

CLINICAL REVIEW

Application Type	sNDA Pediatric Exclusivity Determination
Application Number(s)	22249 / 12
Priority or Standard	6 Month Review
Submit Date(s)	12/27/11
Received Date(s)	12/27/11
PDUFA Goal Date	6/23/12
Division / Office	DHP / OHOP
Reviewer Name(s)	Patricia Dinndorf, M.D.
Review Completion Date	6/7/12
Established Name	Bendamustine Hydrochloride
Trade Name	Treanda
Therapeutic Class	Alkylating Agent
Applicant	Cephalon Inc
Formulation(s)	Single-use vial of bendamustine HCl as lyophilized powder
Dosing Regimen	Not applicable
Indication(s)	None
Intended Population(s)	None

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend that the Pediatric Exclusivity be granted for Treanda (bendamustine) and the pediatric information be included in the Treanda labeling.

My recommendation is based on the review finding that the applicant completely responded to all the elements in the Pediatric Written Request (PWR).

1.2 Risk Benefit Assessment

The risk profile of bendamustine in the pediatric population appears to be similar to that of adult population. However, this submission provided no evidence of efficacy for bendamustine in the pediatric population of patients with relapsed or refractory acute leukemia. Therefore, the risks associated with bendamustine use in the pediatric population are without benefit and such a use is not recommended.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable.

1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: Bendamustine hydrochloride

Proprietary Name: Treanda®

Applicant: Cephalon Inc

Pharmacological Class: Alkylating agent

Proposed Indication: There is no proposed pediatric indication.

Proposed Dosage and Administration: There is no proposed dose or route of administration in pediatric patients

2.2 Tables of Currently Available Treatments for Proposed Indications

There is no proposed indication in pediatric patients.

2.3 Availability of Proposed Active Ingredient in the United States

Bendamustine hydrochloride is available as single-use vials containing either 25 mg or 100 mg of bendamustine HCl as lyophilized powder for injection.

2.4 Important Safety Issues With Consideration to Related Drugs

Not applicable.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Bendamustine hydrochloride is approved for the following indications in adults:

- Chronic lymphocytic leukemia (CLL)
- Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab containing regimen.

Table 1: Regulatory History

Regulatory History	
July 2003	Original IND 67554 allowed to proceed
March 2008	Original NDA 22249 approval for the treatment of patients with CLL
October 2008	Original NDA 22303 approval for the treatment of patients with

	indolent B-cell NHL that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen
Jan 2010	FDA issues original PWR
April 2010	Pediatric ALL protocol submitted to IND 67554
March 2010	Cephalon request for changes in PWR <ul style="list-style-type: none"> ▪ Modification of the criteria to determine the number of patients required in specific age groups to study pharmacokinetics (PK) ▪ Decrease the minimum number of subjects to be studied at the recommended phase 2 dose (b) (4) to 26
September 2010	FDA reissues PWR amendment 2 <ul style="list-style-type: none"> ▪ Number of patients to be treated at the recommended phase 2 dose 26 not counting the patients treated at the recommended phase 2 dose during the phase 1 portion of the study ▪ Specify at least 10 patients treated within each of the following age groups; 1-6, 7-11, 12-21. ▪ The effect of age on PK must be assessed in the overall pediatric population (the specific requirement for the number of PK patients by age groups removed) ▪ A dose de-escalation required if maximum tolerated dose (MTD) exceeded in first group tested ▪ Phase 2 efficacy endpoint will be complete remission not complete response
March 2011	Cephalon request for changes in PWR Amendment 2 <ul style="list-style-type: none"> ▪ Number of patients studied at the recommended phase 2 dose in the phase 2 portion of the trial be (b) (4) from 26 (b) (4) ▪ Change the number included in specific age groups (b) (4) ▪ Time from for submitting the report changed from 12/20/11 to 3/20/12 ▪ Exclusivity determination be extended from 180 days (b) (4)
July 2011	FDA reissues PWR amendment 3 <ul style="list-style-type: none"> ▪ Time for submitting report changed to 3/20/12
December 2011	Cephalon submits Study Report from Trial C188083/2046 "An Open-Label Study of Bendamustine Hydrochloride for the Treatment of Pediatric Patients With Relapsed or Refractory Acute Leukemia." Based on this submission Cephalon requests determination of the FDA on pediatric exclusivity.

2.6 Other Relevant Background Information

The applicant is not seeking approval of bendamustine for any pediatric indications.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission contains the debarment certificate, sufficient datasets, and relevant clinical report forms (CRFs). The overall quality and integrity of the submission is adequate to allow substantive review.

3.2 Compliance with Good Clinical Practices

The cover page of the Clinical Study Report has the following statement. “This study was performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation is archived as required by regulatory authorities.”

3.3 Financial Disclosures

Form 3454 was submitted 3/13/12 and indicates that “No clinical investigators involved received compensation whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). No clinical investigator involved disclosed a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b). No clinical investigator involved was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).”

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Not applicable.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Not applicable.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

(copied from submission eCTD Efficacy Supplement submitted 12/22/11 Section 2.5 Clinical Overview page 3)

Bendamustine is an alkylating agent with a novel chemical structure. In addition to the bifunctional mechlorethamine alkylating group, the molecule contains a purine-like benzimidazole heterocyclic ring and a butyric acid substituent.

4.4.2 Pharmacodynamics (PD)

See clinical pharmacology review.

4.4.3 Pharmacokinetics (PK)

See clinical pharmacology review.

5 Sources of Clinical Data

One trial was conducted in support of this application. This trial was conducted under IND 67554.

5.1 Tables of Studies/Clinical Trials

(copied from submission eCTD Efficacy Supplement submitted 12/27/11 Section 2.7.6 Synopsis of Individual Studies)

Table 2: Synopsis of Trial Conducted to Support This Application
Synopses of Individual Studies

Study number Study title (design) Phase	No. of centers Location	Status Dates	Study population Variables	Dose regimen Duration of treatment	Formulation (Batch/ Lot no.)	No. treated Age (yr): mean (range) M/F (%) W/NW/U (%) Weight (kg): mean (range)
Efficacy and Safety Studies: Uncontrolled Clinical Studies						
C18083/2046 An Open-Label Study of Bendamustine Hydrochloride for the Treatment of Pediatric Patients With Relapsed or Refractory Acute Leukemia Phase 1/Phase 2	24 centers Australia Belarus Brazil Israel Mexico South Korea USA	Completed 05 Aug 10- 08 Aug 11	Patients, 1-20 y of age, with relapsed/refractory ALL or AML Primary efficacy: ORR for patients treated at RPD Secondary efficacy: Best response of PR or better DOR in patients treated at RPD Safety: adverse events clinical laboratory tests results (hematology, and serum chemistry) vital signs measurements Karnofsky or Lansky performance status physical examination findings concomitant medication usage Pharmacokinetics: C_{max} t_{max} AUC_{0-4} AUC_{0-24}	Bendamustine (Phase 1 dose-escalation): administered at starting dose of 90 mg/m ² as a 60-minute iv infusion on days 1-2 of each 21-day cycle, dose then escalated to 90 mg/m ² (cohort 1) and 120 mg/m ² (cohort 2) Bendamustine (Phase 2): administered at the RPD determined in Phase 1 Up to 12 cycles	Bendamustine (09P005A503, 10P004A503)	N=43 9.2 (1, 19) 30/13 (70/30) 25/14/4 (58/33/9) 34.9 (10.5, 71.0)

Abbreviations:

ALL=acute lymphocytic leukemia; AML=acute myeloid leukemia; AUC_{0-t} = area under the plasma drug concentration by time curve from time 0 until the last measurable plasma concentration; AUC_{0-24} =area under the plasma drug concentration by time curve from time 0 until 24 hours after study drug administration; C_{max} =maximum observed plasma drug concentration; DOR= duration of remission; F=female; M=male; NW=nonwhite; ORR=overall response rate; PR=partial response; RPD=recommended pediatric dose; t_{max} =time to maximum plasma drug concentration; U=unknown; USA=United States of America; W=white; y=years.

5.2 Review Strategy

The main focus of this review is to evaluate whether the applicant has successfully fulfilled the requirements set forth in the issued PWR for the eligibility determination on the pediatric exclusivity. To that end, the study report submitted in this supplement was

reviewed. The PWR and the 2 amended PWRs are included in the appendices 9.2, 9.3, and 9.4 of this review.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Trial C18083/2046 An Open-Label Study of Bendamustine Hydrochloride for the Treatment of Pediatric Patients With Relapsed or Refractory Acute Leukemia

Schema

Table 3: Trial C18083 / 2046

Study Design	Multicenter, International, Non-randomized, Open label Phase I/II
Trial Opened to Subject Entry:	August 2010
Trial Closed to Entry:	August 2011
Dose and Route:	90, 120, 150 mg/m ² intravenous (IV) over 60 minutes day 1 and 2 of a 21 day cycle
Indication:	Relapsed or Refractory Acute Leukemia in Pediatric Patients
Planned enrollment:	Phase I - 6 to 18; Phase II - additional 26; Total 32 to 44
Actual enrollment:	43
Terminated early (YES/NO):	No

Figure 1: Study Schema for Induction Cycle

(copied from submission eCTD Efficacy Supplement submitted 12/27/11 Section 5.3.5.2.4 Protocol Am 01 Study 2046 page 39)

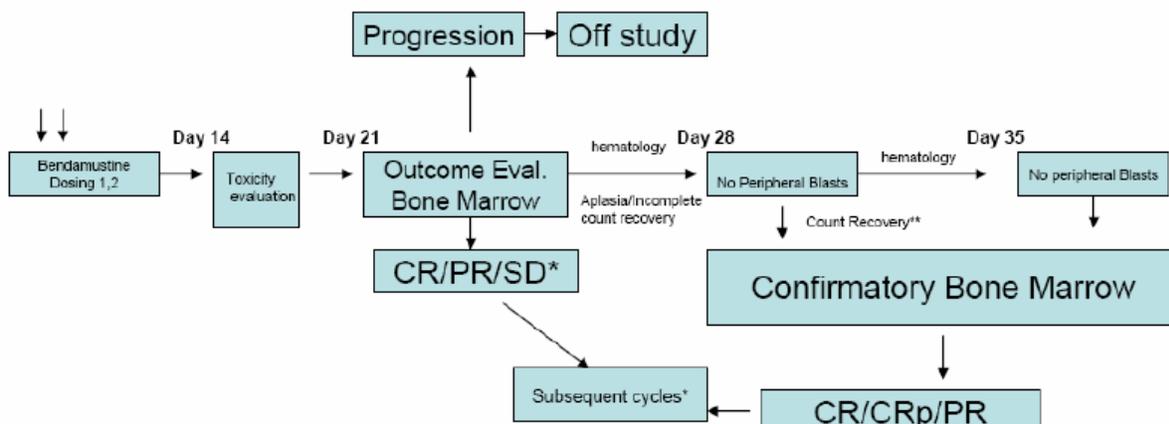
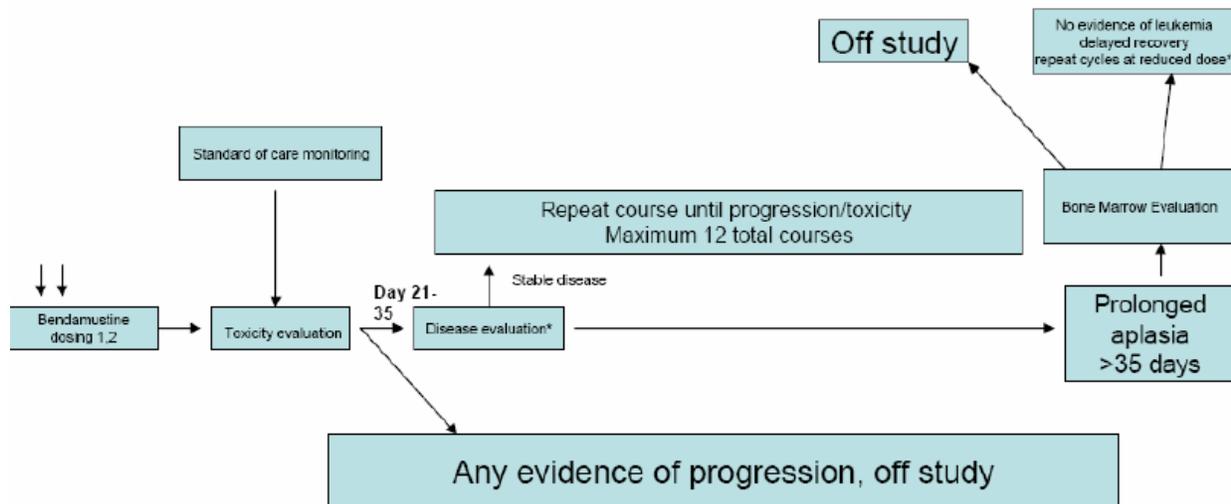


Figure 2: Study Schema for Subsequent Cycles (up to 11 subsequent cycles)

(copied from submission eCTD Efficacy Supplement submitted 12/27/11 Section 5.3.5.2.4 Protocol Am 01 Study 2046 page 40)



Study Objectives:

(copied from submission eCTD Efficacy Supplement submitted 12/27/11 Section 5.3.5.2.4 Protocol Am 01 Study 2046 page 35)

Primary objective

The primary objective of part 1 of this study is to establish the recommended pediatric dose (RPD). The primary objective of part 2 of this study is to evaluate the safety and efficacy (overall response rate [ORR]) of bendamustine at the recommended pediatric dose for the treatment of pediatric patients with relapsed or refractory acute leukemia.

ORR includes complete remission (CR) and complete remission without platelet recovery (CRp).

Secondary objective

- To determine the pharmacokinetic profile of bendamustine and its metabolites, M3 and M4, in this pediatric population
- To determine biological activity, defined as achieving a best response of partial remission (PR) or better
- To determine the duration of remission (DOR) of CR and CRp to bendamustine therapy in this pediatric population
- To evaluate the safety of bendamustine treatment as assessed by the following:
 - occurrence of adverse events throughout the study
 - hematology laboratory tests weekly throughout induction therapy and on days 1, 21, 28 (as applicable), and 35 (as applicable) during subsequent therapy
 - serum chemistry test results weekly throughout induction therapy and on days 1, 21, 28 (as applicable), and 35 (as applicable) during subsequent therapy
 - vital signs (blood pressure, heart rate, temperature, and respiratory rate) measurements on days 1 and 2 of induction treatment
 - physical examination findings on days 1 and 21 of each cycle of induction treatment
 - concomitant medication usage throughout the study

Eligibility Criteria:

(copied from submission eCTD Efficacy Supplement submitted 12/27/11 Section 5.3.5.2.4 Protocol Am 01 Study 2046 page 52 - 53)

Inclusion Criteria

- The patient has histologically proven acute lymphocytic leukemia (ALL) or acute myeloid leukemia (AML) (by French-American-British classification) that has relapsed or is refractory to the last regimen, and the patient is without alternative curative therapy.
- The patient is 1 through 20 years of age inclusive.
- The patient's last myelosuppression therapy ended at least 2 weeks before the first dose of study drug
- Nonhematologic acute toxic effects of prior therapy have resolved to grade 2 or less according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
- The patient has adequate liver function with bilirubin values less than or equal to 1.5 times the upper limit of normal (ULN) and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values less than or equal to 5 times the age-appropriate ULN.

- The patient has adequate renal function with serum creatinine values less than 2 times ULN.
- The patient has Karnofsky or Lansky performance status of 60 or greater. Patients older than 16 years of age will be scored according to the Karnofsky scale and patients 16 years of age or younger will be scored according to the Lansky scale.
- The patient may have had hematopoietic stem cell transplantation [HSCT].

Exclusion Criteria

- The patient has any active, uncontrolled systemic infection, severe concurrent disease, or symptomatic untreated central nervous system (CNS) involvement.
- The patient has evidence of active graft versus host disease.
- The patient has a known human immunodeficiency virus (HIV) infection.
- The patient has active hepatitis B or hepatitis C infection.
- The patient is a pregnant or lactating woman. (Any women becoming pregnant during the study will be withdrawn from the study immediately.)
- The patient has any serious uncontrolled medical or psychological disorder that would impair the ability of the patient to receive study drug.
- The patient has any condition that places the patient at unacceptable risk or confounds the ability of the investigators to interpret study data.
- The patient has received any other investigational agent within 30 days of study entry.
- The patient has known hypersensitivity to bendamustine or mannitol.

Demographics and Baseline Characteristics

Table 4: Demographics and Baseline Characteristics

Demographics and Baseline Characteristics	
N= 43	
Sex	
Male	30 (70%)
Female	13 (30%)
Age in Years	
1 – 6	14 (33%)
7 - 11	13 (30%)
12 - 19	16 (37%)
Mean	9.1
Median	10
Range	1 – 19
Race Ethnicity	
White Non-Hispanic	16 (37%)
White Hispanic	9 (21%)
Asian	11 (26%)
Black Non-Hispanic	2 (5%)
Black Hispanic	1 (2%)
Other	4 (9%)
Diagnosis	
ALL	27 (63%)
AML	16 (37%)
Treatment Cohort	
Phase 1 90 mg/m ²	5 (12%)
Phase 1 120 mg/m ²	6 (14%)
Phase 2 120 mg/m ²	32 (74%)

Disposition

Table 5: Patient Disposition by Phase

(copied from submission eCTD Efficacy Supplement submitted 12/27/11 Section 5.3.3.2.3 2046 eCTD Body page 50)

Patient disposition	Number (%) of patients ^a		
	Phase 1 (N=11)	Phase 2 (N=32)	Total (N=43)
Enrolled	11 (100)	32 (100)	43 (100)
Dose cohort	11 (100)	32 (100)	43 (100)
90 mg/m ²	5 (45)	0	5 (12)
120 mg/m ²	6 (55)	32 (100)	38 (88)
Safety analysis set	11 (100)	32 (100)	43 (100)
Primary analysis set	0	32 (100)	32 (74)
Pharmacokinetic analysis set	11 (100)	32 (100)	43 (100)
Treatment completion	11 (100)	32 (100)	43 (100)
Death	1 (9)	3 (9)	4 (9)
Consent withdrawn	0	1 (3)	1 (2)
Disease progression	8 (73)	27 (84)	35 (81)
Other	2 (18)	1 (3)	3 (7)
Study completion	11 (100)	32 (100)	43 (100)
Death	3 (27)	5 (16)	8 (19)
Consent withdrawn	0	1 (3)	1 (2)
Disease progression	6 (55)	25 (78)	31 (72)
Other	2 (18)	1 (3)	3 (7)
Death	3 (27)	14 (44)	17 (40)
Within 30 days of last dose of study drug	2 (18)	5 (16)	7 (16)
Greater than 30 days of last dose of study drug	1 (9)	9 (28)	10 (23)

Other=Elected to withdraw patient from study to receive additional chemotherapy in preparation for an unrelated bone marrow transplant (patient 001001, Phase 1); bone marrow on day 21 showed 40% blast reduction and investigator decided that study drug response was not effective enough to remain in study (patient 502001, Phase 1); and patient without hematologic response (patient 613003, Phase 2).

Nine subjects received 2 cycles, One subject received a total of 8 cycles.

Exposure to Bendamustine

Cycle 1

The dose for each subject in cycle 1 was calculated based on the body surface area (BSA) derived from the reported height, weight, and assigned dose. The dose administered was within $\pm 3\%$ for 42 subjects. One subject 611001 received 123% of the correct dose because the investigator used 150 mg/m² instead of 120 mg/m² for the dose calculation.

Result of Phase I Dose finding

- Definition of RPD - The dose level at which at least 2 of 3 or 2 of 6 patients have a dose limiting toxicity (DLT) will be considered as exceeding the RPD. The RPD will be the dose 1 step below that level. Only doses of 90, 120, and 150 mg/m² were explored. The dose of 150 mg/m² was only to be explored if the 120 mg/m² dose was deemed safe and PK data indicated that this level resulted in subtherapeutic exposure compared with adults. If 90 mg/m² exceeded the RPD then 60 mg/m² level would also be explored.
- Definition of DLT - Study-drug-related nonhematologic adverse event that is grade 4 for toxicity by NCI CTCAE version 4.0; ≥ grade 3 allergic reaction or skin rash. Hematologic adverse events will not be considered DLT. DLT will be assessed in the first cycle.

Phase I - 90 mg/m²

There were 5 subjects treated at this dose. An initial cohort of 3 subjects was treated with at a dose of 90 mg/m² of bendamustine. The cohort size was expanded from 3 subjects to 5 subjects to replace subjects who were nonevaluable due to early disease progression. There were no DLTs in this cohort.

Phase I – 120 mg/m²

There were 6 phase I subjects treated at this dose. The cohort size was expanded from 3 subjects to 6 subjects to replace subjects who were nonevaluable due to early disease progression. There were no DLTs in this cohort.

The PK data from subjects treated with bendamustine at 120 mg/m² demonstrated that the plasma concentrations within the therapeutic range previously determined for adults. For this reason, escalation of bendamustine to 150 mg/m² did not occur, and 120 mg/m² day 1 and 2 of a 21 day cycle was determined to be the RPD of bendamustine

REVIEWER COMMENT: This conclusion was confirmed in the FDA clinical pharmacology reviewer.

Efficacy

Phase 2 – 120 mg/m²

The primary efficacy variable for this trial is ORR (CR plus CRp) for patients treated at the RPD, as determined by hematology laboratory test results and bone marrow evaluation during induction therapy.

The secondary variables are as follows:

- biological activity, defined as patients achieving a best response of PR or better
- DOR in patients treated at the RPD, defined as duration from date of first evidence of remission (of CR or CRp) to date of progression, new antineoplastic therapy, or death

Results

There were no CRs or CRps in the Phase 2 cohort of subjects treated at the RPD. There were 2 subjects with the best response of PR.

- Subject 018001 a 3 year old female with ALL who achieved a PR after the first cycle of bendamustine. Progressive disease was documented after the second cycle of bendamustine.
- Subject 300002 was a 5 year old male with ALL with a PR documented after the first cycle of bendamustine. Consent was withdrawn after the first cycle of therapy.

Of note there were 2 CRs documented in subjects treated in the Phase I - 90 mg/m² cohort.

- Subject 300001 was a 14 year old male with ALL with a CR documented after the first cycle of bendamustine. He received a total of 8 cycles. Relapse was documented after the last cycle.
- Subject 001001 was a 12 year old male with ALL with a CR documented after the second cycle of bendamustine. He was removed from the study for an HSCT.

Safety

See Section 7.

PK

(copied from submission eCTD Efficacy Supplement submitted 12/27/11 Section 5.3.3.2.3 2046 eCTD Body page 68)

The PK profile of bendamustine was similar across the entire pediatric population (1 through 19 years of age) and was comparable to that in adults, demonstrating that exposures reflective of the therapeutic range in adults were attained following administration of bendamustine at 120 mg/m² (infused over 60 minutes) to pediatric patients.

REVIEWER COMMENT:

The FDA clinical pharmacology reviewer determined that single and multiple dose bendamustine administered in doses ranging from 90 to 120 mg/m² resulted in total systemic exposure (AUC) of bendamustine and its metabolites that were dose-proportional over the dose range studied. The geometric mean BSA adjusted clearance of bendamustine was 14.2 L/h/m². The exposures (AUC₀₋₂₄ and C_{max}) to bendamustine in pediatric patients following a 120-mg/m² IV infusion over 60-minutes were similar to those in adult patients following the same 120-mg/m² dose.

Conclusions

There was no treatment response defined as CR or CRp documented in pediatric subjects with ALL or AML treated at the RPD. Activity was documented in 2 pediatric subjects with ALL treated at the 90 mg/m² on day 1 and 2.

5.4 Evaluation of the Applicant’s Fulfillment of the Pediatric Written Request Requirement

Written Request Items	Information Submitted/ Sponsor’s response
<p>Types of studies/ Study Design: A Phase 1/2 Study of Bendamustine Hydrochloride for the Treatment of Pediatric Patients With Relapsed or Refractory Acute Leukemia</p> <p>A 2-part study design will be used. A minimum of 6 and a maximum of 18 pediatric patients will be enrolled during the dose-escalation, Phase 1 part of this study. After the recommended Phase 2 dose (RP2D) has been determined, an additional 26 patients must be treated at the RP2D (not including the patients treated at RP2D in Phase 1).</p>	<p>Types of studies: This was a multicenter, open-label, nonrandomized, 2-part study (Phase 1/Phase 2) of bendamustine in pediatric patients with relapsed or refractory acute leukemia. (Section 9.1 Overall Study Design and Plan from study report for Study 2046)</p> <p>Phase 1 followed a traditional 3+3 dose escalation scheme and was designed to determine the RPD and dose limiting toxicities (DLTs) of bendamustine in this patient population. The dose level at which at least 2 of 3 or 2 of 6 patients had DLT was considered as exceeding the RPD. The RPD was the dose 1 level below that level. (Section 9.1 Overall Study Design and Plan from study report for Study 2046)</p> <p>Phase 2 of the study was initiated once the RPD had been determined. This second part of the study was designed to evaluate the efficacy and safety of bendamustine in this pediatric patient population at the RPD. An additional 26 patients were to be enrolled, although this number was subsequently expanded to ensure the enrollment of at least 10 patients at each of the 3 age groups: 1 through 6, 7 through 11, and 12 through 21 years of age. (Section 9.1 Overall Study Design and Plan from study report for Study 2046)</p>

REVIEWER COMMENT:

Agree that the type of study and study design conducted were in exact accordance with the PWR.

Written Request Items	Information Submitted/ Sponsor’s response
<p>Indication(s) to be studied: Treatment of pediatric patients with relapsed or refractory acute leukemia defined as patients who have received or who are unable to receive all standard therapies for their disease. Standard therapy is defined as all medications which have been shown to provide clinical benefit in this disease.</p>	<p>Indication(s) studied: Treatment of pediatric patients with relapsed or refractory acute leukemia defined as patients who have received or who are unable to receive all standard therapies for their disease. Standard therapy is defined as all medications which have been shown to provide clinical benefit in this disease. (Section 7 Introduction from study report for Study 2046)</p>

REVIEWER COMMENT:

Agree that the subjects treated on this trial met this indication. See Table 4: Demographics and Baseline Characteristics.

Written Request Items	Information Submitted/ Sponsor's response
<p>Objectives of the study: Primary objectives:</p> <ul style="list-style-type: none"> • Phase 1: To determine the recommended Phase 2 dose of bendamustine in pediatric patients with relapsed or refractory acute leukemia. • Phase 2: To evaluate the safety and efficacy of bendamustine for the treatment of pediatric patients with relapsed or refractory acute leukemia. Efficacy assessment will include complete remission (CR) and complete remission with inadequate platelet recovery (CRp). <p>Secondary objectives:</p> <ul style="list-style-type: none"> • To determine the pharmacokinetic profile of bendamustine in pediatric population • To determine the duration of remission (CR + CRp) to bendamustine therapy in this pediatric population. 	<p>Objectives of the study: Primary Objectives:</p> <ul style="list-style-type: none"> • The primary objective of Phase 1 of this study was to establish the recommended pediatric dose (RPD). • The primary objective of Phase 2 of this study was to evaluate the safety and efficacy (overall response rate [ORR]) of bendamustine at the RPD for the treatment of pediatric patients with relapsed or refractory acute leukemia. Overall response rate included complete remission (CR) and complete remission without platelet recovery (CRp). <p>Secondary Objectives</p> <ul style="list-style-type: none"> • to determine the pharmacokinetic profile of bendamustine and its metabolites, M3 and M4, in this pediatric population • to determine biological activity, defined as achieving a best response of partial response (PR) or better • to determine the duration of remission (DOR) of CR and CRp to bendamustine therapy in this pediatric population • to evaluate the safety of bendamustine treatment as assessed by the following: <ul style="list-style-type: none"> – occurrence of adverse events throughout the study – hematology laboratory tests weekly throughout induction therapy and on days 1, 21, 28 (as applicable), and 35 (as applicable) during subsequent therapy – serum chemistry test results weekly throughout induction therapy and on days 1, 21, 28 (as applicable), and 35 (as applicable) during subsequent therapy – vital signs (blood pressure, heart rate, and temperature) measurements on days 1 and 2 of induction treatment – physical examination findings on days 1 and 21 of induction treatment – concomitant medication usage throughout the study (Section 8 Study Objectives from study report for Study 2046)

REVIEWER COMMENT:

Agree that the trial evaluated the objectives as outlined in the PWR.

Written Request Items	Information Submitted/ Sponsor's response
<p>Age group and population in which study will be performed: 1-21 years. At least 10 patients must be treated within each of the following specified age groups (1-6, 7-11, and 12-21 years old).</p>	<p>Age group and population in which study was performed: Overall, 43 pediatric patients with relapsed or refractory leukemia (11 patients in Phase 1 and 32 patients in Phase 2) were enrolled in the study.</p> <p>The 32 patients in Phase 2 who were treated with bendamustine at 120 mg/m² (10 patients in the 1- through 6-year-old age group; 10 patients in the 7- through 11-year-old age group; and 12 patients in the 12- through 20-year-old age group). (Section 10 Study Patients from study report for Study 2046)</p>

REVIEWER COMMENT:

Agree that the study evaluated the requisite number of subjects in the specified age groups. See Table 4: Demographics and Baseline Characteristics.

Treanda (bendamustine hydrochloride)

Written Request Items	Information Submitted/ Sponsor's response																																																																																																											
<p>Number of patients to be studied or power of study to be achieved: These studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful</p> <p>Phase 1 (dose-escalation portion): A minimum of 6 and a maximum of 18 pediatric patients must be treated to determine the RP2D. In addition, PK profiles must be obtained from a minimum of 6 patients in the RP2D cohort in Phase 1.</p> <p>Phase 2: After the RP2D has been determined, an additional 26 patients must be treated at the RP2D (not including the patients treated at RP2D in Phase 1).</p>	<p>Number of patients studied or power achieved: An initial cohort of 3 pediatric patients was treated with bendamustine at a dose of 90 mg/m² in Phase 1. The cohort size was expanded from 3 patients to 5 patients to replace patients who were nonevaluable due to early disease progression. Since no DLTs were observed in the patients treated with bendamustine at 90 mg/m², the dose of bendamustine was escalated to 120 mg/m². The cohort size was subsequently expanded, this time from 3 patients to 6 patients for the same reasons the cohort size was expanded in the 90-mg/m² cohort. Again, no DLTs were observed in patients treated with bendamustine at 120 mg/m² (Section 10.1.1.1 Disposition by Phase from study report for Study 2046)</p> <p>An analysis of pharmacokinetic data from the patients treated with bendamustine 120 mg/m² in phase 1 of the study demonstrated that the plasma concentrations attained from these pediatric patients were within the therapeutic range previously determined for adults. For this reason, escalation of bendamustine to the 150 mg/m² dose level did not occur, and 120 mg/m² was determined to be the RPD of bendamustine for further evaluation in phase 2 for the treatment of pediatric patients with relapsed or refractory acute leukemia. (Section 10.1.1.1 Disposition by Phase from study report for Study 2046)</p> <p>The primary analysis set was comprised of the 32 patients in Phase 2 who were treated with bendamustine at 120 mg/m² (10 patients in the 1- through 6-year-old age group; 10 patients in the 7- through 11-year-old age group; and 12 patients in the 12- through 20-year-old age group). (Section 10.1.2.2 Demographic Characteristics by Dose Cohort)</p> <p style="text-align: center;">Demographic Information by Dose Cohort and Age Group</p> <table border="1" data-bbox="800 1035 1412 1585"> <thead> <tr> <th rowspan="2">Variable Statistic or category</th> <th colspan="2">Bendamustine at 90 mg/m² (N=5)^a</th> <th colspan="3">Bendamustine at 120 mg/m² (N=38)^b</th> </tr> <tr> <th>7-11 y (N=2)</th> <th>12-20 y (N=3)</th> <th>1-6 y (N=14)</th> <th>7-11 y (N=11)</th> <th>12-20 y (N=13)</th> </tr> </thead> <tbody> <tr> <td>Age, years</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td> Mean</td> <td>9.5</td> <td>12.7</td> <td>3.7</td> <td>8.7</td> <td>14.5</td> </tr> <tr> <td> Standard deviation</td> <td>2.12</td> <td>1.15</td> <td>1.54</td> <td>2.00</td> <td>1.71</td> </tr> <tr> <td> Median</td> <td>9.5</td> <td>12.0</td> <td>3.5</td> <td>7.0</td> <td>14.0</td> </tr> <tr> <td> Min, max</td> <td>8.0, 11.0</td> <td>12.0, 14.0</td> <td>1.0, 6.0</td> <td>7.0, 11.0</td> <td>12.0, 19.0</td> </tr> <tr> <td>Sex, n (%)</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td> Boy</td> <td>1 (50)</td> <td>3 (100)</td> <td>10 (71)</td> <td>7 (64)</td> <td>9 (69)</td> </tr> <tr> <td> Girl</td> <td>1 (50)</td> <td>0</td> <td>4 (29)</td> <td>4 (36)</td> <td>4 (31)</td> </tr> <tr> <td>Race, n (%)</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td> White</td> <td>2 (100)</td> <td>3 (100)</td> <td>7 (50)</td> <td>5 (45)</td> <td>8 (62)</td> </tr> <tr> <td> Black</td> <td>0</td> <td>0</td> <td>2 (14)</td> <td>1 (9)</td> <td>0</td> </tr> <tr> <td> Asian</td> <td>0</td> <td>0</td> <td>4 (29)</td> <td>3 (27)</td> <td>4 (31)</td> </tr> <tr> <td> Other^c</td> <td>0</td> <td>0</td> <td>1 (7)</td> <td>2 (18)</td> <td>1 (8)</td> </tr> <tr> <td>Ethnicity, n (%)</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td> Hispanic or Latino</td> <td>1 (50)</td> <td>1 (33)</td> <td>4 (29)</td> <td>4 (36)</td> <td>4 (31)</td> </tr> <tr> <td> Non-Hispanic and non-Latino</td> <td>1 (50)</td> <td>2 (67)</td> <td>10 (71)</td> <td>7 (64)</td> <td>9 (69)</td> </tr> </tbody> </table> <p>^a Includes 5 patients treated with bendamustine at 90 mg/m² in Phase 1. ^b Includes 6 patients treated with bendamustine at 120 mg/m² in Phase 1 and 32 patients treated with the recommended pediatric dose (RPD) of bendamustine (120 mg/m²) in Phase 2. ^c Other=Spanish (n=1), Latino (n=1), Latin (n=1), and Hispanic (n=1).</p>	Variable Statistic or category	Bendamustine at 90 mg/m ² (N=5) ^a		Bendamustine at 120 mg/m ² (N=38) ^b			7-11 y (N=2)	12-20 y (N=3)	1-6 y (N=14)	7-11 y (N=11)	12-20 y (N=13)	Age, years						Mean	9.5	12.7	3.7	8.7	14.5	Standard deviation	2.12	1.15	1.54	2.00	1.71	Median	9.5	12.0	3.5	7.0	14.0	Min, max	8.0, 11.0	12.0, 14.0	1.0, 6.0	7.0, 11.0	12.0, 19.0	Sex, n (%)						Boy	1 (50)	3 (100)	10 (71)	7 (64)	9 (69)	Girl	1 (50)	0	4 (29)	4 (36)	4 (31)	Race, n (%)						White	2 (100)	3 (100)	7 (50)	5 (45)	8 (62)	Black	0	0	2 (14)	1 (9)	0	Asian	0	0	4 (29)	3 (27)	4 (31)	Other ^c	0	0	1 (7)	2 (18)	1 (8)	Ethnicity, n (%)						Hispanic or Latino	1 (50)	1 (33)	4 (29)	4 (36)	4 (31)	Non-Hispanic and non-Latino	1 (50)	2 (67)	10 (71)	7 (64)	9 (69)
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REVIEWER COMMENT:

Agree that the trial identified an RPD according to the study definition. The trial exceeded the required number of patients to be treated at the RPD. The ethnic and racial characteristics are representative of the disease population.

Treanda (bendamustine hydrochloride)

Written Request Items	Information Submitted/ Sponsor's response
Entry criteria: None listed	Entry criteria used: Since there were no prospective entry criteria detailed in the WR, a comparison to the actual criteria required by the protocol, cannot be made.
	There was however, a list of inclusion/exclusion criteria in the protocol which was repeated in the study report (Section 9.3.1 Inclusion Criteria/Section 9.3.2 Exclusion Criteria from study report for Study 2046). In section 10.2 of the Study Report, Table 13 provides a listing of protocol violations and deviations listing the few patients who did not fully meet these criteria. These deviations had no significant impact on the outcome of the study.

REVIEWER COMMENT:

The trial included subjects between the age of 1 to 21 years with ALL and AML with no available curative therapy. The protocol violations identified in Table 6 below do not significantly impact the outcome of the trial, as the applicant asserts.

Table 6: Applicant's Table (Table 13) Listing Protocol Violations
 (copied from submission eCTD Efficacy Supplement submitted 12/27/11 Section 5.3.3.2.3 2046 eCTD Body page 61)

Criteria for violation	Number (%) of patients	
	Bendamustine 90 mg/m ² (N=5)	Bendamustine 120 mg/m ² (N=38)
Patients with at least 1 violation	1 (20)	12 (32)
Inclusion criteria	0	2 (5)
Total bilirubin was not within normal before study drug administration	0	1 (3)
Assent form was not signed	0	1 (3)
GCP guidelines	0	6 (16)
Late notification of SAE	0	6 (16)
Screening procedure not performed	0	1 (3)
Study drug compliance	0	1 (3)
Incorrect dose administered in cycle 1 due to calculation error	0	1 (3)
Other	1 (20)	3 (8)
Missed laboratory test	1 (20)	0
Protocol noncompliance	0	2 (5)
SAE not reported within 24 hours	0	1 (3)

Treanda (bendamustine hydrochloride)

Written Request Items	Information Submitted/ Sponsor's response
<p>Clinical endpoints: Primary endpoints:</p> <ul style="list-style-type: none"> Phase 1: The recommended Phase 2 dose of bendamustine in children with relapsed or refractory acute leukemia Phase 2: The safety and efficacy, including CR + CRp, of bendamustine for the treatment of pediatric patients with relapsed or refractory acute leukemia <p>Secondary endpoints: The duration of remissions (CR and CRp) to bendamustine therapy in this pediatric population.</p> <p>Pharmacokinetic endpoints: Pharmacokinetic samples must be collected through approaches such as rich sampling or optimal sparse sampling in patients.</p> <p>Such data must then be appropriately analyzed using methods such as nonlinear mixed effects modeling or noncompartmental analysis.</p>	<p>Clinical endpoints used: Primary endpoints: The primary objective of Phase 1 of the study was to determine the RPD of bendamustine for further evaluation in Phase 2. The 120-mg/m² dose of bendamustine was determined in Phase 1 to be the RPD for further evaluation in Phase 2 for the treatment of pediatric patients with relapsed or refractory acute leukemia. (Section 11.4.7 from study report for Study 2046)</p> <p>In the analysis of the primary variable, remission was defined as achieving a best response of CRp or CR. None of the patients in the primary analysis set (patients treated at the RPD in Phase 2 of the study) achieved CRp or CR, thereby confirming the null hypothesis of no worthwhile effect, the latter being defined as a response rate of less than 5%. (Section 11.4.7 Efficacy Conclusions from study report for Study 2046)</p> <p>Secondary endpoint: Duration of response was the other secondary efficacy variable that was to be evaluated in the study. This was defined as duration from date of first response (of CR or CRp) to date of progression, new antineoplastic therapy, or death. However, no duration of response analysis was performed for patients in the primary analysis since no patients treated at the RPD responded. (Section 11.4.7 Efficacy Conclusions from study report for Study 2046)</p> <p>Pharmacokinetic endpoints: Noncompartmental analysis of plasma concentration data over time for bendamustine and its active metabolites from the patients in study 2046 (report DP-2011-123) was performed and standard pharmacokinetic parameters were calculated. (Clinical Pharmacology Summary 2.7.2 Section 1.2.3 Pharmacokinetic Measures and Variables)</p>
<p>Data from the Phase 1 and Phase 2 must be combined to develop pharmacokinetic and pharmacodynamic (PK-PD) models to explore exposure response relationships for measures of safety and effectiveness.</p> <p>The effect of age on the pharmacokinetics of bendamustine within the overall pediatric population must be assessed.</p>	<p>Population pharmacokinetic modeling was also performed using plasma concentration data from patients in study 2046 (38 patients at the 120-mg/m² dose level and 5 patients at the 90-mg/m² dose level). This analysis was performed to characterize the overall pharmacokinetic profile of bendamustine and its active metabolites in pediatric patients with relapsed or refractory acute leukemia. The potential of selected covariates to explain variability on the pharmacokinetics of bendamustine was also assessed. (Clinical Pharmacology Summary 2.7.2 Section 1.2.3 Pharmacokinetic Measures and Variables)</p> <p>Assessment of exposure-response relationships was performed using data from study 2046. Measures of exposure included cycle 1 bendamustine area under the plasma drug concentration by time curve (AUC) and maximum observed plasma drug concentration (C_{max}) and cumulative AUC. Measures of efficacy included remission and best overall response. Measures of safety included adverse events of fatigue, nausea, vomiting, and infection. (Clinical Pharmacology Summary 2.7.2 Section 1.2.4 Pharmacokinetic/Pharmacodynamic Measures and Variables)</p>

REVIEWER COMMENT:

Agree that the trial has identified the RPD, and evaluated the safety and efficacy of bendamustine in the population of interest. FDA clinical pharmacology reviewer concluded adequate data was collected to characterize the PK parameters of bendamustine in the pediatric population.

Treanda (bendamustine hydrochloride)

Written Request Items	Information Submitted/ Sponsor's response
Timing of assessments: if appropriate. None listed.	Timing of assessments: Not applicable

REVIEWER COMMENT:

Not applicable

Written Request Items	Information Submitted/ Sponsor's response
Drug specific safety concerns: The most common non-hematologic adverse reactions for CLL (frequency $\geq 15\%$) are pyrexia, nausea, and vomiting. The most common non-hematologic adverse reactions for NHL (frequency $\geq 15\%$) are nausea, fatigue, vomiting, diarrhea, pyrexia, constipation, anorexia, cough, headache, weight decreased, dyspnea, rash, and stomatitis. The most common hematologic abnormalities for both indications (frequency $\geq 15\%$) are lymphopenia, anemia, leukopenia, thrombocytopenia, and neutropenia.	Drug specific safety concerns evaluated: In this study, safety was assessed by the evaluating the following: reported adverse events, clinical laboratory test results, vital signs measurements, physical examination findings, performance status, and concomitant medication usage. For each safety parameter, all findings (whether normal or abnormal) were recorded in the CRF. The investigator judged the clinical significance of any abnormalities, and abnormalities were described in detail. (Section 9.5.1.2 Safety Measurements from study report for Study 2046)

REVIEWER COMMENT:

Agree that the trial collected the appropriate data to evaluate safety concerns. The analysis of safety in the study report is adequate.

Written Request Items	Information Submitted/ Sponsor's response
Drug information: <ul style="list-style-type: none"> Dosage form: Bendamustine hydrochloride for injection (100 mg/20mL) Route of administration: intravenous infusion (IV) Regimen: Phase 1: The dose escalation scheme, as tolerated, is 90 mg/m ² , 120 mg/m ² , and 150 mg/m ² IV infusion over 60 minutes IV on days 1 and 2 of each 21-day cycle, with delays up to 2 weeks for bone marrow recovery. A 150 mg/m ² dose will be administered only if a 120 mg/m ² dose is deemed safe and the exposure of bendamustine in pediatric patients is less than that in adult patients following administration of 120 mg/m ² bendamustine. A dose de-escalation to 60 mg/m ² may be required if two or more dose limiting toxicities occur at the starting dose. Phase 2: The dose and schedule will depend on the results of the Phase 1 dose escalation study.	Drug information: Phase 1: In Phase 1, the dose escalation scheme, as tolerated, was 90, 120, and 150 mg/m ² of bendamustine by iv infusion over 60 minutes on days 1 and 2 of each 21-day cycle, with delays up to 2 weeks for bone marrow recovery. The 150-mg/m ² dose was to be administered only if the 120-mg/m ² dose was deemed safe and the exposure to bendamustine in pediatric patients was less than that in adult patients following administration bendamustine at 120 mg/m ² . An initial cohort of 3 pediatric patients was treated with bendamustine at a dose of 90 mg/m ² in Phase 1. The cohort size was expanded from 3 patients to 5 patients to replace patients who were nonevaluable due to early disease progression. Since no DLTs were observed in the patients treated with bendamustine at 90 mg/m ² , the dose of bendamustine was escalated to 120 mg/m ² . The cohort size was subsequently expanded, this time from 3 patients to 6 patients for the same reasons the cohort size was expanded in the 90-mg/m ² cohort. Again, no DLTs were observed in patients treated with bendamustine at 120 mg/m ² . (Section 10.1.1.1 Disposition by Phase from study report for Study 2046) Phase 2: In Phase 2, an additional 32 patients were enrolled and treated with bendamustine at the RPD of 120 mg/m ² . (Section 10.1.1.1 Disposition by Phase from study report for Study 2046)

REVIEWER COMMENT:

The doses studied and the analysis of RPD was done in accordance with the PWR.

Treanda (bendamustine hydrochloride)

Written Request Items	Information Submitted/ Sponsor's response
<p>Statistical information (statistical analyses of the data to be performed): This study includes two phases. In Phase 1 of the study, a traditional 3+3 design will be used to determine the maximum tolerated dose (MTD). The MTD will be the RP2D.</p> <p>In Phase 2 of the study, a total sample size of 26 patients (not including patients in the Phase 1 study) will be enrolled into the dose level that has been identified as the RP2D.</p> <p>The efficacy assessment will be based on all patients treated with the RP2D in the Phase 2 study. This will be calculated as the number of patients with CR or CRp divided by the number of patients treated with the RP2D in the Phase 2 study. The null hypothesis is a remission</p>	<p>Statistical information (statistical analyses of the data to be performed): The primary variable for this study is remission, defined as achieving a best response of CRp or CR. The null hypothesis of no worthwhile effect is: $H_0: \leq 5\%$ of the patients achieve remission The alternative hypothesis of a worthwhile effect is: $H_1: \geq 20\%$ of the patients achieve remission An ORR will be calculated as number of patients in the primary analysis set with a best overall response (BOR) of CRp or CR, as determined by the investigator, divided by the number of patients in the primary analysis set. Patients who are treated but have no response data will be analyzed as nonresponders. A 95% confidence interval for the ORR will be calculated based on the binomial distribution. If the lower boundary of this</p>
<p>rate of 5%, which will be tested at a 1-sided alpha level of 0.05. A one-sided 95% confidence interval for the rate of CR or CRp will be calculated based on the binomial distribution, of which the lower boundary of which will be compared with the remission rate of 5% in the null hypothesis (>5% or not). Assuming a true remission rate of 20%, the power of the test would be approximately 80%.</p>	<p>confidence interval is larger than 5%, H_0 as stated above will be rejected. A p-value will also be calculated based on the binomial distribution to test against a response rate of 5%. (Statistical Analysis Plan for Study 2046 Section 7.1 Primary Variables and Analysis)</p>

REVIEWER COMMENT:

The doses studied and the analysis of RPD and efficacy assessment was done in accordance with the PWR.

Written Request Items	Information Submitted/ Sponsor's response
<p>Labeling that may result from the studies: <i>Appropriate sections of the label may be changed to incorporate the findings of the studies.</i></p>	<p>Labeling that may result from the studies: Cephalon submitted proposed revisions to the labeling for Sections 8.4 Pediatric Use, 12.3 Pharmacokinetics and 12.4 Pharmacokinetics/Pharmacodynamics.</p>

REVIEWER COMMENT:

The applicant has submitted labeling incorporating information into the appropriate sections of the label.

Treanda (bendamustine hydrochloride)

Written Request Items	Information Submitted/ Sponsor's response
<p>Format of reports to be submitted:</p> <p>You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) must be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you must use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you must obtain agency agreement.</p> <p>Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. These postmarketing adverse event reports must be submitted as narrative and tabular reports. Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, <i>Providing Regulatory</i></p>	<p>Format of reports submitted:</p> <p>A full study report for Study 2046, not previously submitted to the Agency, included a full analysis, assessment, and interpretation of the data were submitted on December, 27, 2011 in S012. The study report included information on the representation of pediatric patients of ethnic and racial minorities according to the categories and designations in the WR.</p> <p>Included in S-012 were all postmarketing adverse event reports regarding Treanda in narrative and tabular format.</p>
<p><i>Submissions in Electronic Format -Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications at http://www.fda.gov/Cder/guidance/7087rev.htm.</i></p>	

REVIEWER COMMENT:

The full study report was submitted 12/27/11. Postmarketing adverse events were included in section 5.3.6 of the submission.

Written Request Items	Information Submitted/ Sponsor's response
<p>Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before March 20, 2012.</p>	<p>Timeframe for submitting reports of the studies:</p>

REVIEWER COMMENT:

The full study report was submitted 12/27/11.

6 Review of Efficacy

Efficacy Summary

The applicant is not submitting any data that supports efficacy. A review of Trial C18083/2046 “An Open-Label Study of Bendamustine Hydrochloride for the Treatment of Pediatric Patients With Relapsed or Refractory Acute Leukemia” is presented in section 5.3 Discussion of Individual Studies/Clinical Trials. This was a phase 1 / 2 study with the goal of establishing a RPD and an analysis of activity in pediatric ALL and AML. The RPD was determined to be 120 mg/m², there were no CRs or CRps documented in the phase 2 extension using the RPD.

7 Review of Safety

Safety Summary

There were no new safety signals identified in the review of this application. As expected in this patient population all subjects had hematologic abnormalities and the majority of subjects had documented infections. Reported adverse events were similar to those identified in the adult populations with CLL and NHL.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

(copied from submission eCTD Efficacy Supplement submitted 12/27/11 Section 2.7.6 Synopsis of Individual Studies)

Table 7: Synopsis of Trial Conducted to Support This Application
Synopses of Individual Studies

Study number Study title (design) Phase	No. of centers Location	Status Dates	Study population Variables	Dose regimen Duration of treatment	Formulation (Batch/ Lot no.)	No. treated Age (yr): mean (range) M/F (%) W/NW/U (%) Weight (kg): mean (range)
Efficacy and Safety Studies: Uncontrolled Clinical Studies						
C18083/2046 An Open-Label Study of Bendamustine Hydrochloride for the Treatment of Pediatric Patients With Relapsed or Refractory Acute Leukemia Phase 1/Phase 2	24 centers Australia Belarus Brazil Israel Mexico South Korea USA	Completed 05 Aug 10- 08 Aug 11	Patients, 1-20 y of age, with relapsed/refractory ALL or AML Primary efficacy: ORR for patients treated at RPD Secondary efficacy: Best response of PR or better DOR in patients treated at RPD Safety: adverse events clinical laboratory tests results (hematology, and serum chemistry) vital signs measurements Kamofsky or Lansky performance status physical examination findings concomitant medication usage Pharmacokinetics: C_{max} t_{max} AUC_{0-1} AUC_{0-24}	Bendamustine (Phase 1 dose-escalation): administered at starting dose of 90 mg/m ² as a 60-minute iv infusion on days 1-2 of each 21-day cycle, dose then escalated to 90 mg/m ² (cohort 1) and 120 mg/m ² (cohort 2) Bendamustine (Phase 2): administered at the RPD determined in Phase 1 Up to 12 cycles	Bendamustine (09P005A503, 10P004A503)	N=43 9.2 (1, 19) 30/13 (70/30) 25/14/4 (58/33/9) 34.9 (10.5, 71.0)

Abbreviations:

ALL=acute lymphocytic leukemia; AML=acute myeloid leukemia; AUC_{0-t} = area under the plasma drug concentration by time curve from time 0 until the last measurable plasma concentration; AUC_{0-24} =area under the plasma drug concentration by time curve from time 0 until 24 hours after study drug administration; C_{max} =maximum observed plasma drug concentration; DOR= duration of remission; F=female; M=male; NW=nonwhite; ORR=overall response rate; PR=partial response; RPD=recommended pediatric dose; t_{max} =time to maximum plasma drug concentration; U=unknown; USA=United States of America; W=white; y=years.

7.1.2 Categorization of Adverse Events

Adverse events were documented on the CRF using CTCAE v 4 terminology and grading system. In addition to the investigator's own description of the adverse events, each adverse event was encoded by the use of the Medical Dictionary for Regulatory Activities (MedDRA) version 13.0.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The data from Trial CI18083/2046 was the only data derived from a trial included. In the integrated safety summary the applicant includes postmarketing data on pediatric patients included in the Cephalon pharmacovigilance database. See section 8 Postmarketing Experience.

7.2 Adequacy of Safety Assessments

Adverse events were collected from time of study entry through 30 days after the last dose of bendamustine. Adverse events were documented on the CRF using CTCAE v 4 terminology and grading system. In addition to the investigator's own description of the adverse events, each adverse event was encoded using MedDRA version 13.0. This approach was adequate.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 8: Bendamustine Exposure by Dose Cohort

Extent of Exposure Total Number of Cycles	90 mg/m² x 2 doses (n = 5)	120 mg/m² x 2 doses (n = 38)
1	3	31
2	1	7
8	1	0

7.2.2 Explorations for Dose Response

There was no formal exploration for dose response. Of note, there were no responses in subject treated at the RPD of 120 mg/m² on day 1 and 2, but 2 responses were documented in subjects treated at the initial phase 1 dose of 90 mg/m² on day 1 and 2.

7.2.3 Special Animal and/or In Vitro Testing

Not done.

7.2.4 Routine Clinical Testing

Clinical laboratory tests (serum chemistry and hematology) were performed on days 1, 8, 15, and 21 of cycle 1 and day 21 of cycle 2. Serum chemistry laboratory tests included calcium, sodium, potassium, chloride, bicarbonate or carbon dioxide, glucose, blood urea nitrogen (BUN), creatinine, ALT, AST, lactic dehydrogenase (LDH), alkaline phosphatase, and total bilirubin, and uric acid (at screening only). Hematology laboratory tests included hemoglobin, hematocrit, platelet count, absolute neutrophil count (ANC) and white blood cell (WBC) count and differential.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not done.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

No analysis done.

7.3 Major Safety Results

7.3.1 Deaths

All 17 subjects enrolled in this trial who died while on study had evidence of progressive disease at the time of death as would be expected in the study population. No deaths were attributed to the study drug by the investigator.

7.3.2 Nonfatal Serious Adverse Events

The nonfatal adverse events excluding hematologic and infectious that were classified as serious were reported in 5 subjects these included fever (n=3), impaired renal function, back pain and worsening chest pain. One subject who died with progressive leukemia was reported to have tumor lysis syndrome.

As expected in this population subjects with relapsed of resistant leukemia, hematologic cytopenias were documented in virtually every patient, and infections were reported in more than half the subjects enrolled.

7.3.3 Dropouts and/or Discontinuations

The majority of patients (n=41) were removed from the trial due to lack of response and progressive leukemia.

- Subject 001001 in the 90 mg/m² cohort was removed from the trial to undergo an HSCT.

- Subject 300002 in the 120 mg/m² cohort was removed from the trial on day 23 at his parent's request.

7.3.4 Significant Adverse Events

The Warnings and Precautions section of the bendamustine hydrochloride label includes the following: myelosuppression, infections, infusion reactions and anaphylaxis, tumor lysis syndrome, skin reactions specifically Stevens-Johnson Syndrome and toxic epidermal necrolysis, other malignancies, and extravasation.

- Myelosuppression - All subjects had documented myelosuppression.
 - Infection - More than half of the patients had documented infections.
 - Infusion reactions and anaphylaxis – There were 2 reports of allergic reaction. These were associated with antibiotics not bendamustine.
 - Tumor lysis syndrome – There was one report of tumor lysis syndrome, but the details of the incident were not well documented.
 - Skin reactions - There were no reports of Stevens-Johnson Syndrome, or toxic epidermal necrolysis. Rashes were reported in 6 subjects and were considered to be related to bendamustine. These were categorized as grade 1 or 2.
- (b) (4)
- Extravasation – There were no reports of drug extravasations, this would be unlikely because all children with relapsed or refractory leukemia would be expected to have central venous catheters.

7.3.5 Submission Specific Primary Safety Concerns

See section 7.3.4.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The Applicant's tables summarizing the adverse events the occurred in ≥ 15% of patients is presented below. (copied from submission eCTD Efficacy Supplement submitted 12/27/11 Section 5.3.3.2.3 2046 eCTD Body pages 76 to 80)

Table 9: Adverse Events Occurring in at Least 15% of Patients

System organ class MedDRA 13.0 preferred term, n (%)	Number (%) of patients ^a				
	Bendamustine at 90 mg/m ² (N=5) ^b		Bendamustine at 120 mg/m ² (N=38) ^c		
	7-11 y (N=2)	12-20 y (N=3)	1-6 y (N=14)	7-11 y (N=11)	12-20 y (N=13)
Blood and lymphatic system disorders					
Anaemia	1 (50)	2 (67)	9 (64)	6 (55)	10 (77)
Febrile neutropenia	0	0	4 (29)	5 (45)	6 (46)
Neutropenia	0	0	4 (29)	1 (9)	0
Pancytopenia	0	0	1 (7)	2 (18)	1 (8)
Thrombocytopenia	0	2 (67)	4 (29)	4 (36)	4 (31)
Ear and labyrinth disorders					
Ear pain	0	1 (33)	0	1 (9)	0
Tympanic membrane disorder	1 (50)	0	0	0	0
Endocrine disorders					
Adrenal insufficiency	0	1 (33)	0	0	0
Eye disorders					
Eye pruritus	0	1 (33)	0	0	0
Photophobia	1 (50)	0	0	0	0
Gastrointestinal disorders					
Abdominal pain	1 (50)	0	2 (14)	2 (18)	4 (31)
Constipation	0	0	1 (7)	1 (9)	5 (38)
Diarrhoea	0	1 (33)	5 (36)	2 (18)	6 (46)
Lip haemorrhage	0	0	0	0	2 (15)
Mouth ulceration	0	1 (33)	1 (7)	0	0
Nausea	1 (50)	2 (67)	6 (43)	4 (36)	7 (54)
Oral mucosal erythema	1 (50)	0	0	0	0
Oral pain	0	1 (33)	0	0	1 (8)
Tongue coated	1 (50)	0	0	0	0
Vomiting	1 (50)	1 (33)	6 (43)	2 (18)	5 (38)
General disorders and administration site conditions					
Asthenia	0	0	0	0	2 (15)
Catheter site pain	0	2 (67)	1 (7)	0	0
Chest pain	0	0	0	3 (27)	1 (8)
Chills	0	0	0	1 (9)	2 (15)
Fatigue	1 (50)	0	1 (7)	2 (18)	3 (23)
Mucosal dryness	1 (50)	0	0	0	0
Mucosal inflammation	0	0	2 (14)	0	2 (15)
Oedema peripheral	1 (50)	1 (33)	0	0	2 (15)
Pain	0	0	0	2 (18)	1 (8)
Pyrexia	0	1 (33)	8 (57)	6 (55)	6 (46)
Infections and infestations					
Aspergillosis	0	0	0	0	2 (15)
Paronychia	0	1 (33)	0	0	0
Sinusitis	0	1 (33)	0	1 (9)	0
Staphylococcal infection	0	0	0	0	2 (15)
Injury, poisoning and procedural complications					
Incision site pain	0	1 (33)	0	0	0
Procedural pain	0	1 (33)	0	0	1 (8)
Wound	0	1 (33)	0	0	0
Investigations					
Alanine aminotransferase increased	1 (50)	1 (33)	1 (7)	0	2 (15)
Aspartate aminotransferase increased	0	1 (33)	1 (7)	1 (9)	3 (23)
Blood alkaline phosphatase increased	0	0	0	0	2 (15)
Blood bilirubin increased	0	0	0	0	2 (15)
Blood creatinine increased	1 (50)	1 (33)	1 (7)	0	2 (15)
Platelet count decreased	0	0	4 (29)	1 (9)	3 (23)
Weight decreased	1 (50)	0	1 (7)	0	1 (8)
Weight increased	0	0	0	0	2 (15)

Clinical Review
 Patricia Dinndorf
 22249 / 12
 Treanda (bendamustine hydrochloride)

System organ class MedDRA 13.0 preferred term, n (%)	Number (%) of patients ^a				
	Bendamustine at 90 mg/m ² (N=5) ^b		Bendamustine at 120 mg/m ² (N=38) ^c		
	7-11 y (N=2)	12-20 y (N=3)	1-6 y (N=14)	7-11 y (N=11)	12-20 y (N=13)
Metabolism and nutrition disorders					
Decreased appetite	1 (50)	1 (33)	6 (43)	0	1 (8)
Fluid overload	1 (50)	0	1 (7)	1 (9)	0
Hypercalcaemia	1 (50)	1 (33)	0	0	2 (15)
Hyperglycaemia	0	1 (33)	2 (14)	0	2 (15)
Hyperkalaemia	0	0	1 (7)	0	2 (15)
Hypermagnesaemia	1 (50)	0	0	0	0
Hypermatraemia	0	1 (33)	0	0	1 (8)
Hypoalbuminaemia	0	0	0	0	2 (15)
Hypocalcaemia	1 (50)	0	2 (14)	0	3 (23)
Hypoglycaemia	0	1 (33)	0	0	0
Hypokalaemia	2 (100)	0	1 (7)	1 (9)	5 (38)
Hypomagnesaemia	1 (50)	0	2 (14)	2 (18)	3 (23)
Hyponatraemia	2 (100)	1 (33)	1 (7)	1 (9)	1 (8)
Hypophosphataemia	1 (50)	0	2 (14)	0	2 (15)
Tumour lysis syndrome	1 (50)	1 (33)	0	1 (9)	1 (8)
Musculoskeletal and connective tissue disorders					
Arthralgia	0	2 (67)	1 (7)	0	0
Back pain	0	1 (33)	1 (7)	0	1 (8)
Muscle spasms	0	1 (33)	0	0	0
Muscular weakness	0	1 (33)	0	0	1 (8)
Musculoskeletal stiffness	1 (50)	0	0	0	0
Pain in extremity	1 (50)	0	2 (14)	1 (9)	1 (8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Acute myeloid leukaemia	0	0	0	0	3 (23)
B precursor type acute leukaemia	1 (50)	0	0	0	0
Cancer pain	1 (50)	0	0	0	0
Leukaemia	0	0	0	2 (18)	0
Lung neoplasm	0	0	0	0	2 (15)
T-cell type acute leukaemia	1 (50)	0	0	0	0
Nervous system disorders					
Depressed level of consciousness	0	0	0	0	2 (15)
Headache	0	2 (67)	0	4 (36)	3 (23)
Somnolence	1 (50)	0	0	0	1 (8)
Psychiatric disorders					
Agitation	0	0	0	0	2 (15)
Anxiety	0	0	0	0	3 (23)
Confusional state	0	0	0	0	2 (15)
Insomnia	0	0	0	0	2 (15)
Renal and urinary disorders					
Renal failure acute	1 (50)	0	0	0	1 (8)
Renal impairment	0	1 (33)	0	0	1 (8)
Respiratory, thoracic and mediastinal disorders					
Cough	0	1 (33)	4 (29)	3 (27)	4 (31)
Dyspnoea	0	0	1 (7)	1 (9)	3 (23)
Epistaxis	1 (50)	0	2 (14)	2 (18)	1 (8)
Hypoxia	0	0	0	0	2 (15)
Productive cough	0	0	0	1 (9)	2 (15)
Pulmonary oedema	0	0	1 (7)	0	2 (15)
Rhinorrhoea	0	0	3 (21)	0	0
Skin and subcutaneous tissue disorders					
Dry skin	1 (50)	0	0	1 (9)	1 (8)
Ingrowing nail	0	1 (33)	0	0	0
Petechiae	0	0	0	0	2 (15)
Pruritus	0	0	1 (7)	1 (9)	2 (15)
Rash	0	1 (33)	1 (7)	0	3 (23)
Rash erythematous	0	1 (33)	1 (7)	0	0
Vascular disorders					
Hypertension	1 (50)	0	3 (21)	3 (27)	5 (38)
Hypotension	1 (50)	0	2 (14)	1 (9)	4 (31)
Pallor	1 (50)	0	0	0	0

7.4.2 Laboratory Findings

- Hematologic values were abnormal as expected in every subject.
- Elevated transaminases (AST, ALT) were documented in 34 subjects, of these 2 subjects had grade 3 elevations.
- Abnormal (\leq grade 2) bilirubin was documented in 2 subjects
- Elevated creatinine (\leq grade 2) was documented in 6 patients

7.4.3 Vital Signs

Vital sign measurements were performed only during the initial treatment cycle. No specific conclusions can be made from this data.

7.4.4 Electrocardiograms (ECGs)

ECGs were not performed as a component of this trial.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

No allergic reactions related to bendamustine were reported.

7.5 Other Safety Explorations

These were not analyzed.

7.6 Additional Safety Evaluations

These were not analyzed.

8 Postmarket Experience

The applicant includes postmarketing data on pediatric patients included in the Cephalon pharmacovigilance database. A total of 46 reports (44 serious, 2 non-serious) with 94 adverse events were identified in the database. There were 15 fatal case reports identified. None of the 15 fatal outcomes was attributable to bendamustine treatment. In 14 of the 15 reports, the cause of death was associated with progression of the patient's underlying malignancy. In the remaining report, the fatal outcome was due to multi-organ failure associated with *aspergillus* sepsis and to the patient's disease.

The events identified in this review are consistent with the known safety profile of bendamustine and are associated with the patients' underlying disease.

9 Appendices

9.1 Labeling Recommendations

Applicant suggested revision

(b) (4)

FDA
Agree

Applicant suggested revision

Remove apostrophe “s” from Hodgkin throughout label

FDA
Agree

Applicant suggested revision

Change Post-Marketing to Postmarketing throughout label

FDA
Agree

Applicant suggested revision

(b) (4)

FDA

In section 5.2 infections FDA has added adult and pediatric to describe patients in clinical trials

FDA has revised Section 8.4 Pediatric Use

8.4 Pediatric Use

The effectiveness of TREANDA in pediatric patients has not been established. TREANDA was evaluated in a single phase 1/2 trial. The pediatric patients had a safety profile consistent with that seen in adults, and no new safety signals were identified.

The trial included pediatric patients from 1 to 19 years of age with relapsed or refractory acute leukemia, including 27 patients with acute lymphocytic leukemia (ALL) and 16 patients with acute myeloid leukemia (AML). TREANDA was administered as an intravenous infusion over 60 minutes on Days 1 and 2 of each 21 day cycle. Doses of

90 and 120 mg/m² were evaluated. The phase 1 portion of the study determined that the recommended phase 2 dose of TREANDA in pediatric patients was 120 mg/m².

A total of 32 patients entered the phase 2 portion of the study at the recommended dose and were evaluated for response. There was no treatment response (CR+ CRp) in any patient at this dose. However, there were 2 patients with ALL who achieved a CR at a dose of 90 mg/m² in the Phase 1 portion of the study.

In the above mentioned pediatric trial, the pharmacokinetics of TREANDA at 90 to 120 mg/m² were evaluated in 38 patients aged 1 to 19 years (median age of 10 years). The single dose and multiple dose total systemic exposure (AUC) of bendamustine and its metabolites were dose-proportional over the dose range studied.

The geometric mean body surface adjusted clearance of bendamustine was 14.2 L/h/m². The exposures (AUC₀₋₂₄ and C_{max}) to bendamustine in pediatric patients following a 120-mg/m² intravenous infusion over 60-minutes were similar to those in adult patients following the same 120-mg/m² dose.

(b) (4)

Applicant suggested revision 6/6/12

From:

FDA version Section 8.4 Pediatric Use

In the above mentioned pediatric trial, the pharmacokinetics of TREANDA at 90 to 120 mg/m² were evaluated in 38 patients aged 1 to 19 years (median age of 10 years).

To:

In the above-mentioned pediatric trial, the pharmacokinetics of TREANDA at 90 and 120 mg/m² doses were evaluated in 5 and 38 patients, respectively, aged 1 to 19 years (median age of 10 years).

FDA agrees with this revision.

9.2 Original Written Request (1/19/10)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST

NDA 022249

Cephalon, Inc.
Attention: Carol S. Marchione
Senior Director and Group Leader
Regulatory Affairs
41 Moores Rd
P.O.Box 4011
Frazer, PA 19355

Dear Ms. Marchione:

Reference is made to your July 27, 2009, Proposed Pediatric Study Request for Treanda® (bendamustine hydrochloride) for Injection.

To obtain needed pediatric information on bendamustine, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the following study:

- *Background:* Acute leukemia represents the most common malignancy of childhood. Despite significant improvement in cure rates since the 1970s, cure rates for patients with relapsed or refractory leukemia continue to be suboptimal. Standard chemotherapy regimens utilized in the treatment of patients with ALL and AML typically utilize 6-12 cytotoxic agents with select patients receiving stem cell transplantation (depending upon donor availability). Most subjects with pediatric leukemia who are enrolled in a Phase 1 study are refractory to standard induction therapy or have disease that has relapsed 2 or more times. As such the majority of patients have very limited options.

Treanda (bendamustine) is an alkylating agent recently approved for treatment of NHL and CLL in adults. The antileukemic activity of bendamustine hydrochloride has been demonstrated in cell lines and a clinical trial in adults with AML/MDS. There is little clinical experience using Treanda® (bendamustine hydrochloride) in childhood acute leukemia or pediatric patients in general. Therefore, a single arm, Phase 1 dose escalating trial to explore the dose, schedule, and safety profile followed by a Phase 2 trial to determine the anti-leukemic activity in the pediatric population are necessary. After establishing the safety and efficacy of this agent as a single agent, subsequent Phase 1 and 2 studies can be designed to evaluate the role of this agent in multiagent regimens which are the backbone of current ALL therapy in children (e.g BFM and Dana Farber regimens).

Most current pediatric oncology studies enroll subjects between the ages of 1 and 21 years. The reason for the cut off is that most Children's Hospitals in the US treat patients up to age 21. Additionally due to better outcomes on pediatric ALL regimens, patients in the adolescent/young adult subgroups (17-21) are preferentially referred to pediatric oncologists.

However, due to the presence of refractory or resistant disease, this age group also has the worst outcome of any pediatric age group with ALL. Typically by the time these patients become eligible for Phase 1 studies, they have been receiving therapy for 3-5 years. Enrolling patients age 18-21 provides required information that is relevant to drug development for pediatric ALL patients.

- *Type of study(ies):* A Phase 1/2 Study of Bendamustine Hydrochloride for the Treatment of Pediatric Patients With Relapsed or Refractory Acute Leukemia

A 2-part study design will be used. A minimum of 6 and a maximum of 18 pediatric patients will be enrolled during the dose-escalation, Phase 1 part of this study. After the recommended Phase 2 dose (RP2D) has been determined, additional patients will be enrolled in the Phase 2 part of this study, until a total of 26 patients have received bendamustine at the RP2D.

- *Indication(s) to be studied:*

Treatment of pediatric patients with relapsed or refractory acute leukemia defined as patients who have received or who are unable to receive all standard therapies for their disease. Standard therapy is defined as all medications which have been shown to provide clinical benefit in this disease.

- *Objectives of the study:*

Primary objectives:

- Phase 1: To determine the recommended Phase 2 dose of bendamustine in pediatric patients with relapsed or refractory acute leukemia.
- Phase 2: To evaluate the safety and efficacy of bendamustine for the treatment of pediatric patients with relapsed or refractory acute leukemia. Efficacy assessment will include complete response (CR) and complete response without platelet recovery (CRp).

Secondary objectives:

- To determine the pharmacokinetic profile of bendamustine in pediatric population
- To determine the duration of response (CR, CRp) to bendamustine therapy in this pediatric population.

- *Age group in which study(ies) will be performed:* 1-21 years, targeting patients age: 1-6, 7-11, 12-16, and 17-21 years
- *Number of patients to be studied:* Minimum 32 patients

These studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Phase 1 (dose-escalation portion): A minimum of 6 and a maximum of 18 pediatric patients must be enrolled to determine the RP2D. In addition, PK profiles must be obtained from a minimum of 6 patients in the RP2D cohort in Phase 1.

Phase 2: After the RP2D has been determined, additional patients must be enrolled until a total of 26 patients have received bendamustine at the RP2D.

- *Study endpoints:*

Primary endpoints:

- Phase 1: The recommended Phase 2 dose of bendamustine in children with relapsed or refractory acute leukemia
- Phase 2: The safety and efficacy (CR + CRp) of bendamustine for the treatment of pediatric patients with relapsed or refractory acute leukemia

Secondary endpoints:

- The duration of response (CR and CRp) to bendamustine therapy in this pediatric population.
- Pharmacokinetic endpoints:

Pharmacokinetic samples must be collected through approaches such as rich sampling or optimal sparse sampling in patients. Such data must then be appropriately analyzed using methods such as nonlinear mixed effects modeling or noncompartmental analysis. Data from the Phase 1 and Phase 2 must be combined to develop pharmacokinetic and pharmacodynamic (PK-PD) models to explore exposure-response relationships for measures of safety and effectiveness.

The pharmacokinetic studies must be prospectively powered to target a 95% confidence interval within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution for bendamustine in each of the age groups (1-6, 7-11, 12-16, 17-21 years old).

- *Drug information*

- Dosage form: Bendamustine hydrochloride for injection (100 mg/20mL)
- Route of administration: intravenous infusion (IV)
- Regimen:

Phase 1: The dose escalation scheme, as tolerated, is 90 mg/m², 120 mg/m², and 150 mg/m² IV infusion over 60 minutes IV on days 1 and 2 of each 21-day cycle, with delays up to 2 weeks for bone marrow recovery. A 150 mg/m² dose will be administered only if a 120 mg/m² dose is deemed safe and the exposure of bendamustine in pediatric patients is less than that in adult patients following administration of 120 mg/m² bendamustine.

Phase 2: The dose and schedule will depend on the results of Phase 1 dose escalation study.

- *Drug specific safety concerns:*

The most common non-hematologic adverse reactions for CLL (frequency ≥15%) are pyrexia, nausea, and vomiting. The most common non-hematologic adverse reactions for NHL (frequency ≥ 15%) are nausea, fatigue, vomiting, diarrhea, pyrexia, constipation, anorexia, cough, headache, weight decreased, dyspnea, rash, and stomatitis. The most common hematologic abnormalities for both indications (frequency ≥ 15%) are lymphopenia, anemia, leukopenia, thrombocytopenia, and neutropenia.

- *Statistical information, including power of study(ies) and statistical assessments:*
This study includes two phases. In Phase 1 of the study, a traditional 3+3 design will be used to determine the maximum tolerated dose (MTD). The MTD will be the RP2D. In Phase 2 of the study, additional patients will be enrolled into the dose level that has been identified as the RP2D until a total sample size of 26 patients exposed to the RP2D is reached. The efficacy assessment will be based on all patients treated with the RP2D. This will be calculated as the percentage of patients with CR or CRp divided by the number of patients treated with the RP2D. If 4 or more overall responses are observed, the null hypothesis of a true response rate of 5% is rejected at 1-sided alpha level of 0.05, and it is concluded that the study drug has activity in this pediatric patient population. Assuming a true effect of 20%, the power would be approximately 80%.
- *Labeling that may result from the study(ies):* You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that Bendamustine is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).
- *Format and types of reports to be submitted:* You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) must be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you must use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you must obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. These postmarketing adverse event reports must be submitted as narrative and tabular reports.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at <http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf> and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at <http://www.fda.gov/Cder/guidance/7087rev.htm>.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before December 20, 2011. Please keep in mind that pediatric

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exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

Response to Written Request: Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at <http://www.fda.gov/cder/pediatric/index.htm>

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request must be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR**

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PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Alberta Davis-Warren, Regulatory Project Manager, at 301-796-3908

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products, HFD-150
Center for Drug Evaluation and Research

9.3 Revised Written Request Amendment 2 (9/23/10)

WRITTEN REQUEST – AMENDMENT 2

NDA 022249

Cephalon, Inc.
Attention: Carol S. Marchione
Senior Director and Group Leader
Regulatory Affairs
41 Moores Rd
P.O. Box 4011
Frazer, PA 19355

Dear Ms. Marchione:

Please refer to your correspondence dated March 8, 2010, requesting changes to FDA's January 19, 2010 Written Request for pediatric studies for Treanda® (bendamustine hydrochloride) for Injection.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on January 19, 2010, remain the same. (Text added is underlined. Text deleted is strikethrough.)

Alkylating agents have been used for cancer treatments including acute leukemia over decades. The safety and efficacy experience of agents of this class are well documented in adult and pediatric acute leukemia patients. Treanda (bendamustine) Bendamustine is an alkylating agent that has been used for decades in Europe and was recently approved for treatment of NHL and CLL in adults in the United States for treatment of adult patients with non-Hodgkin's lymphoma and chronic lymphocytic leukemia. The antileukemic activity of bendamustine hydrochloride has been demonstrated in cell lines and a clinical trial in adults with AML/MDS acute myelogenous leukemia/myelodysplastic syndrome. There is little clinical experience using Treanda® (bendamustine hydrochloride) in childhood acute leukemia or pediatric patients in general. Therefore, a single arm, Phase 1 dose escalating trial to explore the dose, schedule, and safety profile followed by a Phase 2 trial to determine the anti-leukemic activity in the pediatric population is ~~are~~ necessary. After establishing the safety and efficacy of this agent bendamustine as a single agent, subsequent Phase 1 and 2 studies can be designed to evaluate the role of this agent in multiagent regimens which are the backbone of current acute lymphoblastic leukemia (ALL) therapy in children (e.g., Berlin-Frankfurt-Münster (BFM) and Dana Farber regimens).

- *Type of study(ies):* A Phase 1/2 Study of Bendamustine Hydrochloride for the Treatment of Pediatric Patients With Relapsed or Refractory Acute Leukemia

A 2-part study design will be used. A minimum of 6 and a maximum of 18 pediatric patients will be enrolled during the dose-escalation, Phase 1 part of this study. After the recommended Phase 2 dose (RP2D) has been determined, an additional 26 patients ~~will~~ must be ~~enrolled~~

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treated in the Phase 2 part of this study, until a total of 26 patients have received bendamustine at the RP2D (not including the patients treated at RP2D in Phase 1).

- *Objectives of the study:*

Primary objectives:

- Phase 1: To determine the recommended Phase 2 dose of bendamustine in pediatric patients with relapsed or refractory acute leukemia.
- Phase 2: To evaluate the safety and efficacy of bendamustine for the treatment of pediatric patients with relapsed or refractory acute leukemia. Efficacy assessment will include complete remission response (CR) and complete remission response without inadequate platelet recovery (CRp).

- *Age group in which study(ies) will be performed:* ~~1-21 year targeting patients age: 1-6, 7-11, 12-16, and 17-21 years. At least 10 patients must be treated within each of the following specified age groups (1-6, 7-11, and 12-21 years old).~~

- *Number of patients to be studied:* ~~Minimum 32 patients~~

These studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Phase 1 (dose-escalation portion): A minimum of 6 and a maximum of 18 pediatric patients must be ~~enrolled~~ treated to determine the RP2D. In addition, PK profiles must be obtained from a minimum of 6 patients in the RP2D cohort in Phase 1.

Phase 2: After the RP2D has been determined, an additional 26 patients must be enrolled treated until a total of 26 patients have received bendamustine at the RP2D (not including the patients treated at RP2D in Phase 1).

- *Study endpoints:*

Primary endpoints:

- Phase 1: The recommended Phase 2 dose of bendamustine in children with relapsed or refractory acute leukemia
- Phase 2: The safety and efficacy, including CR + CRp, of bendamustine for the treatment of pediatric patients with relapsed or refractory acute leukemia

Secondary endpoints:

- The duration of ~~response~~ remissions (CR and CRp) to bendamustine therapy in this pediatric population.
- Pharmacokinetic endpoints:

Pharmacokinetic samples must be collected through approaches such as rich sampling or optimal sparse sampling in patients. Such data must then be appropriately analyzed using methods such as nonlinear mixed effects modeling or noncompartmental analysis. Data

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from the Phase 1 and Phase 2 must be combined to develop pharmacokinetic and pharmacodynamic (PK-PD) models to explore exposure-response relationships for measures of safety and effectiveness.

The pharmacokinetic studies must be prospectively powered to target a 95% confidence interval within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution for bendamustine in each of the age groups (1-6, 7-11, 12-16, 17-21 years old). The effect of age on the pharmacokinetics of bendamustine within the overall pediatric population must be assessed.

- *Drug information*

- Dosage form: Bendamustine hydrochloride for injection (100 mg/20mL)
- Route of administration: intravenous infusion (IV)
- Regimen:

Phase 1: The dose escalation scheme, as tolerated, is 90 mg/m², 120 mg/m², and 150 mg/m² IV infusion over 60 minutes IV on days 1 and 2 of each 21-day cycle, with delays up to 2 weeks for bone marrow recovery. A 150 mg/m² dose will be administered only if a 120 mg/m² dose is deemed safe and the exposure of bendamustine in pediatric patients is less than that in adult patients following administration of 120 mg/m² bendamustine. A dose de-escalation to 60 mg/m² may be required if two or more dose limiting toxicities occur at the starting dose.

Phase 2: The dose and schedule will depend on the results of the Phase 1 dose escalation study.

- *Statistical information, including power of study(ies) and statistical assessments:*

This study includes two phases. In Phase 1 of the study, a traditional 3+3 design will be used to determine the maximum tolerated dose (MTD). The MTD will be the RP2D. In Phase 2 of the study, a total sample size of 26 additional patients (not including patients in the Phase 1 study) will be enrolled into the dose level that has been identified as the RP2D until a total sample size of 26 patients exposed to the RP2D is reached. The efficacy assessment will be based on all patients treated with the RP2D in the Phase 2 study. This will be calculated as the percentage number of patients with CR or CRp divided by the number of patients treated with the RP2D in the Phase 2 study. If 4 or more overall responses are observed, The null hypothesis is a remission rate of 5%, which will be tested at a of a true response rate of 5% is rejected at 1-sided alpha level of 0.05, and it is concluded that the study drug has activity in this pediatric patient population. A one-sided 95% confidence interval for the rate of CR or CRp will be calculated based on the binomial distribution, the lower boundary of which will be compared with the remission rate of 5% in the null hypothesis (>5% or not). Assuming a true effect remission rate of 20%, the power of the test would be approximately 80%.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated January 19, 2010, as amended by this letter must be submitted to the Agency on or before December 20, 2011, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports,

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clearly mark your submission “**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**” in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request “**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**” in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, call Alberta Davis-Warren Regulatory Project Manager, at 301-796-3908

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products, HFD-150
Center for Drug Evaluation and Research

Attachment (Complete Clean Copy of Written Request as amended)

WRITTEN REQUEST

NDA 022249

Cephalon, Inc.
Attention: Carol S. Marchione
Senior Director and Group Leader
Regulatory Affairs
41 Moores Rd
P.O.Box 4011
Frazer, PA 19355

Dear Ms. Marchione:

Reference is made to your July 27, 2009, Proposed Pediatric Study Request for Treanda® (bendamustine hydrochloride) for Injection.

To obtain needed pediatric information on bendamustine, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the following study:

- *Background:* Acute leukemia represents the most common malignancy of childhood. Despite significant improvement in cure rates since the 1970s, cure rates for patients with relapsed or refractory leukemia continue to be suboptimal. Standard chemotherapy regimens utilized in the treatment of patients with ALL and AML typically utilize 6-12 cytotoxic agents with select patients receiving stem cell transplantation (depending upon donor availability). Most subjects with pediatric leukemia who are enrolled in a Phase 1 study are refractory to standard induction therapy or have disease that has relapsed 2 or more times. As such the majority of patients have very limited options.

Alkylating agents have been used for cancer treatments including acute leukemia over decades. The safety and efficacy experience of agents of this class are well documented in adult and pediatric acute leukemia patients. Bendamustine is an alkylating agent that has been used for decades in Europe and was recently approved in the United States for treatment of adult patients with non-Hodgkin's lymphoma and chronic lymphocytic leukemia. The antileukemic activity of bendamustine hydrochloride has been demonstrated in cell lines and a clinical trial in adults with acute myelogenous leukemia/myelodysplastic syndrome. There is little clinical experience using bendamustine hydrochloride in childhood acute leukemia or pediatric patients in general. Therefore, a single arm, Phase 1 dose escalating trial to explore the dose, schedule, and safety profile followed by a Phase 2 trial to determine the anti-leukemic activity in the pediatric population is necessary. After establishing the safety and efficacy of bendamustine as a single agent, subsequent Phase 1 and 2 studies can be designed to evaluate the role of this agent in multiagent regimens which are the backbone of current acute lymphoblastic leukemia (ALL) therapy in children (e.g., Berlin-Frankfurt-Münster (BFM) and Dana Farber regimens).

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Most current pediatric oncology studies enroll subjects between the ages of 1 and 21 years. The reason for the cut off is that most Children's Hospitals in the US treat patients up to age 21. Additionally due to better outcomes on pediatric ALL regimens, patients in the adolescent/young adult subgroups (17-21) are preferentially referred to pediatric oncologists. However, due to the presence of refractory or resistant disease, this age group also has the worst outcome of any pediatric age group with ALL.

- *Type of study(ies):* A Phase 1/2 Study of Bendamustine Hydrochloride for the Treatment of Pediatric Patients With Relapsed or Refractory Acute Leukemia

A 2-part study design will be used. A minimum of 6 and a maximum of 18 pediatric patients will be enrolled during the dose-escalation, Phase 1 part of this study. After the recommended Phase 2 dose (RP2D) has been determined, an additional 26 patients must be treated at the RP2D (not including the patients treated at RP2D in Phase 1).

- *Indication(s) to be studied:*

Treatment of pediatric patients with relapsed or refractory acute leukemia defined as patients who have received or who are unable to receive all standard therapies for their disease. Standard therapy is defined as all medications which have been shown to provide clinical benefit in this disease.

- *Objectives of the study:*

Primary objectives:

- Phase 1: To determine the recommended Phase 2 dose of bendamustine in pediatric patients with relapsed or refractory acute leukemia.
- Phase 2: To evaluate the safety and efficacy of bendamustine for the treatment of pediatric patients with relapsed or refractory acute leukemia. Efficacy assessment will include complete remission (CR) and complete remission with inadequate platelet recovery (CRp).

Secondary objectives:

- To determine the pharmacokinetic profile of bendamustine in pediatric population
- To determine the duration of remission (CR + CRp) to bendamustine therapy in this pediatric population.

- *Age group in which study(ies) will be performed:* 1-21 years. At least 10 patients must be treated within each of the following specified age groups (1-6, 7-11, and 12-21 years old).

- *Number of patients to be studied:*

These studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Phase 1 (dose-escalation portion): A minimum of 6 and a maximum of 18 pediatric patients must be treated to determine the RP2D. In addition, PK profiles must be obtained from a minimum of 6 patients in the RP2D cohort in Phase 1.

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Phase 2: After the RP2D has been determined, an additional 26 patients must be treated at the RP2D (not including the patients treated at RP2D in Phase 1).

- *Study endpoints:*

Primary endpoints:

- Phase 1: The recommended Phase 2 dose of bendamustine in children with relapsed or refractory acute leukemia
- Phase 2: The safety and efficacy, including CR + CRp, of bendamustine for the treatment of pediatric patients with relapsed or refractory acute leukemia

Secondary endpoints:

- The duration of remissions (CR and CRp) to bendamustine therapy in this pediatric population.

- Pharmacokinetic endpoints:

Pharmacokinetic samples must be collected through approaches such as rich sampling or optimal sparse sampling in patients. Such data must then be appropriately analyzed using methods such as nonlinear mixed effects modeling or noncompartmental analysis. Data from the Phase 1 and Phase 2 must be combined to develop pharmacokinetic and pharmacodynamic (PK-PD) models to explore exposure-response relationships for measures of safety and effectiveness.

The effect of age on the pharmacokinetics of bendamustine within the overall pediatric population must be assessed.

- *Drug information*

- Dosage form: Bendamustine hydrochloride for injection (100 mg/20mL)
- Route of administration: intravenous infusion (IV)
- Regimen:

Phase 1: The dose escalation scheme, as tolerated, is 90 mg/m², 120 mg/m², and 150 mg/m² IV infusion over 60 minutes IV on days 1 and 2 of each 21-day cycle, with delays up to 2 weeks for bone marrow recovery. A 150 mg/m² dose will be administered only if a 120 mg/m² dose is deemed safe and the exposure of bendamustine in pediatric patients is less than that in adult patients following administration of 120 mg/m² bendamustine. A dose de-escalation to 60 mg/m² may be required if two or more dose limiting toxicities occur at the starting dose.

Phase 2: The dose and schedule will depend on the results of the Phase 1 dose escalation study.

- *Drug specific safety concerns:*

The most common non-hematologic adverse reactions for CLL (frequency ≥15%) are pyrexia, nausea, and vomiting. The most common non-hematologic adverse reactions for NHL (frequency ≥ 15%) are nausea, fatigue, vomiting, diarrhea, pyrexia, constipation, anorexia, cough, headache, weight decreased, dyspnea, rash, and stomatitis. The most

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common hematologic abnormalities for both indications (frequency $\geq 15\%$) are lymphopenia, anemia, leukopenia, thrombocytopenia, and neutropenia.

- *Statistical information, including power of study(ies) and statistical assessments:*
This study includes two phases. In Phase 1 of the study, a traditional 3+3 design will be used to determine the maximum tolerated dose (MTD). The MTD will be the RP2D. In Phase 2 of the study, a total sample size of 26 patients (not including patients in the Phase 1 study) will be enrolled into the dose level that has been identified as the RP2D. The efficacy assessment will be based on all patients treated with the RP2D in the Phase 2 study. This will be calculated as the number of patients with CR or CRp divided by the number of patients treated with the RP2D in the Phase 2 study. The null hypothesis is a remission rate of 5%, which will be tested at a 1-sided alpha level of 0.05. A one-sided 95% confidence interval for the rate of CR or CRp will be calculated based on the binomial distribution, of which the lower boundary of which will be compared with the remission rate of 5% in the null hypothesis ($>5\%$ or not). Assuming a true remission rate of 20%, the power of the test would be approximately 80%.
- *Labeling that may result from the study(ies):* You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that Bendamustine is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).
- *Format and types of reports to be submitted:* You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) must be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you must use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you must obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. These postmarketing adverse event reports must be submitted as narrative and tabular reports.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at <http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf> and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at <http://www.fda.gov/Cder/guidance/7087rev.htm>.

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- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before December 20, 2011. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

Response to Written Request: Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at <http://www.fda.gov/cder/pediatric/index.htm>

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If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request must be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Alberta Davis-Warren, Regulatory Project Manager, at 301-796-3908.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products, HFD-150
Center for Drug Evaluation and Research

9.4 Revised Written Request Amendment 3 (7/7/11)

NDA 022249

REVISED WRITTEN REQUEST AMENDMENT 3

Cephalon, Inc.
Attention: Carol S. Marchione
Senior Director and Group Leader
Regulatory Affairs
41 Moores Rd.
P.O. Box 4011
Frazer, PA 19355

Dear Ms. Marchione

Please refer to your correspondence dated March 31, 2011, requesting changes to FDA's September 23, 2010 Written Request for pediatric studies for Treanda® (bendamustine hydrochloride) for injection.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on January 19, 2010, and as amended on September 23, 2010, remain the same. (Text added is underlined. Text deleted is strikethrough.)

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before March 20, 2012 ~~December 20, 2014~~. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated January 19, 2010, as amended by this letter and by previous amendment(s) dated September 23, 2010, must be submitted to the Agency on or before March 20, 2012, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

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Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **“SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED”** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **“PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES”** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, call Theresa Ferrara, Regulatory Project Manager, at 301-796-2848.

Sincerely,

(See appended electronic signature page)

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products, HFD-150
Center for Drug Evaluation and Research

Clinical Review
Patricia Dinndorf
22249 / 12
Treanda (bendamustine hydrochloride)

9.5 Pediatric Exclusivity Board Meeting

This application was discussed at the Pediatric Exclusivity Board on 5/22/12. The decision was made to grant exclusivity.

From: Ferrara, Theresa [mailto:Theresa.Ferrara@fda.hhs.gov]
Sent: Tuesday, May 22, 2012 02:45 PM
To: Carol Marchione
Subject: Treanda, NDA 22249 / S-12 Pediatric Exclusivity granted

Dear Carol,
Please refer to Treanda, NDA 22249 / S-12 and Cephalon's request for determination of pediatric exclusivity.

This email serves to inform you that Pediatric Exclusivity has been granted for studies conducted on **bendamustine**, effective **May 22, 2012**, under section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a), as amended by the Best Pharmaceuticals for Children Act (BPCA). This information will be reflected on CDER's pediatric web site and in the monthly update of the Orange Book. For additional information, please see the Guidance for Industry - Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080558.pdf>).

In accordance with section 505A(e)(1) of the Act, as amended by FDAAA (Pub. L. No. 110-85), approved drugs for which a pediatric exclusivity determination was made, on or after September 27, 2007, shall have a copy of the Written Request and any amendments posted on CDER's pediatric web site.

In addition, we remind you that section 17 of the BPCA, as reauthorized and amended under the FDA Amendments Act of 2007, requires for one year after pediatric labeling is approved, any report received by FDA of an adverse event associated with the drug granted exclusivity will be referred to the Office of Pediatric Therapeutics. This process occurs for all products granted Pediatric Exclusivity regardless of the regulatory action taken. The Director of that Office will provide for a review of the adverse event reports by the Pediatric Advisory Committee (PAC) and will obtain recommendations from that Committee on action FDA should take.

Please contact me should you have any questions. Kindly confirm receipt of this email correspondence. Thank you.

Kind regards,
Theresa

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/s/

THERESA A FERRARA
05/22/2012

9.6 Abbreviations

ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ANC	Absolute neutrophil count
BSA	Body surface area
BUN	Blood urea nitrogen
CLL	Chronic lymphocytic leukemia
CR	Complete response
CRp	Complete response without platelet recovery
CRF	Clinical report form
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of remission
DLT	Dose limiting toxicity
ECG	Electrocardiograms
GCP	Good clinical practice
HSCT	Hematopoietic stem cell transplantation
ICH	International Conference on Harmonization
IV	Intravenous
LDH	Lactic dehydrogenase
MTD	Maximum tolerated dose
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NHL	Non Hodgkin lymphoma
ORR	Overall response rate
PD	Pharmacodynamic
PK	Pharmacokinetic
PR	Partial response
PWR	Pediatric Written Request
RPD	Recommended pediatric dose
ULN	Upper limit of normal
WBC	White blood cell

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/s/

PATRICIA A DINNDORF
06/07/2012

ALBERT B DEISSEROTH
06/07/2012