - ***Revised to emphasize the safety population included patients regardless of PIK3CA mutation status*** - ***Removed*** (b) (4) ***to focus on deaths due to adverse reactions (ARs)*** - ***Added serious adverse reaction information (and grouped with ONJ ARs)*** - ***Moved diabetic patient demographics and hyperglycemia information to the hyperglycemia W&P (5.3)*** - ***Removed*** (b) (4) - ***Condensed low grade rash information and moved to a subsection below the most common AR table*** - ***Added information to describe patients who were permanently discontinued due to ARs and who required dose reductions due to ARs.*** - ***Reformatted the adverse reactions table (Table 6) to combine Grade 3-4 adverse reactions; and revised subheadings to reflect lack of Grade 4 ARs for some ARs listed in the table*** - ***Removed*** (b) (4) - ***Revised the laboratory abnormality table (Table 7) to use consistent terminology and remove units and redundant synonyms.***
7 Drug Interactions	Novartis provided extensive details on the Drug Interactions section	***FDA rewrote this section due to the inclusion of non-actionable information, uninformative statements*** (b) (4) ***unqualified or unclear information*** (b) (4)

		(b) (4). ***Extensive revisions were made to be more consistent with best labeling practices and more recently approved prescribing information. See the final approved labeling for full details.***
8.1 Pregnancy	---	***FDA added a cross reference to the fulvestrant prescribing information to be consistent with the approved indications for use.*** ***FDA removed*** (b) (4) ***and replaced with "There are no available data in pregnant women to inform the drug-associated risk."*** ***FDA revised the proposed fetal toxicity information to add "adverse developmental outcomes including embryo-fetal mortality (post-implantation loss), reduced fetal weights, and increased incidences of fetal malformations at maternal exposures ≥0.8 times the exposure in humans based on AUC at the recommended dose of 300 mg/day."*** ***FDA removed*** (b) (4) ***FDA revised the*** (b) (4) ***based on FDA Nonclinical Review findings.***
8.2 Lactation, 8.3 Females and Males of Reproductive Potential, 17 Patient Counseling Information, PPI	Included instructions to use contraception during treatment and not breastfeed for (b) (4) after the last dose	***FDA added a cross reference to the fulvestrant prescribing information to be consistent with the approved indications for use.*** ***FDA revised the breast feeding statement to increase from*** (b) (4) ***to 7 days after discontinuation.*** ***Additional minor edits in terminology and format were made throughout 8.2 and 8.3 to be consistent with current PLLR***

		guidance and best labeling practices.
11 Description	…	***FDA revised the pharmacological class from*** (b) (4) ***to "kinase inhibitor".***
12 Clinical Pharmacology	Novartis provided extensive details on the Clinical Pharmacology section	***12.1 Mechanism of Action*** ***FDA revised this section to remove terms or information not related to the MOA for the indicated population and undefined or potentially speculative claims of untested MOAs consistent with the FDA Guidance for the Clinical Pharmacology Section of Labeling.*** ***12.2 Pharmacodynamics*** ***FDA removed*** (b) (4) ***12.3 Pharmacokinetics*** ***Multiple revisions were made based on the Clinical Pharmacology Review findings and to format the proposed information consistently with the FDA Labeling Guidance for this subsection.***
13 Nonclinical Toxicology	Novartis provided extensive details on the Nonclinical Toxicology section	***FDA made minor revisions and removed*** (b) (4) ***FDA removed*** (b) (4)
14 Clinical Studies	Text was organized in a different order Included ORR data for all patients and those with measurable disease	***FDA made the following revisions to the study description and demographic results:*** - ***Added "Patients were excluded if they had inflammatory breast cancer, diabetes mellitus Type 1 or uncontrolled Type 2, or pneumonitis."*** - ***FDA added demographic information to describe the percentage of patients with PIK3CA mutations, liver/lung metastasis, and who had been previously treated with a***

		CDK4/6 inhibitor. - ***FDA revised the companion diagnostic information to clarify the process used and limitations for both devices when determining PIK3CA status.*** - ***FDA added "The median duration of exposure to PIQRAY plus fulvestrant was 8.2 months with 59% of patients exposed for > 6 months."*** - ***FDA revised the major efficacy and other endpoint information statements to include the endpoints and populations used to support the approved indication (e.g., PFS, ORR, OS in the PIK3CA cohort) and removed*** (b) (4) ***FDA made the following revisions to the study results:*** - ***FDA revised the results from the BICR findings to remove*** (b) (4) ***The results were described as consistent with the investigator assessment results for PFS.*** - ***FDA removed*** (b) (4) - ***From the efficacy results table (Table 8), FDA removed*** (b) (4) - ***FDA revised the proposed stopping boundary in the table footnote*** (b) (4) ***to a two sided p-value (<0.0398)*** - ***For Figure 1 (Kaplan Meier curve), FDA removed***

		(b) (4) [redacted]
17 Patient Counseling Information	…	***FDA added patient counseling topics and information for diarrhea and infertility.***
PPI	Text and side effects were organized in a different order and format	***Reformatting and multiple content revisions were made to the proposed Patient Package Insert (PPI). Additional updates were made to be consistent with revisions to the Full Prescribing Information (FPI) (e.g., added serious side effect information for hyperglycemia).*** ***See the approved PPI and the FDA OPDP/DMP reviews for full details.***

12 Risk Evaluation and Mitigation Strategies (REMS)

The Applicant's Position:

No REMS is recommended.

The FDA's Assessment:

No REMS is recommended.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

There were no postmarketing requirements. Three postmarketing commitments are as follows:

PMC #1:

Submit the final overall survival (OS) analysis and datasets with the final report from the ongoing clinical trial BYL719C2301, SOLAR-1, entitled "A Phase III randomized double-blind, placebo-controlled study of alpelisib in combination with fulvestrant for men and postmenopausal women with HR-receptor positive, HER2-negative advanced breast cancer with progressed on or after aromatase inhibitor treatment".

PMC Schedule Milestones
Final Protocol Submission: 12/2017
Trial Completion: 08/2021
Final Report Submission: 02/2022

PMC #2:

Conduct a clinical trial to evaluate the effect of repeat doses of a strong CYP3A4 inducer on pharmacokinetics of alpelisib to assess the magnitude of decreased alpelisib exposure and to determine appropriate dosing recommendations. Design and conduct the trial in accordance with the FDA Guidance for Industry; "Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications."

PMC Schedule Milestones
Final Protocol Submission: 07/2020
Trial Completion: 10/2021
Final Report Submission: 04/2022

PMC #3:

Conduct a clinical trial to evaluate the effect of repeat doses of alpelisib on the single dose pharmacokinetics of sensitive probe substrates to assess the magnitude of exposure change for sensitive substrates of CYP2B6, CYP3A4 and CYP2C-family enzymes (CYP2C9, CYP2C19 and / or CYP2C8) and to determine appropriate dosing recommendations. Design and conduct the trial in accordance with the FDA Guidance for Industry; "Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications."

PMC Schedule Milestones
Final Protocol Submission: 09/2020
Trial Completion: 03/2022
Final Report Submission: 09/2022

14 Division Director (OCP)

X

Nam Atiqur Rahman

15 Division Director (OB)

X

Rajeshwari Sridhara

16 Division Director (Clinical)

X

Julia Beaver

17 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_____

Gideon Blumenthal

18 Appendices

18.1. References

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Vora SR et al (2014) CDK 4/6 inhibitors sensitize PIK3CA mutant breast cancer to PI3K inhibitors. Cancer Cell ;26(1):136-49.

Zhang et al (2014) pH-dependent drug-drug interactions for weak base drugs: potential implications for new drug development. Clin Pharmacol Ther; 96(2):266-77.

FDA reviews and the most recent package inserts needed for review of this NDA were accessed via: https://www.accessdata.fda.gov/scripts/cder/daf/

18.2. Financial Disclosure

The Applicant's Position:

The Applicant provided financial disclosure for all clinical investigators involved in the studies included in this submission in Form 3455. No concerns were raised regarding the overall integrity of the data.

There were two investigators with disclosable financial arrangements (Table 27). Neither of these investigators was a principal investigator. One investigator (who unfortunately died) participated at a (b) (6) that contributed (b) (6) to Study CBYL719C2301; this was a US site. (b) (6)

Table 27: Summary of Disclosable Financial Arrangements and Interest

Investigator	Study No.	Center No.	Amount Disclosed	Category of Disclosure
(b) (6)	BYL719C2301	(b) (6)	Unknown	Details unspecified
	BYL719C2301		>$25,000	Supporting subjects

The FDA's Assessment:

The FDA agrees with the applicant's assessment.

Covered Clinical Study (Name and/or Number): SOLAR-1

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2607		
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): 2		
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: 1 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 1 Significant equity interest held by investigator: 1		

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) 0		
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.

The FDA's Assessment

The FDA agrees with the applicant's entries in Table above. One investigator for the SOLAR-1 trial had a significant equity interest that could be influenced by the outcome of the study. Bias on the part of a single investigator in this global study is unlikely to have significantly impacted the results of this global study and would not change the conclusions on the findings of efficacy and safety.

18.3. OCP Appendices by the FDA (Technical documents supporting OCP recommendations)

18.3.1. Summary of Bioanalytical Method Validation and Performance

In the pivotal study CBYL719C2301, alpelisib and its major metabolite BZG791 were measured using 2 validated LC-MS/MS methods (Table 28 and Table 29). In other studies, alpelisib and BZG791 were measured using LC-MS/MS methods with minimal modifications. Additionally, methods to measure total radiolabeled alpelisib in human plasma, whole blood, urine and feces were also developed.

Table 28: Summary method performance of a bioanalytical method to measure alpelisib and BZG791 in human plasma human plasma

Bioanalytical method validation report name, amendments, and hyperlinks	[DMPK R1400105-a-01], Quantitative determination of BYL719 and BZG791 in human plasma (K3EDTA) by LC-MS/MS and amendment no. 1 to the method validation report		
Method description	The method consists of a protein precipitation extraction with acetonitrile and analysis of the processed sample by liquid chromatography - tandem mass spectrometry (LC-MS/MS) in MRM mode using ESI as the ionization technique		
Materials used for calibration curve & concentration	Human plasma with K_3EDTA from healthy donors Alpelisib and BZG791 (analytes) [M+6]BYL719 and [M+6]BZG791 (stable labeled internal standards)		
Validated assay range	5.00 to 5000 ng/mL for alpelisib and 1.00 to 1000 ng/mL for BZG791 using 50.0 µL of human plasma		
Material used for QCs & concentration	Human plasma with K_3EDTA from healthy donors Alpelisib and BZG791 (analytes) [M+6]BYL719 and [M+6]BZG791 (stable labeled internal standards)		
Minimum required dilutions (MRDs)	Not applicable		
Source & lot of reagents (LBA)	Not applicable		
Regression model & weighting	Linear regression (y =ax + b) with $1/x^2$ as weighting factor		
Validation parameters	**Method validation summary**		**Acceptability**
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	8	Acceptable
	Cumulative accuracy (%bias) from LLOQ to ULOQ alpelisib BZG791	 -1.0 to 1.5% -2.5 to 2.3%	Acceptable
	Cumulative precision (%CV) from LLOQ to ULOQ alpelisib BZG791	 ≤ 5.3% ≤ 4.9%	Acceptable
QCs performance during accuracy & precision	**<u>Cummulative accuracy (%bias) in 4 QCs</u>** QCs: alpelisib BZG791	 0.0 to 6.8% -0.3 to 5.0%	Acceptable

	Inter-batch %CV QCs: alpelisib BZG791	 ≤ 5.4% ≤ 4.8%	Acceptable
	Total error QCs: alpelisib BZG791	Not applicable	
Selectivity & matrix effect	6 lots were tested for selectivity without any observation. 6 lots were tested for matrix effect.		Acceptable
Interference & specificity	1 lot was used to test interferences and contribution of alpelisib to BZG791 observed which does not impact the method as long as the BZG791 is not less than 0.1105% of the alpelisib concentration. 1 lot was used to test specificity against letrozole, buparlisib, fulvestrant and tamoxifen %bias from -4.3 to 8.0 for alpelisib and from -2.9 to 4.0 for BZG791		Acceptable
Hemolysis effect	Not applicable		
Lipemic effect	Not applicable		
Dilution linearity & hook effect	Not applicable		
Bench-top/process stability	25 hours stability at room temperature on bench Bias% from -2.8 to 1.1 with CV% ≤ 2.3 for alpelisib Bias% from 0.6 to 0.8 with CV% ≤ 4.3 for BZG791 145 hours stability at 8°C of processed samples in the autosampler Bias% from 1.1 to 4.4 with CV% ≤ 2.7 for alpelisib Bias% from -3.8 to 5.0 with CV% ≤ 2.6 for BZG791		Acceptable
Freeze-Thaw stability	5 freeze-thaw cycles with storage at -20°C Bias% from -2.4 to 2.5 with CV% ≤ 2.1 for alpelisib Bias% from -3.2 to 4.0 with CV% ≤ 4.9 for BZG791 5 freeze-thaw cycles with storage at -70°C Bias% from -0.9 to 1.3 with CV% ≤ 2.7 for alpelisib Bias% from 1.0 to 1.7 with CV% ≤ 3.8 for BZG791		Acceptable
Long-term storage	365 days of storage at -20°C Bias% from -0.4 to 12.0 with CV% ≤ 4.0 for alpelisib Bias% from -6.5 to 11.1 with CV% ≤ 3.3 for BZG791 254 days of storage at -70°C Bias% from -1.2 to 5.6 with CV% ≤ 2.9 for alpelisib Bias% from -4.6 to 5.3 with CV% ≤ 10.0 for BZG791		Acceptable
Parallelism	Not applicable		
Carry over	Carryover was exceeded in some of the validation runs. It was higher than 20% of LLOQ in 1 out of 10 runs for alpelisib and higher than 20% of LLOQ in 1 out of 9 runs for BZG791		Acceptable
Method performance in study CBYL719C2301 [DMPK RCBYL719C2301], Bioanalytical data report: Determinations of Alpelisib (BYL719) and Fulvestrant in human plasma			
Assay passing rate	89.7% 5 out of 6 failed runs had instrument/system issues		Acceptable
Standard curve performance	• Cumulative bias range: -5.4 to 3.3% • Cumulative precision: ≤ 4.5% CV		Acceptable

QC performance	• Cumulative bias range: -3.2 to 6.5% • Cumulative precision: ≤ 4.7% CV	Acceptable
Method reproducibility	Incurred sample reanalysis was performed in 5.1% of study samples and 100 % of these samples met the pre-specified criteria	Acceptable
Study sample analysis/ stability	Alpelisib in human plasma is stable for 1455 days at -70°C. All samples were analyzed within the demonstrated stability period	

Table 29: Summary method performance of a bioanalytical method DMPK R1600667 to measure alpelisib and BZG791 in human plasma

Bioanalytical method validation report name, amendments, and hyperlinks	[DMPK R1600667-01] - Quantitative Determination of BYL719 and BZG791 in K_3EDTA Human Plasma by LC- MS/MS and amendment no. 1 to the method validation report		
Method description	The method consists of protein precipitation and analysis of the processed samples by liquid chromatography - tandem mass spectrometry (LCMS/ MS) in MRM mode using ESI as the ionization technique.		
Materials used for calibration curve & concentration	Human plasma (K_3-EDTA) Alpelisib and BZG791 (analyte) [M+6]BYL719 and [M+6]BZG791 (stable labeled internal standard)		
Validated assay range	Alpelisib: 5.00 (LLOQ) to 5000 ng/mL using 50 µL of human plasma BZG791: 1.00 (LLOQ) to 1000 ng/mL using 50 µL of human plasma		
Material used for QCs & concentration	Human plasma (K_3-EDTA) Alpelisib and BZG791 (analyte) [M+6]BYL719 and [M+6]BZG791 (stable labeled internal standard)		
Minimum required dilutions (MRDs)	Not applicable		
Source & lot of reagents (LBA)	Not applicable		
Regression model & weighting	Linear regression (y =ax + b) with $1/x^2$ as weighting factor		
Validation parameters	**Method validation summary**		**Source location**
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	10	Acceptable
	Cumulative accuracy (%bias) from LLOQ to ULOQ alpelisib BZG791	 -2.4 to 2.0% -2.6 to 1.6%	Acceptable
	Cumulative precision (%CV) from LLOQ to ULOQ alpelisib BZG791	 ≤ 5.5% ≤ 4.5%	Acceptable
QCs performance during accuracy & precision	**Cumulative accuracy (%bias) in 4 QCs** QCs: alpelisib BZG791	 -3.0 to 3.3% -1.0 to 4.3%	Acceptable
	Inter-batch %CV QCs: alpelisib BZG791	 ≤ 5.7% ≤ 5.4%	Acceptable

	Total error QCs: alpelisib BZG791	Not applicable	
Selectivity & matrix effect	6 lots were tested for selectivity without any observation 6 lots were tested for matrix effect.		Acceptable
Interference & specificity	Contribution of alpelisib to BZG791 was observed and investigated. It was concluded that alpelisib itself contains BZG791 and does not affect the quantification of alpelisib and BZG791. The interference from LSZ102, MHP303, LEE011 and LEQ803 to alpelisib and BZG791 was tested (low and high QC) - No interference observed (% Bias from -8.7 to 0.8% for alpelisib, %Bias from -5.0 to 1.3% for BZG791)		Acceptable
Hemolysis effect	1 heamolysed lot was tested (low and high QC). alpelisib: %Bias range from -0.8 to 3.3% with %CV <3.0% BZG791: %Bias range from 3.6 to 6.0% with %CV <2.8%		Acceptable
Lipemic effect	1 lipemic lot was tested (low and high QC). alpelisib: %Bias range from -3.0 to 3.3% with %CV <3.5% BZG791: %Bias range from 0.8 to 7.4% with %CV <2.6%		Acceptable
Dilution linearity & hook effect	10-fold (from 255000 for alpelisib and 5100 ng/mL for BZG791) Bias% -2.0 with CV% 2.4 for alpelisib Bias% -0.2 with CV% 1.6 for BZG791		Acceptable
Bench-top/process stability	17 hours stability at room temperature on bench Bias% from -3.8 to 3.3 for alpelisib Bias% from -4.6 to 0.0% for BZG791 124 hours stability at 5°C of processed samples in the autosampler Bias% from –4.3 to 2.7 for alpelisib Bias% from -3.1 to 1.0 for BZG791 Post prep stability in extracts for 4h at room temperature Bias% from –3.0 to 0.0 for alpelisib Bias% from -2.9 to -1.3 for BZG791 Stability in dry extract for 118h at -20°C Bias% from –3.0 to -0.7 for alpelisib Bias% from -3.3 to -2.0 for BZG791 Stability in whole blood for 2h on wet ice and at Room temperature %Stability ranges from 98.8% to 99.4% (Ice) and from 98.9% to 99.8% (RT) with %CV <3.5% for alpelisib %Stability ranges from 98.6% to 100.4% (Ice) and from 99.2% to 100.2% (RT) with %CV <2.7% for BZG791		Acceptable
Freeze-Thaw stability	5 freeze-thaw cycles with storage at -78°C Bias% from -3.5 to 2.0 for alpelisib Bias% from -3.9 to 2.0 for BZG791 5 freeze-thaw cycles with storage at -20°C Bias% from -3.8 to 2.0 for alpelisib Bias% from -3.4 to 3.0 for BZG791		Acceptable
Long-term storage	377 days of storage at -78°C and -20°C Bias% from -4.0 to -3.0 for alpelisib Bias% from -6.3 to -5.1 for BZG791 377 days of storage at -78°C and -20°C Bias% from -9.3 to -2.8 for alpelisib Bias% from -9.7 to -4.6 for BZG791		Acceptable
Parallelism	Not applicable		

Carry over	Response after injection in blank samples following each injection of the ULOQ ≤20% of the mean response observed for the LLOQ for alpelisib and BZG791 Response after injection of [M+6]BYL719 and [M+6]BZG791 at the working concentration in blank samples following each injection of ULOQ ≤5% of the [M+6]BYL719 and [M+6]BZG791 mean response observed at the working concentration	Acceptable
Method performance in study CBYL719C2301 - report number [DMPK RCBYL719C2301a] (Bioanalytical data report: Determination of BYL719 in human plasma)		
Assay passing rate	91.7%	Acceptable
Standard curve performance	• Cumulative bias range: -2.5% to 2.1% • Cumulative precision: ≤ 5.4% CV	Acceptable
QC performance	• Cumulative bias range: -1.7% to 1.6% • Cumulative precision: ≤ 6.5% CV	Acceptable
Method reproducibility	Incurred sample reanalysis was performed with 7.3% of study samples (20 samples) and 85.0% of samples met the pre-specified criteria.	Acceptable
Study sample analysis/ stability	Alpelisib in human plasma is stable for 1455 days at -65°C. The stability data can cover the period (a total of 975 days) from sampling to analysis of all study samples.	

18.3.2. Pharmacometrics Review

Part A : Population PK analysis

Introduction

The primary objectives of this analysis were to:

1. ***Characterize the pharmacokinetics of alpelisib when administered as a single agent and in combination with fulvestrant and to obtain key exposure metrics***
2. ***Explore factors influencing alpelisib pharmacokinetics***

The Applicant's Analysis:

a. Data

The Phase I analysis was based on PK data from 2 studies and the Phase III analysis was based on PK data from one study. The study design, study population, and timing of blood samples varied among the 3 clinical studies. Brief descriptions of the studies included are presented in Table 30.

The final data file for analysis contained 6987 PK observations from 254 subjects for the Phase I analysis and the final data file for analysis contained 1487 PK observations from 271 subjects for the Phase III analysis.

Summary statistics of the baseline demographic covariates in the analysis dataset is provided in Table 31.

Table 30: Summary of Studies with PK Sampling Included in Population PK Analysis

Protocol # & Study Design	Dosage Regimen & Study Description	Number of Subjects in PopPK Analysis, Subject Type and Food Status	Dose(s) [mg]
CBYL719X1101: A phase I study of BYL719, in adult patients with advanced solid Malignancies (Japanese)	Administered orally as single ascending dose to evaluate PK, safety & tolerability	33 patients with solid malignancies	Single agent (QD): 90, 180, 270, 350 and 400
CBYL719X2101: A phase IA, multicenter, open-label Dose escalation study of oral BYL719, in adult patients with advanced solid malignancies, whose tumors have an alteration of the PIK3CA gene	Administered orally as single or combo to evaluate PK, safety & tolerability and find optimal dose	221 patients (134 on single agent + 87 combo)	Single agent (QD): 30, 60, 90, 180, 270, 300, 350, 400, 450 mg Single agent (BID): 120, 150, 200 mg Fulvestrant (QD) combo: 300, 350, 400 mg
CBYL719C2301: A phase III randomized double-blind, placebo controlled study of alpelisib in combination with fulvestrant for men and postmenopausal women	Administered orally as single or combo to evaluate efficacy, safety & PK.	271 patients on combo	Alpelisib 300 mg daily Fulvestrant 500 mg every 28 days with 1 additional dose on Day 15 of each Cycle

Source: Applicant's Tabular listing of all clinical studies, Table 5.2

Table 31: **Summary of Baseline Demographic Covariates for Analysis**

Study	X1101 Single agent	X2101 Fulvestrant + BYL	X2101 Single agent
Subject			
All	25 (10.2%)	87 (35.5%)	133 (54.3%)
Gender			
Male	15 (6.1%)	1 (0.4%)	36 (14.7%)
Female	10 (4.1%)	86 (35.1%)	97 (39.6%)
Age [y]			
median [min-max]	55 [24 - 76]	59 [37 - 79]	59 [21 - 82]
25th-75th percentile	44 - 63	50.5 - 64	50 - 66
Weight [kg]			
median [min-max]	61.4 [44.7 - 78.9]	66.5 [42.3 - 107]	70 [36.7 - 181]
25th-75th percentile	52.8 - 67.1	60.7 - 78.7	59 - 79.6
CrCL [mL/min]			
median [min-max]	89 [52 - 201.5]	92.8 [27 - 200.5]	101.7 [39.4 - 274.2]
25th-75th percentile	69.2 - 112.8	73.6 - 119.5	80.6 - 123.5
Race			
Caucasian	NA	75 (30.6%)	124 (50.6%)
Asian	25 (10.2%)	1 (0.4%)	4 (1.6%)
Black	NA	7 (2.9%)	1 (0.4%)
Other	NA	4 (1.6%)	3 (1.2%)
Renal impairment			
Normal	11 (4.5%)	50 (20.4%)	90 (36.7%)
Mild	11 (4.5%)	32 (13.1%)	29 (11.8%)
Moderate	3 (1.2%)	4 (1.6%)	13 (5.3%)
Severe	NA	1 (0.4%)	NA
Hepatic impairment			
Normal	23 (9.4%)	57 (23.3%)	96 (39.2%)
Mild	2 (0.8%)	28 (11.4%)	36 (14.7%)
Moderate	NA	2 (0.8%)	NA

Source: Applicant's Population Phase I popPK report, Table 5-1

Study	SOLAR-1 (C2301)
Subject	
All	271 (100%)
Gender	
Male	1 (0.4%)
Female	270 (99.6%)
Age [y]	
median [min-max]	62 [25 - 87]
25th-75th percentile	57 - 69
Weight [kg]	
median [min-max]	67.1 [38.5 - 120]
25th-75th percentile	58.1 - 78
CrCL [mL/min]	
median [min-max]	85.6 [31.8 - 211]
25th-75th percentile	68.6 - 105.4
Race	
Caucasian	192 (70.8%)
Asian	54 (19.9%)
Black	2 (0.7%)
Other	9 (3.3%)
Renal impairment	
Normal	117 (43.2%)
Mild	108 (39.9%)
Moderate	45 (16.6%)
Severe	NA
Hepatic impairment	
Normal	230 (84.9%)
Mild	41 (15.1%)
Moderate	NA

Source: Applicant's Population Phase III popPK report, Table 5-1

b. Base model

The final base model was a one-compartment model with a delayed first-order absorption and linear elimination. The effect of body weight was included as an allometric exponent on CL/F and V/F.

Inter-individual variability (IIV) for log-transformed PK parameters was modelled assuming a normal distribution for patient level random effects. Residual variability was tested as additive, proportional or both on the dependent variable. Model evaluation and selection of the base model were based on standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value (OFV), accuracy of parameter estimation (i.e., 95% confidence interval excluding 0), successful model convergence, and diagnostic plots.

c. Covariate analysis

Clinical judgment, physiologic relevance, prior knowledge and mechanistic plausibility were used to determine which covariates should be tested with the various PK parameters. A systematic covariate search was performed that led to the final model in the Phase I population PK analysis. Covariate parameters, including age, Hispanic, renal impairment and hepatic on CL/F, and Japanese ethnicity on Vc/F, were investigated in the Phase III population PK analysis.

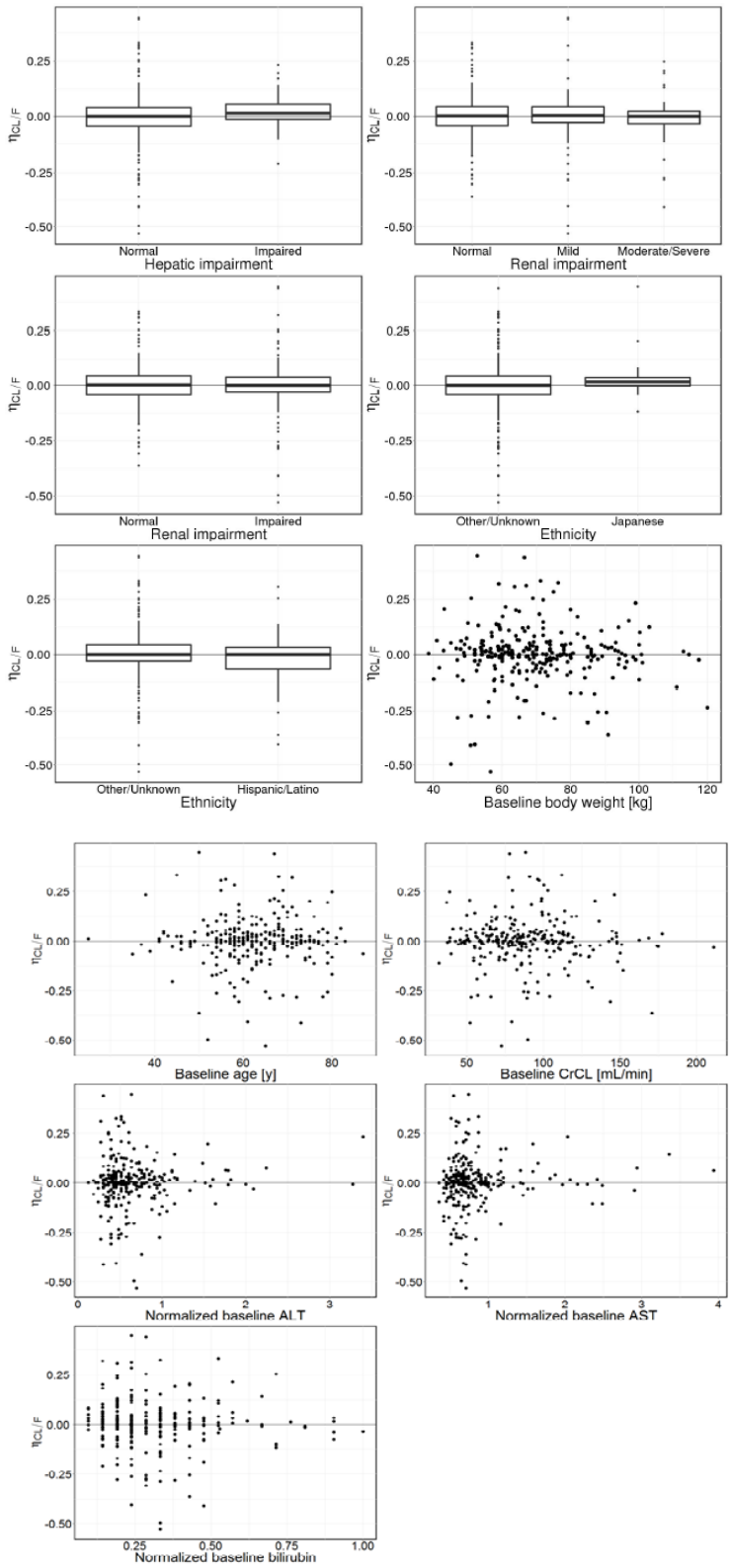
The reviewer's analysis of covariates effect on PK was similar to that of the applicant. The effects of body weight, renal impairment, hepatic impairment, and Ethnicity on clearance (CL/F) are explored in Figure 11. The model estimated covariate effects on PK parameters are illustrated in Table 32.

Table 32: Covariate Effects on PK parameters

	CL [L/h]	V [L]	t ½ [h]	Cmin [ng/mL]	Cmax [ng/mL]	AUC [ng.h/mL]
Typical	9.18	113.88	8.60	516	2400	32680
50 kg	7.64	97.88	8.88	642	2840	39257
90 kg	11.04	132.67	8.33	413	2026	27162
52 y	9.64	113.88	8.19	465	2340	31119
72 y	8.74	113.88	9.03	571	2463	34319

Source: Applicant's Population Phase III popPK report, Table 5-5

Figure 11: Parameter-Covariate plots



Source: Applicant's Population Phase III popPK report, Figure 9-1 and Figure 9-2.

d. Model results

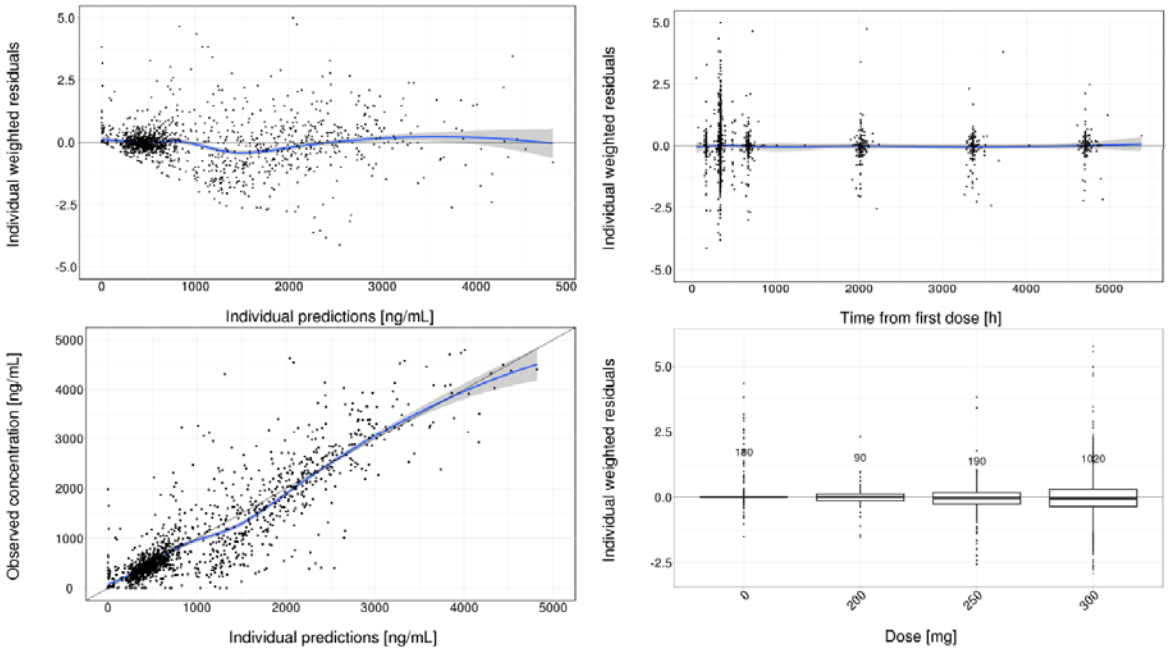
The parameter estimates for the final covariate model in the Phase III population PK analysis are listed in Table 33. The goodness-of-fit plots for the final covariate model for all data are shown in Figure 12. The Visual Predictive Check (VPC) plot for the final covariate model with all data is shown in Figure 13.

Table 33: Parameter Estimates for the Final Model

	Estimate	%CV	Estimate (log scale)	SE (log scale)
KA [1/h]	0.75	5.5	-0.284	0.055
theta[CL]	0.63	16.1	-0.467	0.16
Theta[V]	0.52	Fixed	-0.659	Fixed
CL [L/h]	9.18	2.3	2.217	0.023
Age on CL [L/hr/y]	1	0.2	-0.005	0.002
V [L]	113.88	4.8	4.735	0.048
sigma[CL]	0.21			
sigma[V]	0.46			
sigma[epsilon]	518.46			
# Subjects	271			
# Observations	1487			
Log Lik.	-11588			

Source: Applicant's Population Phase III popPK report, Table 5-4

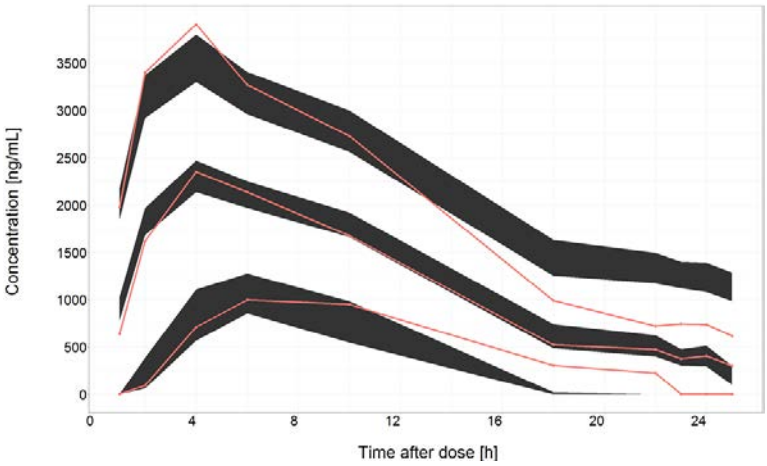
Figure 12: Goodness-of-fit plots for final covariate model



Source: Applicant's Population Phase III popPK report, Figure 5-8 and Figure 5-9

The black line in the observed vs IPRED plots represents the line of unity (y=x). The black line in the IWRES vs PRED/TIME/Dose plots represents the horizontal line (y=0). The blue line represents a smooth regression line.

Figure 13: VPC plots for final covariate model



The solid lines represent the 10th, 50th and 90th percentiles of the observed concentrations. The shaded areas are the 90 % prediction intervals for the 500 simulated datasets.
Source: Applicant's Population Phase III popPK report, Figure 5-10

The FDA's Assessment:

The applicant's population PK analysis is acceptable. The goodness-of-fit plots and the visual predictive check indicate that the updated population PK model is adequate in characterizing the PK profile of alpelisib in subjects with advanced breast cancer. The inter-individual variability for CL/F and Vc/F are modest. The estimated PK parameters, such as CL/F and Vc/F appear reasonable. The applicant's analyses were verified by the reviewer, with no significant discordance identified. The applicant did not formally evaluate the covariate effect of PPI on PK of alpelisib, the results from post-hoc analysis are inconclusive without the complete record for specific timing of PPI dosing information. More specifically, the developed model was used to support the current submission as outlined in Table 34.

Table 34: Specific Comments on Applicant's Final Population PK model

Utility of the final model			Reviewer's Comments
Support labeling statements about intrinsic and extrinsic factors	**Intrinsic factor**	(b) (4)	The statement is generally acceptable. Covariate analysis using the sponsor's final model demonstrates that no evident difference (greater than 80-125%) exists based on ethnicity, age, body

		(b) (4)	weight, and renal impairment (moderate or mild). (b) (4)
	Extrinsic factor		No definitive conclusion can be made with regard to the effect of PPI on alpelisib PK.
Derive exposure metrics for Exposure-response analyses	Cmin, Cmax, AUC		The applicant's final model is generally acceptable for generating exposure metrics for exposure-response analyses.
Predict exposures at alternative dosing regimen	N.A.		N.A.

Appears this way on original

Part B: Exposure Response Analysis

Exposure-efficacy relationship

<u>The Applicant's Analysis:</u>

The impact of alpelisib exposure on PFS was investigated using an extended Cox PH model with log-transformed and time-normalized Cmin, which is defined as the sum of projected Cmin values up to the PFS event (or censoring) divided by the time to PFS, as a time-dependent covariate. Therefore, exposure levels at 0 were not included in the analysis. The reference exposure is log of exposure at 1. The hazard ratio for a 1.5-fold increase in exposure in the PIK3CA mutant cohort: 0.91 (0.72, 1.13) and the PIK3CA non-mutant cohort 0.92: (0.68, 1.26) did not indicate any significant impact of alpelisib exposure on PFS using this exposure metric.

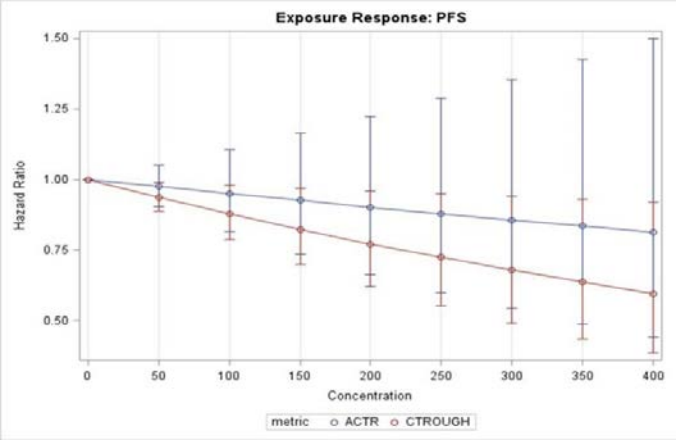
<u>The FDA's Assessment:</u>

Comparison of Ctrough vs. Time-normalized Cmin

This reviewer made comparison between the two exposure-metrics: Ctrough, which is observed up to the PFS event (or censoring) and Time-normalized Cmin (ACTR), which is defined as the sum of projected Cmin values up to the PFS event (or censoring) divided by the time to event. Ctrough has two modes and one of them is at 0; while ACTR has one mode and is more centralized after transformation.

This reviewer further did exposure response analyses with Ctrough as the time-varying dependent variable. As shown in Figure 14, the slope of ER for Ctrough is steeper than the one for ACTR. Using Ctrough, each exposure > 0 on the list significantly reduces hazard comparing with exposure 0 at a given time point. ATCR also reduces hazard but not significantly with wider confidence intervals. Although there is a positive trend of better efficacy with increasing exposure, no definitive conclusions about ER relationship for efficacy can be made given the possible confounding effect due to frequent dose reduction in trials.

Figure 14: Exposure responses for Ctrough and ACTR



Source: FDA Reviewer's analysis.

Exposure-safety relationship

The Applicant's Analysis:

The impact of alpelisib exposure, characterized by either time-normalized Cmin or instantaneous Cmin, on the time to first onset of grade ≥ 2 AESIs was investigated using a Cox model. Time-normalized Cmin as a time-dependent covariate was investigated using an extended Cox model, and the instantaneous effect of Cmin as a fixed covariate was investigated using a standard Cox model. The AESIs were: hyperglycemia (grade ≥ 2 and grade ≥ 3), hypersensitivity (grade ≥ 2), pancreatitis (grade ≥ 2), pneumonitis (grade ≥ 2), rash (grade ≥ 2 and grade ≥ 3), severe cutaneous reaction (grade ≥ 2), GI toxicity (nausea (grade ≥ 2), vomiting (grade ≥ 2), and diarrhea (grade ≥ 2).

The results as in Table 35 and Table 36 showed that increasing alpelisib exposure (measured as time-normalized Cmin) increased the risk of hyperglycemia events (of grade ≥ 2 and grade ≥ 3). Increasing exposure did not significantly impact the hazard rate of other AESIs mentioned above. The instantaneous effect of Cmin on AESIs showed an increased risk of hyperglycemia events of grade ≥ 3. The hazard rate for other AESIs was either low (hyperglycemia events of grade ≥ 2, rash, nausea, vomiting, and diarrhea) or not significant.

Table 35: Exposure safety response for log-transformed instantaneous Cmin.

PK parameter	Endpoint	Estimate of hazard ratio	95% CI	
			Lower	Upper
log(instantaneous Cmin)	Hyperglycaemia (at least grade 2)	1.053	1.030	1.076
	Hyperglycaemia (at least grade 3)	1.152	1.055	1.258
	Hypersensitivity (at least grade 2)	1.025	0.996	1.055
	Pancreatitis (at least grade 2)	1.009	0.997	1.021
	Pneumonitis (at least grade 2)	1.005	0.984	1.027
	Rash (at least grade 2)	1.044	1.024	1.065
	Rash (at least grade 3)	1.079	1.027	1.133
	Severe cutaneous reaction (at least grade 2)	1.211	0.718	2.043
	Nausea, vomiting, diarrhea (at least grade 2)	1.036	1.019	1.053

Log instantaneous Cmin is defined as log of projected Cmin on the event day or censoring time
Projected Cmin is a predicted value based on dosing history, observed trough concentrations and pharmacokinetic properties of alpelisib.
Source: Applicant's Study C2301 CSR Table 14.2-6.5.

Table 36: Exposure safety response for log-transformed time-normalized Cmin.

PK parameter	Endpoint	Estimate of hazard ratio	95% CI	
			Lower	Upper
log(Cmin,TN)	Hyperglycaemia (at least grade 2)	1.223	1.014	1.475
	Hyperglycaemia (at least grade 3)	1.331	1.058	1.675
	Hypersensitivity (at least grade 2)	1.055	0.721	1.544
	Pancreatitis (at least grade 2)	0.968	0.697	1.345
	Pneumonitis (at least grade 2)	1.760	0.599	5.165
	Rash (at least grade 2)	1.160	0.907	1.485
	Rash (at least grade 3)	1.150	0.841	1.574
	Severe cutaneous reaction (at least grade 2)	0.674	0.225	2.021
	Nausea, vomiting, diarrhea (at least grade 2)	1.076	0.902	1.284

Time-normalized Cmin,TN is defined as the sum of projected Cmin values up to the adverse event (or censoring) divided by the time to onset of first Grade 2 [Grade 3] or worse event.
Source: Applicant's Study C2301 CSR Table 14.2-6.4.

The FDA's Assessment:

This reviewer did exposure safety response analyses using Ctrough and TN as exposure metrics. As shown in Table 37 and Table 38, the results are similar to the corresponding log-transformed metrics.

Table 37: Exposure safety response for Cmin

PK parameter	Endpoint	Estimate of hazard ratio	95% CI	
			Lower	Upper
Cmin	Hyperglycaemia (at least grade 2)	1.180	1.137	1.224
	Hyperglycaemia (at least grade 3)	1.196	1.148	1.246
	Hypersensitivity (at least grade 2)	1.100	0.969	1.248
	Pancreatitis (at least grade 2)	1.078	0.973	1.195
	Pneumonitis (at least grade 2)	0.952	0.719	1.261
	Rash (at least grade 2)	1.180	1.128	1.235
	Rash (at least grade 3)	1.203	1.133	1.277
	Severe cutaneous reaction (at least grade 2)	1.200	0.973	1.479
	Nausea, vomiting, diarrhea (at least grade 2)	1.141	1.091	1.194

Source: FDA Reviewer's analysis.

Table 38: Exposure safety response for TN Cmin

PK parameter	Endpoint	Estimate of hazard ratio	95% CI	
			Lower	**Upper**
(Cmin,TN)	Hyperglycaemia (at least grade 2)	1.045	0.994	1.099
	Hyperglycaemia (at least grade 3)	1.060	1.000	1.124
	Hypersensitivity (at least grade 2)	0.953	0.783	1.161
	Pancreatitis (at least grade 2)	0.932	0.796	1.092
	Pneumonitis (at least grade 2)	1.109	0.882	1.395
	Rash (at least grade 2)	1.013	0.942	1.090
	Rash (at least grade 3)	1.017	0.923	1.121
	Severe cutaneous reaction (at least grade 2)	0.783	0.474	1.291
	Nausea, vomiting, diarrhea (at least grade 2)	0.996	0.931	1.066

Source: FDA Reviewer's analysis.

Additional Exposure-Response Analyses

The Applicant's Analysis:

In response to Question 3 of IR on date 1/11/2019, "Conduct exposure-response analyses for the first dose modification and discontinuation of alpelisib with time-varying Cmin as the exposure metric. Robust evaluation of baseline risk factors and other potential time-varying covariates should be performed. Provide analysis results with codes and datasets.", the sponsor conducted the analyses as requested.

The analyses showed that there is no evidence that increasing exposure would lead to an increase in the risk of dose interruption, dose reduction, and discontinuation even when incorporating additional risk factors such as baseline FPG and use of concomitant medication.

In response to Question 4 of IR on date 1/11/2019, "Provide exposure-response analysis for time to first onset adverse event of special interest by evaluation grade (e.g., Grade 1, 2, 3 and 4, separately)." , the sponsor conducted ER analysis for grade=1, grade=2, grade=3, and grade=4 separately, if the number of events is sufficient.

The analyses showed that increasing exposure (defined by average projected trough alpelisib concentration) by 50% increased the risk of hyperglycemia by up to 34% for grade 1 and grade 3, but not for grade 2 or 4. Increasing exposure by 50% did not significantly impact the hazard ratio for grade 1, 2, or 3 rash. There were no grade 4 rash events. This analysis, where AESI grades were evaluated separately (i.e. grade = 1, grade = 2, grade =3 and grade=4) should however be interpreted with caution.

The FDA's Assessment:

FDA has no objection to the Applicant's additional exposure-response analysis results.

18.3.3. Physiologically based Pharmacokinetic Modeling Review

Executive Summary

The objective of this review is to evaluate the adequacy of the applicant's following PBPK study reports to support the intended uses.

- ***Report No. DMPK R1400676, entitled "Simcyp interaction predictions of BYL719 (alpelisib) with typical CYP3A substrates and perpetrators";***
- ***Report No. DMPK R17011116, entitled "Predictions of systemic exposure of substrates for CYP3A4 and CYP2C9 when co-administered with alpelisib (BYL719)";***
- ***Report No. DMPK R1300572, entitled "Simcyp predictions of RAD001(everolimus) pharmacokinetics and drug interactions"; and***
- ***Report No. DMPK R1701118, entitled "Oral absorption modeling of BYL719 in GastroPlus".***

The Division of Pharmacometrics has reviewed the PBPK reports, supporting modeling files, and the applicant's responses to FDA's information requests (IRs) submitted on Jan. 11, 2019, Jan. 31, 2019 and Feb.12, 2019 and concluded the followings.

- ***The PBPK analysis is inadequate to predict the effect of alpelisib on the PK of a sensitive CYP3A substrate (midazolam). The applicant verified the model by comparing the model prediction with the observed DDI effects of alpelisib on everolimus PK. However, in vitro alpelisib is a P-gp inhibitor and inducer, and everolimus is a P-gp substrate and inhibitor. Both the alpelisib and everolimus models did not account for the potential interaction via P-gp. Therefore, the estimated net CYP3A effects may be biased.***
- ***The PBPK analyses are inadequate to predict the effects of alpelisib on the PK of a CYP3A auto-inducer (rifampicin), and CYP3A auto-inhibitors (ribociclib and ritonavir). The PBPK analyses are inadequate to predict the effects of a CYP3A inducer (rifampicin) on the PK of alpelisib. In vitro, alpelisib is a time-dependent inhibitor and inducer of CYP3A. The clinical DDI study between alpelisib and everolimus cannot provide adequate information to differentiate the CYP3A induction and CYP3A inhibition effects of alpelisib because the study results only reflected the net effect of DDI involving both CYP3A and P-gp. Due to the uncertainty associated with the alpelisib-mediated in vivo CYP3A induction and inhibition effect, the model could not be appropriately verified to predict the DDI between alpelisib and CYP3A modulators.***
- ***The PBPK analyses are inadequate to predict the effects of a CYP3A inhibitor (ritonavir) on the PK of alpelisib. However, due to the minor contribution of CYP3A to the alpelisib systemic clearance (fm~ 0.12), the effect of CYP3A inhibitor on alpelisib PK is expected to be low.***

- ***The PBPK analysis cannot be used to quantitatively predict the effects of alpelisib on the PK of a CYP2C9 substrate (warfarin) due to the lack of in vitro to in vivo extrapolation of the K_I (inhibition constant). The model could be used as a risk assessment tool to evaluate a worst-case scenario with regards to the change in PK of a CYP2C9 substrate when it is co-administered with alpelisib.*** (b) (4)

- ***The PBPK analysis cannot be used to predict the effects of alpelisib on the PK of a CYP2B6 substrate (bupropion) due to the lack of in vitro to in vivo extrapolation of the K_I (inhibition constant). The model could be used as a risk assessment tool to evaluate a worst-case scenario with regards to the change in PK of a CYP2B6 substrate when it is co-administered with alpelisib. The model predicted that bupropion plasma AUC ratio with and without coadministration of alpelisib was 0.88.***

- ***The PBPK analysis is inadequate to predict the effects of BCRP inhibitors (itraconazole or cyclosporin A) on the PK of alpelisib. Itraconazole and cyclosporine A are dual inhibitors of CYP3A4 and BCRP. Both itraconazole and cyclosporine A are CYP3A substrates. The itraconazole or cyclosporine A PK may be affected by alpelisib due to its effect on CYP3A activity. Without prior knowledge of the net effect of alpelisib on CYP3A activity, it is not able to estimate the net CYP3A activity in the system containing both alpelisib and itraconazole or cyclosporine A. Thus, the BCRP mediated DDI between alpelisib and itraconazole or cyclosporin A cannot be estimated.***

- ***The alpelisib PBPK absorption model is not adequate to predict the fraction absorbed of alpelisib under fed conditions (low-fat low-calorie [LFLC] or high-fat low-calorie [HFLC]) due to the possibility of enterohepatic circulation involved in alpelisib absorption.*** (b) (4)

Background

<u>Pharmacokinetics</u>

Alpelisib has low and pH-dependent solubility where the solubility decreases with the increasing pH. The apparent permeability of alpelisib was high in the absence of transporter and moderate to high in the presence of unsaturated efflux transporter (BCRP). The absorption of alpelisib was at least 53.5% under the fasted state after a single oral dose of 400 mg alpelisib (mass balance Study X2107). The alpelisib C_{max} and AUC_{inf} were significantly increased under the fed state by an average of 84-145% and 73-77%, respectively, in healthy subjects.

Alpelisib distributes widely into tissues with the apparent volume of distribution of 114 L. Alpelisib moderately binds to protein with a free fraction of plasma protein binding (f_u) of 0.108, and a mean blood to plasma ratio of 1.03 (Summary of Clinical Pharmacology Studies - Breast Cancer-1).

Alpelisib's primary metabolism pathway in vivo is amide hydrolysis to BZG791, which is the major circulating metabolite in the plasma. Formation of BZG791 is governed by multiple, ubiquitously expressed, high-capacity enzymes (esterases, amidases, and choline esterase) that are unlikely to become subject to CYP enzymes mediated drug-drug-interactions (DDIs). The overall contribution of cytochrome P450 (CYP) family 3A4 is low with an estimated fraction metabolism (f_m CYP3A4) of ~12% based on the result that the CYP3A4-mediated metabolites represented ~12% of the dose in excreta. The primary metabolite BZG791 had similar PK characteristics as the parent drug with concentration time course of the metabolite being parallel to that of the parent (formation-rate limited metabolite). In the systemic circulation, the relative exposure of BZG791 was between 20% and 30% of alpelisib (Summary of Clinical Pharmacology Studies - Breast Cancer-1).

Alpelisib and its metabolites are almost exclusively excreted in the feces (81.0%) after oral administration, most likely through hepatobiliary export and/or intestinal secretion of either unchanged parent (36.2%) or metabolite BZG791under fasting condition. Excretion in the urine is minor (13.5%), with only a fraction of the dose being excreted as unchanged alpelisib (2%) (Summary of Clinical Pharmacology Studies - Breast Cancer-1).

Drug Interaction

In vitro studies

In vitro alpelisib is a time-dependent inhibitor and an inducer for CYP3A, a competitive inhibitor and inducer for CYP2C9, an inducer for CYP2B6, and an inhibitor for P-gp. Table 39and Table 40 list the results of applicant conducted in vitro studies which are pertaining to alpelisib DDI assessment.

Table 39: Identification of CYP enzymes and transporters involved in alpelisib ADME

Enzymes /Transporters	In vitro System	Parameters	Sources
CYP3A4	Human liver microsomes	K_m=24.95 μM V_{max}=63.21 pmol/min/mg CL_{int}=2.54 μL/min/mg	R1200505
CYP3A4	Recombinant human CYP3A4	K_m=5.75 μM V_{max}=2428 pmol/min/nmol CL_{int}=0.422 μL/min/pmol	R1200505
BCRP	Caco-2 cells	K_m=2 μM V_{max}=3.4 pmol/min/mg	R0900464
BCRP	MDCKII	K_m~15 μM	R0900828

Table 40: Evaluation of alpelisib as a modulator of drug metabolizing enzymes or P-gp

Enzymes /Transporters	Probe substrate/ metabolite	In vitro System	Mechanism	Parameters	Sources
CYP3A4	Midazolam/1'-hydroxymidazolam	Human liver microsomes	Time-dependent inhibition	K_I=5.6±1.0 μM k_{inact}=0.011 ± 0.0006 min^{-1}	R0900218
CYP3A4	Midazolam/1'-hydroxymidazolam	Human hepatocytes	mRNA induction	EC_{50}= 1.7 μM E_{max}= 0.83[b]	R1300942
CYP2B6	Bupropion/ hydroxybupropion	Human hepatocytes	mRNA induction	EC_{50}= 3.0 μM E_{max}= 0.51[b]	R1300942
CYP2C9	Diclofenac/4'-hydroxydiclofenac	Human hepatocytes	mRNA induction	EC_{50}= 2.2 μM E_{max}= 1.57[b]	R1300942
CYP2C9	Diclofenac/4'-hydroxydiclofenac	Human liver microsomes	Competitive inhibition	K_i=22 μM	R0900502
P-gp	NR[a]	NR[a]		K_i=96.7 μM	R0900459

a: NR: not reported
b: Maximal mRNA induction relative to the maximal mRNA induction by the positive control

Relevant clinical DDI studies

One clinical study was conducted by the applicant to evaluate the effects of alpelisib on the PK of everolimus in cancer patients (Study Z2102). Refer to the Clinical pharmacology review regarding the study design (No. BYL719A2102) and study results. Overall, there is no clinically relevant DDI observed between alpelisib and everolimus. The PK of 2.5 mg everolimus was largely unchanged in the presence of alpelisib independent of the dose of alpelisib (250 mg or 300 mg). This study was used for model verification.

Part A: DDI assessment

The Applicant's Analysis:

PBPK software

Simcyp V14 (Simcyp Ltd, UK) was used to develop the PBPK models and predict the effects of alpelisib on the PK of midazolam, ritonavir, ribociclib, rifampicin, warfarin, and bupropion, and the effects of ritonavir, rifampicin, itraconazole and cyclosporine A on the PK of alpelisib. Simcyp V15 and V16 were used, respectively, to predict the effects of alpelisib on the PK of a CYP3A4 auto-inhibitor (ritonavir) and a CYP3A4 substrate (everolimus).

Model development

Alpelisib

The alpelisib PBPK model was developed based on in vitro and in vivo ADME data. The first-order absorption model was selected with a fraction absorbed (f_a) (model predicted), a first-order rate constant (k_a) (estimated based on observed alpelisib PK profiles), and an effective permeability (P_{eff}) in human (predicted based on in vitro parallel artificial *membrane* permeability assay (PAMPA) data) as input parameters. Although the in vitro study results showed that alpelisib is a weak P-gp substrate and a relatively strong BCRP substrate with a K_m of 2 -15 μM, both P-gp and BCRP were saturated during the absorption phase due to the high luminal alpelisib concentration of 724 μM. Therefore, absorption is governed by the passive permeability. Due to the minor contribution of CYP3A4 to the systemic clearance (f_m~ 0.12), intestinal metabolism attributing to the first-pass effect was expected to be low.

The steady state volume of distribution (1.87 L/kg) was predicted using Poulin and Theil (2002) method which was comparable to the respective estimate based on population pharmacokinetic analysis (1.54-1.69 L/kg).

In vitro studies demonstrated that enzymatic amide hydrolysis was a major metabolism pathway to form the major metabolite BZG 791, whereas the CYP3A4 contribution to alpelisib clearance is minor. Mass balance study showed that the excretion ratio of CYP3A4-mediated metabolites and BZG791 was accounted for ~12% and ~40% of the dose, respectively. The intrinsic clearance via CYP3A4 was estimated using the Simcyp retrograde model and based on the total clearance and f_mCYP3A4 of 0.12.

CL_{others} (additional systemic clearance) was used in the alpelisib model representing the contribution of intestinal/biliary elimination mediated by efflux transporters in addition to the BZG791 formation, which was optimized based on the observed clinical PK data and accounted for about 80% of total clearance. Contribution of renal excretion to total elimination was negligible given only 2% of the radioactivity was excreted into urine as the parent drug after oral administration of [^{14}C]alpelisib in human.

The CYP3A inhibitory parameters (KI and kinact) obtained from an in vitro study (Table 40, R0900218) were used in the model to describe the alpelisib-mediated CYP3A4 inhibition kinetics. The CYP3A induction parameter (IndC50=1.7 μM) estimated from an in vitro study based on the changes in mRNA levels relative to the vehicle control was used in the model (Table 40, R1300942), whereas the Indmax (=15), the maximal CYP3A induction potential, was optimized based on the clinical PK data following single and multiple oral dosing of alpelisib over the dose range of 60-450 mg.

The CYP2C9 inhibitory parameters and CYP2B6 and CYP2C9 induction parameters obtained from in vitro studies (Table 40, R1300942 and R0900502) were used in the model to describe alpelisib-mediated inhibitory or induction kinetics of these enzymes.

The FDA's Assessment:

1. ***The alpelisib model did not account for alpelisib mediated P-gp induction and inhibition effect, which may contribute to the DDI between alpelisib and everolimus.***
2. ***In the in vitro study, alpelisib was characterized as a relative strong BCRP substrate with a K_m of 2 -15 mM. The intestine BCRP transport may be completely saturated due to the high intestinal concentration and may not have impact on alpelisib absorption. However, the potential DDI between alpelisib and a BCRP inhibitor in the liver need to be evaluated given the lower alpelisib unbound plasma concentration relative to the K_m of BCRP mediated biliary excretion of alpelisib. On Jan. 11, 2019, an information request was issued requesting the evaluation of the potential DDI between alpelisib and a BCRP inhibitor in the liver.***

Perpetrator drugs

The default PBPK models of perpetrator drugs (ritonavir, rifampicin, itraconazole and cyclosporine A) in SimCYP V13 and V14 were used for DDI prediction. The Simcyp rifampicin model (V13) were refined by incorporating the CYP3A enzyme kinetics and updating the CYP3A4 enzyme induction parameters based on the clinical DDI study results. Compatibility of the simulation performance using these perpetrator files between Simcyp V13 and V14 was confirmed.

Victim drugs

The default PBPK models of victim drugs (midazolam, ritonavir, ribociclib, rifampicin, warfarin, and bupropion) in SimCYP V14 were used for DDI prediction. The Simcyp rifampicin model (V13) were refined by incorporating the CYP3A enzyme kinetics and updating the CYP3A4 enzyme induction parameters based on the clinical DDI study results. The compatibility of the simulation performance between Simcyp V12 and 14 was confirmed.

Everolimus drug model

The first-order absorption model was selected, and the f_a and k_a were defined as 1 to fit the everolimus PK profiles. Everolimus is a P-gp substrate. The P-gp may not play an important role for everolimus absorption, since the passive permeability of everolimus was found to be high and P-gp is likely to be saturated in the intestine at doses > 1mg (4μM) based upon the measured K_m value of 1 μM. The P-gp was therefore not incorporated in the GI tract of the everolimus model.

Parameter sensitivity analysis was performed on Q_{gut} and $f_{u,gut}$ values to minimize the F_g to fit the in vivo DDI study results with ketoconazole and erythromycin.

The minimal PBPK model was used with a k_{in} value of 0.55 h^{-1}, k_{out} value of 0.10 h^{-1}, and the volume of the single adjusting compartment (V_{sac}) was assigned a value of 10 L/kg. The V_{ss} was predicted to be 13.2 L/kg using Rodgers and Rowland method with a K_p scalar of 0.14.

The everolimus clearance was described by enzyme kinetics with a recombinant CYP3A4-mediated CL_{int} of 0.1 μL/min/pmol CYP, which was optimized based on the clinical PK data (top-down approach).

To best predict the DDI between everolimus and ketoconazole, an active update factor of 2.5 was assigned in the everolimus model to account for higher drug concentrations in the liver and lower

F_h. There is no evidence of involvement of hepatic uptake transporters in everolimus transport into the liver.

Everolimus has been identified as a CYP2C9, CYP2D6 and CYP3A4 inhibitor based on in vitro studies. The inhibitory parameter K_i values (50.3, 1.7 and 2.3 μM for CYP2C9, CYP2D6 and CYP3A4, respectively) obtained from in vitro studies were used in the model to predict the in vivo DDI. Everolimus was also identified as an inhibitor of P-gp with an IC_{50} value of 9.4 μM and OATP1B1 and OATP1B3 with IC_{50} values of 0.1 and 0.63 μM, respectively. However, the everolimus model did not incorporate the interaction between everolimus and transporters.

Everolimus model was originally developed in Simcyp V12. The model was updated using Simcyp V16 to predict the effects of alpelisib on the PK of everolimus.

The FDA's Assessment:

1. ***The model did not account for everolimus mediated P-gp inhibition effect, which may contribute to the DDI between alpelisib and everolimus.***
2. ***The model did not include P-gp mediated luminal efflux and biliary excretion of everolimus. Everolimus may act as a potential P-gp substrate and the interaction with P-gp modulators may cause the change in exposure of everolimus.***

DDI potential of BZG791

BZG791 (a hydrolyzed metabolite) systemic exposure accounted for ~26.7% of total radioactivity after a single oral administration of [^{14}C] alpelisib to human (CBYL719X2107). No in vivo interaction potential of BZG791 with alpelisib or other substrates could be expected based on the in vitro studies. The BZG791 PBPK model was not developed in this study.

Route of administration

In this analysis, alpelisib and all the perpetrator and victim drugs were orally administered.

PBPK model verification

a. Ritonavir, itraconazole, cyclosporine A, midazolam, ribociclib, warfarin, and bupropion

The default PBPK models in Simcyp for ritonavir, itraconazole, cyclosporine A, midazolam, ribociclib, warfarin, and bupropion were used for DDI predictions without further model verification.

b. Rifampicin

The default Simcyp V13 rifampicin model was refined by incorporating the CYP3A enzyme kinetics (V_{max}=0.209 pmol/min/pmol and K_m=16.2 μM) based on the in vivo auto-induction potential for

CYP3A4 observed in clinical studies[1]. The CYP3A4 induction parameters for rifampicin were also refined based on the clinical DDI study results using victim drugs with a wide range of $f_{m,CYP3A4}$ values (0.18 (predonisolone) $<f_{m,CYP3A4}<$ 1.00 (simvastatin)[2]. The predicted AUCRs (ratios of the substrate AUC with or without a perpetrator) were comparable to those observed with a median of 1.16-fold and a range of 0.71-2.68. The original parameters in the Simcyp rifampicin model (Ind_{max}=8, $IndC_{50}$=0.320 µM) were replaced by the latest information (Ind_{max}=15.8, $IndC_{50}$=0.281 µM). The updated induction parameters were close to the rifampicin CYP3A induction parameters (Ind_{max}=16, $IndC_{50}$=0.32 µM) implemented in Simcyp V17.

c. Alpelisib

The alpelisib model was verified against observed PK following single or multiple dose of oral administration in healthy subjects, and the DDI study between alpelisib and everolimus.

PBPK model application

The developed PBPK models were used to simulate the DDIs for alpelisib in the following scenarios.

1. To predict the effect of alpelisib on everolimus (a sensitive CYP3A and P-gp substrate) and midazolam (a sensitive CYP3A substrate) PK at steady-state in healthy subjects;
2. To predict the effect of alpelisib on ribociclib (a weak CYP3A auto-inhibitor), ritonavir (a strong CYP3A auto-inhibitor), and rifampicin (a CYP3A auto-inducer) PK at steady-state in healthy subjects;
3. To predict the effect of ritonavir (a CYP3A auto-inhibitor) and rifampicin (a CYP3A auto-inducer) on alpelisib PK at steady-state in healthy subjects;
4. To predict the effect of alpelisib on warfarin (a sensitive CYP2C9 substrate) or bupropion (a CYP2B6 substrate) PK at steady-state in healthy subjects;
5. To predict the effects of itraconazole (a CYP3A substrate, CYP3A inhibitor, and BCRP inhibitor) and cyclosporine A (a CYP3A substrate, CYP3A inhibitor and BCRP inhibitor) on alpelisib PK at steady-state in healthy subjects.

[1] Baneyx G, Parrott N, Meille C, Iliadis A, Lavé T. Physiologically based pharmacokinetic modeling of CYP3A4 induction by rifampicin in human: influence of time between substrate and inducer administration. Eur J Pharm Sci. 2014 Jun 2; 56:1-15.

[2]Yamashita F, Sasa Y, Yoshida S, Hisaka A, Asai Y, Kitano H, Hashida M, Suzuki H. PLoS One. Modeling of rifampicin-induced CYP3A4 activation dynamics for the prediction of clinical drug-drug interactions from in vitro data. 2013 Sep 24;8(9): e70330.

Results

a. Version difference

The reviewer noticed that there is minor difference in the predicted C_{max} and AUC values of alpelisib or everolimus between SimCYP V17 vs SimCYP V14, 15 or 16. However, the predicted victim drug C_{max} and AUC ratios in the presence and absence of perpetrators are the same between SimCYP V17 and other versions. Therefore, in the following sections, the Applicant submitted results were presented which were obtained using SimCYP V 14, 15 or 16 based on the Applicant submitted PBPK models. In the FDA analyses, the reviewer conducted the PBPK analyses based on the Applicant submitted PBPK models using SimCYP V17.

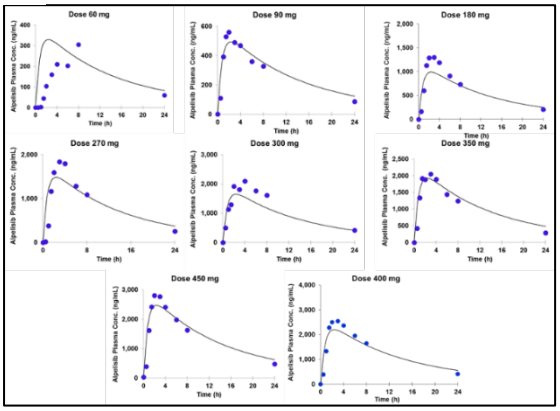
b. Alpelisib model verification

The in vitro CYP3A inhibitory parameters (KI and kinact) were used in the model to describe the alpelisib-mediated CYP3A inhibitory kinetics (Table 40, R0900218). One of the CYP3A induction parameter (Ind50) value in the model was obtained from in vitro study (Table 40, R1300942), while the other CYP3A induction parameter (Indmax) was manually optimized to fit the clinical observed PK data following multiple administration of alpelisib.

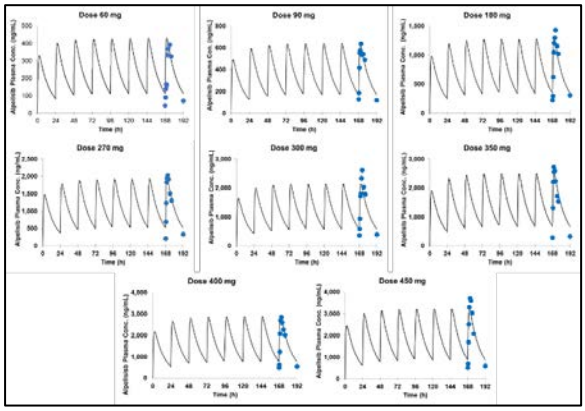
Figure 15 A and B show the simulated alpelisib PK profiles following a single or multiple administration of alpelisib. The Cmax and AUC values obtained from model simulation and clinical studies (Study Z2102 and Study Z2107) were presented in Table 41. The simulated AUC values are in line with the observed data after a single dose or multiple dose administration of alpelisib over a dose range of 60-450 mg. The simulated Cmax, however, was underestimated and within 40%.

Figure 15: Observed and simulated alpelisib PK profiles following a single (A) or multiple dose (B) administration of alpelisib in humans

A



B



*Observed and simulated alpelisib concentration-time profiles are presented as dots and lines, respectively.
Source: based on the Applicant's simulations

Table 41: Observed and simulated alpelisib C_{max}, AUC and the C_{max} and AUC ratios following a single or multiple administration of alpelisib.

	Dose (mg)	N in Clinical Studies	C_{max} (ng/mL)[b] Observed/Predicted/$R_{Pred/Obs}$	AUC (ng*h/mL)[b] Observed/Predicted/$R_{Pred/Obs}$
Single dose	60	3	338 / 326 / 0.96	4816[a] / 5864 / 1.22
	90	6	759 / 489 / 0.64	8220 / 8772 /1.07
	180	6	1545 / 979 / 0.63	18457 / 17442 / 0.95
	270	4	1950 / 1469 / 0.75	24363 / 26073 / 1.07
	300	8	2180 / 1633 / 0.75	26179 / 28947 / 1.11
	350	6	3150 / 1906 / 0.61	29972 / 33742 / 1.13
	400	55	2880 / 2179 / 0.76	36970 / 38536 / 1.04
	450	9	2850 / 2452 / 0.86	42098 / 43334 / 1.03
Multiple dose q.d. for 8 days	60	3	475 / 423 / 0.89	4770 / 5771 / 1.21
	90	6	849 / 639 / 0.75	8520 / 8610 /1.01
	180	6	1740 / 1295 / 0.74	20600 / 17096 / 0.83
	270	4	2880 / 1958 / 0.68	25900 / 25605 / 0.99
	300	8	3160 / 2181 / 0.69	33200 / 28453 / 0.86
	350	6	3200 / 2553 / 0.80	29500 / 33213/ 1.13
	400	65	3560 / 2927 / 0.82	39600 / 37990 / 0.96
	450	9	3550 / 3301 / 0.93	46000 / 42786/ 0.93

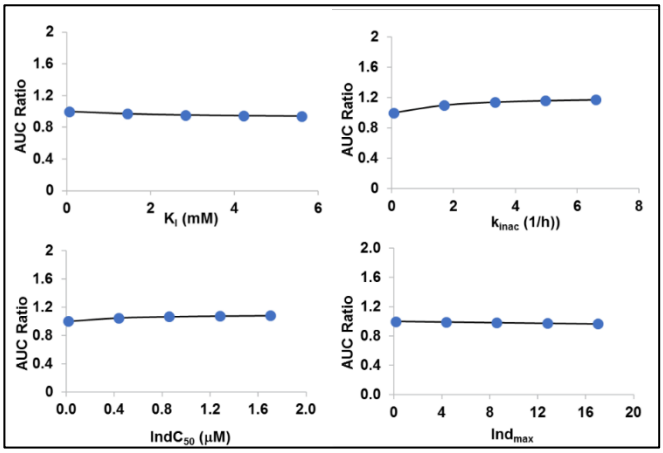
a: n=1;
b: Both simulated and observed C_{max} and AUC values are presented as median values. Observed values were obtained from Study Z2102 (multiple dose in cancer patients) or Study Z2107 (single dose in healthy subjects).
*The number of subjects in the simulation is 24 healthy subjects.
Source: Applicant's PBPK report DMPK R1400676 Table 6-9.

The FDA's Assessment:

The simulated alpelisib PK profiles agreed relatively well with the observed data over a dose range of 60-450 mg following multiple administration using the Applicant's model. The lack of systemic exposure accumulation of alpelisib over time was also captured by the Applicant's model. However, considering the minor contribution of CYP3A to the alpelisib systemic clearance (fm~ 0.12), alpelisib is not a sensitive substrate to test its inhibitory and induction effects on CYP3A. The reviewer conducted a sensitivity analysis to assess the effects of alpelisib

CYP3A induction and inhibition on itself systemic exposure. Simulation suggested that the alpelisib plasma AUC was not sensitive to the changes in its CYP3A induction and inhibitory parameters when varying the KI and IndC50 values in a range of 0.01-fold to 1-fold and kinact and Indmax values in a range of 0.1-fold to10-fold of the values obtained from in vitro studies (Figure 16). The uncertainty associated with the alpelisib-mediated in vivo CYP3A induction and inhibitory effect, therefore, may compromise the capability of alpelisib model for DDI assessment with CYP3A substrates and modulators.

Figure 16: Sensitivity analysis of alpelisib CYP3A induction and inhibitory parameters on the simulated alpelisib AUC



* PBPK simulation was conducted following multiple dose administration of 300 mg alpelisib in healthy subjects
Source: FDA reviewer's analysis.

c. Model DDI predictive performance evaluation

DDI assessment of the perpetrator potential of alpelisib on everolimus PK at steady-state in healthy subjects

The applicant performed simulations to explore the effect of alpelisib on everolimus PK at steady state in healthy subjects and compared them to the clinical DDI study results. The simulated everolimus AUC ratio (geometric mean ratio) at the last dose after oral administration of 2.5 mg everolimus, q.d. for 28 days was 1.13-fold with co-administration of alpelisib (300 mg p.o., q.d. for 21 days). The clinical observed AUC ratio was 0.766 (geometric mean ratio) or 0.888 (estimated based on a linear mixed-effect model). The Applicant stated that both observed and simulated results support the conclusion that there is a lack of meaningful change in everolimus PK when co-administered with alpelisib. (Applicant's response to FDA's Information Request on Jan 11, 2019)

<u>The FDA's Assessment:</u>

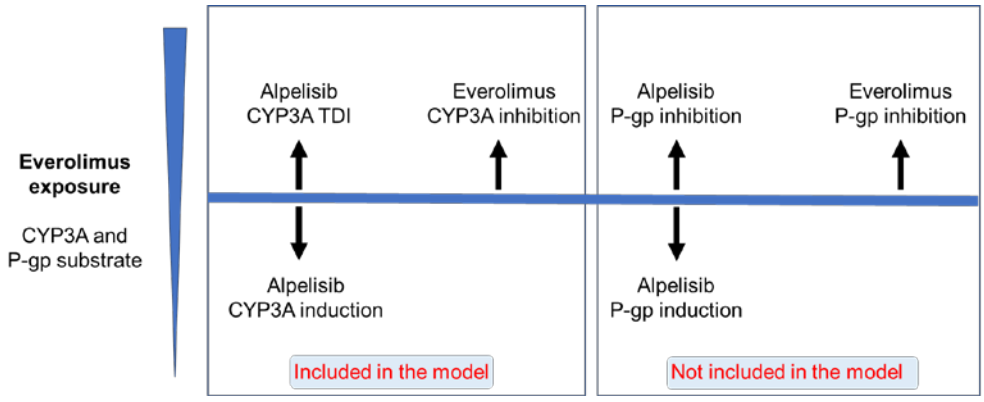
The in vitro study result indicated that alpelisib is a weak P-gp inhibitor with a K_i of 98.6 µM (R0900459), which may translate into clinical significance based on an expected alpelisib gut concentration of 724 µM following the administration of 300 mg alpelisib. Due to alpelisib's

own CYP3A induction potential it may also induce P-gp. Everolimus is a substrate for both P-gp and CYP3A. It is also a CYP3A inhibitor with a K_i of 9.4 µM (competitive inhibition) and a P-gp inhibitor. The interaction between alpelisib and everolimus was summarized in Figure 17.

1. ***The applicant's model incorporated CYP3A induction and time-dependent inhibition properties of alpelisib and CYP3A competitive inhibition property of everolimus. However, the model did not incorporate parameters describing alpelisib-mediated P-gp induction and inhibition and everolimus-mediated P-gp inhibition. In addition, the everolimus model did not include P-gp mediated luminal efflux and biliary excretion of everolimus. As shown in Table 42, the Applicant's everolimus substrate model constantly under-predicted the observed effects of CYP3A and P-gp dual modulators (ketoconazole, verapamil, and rifampicin) on everolimus PK by considering the contribution from CYP3A alone. These results indicated that everolimus may act as a potential P-gp substrate and the interaction with P-gp modulators may cause the change in exposure of everolimus. Without the prior knowledge of the effect of alpelisib and everolimus on P-gp, the effect of both alpelisib and everolimus on everolimus exposure mediated by P-gp cannot be excluded.***
2. ***As aforementioned in the 'alpelisib model verification' section, the uncertainty associated with CYP3A induction and inhibitory parameters also rendered the alpelisib model inadequate for CYP3A-mediated DDI assessment.***
3. ***In addition, both predicted everolimus AUCR (1.13) and observed AUCR (0.766, geometric mean ratio) or 0.888 (estimated based on a linear mixed-effect model) were not considered significant regarding the magnitude of the effects of alpelisib on everolimus PK. However, the direction of observed (net induction) and predicted (net inhibition) DDI is opposite. This could be due to the uncertainties in the model described above.***

As indicated above, as there are multiple gaps existing in the current model validation, the reviewer concludes that the effects of alpelisib on a CYP3A substrate cannot be assessed by the current model.

Figure 17: FDA analysis of pathways involved in alpelisib and everolimus DDI



Source: FDA reviewer's analysis.

Table 42: Observed and simulated C_{max} and AUC ratios of everolimus in the presence and absence of ketoconazole, erythromycin, verapamil and rifampin.

	Ketoconazole[a]		Erythromycin[b]		Verapamil[c]		Rifampin[d]	
	C_{max}R	AUCR	C_{max}R	AUCR	C_{max}R	AUCR	C_{max}R	AUCR
Observed	3.9	15	2.0	4.5	2.2	3.4	0.42	0.37
Simulated	1.6	8.9	1.5	4.6	1.3	1.7	0.45	0.19
Simulated / Observed	0.41	0.59	0.75	1.02	0.59	0.5	1.07	0.51

a: Period 1: everolimus, 2 mg on day 1 through day 6; Period 2: ketoconazole, 200 mg, b.i.d. on day 10 through day 17 and everolimus, 2 mg, q.d. on day 13 through day 18[3].

b: everolimus, 2 mg, on day 1 and day 14; erythromycin 500 mg, t.i.d. on day 10 through day 18[4].

c: Period 1: everolimus, 2 mg on day 1 through day 6; Period 2: verapamil, 80 mg, t.i.d. on day 10 through day 15 and everolimus, 2 mg, q.d. on day 11 through day 16[5].

d: Period 1: everolimus, 2 mg on day 1; Period 2: rifampin, 600 mg, q.d. on day 7 through day 19 and everolimus, 2 mg, on day 15[6].

Source: FDA reviewer's analysis. Data were obtained from published articles and summarized in DMPK-R1300572 report. Everolimus is administered orally.

d. Model application evaluation

1. Assessment of the effects of alpelisib on midazolam PK at steady-state in healthy subjects

The FDA's Assessment:

The applicant developed alpelisib model was used to predict the effects of alpelisib on midazolam (a sensitive CYP3A4 substrate) PK. As stated in previous sections, the net effect of alpelisib on the PK of a sensitive CYP3A substrate cannot be estimated using the current PBPK model due to the gaps existing in the model, and lack of appropriate model validation.

2. Assessment of the effects of alpelisib on rifampicin (a CYP3A auto-inducer) PK at steady-state in healthy subjects

The FDA's Assessment:

[3] Kovarik JM, Beyer D, Bizot MN, Jiang Q, Shenouda M, Schmouder RL. Blood concentrations of everolimus are markedly increased by ketoconazole. J Clin Pharmacol. 2005;45(5):514-8.

[4] Kovarik JM, Beyer D, Bizot MN, Jiang Q, Shenouda M, Schmouder RL. Effect of multiple-dose erythromycin on everolimus pharmacokinetics. Eur J Clin Pharmacol. 2005;61(1):35-8.

[5] J M Kovarik, D Beyer, M N Bizot, Q Jiang, M J Allison, and R L Schmouder. Pharmacokinetic interaction between verapamil and everolimus in healthy subjects. Br J Clin Pharmacol. 2005; 60(4): 434–437.

[6] Kovarik JM, Hartmann S, Figueiredo J, Rouilly M, Port A, Rordorf C. Effect of rifampin on apparent clearance of everolimus. Ann Pharmacother. 2002;36(6):981-5.

The applicant developed alpelisib model was used to predict the effects of alpelisib on the PK of rifampicin (a CYP3A auto-inducer). The predicted rifampicin plasma AUCR with and without coadministration of alpelisib is 1.35. The current available information is not enough to differentiate the contribution of alpelisib mediated-CYP3A induction and alpelisib-mediated CYP3A inhibition to the CYP3A-mediated DDI. The net effect of alpelisib on CYP3A activity, the alpelisib-mediated-pure TDI of CYP3A, and alpelisib-mediated pure CYP3A induction are all the critical determinants of potential DDI between alpelisib and a CYP3A auto-inducer. In addition, literature reported clinical DDI study assessing the effect of alpelisib on the PK of encorafenib, a CYP3A4 substrate and inducer, showed that the exposure of encorafenib was increased by about 2-fold in the presence of 300 mg alpelisib (C_{max} 2394 vs. 1427 ng/mL and AUC_{tau} 12948 vs 7172 h·ng/mL) compared to the administration of 200 mg encorafenib alone at steady state[7]. The results indicated that the exposure of a CYP3A inducer may be increased due to the interaction with alpelisib. Based on the gaps discussed previously in this section, the reviewer concluded that the applicant's alpelisib model is not adequate to assess the effect of alpelisib on the PK of a CYP3A auto-inducer.

3. Assessment of the effects of alpelisib on ribociclib and ritonavir (CYP3A auto-inhibitors) PK at steady-state in healthy subjects

<u>The FDA's Assessment:</u>

Due to the reasons outlined in previous sections, both the net effect of alpelisib on CYP3A activity, and the alpelisib mediated-pure TDI of CYP3A and alpelisib-mediated pure CYP3A induction are the critical determinants to evaluate the effect of alpelisib on the PK of a CYP3A auto-inhibitor. Therefore, the reviewer concluded that the Applicant's alpelisib model is not adequate for the DDI assessment of the effect of alpelisib on the PK of a CYP3A auto-inhibitor.

(b) (4)

4. Assessment of the effects of ritonavir (a CYP3A auto-inhibitor) on alpelisib PK at steady-state in healthy subjects

<u>The FDA's Assessment:</u>

[7] van Geel RMJM1, Tabernero J, Elez E, Bendell JC, Spreafico A, Schuler M, Yoshino T, Delord JP, Yamada Y, Lolkema MP, Faris JE, Eskens FALM, Sharma S, Yaeger R, Lenz HJ, Wainberg ZA, Avsar E, Chatterjee A, Jaeger S, Tan E, Maharry K, Demuth T, Schellens JHM. A Phase Ib Dose-Escalation Study of Encorafenib and Cetuximab with or without Alpelisib in Metastatic BRAF-Mutant Colorectal Cancer. Cancer Discov. 2017 Jun;7(6):610-619.

As aforementioned, due to the minor contribution of CYP3A to the alpelisib systemic clearance (fm~ 0.12), the effect of ritonavir, a CYP3A substrate and strong inhibitor, on alpelisib PK is expected to be low. The reviewer conduced a worst-case scenario analysis assuming complete inhibition of CYP3A mediated metabolic pathway. The simulated alpelisib plasma C_{max} and AUC were increased by 1.08 and 1.16-fold, respectively. Based on the simulation, the reviewer concluded that the effect of a strong CYP3A inhibitor on the PK of alpelisib is minimal.

5. Assessment of the effects of rifampicin (a strong CYP3A inducer) on alpelisib PK at steady-state in healthy subjects

<u>The FDA's Assessment:</u>

The Applicant assessed the effects of rifampicin (a CYP3A auto-inducer) on alpelisib PK using the modified Simcyp rifampin model. When the in vivo alpelisib CYP3A inhibitory effect and induction effect were both over-estimated or both under-estimated, the simulated alpelisib PK and the simulated effects of alpelisib on everolimus PK would maintain the same. However, the effects of a strong CYP3A inducer (such as rifampin) on alpelisib could be over- or under-estimated. The uncertainty in alpelisib CYP3A inhibitory and induction potential estimation could introduce uncertainties in the prediction of the effects of a strong CYP3A inducer (e.g. rifampin) on alpelisib PK. Two potential scenarios are discussed in more detail as follows using simulations.

Scenario 1: Both in vivo alpelisib CYP3A inhibitory effect and induction effect are over-estimated.

In the Applicant's response to FDA information request on Jan. 31, 2019, the Applicant conducted a sensitivity analysis by increasing the alpelisib CYP3A inactivation rate (k_{inact}) values by 2, 5, 10 and 20-fold and simultaneously, increasing the CYP3A maximal fold induction (Ind_{max}) values by the same factors to maintain the net CYP3A activity the same as the default level. The K_I (concentration of inhibitor that supports half maximal inhibition) and $IndC_{50}$ (drug concentration that supports half maximal induction) values in the model remained unchanged in this analysis.

As shown in Table 43, although the CYP3A k_{inact} and Ind_{max} parameter values were increased by 2-20-fold, the predicted alpelisib PK and the effects of alpelisib on everolimus PK were unchanged, indicating that the net CYP3A activity was maintained when increasing the magnitude of the alpelisib CYP3A inhibition and induction effects simultaneously. The effect of rifampicin on alpelisib PK decreased as evidenced by the increased AUC ratios from 0.79 to 1.00 with increasing alpelisib CYP3A k_{inact} and Ind_{max} values. These simulation results indicated that the effect of alpelisib on CYP3A activity superseded and finally completely masked the induction effect of rifampicin on CYP3A. As such, in this scenario, the effect of a strong CYP3A inducer on alpelisib could be reduced and further completely blocked.

Scenario 2: Both in vivo alpelisib CYP3A inhibitory effect and induction effect are under-estimated.

In the Applicant's response to FDA information request on Feb. 12, 2019, the Applicant conducted a sensitivity analysis by increasing the alpelisib CYP3A K_I values or decreasing the k_{inact} values by 2,5,10 and 20-fold. To maintain the net effect of alpelisib on CYP3A activity unchanged, the change of CYP3A K_I or k_{inact} was balanced by simultaneously decreasing the CYP3A $IndC_{50}$ or Ind_{max} values.

As shown in Table 43, the net CYP3A activity was maintained when decreasing the magnitude of CYP3A inhibition and induction effects since the predicted alpelisib PK and DDI potential of alpelisib with everolimus were consistent with the prediction by using the Applicant submitted model in the original PBPK report. The effect of rifampicin on alpelisib PK increased as evidenced by the decreased AUC ratios from 0.79 to 0.59 with increasing alpelisib CYP3A K_I values or decreasing CYP3A k_{inact} values by 2,5,10 and 20-fold. These simulation results indicated that the CYP3A induction effect of rifampicin superseded the effect of alpelisib on CYP3A activity.

In addition, the literature reported clinical PK study of alpelisib with a CYP3A inducer encorafenib indicated that alpelisib (300 mg) exposure was reduced by 1.75-fold with coadministration of 200 mg encorafenib compared to those with coadministration of 300 mg encorafenib[8]. However, due to the insufficient number of subjects included in the data analysis (n=2), the conclusion of this study regarding the DDI of alpelisib as victim with CYP3A inducer needs to be further verified with the dedicated clinical DDI study data.

In conclusion, the uncertainty associated with alpelisib in vivo inhibition and induction potential estimation will affect the simulation of the effect of rifampicin on alpelisib PK.

[8] van Geel RMJM, Tabernero J, Elez E, Bendell JC et. al. A Phase Ib Dose-Escalation Study of Encorafenib and Cetuximab with or without Alpelisib in Metastatic BRAF-Mutant Colorectal Cancer. Cancer Discov. 2017 Jun;7(6):610-619.

Table 43: DDI simulations of either alpelisib as perpetrator with everolimus or rifampicin as perpetrator with alpelisib

		Model Validation			Model Prediction
	Fold increases in both CYP3A induction and inhibition parameter values	**Effect of changes in CYP3A induction/inhibition parameter values on alpelisib PK[a]**		**Victim: everolimus Perpetrator: alpelisib[b]**	**Victim: alpelisib Perpetrator: rifampicin[c]**
	A: k_{inact} and Ind_{max} (fold increased)	Alpelisib C_{max} ratio	Alpelisib AUC ratio	Everolimus AUC_{tau} ratio	Alpelisib AUC_{tau} ratio
Predicted using the alpelisib model in the original submission	1	1	1	1.11[d]	0.79[d]
Scenario 1	2	0.99	0.99	1.09	0.89
	5	0.99	0.98	1.08	0.98
	10	0.99	0.98	1.09	1.00
	20	0.99	0.98	1.10	1.00

		Model Validation			Model Prediction
	Fold changes in both CYP3A induction and inhibition parameter values	**Effect of changes in CYP3A induction/inhibition parameter values on alpelisib PK[a]**		**Victim: everolimus Perpetrator: alpelisib[b]**	**Victim: alpelisib Perpetrator: rifampicin[c]**
	B: K_I /Ind_{50} (fold increased)	**Alpelisib C_{max} ratio**	**Alpelisib AUC ratio**	**Everolimus AUC_{tau} ratio**	**Alpelisib AUC_{tau} ratio**
Predicted using the alpelisib model in the original submission	1/1	1	1	1.11[d]	0.79[d]
Scenario 2	2/2.35	1	1	1.11	0.70
	5/7.06	1	1	1.10	0.63
	10/16.5	1	1	1.08	0.60
	20/44.1	1	1	1.08	0.59
	C: k_{inact} and Ind_{max} (fold decreased)				
	2/2	1[e]	1[e]	1.12	0.70
	5/4.3	0.99[e]	0.99[e]	1.09	0.63
	10/7.5	1[e]	1[e]	1.11	0.60
	20/11.5	1[e]	1[e]	1.10	0.58

a: alpelisib (300mg, q.d for 15 days)
b: alpelisib (300mg, q.d for 15 days), everolimus (2.5 mg, q.d. for 15 days)
c: rifampicin (600mg, q.d for 7 days), alpelisib (300mg, q.d for 7 days)
d: predicted results by using Applicant alpelisib model in the original submission
e: these values were calculated based on reviewer's simulations. The calculated values based on the simulation results in the response to FDA's information request were 0.83. The Applicant simulated everolimus and rifampicin AUC ratio with and without coadministration of alpelisib are consistent with those simulated by the reviewer.
*A: Both k_{inact} and Ind_{max} values were increased by 2, 5, 10 and 20-fold. The K_I and $IndC_{50}$ values in these simulations remained unchanged; B: K_I values were increased by 2, 5, 10 and 20-fold and Ind_{50} values were increased by 2.35, 7.06, 16.5, and 44.1-fold, k_{inact} and Ind_{max} values in these simulations remained unchanged; C: k_{inact} values were decreased by 2, 5, 10 and 20-fold and Ind_{max} values were decreased by 2, 4.3, 7.5 and 11.5-fold. The K_I and $IndC_{50}$ values in these simulations remained unchanged.
Source: Applicant and FDA reviewer's analysis.

6. Assessment of the effects of alpelisib on warfarin (a CYP 2C9 substrate) PK at steady-state in healthy subjects

The FDA's Assessment:

The applicant developed alpelisib model was used to predict effects of alpelisib on warfarin (a sensitive CYP2C9 substrate) PK. The CYP2C9 induction parameters (IndC50=2.2 µM, Indmax=1.57) in alpelisib model were obtained from in vitro study (Table 40, R1300942). The predicted warfarin plasma AUCR with and without coadministration of alpelisib was 0.91. The Applicant further conducted a sensitivity analysis of CYP2C9 induction parameters IndC50 (0.1-20 µM) and Indmax (1-20) on the predicted warfarin AUCR. A minimal warfarin (10 mg) AUCR of 0.2 was estimated when it was coadministered with alpelisib (300 mg, q.d. for 20 days). The Applicant concluded that there is no or weak induction potential of alpelisib on warfarin. Warfarin exposure may be reduced with the coadministration of alpelisib under worst-case scenario.

In the alpelisib model, the Indmax (maximal fold induction, equal to Emax +1) was estimated based on the Emax obtained from the in vitro study (Table 40, R1300942), where Emax was defined as the maximal mRNA induction relative to the maximal induction by the positive control. The Indmax in Simcyp was defined as the maximal fold induction over the vehicle control. The Applicant incorporated the Indmax relative to the positive control rather than the vehicle control in the alpelisib model which may lead to an underestimation of the alpelisib's induction effect. In general, there is lack of evidence and experience that model may provide reasonable estimates of in vivo induction effects by directly using the in vitro induction parameters. In the current submission, there is no in vivo DDI study to verify that using the in vitro induction parameters can directly predict the in vivo DDI. Therefore, the in vitro-in vivo extrapolation of CYP2C9 induction effect mediated by alpelisib has not been established for quantitative prediction. The Applicant's sensitivity analysis did flag a potential risk of in vivo DDI between alpelisib and warfarin.

Based on the sensitivity analysis, the reviewer concluded that exposure of warfarin may be reduced with the coadministration of alpelisib. However, due to the uncertainty associated with the in vitro-in vivo extrapolation of CYP2C9 induction potentials mediated by alpelisib, the analysis is considered as a risk assessment.

7. Assessment of the effects of alpelisib on bupropion (a CYP 2B6 substrate) PK at steady-state in healthy subjects

The FDA's Assessment:

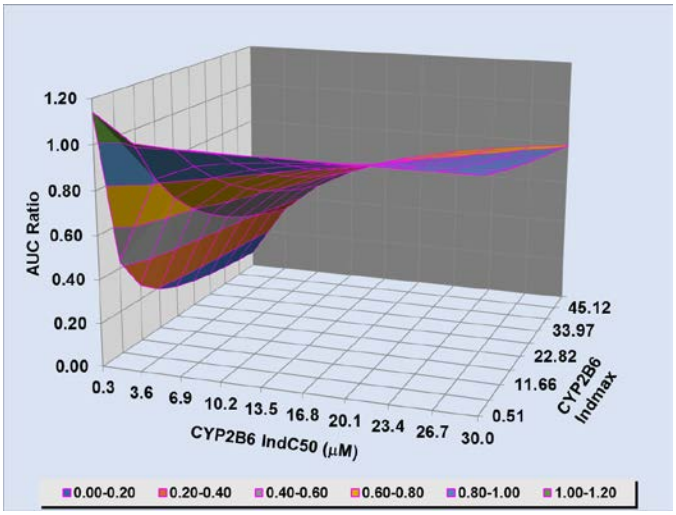
The applicant conducted PBPK simulation to assess the effect of alpelisib on the PK of bupropion (a CYP2B6 substrate) in response to FDA IR, and submitted a Simcyp output excel file, in which the simulation design, model parameter input values, and simulated results were provided.

The CYP2B6 induction parameter (IndC50=3.0 µM) in the alpelisib model was obtained from the in vitro study. The reported Emax was 0.51 in the in vitro study report (Table 40, DMPK R1300942).

A value of 5.07 was used for Ind_{max} in the model and no justification was provided. The predicted bupropion plasma AUC ratio with and without coadministration of alpelisib was 0.88.

The applicant did not provide justification for the choice of 5.07 for CYP 2B6 Indmax used in the alpelisib model. Since the in vitro-in vivo extrapolation of CYP2B6 induction effect mediated by alpelisib has not been established, the reviewer conducted a sensitivity analysis of CYP2B6 induction parameters IndC50 (0.3-30 µM) and Indmax (0.51-50.7) to assess the effects on the predicted bupropion AUCRs. A minimal bupropion (150 mg, on day 11) AUCR of 0.07 was estimated with the coadministration of alpelisib (300 mg, q.d. for 15 days) (Figure 18). The sensitivity analysis result indicated that the potential DDI risk between bupropion and alpelisib should not be excluded without further investigation. Based on the sensitivity analysis, the reviewer concluded that exposure of bupropion may be reduced with the coadministration of alpelisib.

Figure 18: Sensitivity analysis of alpelisib CYP2B6 induction parameters $IndC_{50}$ and Ind_{max} on the predicted bupropion AUCRs



*PBPK simulation is conducted following a single dose of 150 mg bupropion on day 11 and multiple dose of 300 mg alpelisib, q.d. for 15 days.
Source: FDA reviewer's analysis.

8. Assessment of the effects of itraconazole or cyclosporine A (BCRP inhibitors) on alpelisib PK at steady-state in healthy subjects

<u>The FDA's Assessment:</u>

The applicant submitted the DDI assessment evaluating the effects of BCRP inhibitors on the PK of alpelisib along with the model files in their response to FDA IR on Jan 11. 2019. The Applicant developed alpelisib model was slightly modified in order to account for BCRP mediated transport in the liver. The modification included 1) adding BCRP for the biliary secretion which was assigned to 40% of total clearance (Summary of Clinical Pharmacology Studies - Breast Cancer-1), and 2) changing the distribution model from a minimal PBPK model to a full PBPK model.

Biliary secretion was summed up together with the alpelisib hydrolysis under "Additional Systemic Clearance" (CL_{others}) in the original alpelisib model. In the updated model with BCRP, CL_{others} value was reduced to 4.34 L/h and a CL_{int} value of 3.86 µL/min/10^6 hepatocytes was assigned to the BCRP secretion. To implement BCRP transport, the alpelisib distribution model had to be switched from a minimal to a full PBPK model and the prediction method for volume of distribution had to be "method 2" Rodger/Rowland. K_p scalar was scaled to result in a V_{ss} of 1.86 L/kg. As T_{max} was appearing earlier with these new settings, k_a and lag time were modified accordingly. The alpelisib PK profile predicted using the modified alpelisib model agreed well with the one predicted using the alpelisib model without modification.

The followings are the three scenarios that have been considered in the Applicant simulations regarding the assessment of the effects of BCRP inhibitors on the PK of alpelisib.

Scenario 1: Literature reported BCRP K_I values of itraconazole (K_i=IC_{50}/2, IC_{50}= 1.9 µM) and its major metabolite hydroxy-itraconazole (K_I=IC_{50}/2, IC_{50}= 0.44 µM) and the BCRP K_I value of 0.5 µM in Simcyp default cyclosporine A model were used in simulations.

Scenario 2: 10-fold lower K_I values for itraconazole, hydoxy-itroconazole and cyclosporine A were used in simulations.

Scenario 3: BCRP transport pathway in alpelisib model was completely inhibited in simulations.

The applicant simulated alpelisib AUC ratios with and without coadministration of BCRP inhibitors under different scenarios. It was shown that the alpelisib AUC was increased by 1.69-fold under worst-case scenario with complete inhibition of the BCRP pathway.

Itraconazole and cyclosporine A may potentially affect alpelisib PK via both CYP3A and BCRP pathways. Both itraconazole and cyclosporine A are CYP3A substrates, CYP3A inhibitors and BCRP inhibitors. The itraconazole or cyclosporine A PK may also be affected by alpelisib due to its effect on CYP3A activity. Without prior knowledge of the net effect of alpelisib on CYP3A activity, it is not able to estimate the net CYP3A activity in the system containing both alpelisib and itraconazole or cyclosporine A. Thus, the BCRP mediated DDI between alpelisib and itraconazole or cyclosporin A cannot be estimated.

Conclusions

The applicant submitted alpelisib PBPK model is not adequate to predict CYP3A-mediated DDI potential of alpelisib as a victim or perpetrator due to the multiple pathways (CYP3A, P-gp, and BCRP) involved, and lack of appropriate model validation. Based on worst-case scenario analysis, the model predicted that alpelisib may decrease the exposure of a sensitive CYP2C9 substrate (warfarin) by 80% or a CYP2B6 substrate (bupropion) by 97%.

Part B: Prediction of fraction absorbed of alpelisib under fed condition in healthy subjects

The Applicant's Analysis:

PBPK software

GastroPlus^{TM} V9.5 (Simulation Plus, US) was used to develop the oral absorption PBPK model for alpelisib and predict the fraction absorbed under fasted and fed conditions with or without coadministration of ranitidine in healthy subjects.

Model development

The applicant's model consists of an advanced compartment and transit (ACAT) absorption Model and a 2-compartmental model with a systemic clearance of 20.4 L/h, and a volume of distribution of 90.9 L estimated from the population pharmacokinetic (pop-PK) analysis. The measured pH-solubility in buffers was used to simulate absorption of 300 mg of alpelisib under fasted conditions and when coadministered with ranitidine; whereas adjusted pH-solubility profile (adjusted based on the pKa function fitting using measured solubility data) was used for simulating absorption under fed conditions. In vitro dissolution data of alpelisib generated under fasted-state simulated intestinal fluid (FaSSIF) and fed-state simulated intestinal fluid (FeSSIF) conditions were used to fit constant Z-factor (Takano dissolution model) and obtained a Z-factor of 7.48E-3 mL/mg/s for fasted and 6.0E-3 mL/mg/s for fed conditions.

GastroPlus ACAT default physiological parameters such as pH, transit times and volumes across the intestinal tract were used to simulate the alpelisib PK under fasted and HFHC meal conditions. To simulate the food effect with high-fat low-calorie (HFLC) meal, several adjustments in the ACAT model were made according to Sutton et al 2017 (Table 44). For co-administration with ranitidine, pH in stomach was set to 6.50 (when fasted and fed).

Table 44: ACAT physiology for a 70-kg subject under fasted condition (A) and under fed (LFLC meal) (B) condition

A

Compartment	pH	Transit time (h)	Volume (mL)	Bile salt (mM)
Stomach	Fasted: 1.30 Fed: 4.90	Fasted: 0.25 Fed: 1.00	Fasted: 46.56 Fed: 931.2	0
Duodenum	Fasted: 6.00 Fed: 5.40	0.26	41.56	Fasted: 2.80 Fed: 14.44
Jejunum 1	Fasted: 6.20 Fed: 5.40	0.93	154.2	Fasted: 2.33 Fed: 12.02
Jejunum 2	Fasted: 6.40 Fed: 6.00	0.74	122.3	Fasted: 2.03 Fed: 10.46
Ileum 1	6.60	0.58	94.29	Fasted: 1.41 Fed: 7.28
Ileum 2	6.90	0.42	70.53	Fasted: 1.16 Fed: 5.99
Ileum 3	7.40	0.29	49.83	Fasted: 0.14 Fed: 0.73
Caecum	6.40	4.19	47.49	0
Asc Colon	6.80	12.57	50.33	0

B

Compartment	pH	Transit time (h)	Volume (mL)	Bile salt (mM)
Stomach	LFLC: 1.30 HFLC: 4.75	LFLC: 0.70 HFLC: 0.65	LFLC: 600 HFLC: 495	0
Duodenum	5.40	0.26	41.56	LFLC: 2.80 HFLC: 14.44
Jejunum 1	5.40	0.93	154.2	LFLC: 2.33 HFLC: 12.02
Jejunum 2	6.00	0.74	122.3	LFLC: 2.03 HFLC: 10.46
Ileum 1	6.60	0.58	94.29	LFLC: 1.41 HFLC: 7.28
Ileum 2	6.90	0.42	70.53	LFLC: 1.16 HFLC: 5.99
Ileum 3	7.40	0.29	49.83	LFLC: 0.14 HFLC: 0.73
Caecum	6.40	4.19	47.49	0
Asc Colon	6.80	12.57	50.33	0

*****Sutton SC, Nause R, Gandelman K (2017) The impact of gastric pH, volume, and emptying on the food effect of ziprasidone oral absorption. The AAPS J.; 19 (4): 1084 – 1090.
Source: Applicant's PBPK report DMPK R1701118 Table 3-3 and Table 3-4.

PBPK model verification

The alpelisib PBPK models were verified with the clinical PK study data under fasting and fed conditions with and without ranitidine.

PBPK model application

The developed PBPK models were used to predict the fraction absorbed under fasted and fed conditions with or without coadministration of ranitidine in healthy subjects.

The FDA's Assessment:

As there was a dedicated DDI study evaluating the effects of ranitidine on the PK of alpelisib, the PBPK analyses evaluating the same effects were not reviewed due to the short review timeline. The fraction absorbed prediction under the fasting condition was not relevant as alpelisib was proposed to be given with food.

Results

Fraction absorbed of alpelisib under fed conditions (LFLC or HFLC) Source: Applicant's PBPK report DMPK R1701118 Table 7-2.

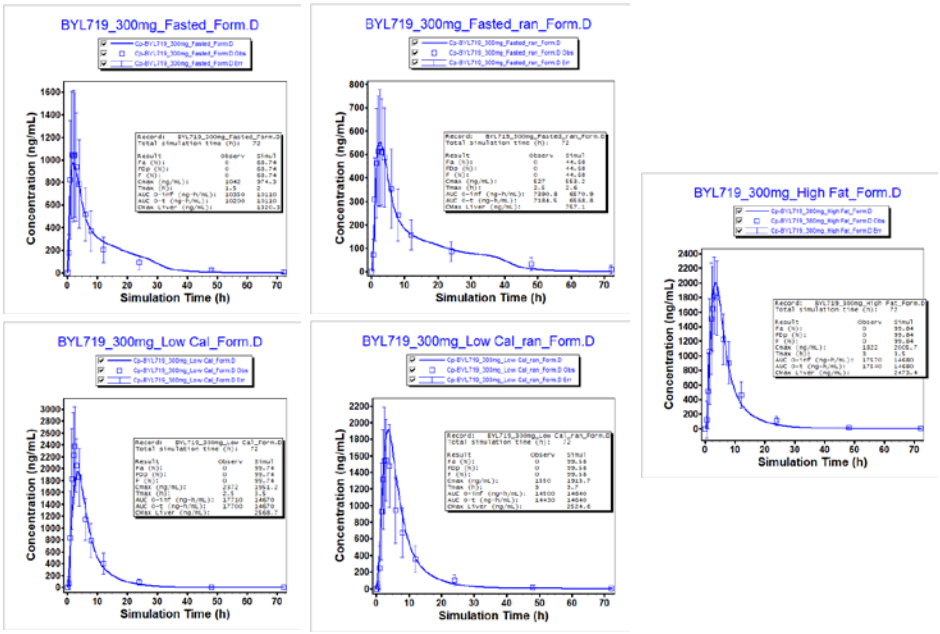
Figure 19 and Table 45 summarized the predicted and observed alpelisib PK parameters under various conditions. The model estimated fraction absorbed of alpelisib was about 99.9% in both LFLC or HFLC conditions.

Table 45: Observed and simulated alpelisib C_{max} and AUC, the C_{max} and AUC ratios and predicted fraction absorbed of alpelisib

		Fasted	LFLC	Fasted+ Ranitidine	LFLC+ Ranitidine	HFHC
AUC (ng*hr/mL)	Obs.	10350	17700	7390	14500	17570
	Pred.	10110	14670	6570	14640	14680
	$R_{pred./obs.}$	0.97	0.82	0.89	1.00	0.84
C_{max} (ng/mL)	Obs.	1042	2372	527	1550	1822
	Pred.	974	1951	553	1913	2005
	$R_{pred./obs.}$	0.93	0.82	1.05	1.23	1.10
Fraction absorbed	Pred.	69%	99.8%	45%	99.7%	99.8%

Source: Applicant's PBPK report DMPK R1701118 Table 7-2.

Figure 19: Observed and simulated alpelisib PK with or without food, and with or without concurrent ranitidine



*PBPK simulations are conducted following a single administration of 300 mg alpelisib under fasting condition with and without ranitidine, under fed condition (LFLC) with and without ranitidine, and under fed condition (HFHC).
Source: Applicant's PBPK report DMPK R1701118 Figure 8-4 and Figure 8-5.

<u>The FDA's Assessment:</u>

It is possible that the fraction absorbed of alpelisib in healthy subjects under LFLC and HFLC conditions could be greater than 1 based on the reasons outlined below.

1. ***The preclinical study result (DMPK R0900368) indicated that efflux transporter (BCRP) functionally mediates the transport of alpelisib back to lumen as evidenced by the results that parent drug was identified in the bile (8.66% of the dose) and feces (10.9% of the dose) in the bile duct cannulated rats after iv administration.***

2. ***In addition, double peaks in alpelisib plasma concentration-time profiles were observed in some subjects.***

Therefore, the possibility of enterohepatic circulation in alpelisib absorption could not be excluded.

a. Absolute bioavailability prediction

<u>The FDA's Assessment:</u>

The applicant did not intend to use PBPK model to predict the alpelisib absolute bioavailability. The values, 69% and 99% were the estimated fraction absorbed of alpelisib, not the bioavailability under fasted and fed conditions, respectively as stated in PBPK report No. DMPK R1701118, entitled "Oral absorption modeling of BYL719 in GastroPlus". In addition, the applicant-developed alpelisib model consisted of a 2-compartmental model instead of a PBPK model to characterize alpelisib disposition in the body, while the PBPK model is generally used to enable the bioavailability prediction after incorporating the enzyme and transposer information into the model. (b) (4)

Conclusions

The alpelisib PBPK absorption model is not adequate to predict the fraction absorbed of alpelisib under fed conditions (low-fat low-calorie [LFLC] or high-fat low-calorie [HFLC]) due to the possibility of enterohepatic circulation involved in alpelisib absorption. (b) (4)

18.3.4. Static DDI risk assessment

Part A: Assessment of the effect of alpelisib on other drug metabolizing enzymes and transporters

The Applicant's Analysis:

The applicant used static DDI risk assessment with experimentally determined in vitro Ki values for alpelisib. Alpelisib displayed potential for P-gp inhibition based high luminal concentration in the intestine. Alpelisib showed low potential to inhibit SULT, BSEP, OATP1B1, OATP1B3, OCT1, OAT3, MATE1, and MATE2K at clinically relevant concentrations (Table 46). In vitro assays also suggested that alpelisib didn't show signal in reversible inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2D6 and CYP2E1, time-dependent inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6, induction of CYP1A2, as well as inhibition of UGTs, OAT1, OCT2, MRP2 and BCRP (tested up to 100 – 200 μM alpelisib).

Table 46: Static DDI risk assessment for alpelisib as inhibitors of enzymes and transporters

	Protein	Ki (μM)	DDI Risk Assessment		
			$R_{unbound}$	$R_{unbound\ (net\ effect)}$	AUCR
Hepatic	SULT	36 (IC50/2)	1.02	1.02	1.02
	OCT1	91.60	1.01	N/A	N/A
	OATP1B1	20.90	1.04	N/A	N/A
	OATP1B3	40.00	1.02	N/A	N/A
	P-gp	96.70	1.01	N/A	N/A
	BSEP	74.50	1.01	N/A	N/A
Renal	OAT3	29.40	1.02	N/A	N/A
	MATE1	101.5	1.01	N/A	N/A
	MATE2K	>175	1.00	N/A	N/A
Intestinal	P-gp	96.70	29.1	N/A	N/A

Source: Applicant's Summary of Clinical Pharmacology Table 5-2

The FDA's Assessment:

The FDA agrees with the Applicant's assessment of the effect of alpelisib on other drug metabolizing enzymes and transporters.

Part B: Assessment of the effect of BZG791 on drug metabolizing enzymes and transporters

The Applicant's Analysis:

The applicant used static DDI risk assessment with experimentally determined in vitro Ki values. BZG791 showed low potential to induce CYP2B6 and CYP2C9. BZG791 showed low potential to inhibit CYP2C8, OCT1, OATP1B1, OATP1B3, BCRP, BSEP, OAT1, OAT3, MATE1 and BCRP (Table 47). In vitro assays also suggested that alpelisib didn't show signal in reversible inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4, time-dependent inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, CYP induction of CYP1A2 and CYP3A4, as well as inhibition of BCRP, MATE2K, OCT2 and MRP2 (tested up to 100 - 400 μM BZG791).

Table 47: Static DDI risk assessment for BZG791 as inhibitors of enzymes and transporters

	Protein	Ki (μM)	DDI Risk Assessment		
			$R_{unbound}$	$R_{unbound\ (net\ effect)}$	AUCR
Hepatic	CYP2B6	26 (EC50) 3.23 (Emax)	0.91	0.99	0.99
	CYP2C8	34 (EC50/2)	1.00	1.00	1.00
	CYP2C9	66 (EC50) 2 (Emax)	0.98	1.00	1.00
	OCT1	190.8	1.00	N/A	N/A
	OATP1B1	8.59	1.01	N/A	N/A
	OATP1B3	42.40	1.00	N/A	N/A
	BCRP	77.60	1.00	N/A	N/A
	BSEP	49.60	1.00	N/A	N/A
Renal	OAT1	139.6	1.00	N/A	N/A
	OAT3	1.38	1.06	N/A	N/A
	MATE1	215.5	1.00	N/A	N/A
Intestinal	BCRP	77.60	1.00	N/A	N/A

Source: Applicant's Summary of Clinical Pharmacology Table 5-3

The FDA's Assessment:

The FDA agrees with the applicant's assessment of the effect of BZG791 on drug metabolizing enzymes and transporters

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