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/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.

    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 $\geq$ 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.

- *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

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**

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22249	GI-1	CEPHALON INC	TREANDA

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/s/

RICHARD PAZDUR
01/19/2010