

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: October 3, 2008

TO: Virginia Kwitowski, Reviewing Medical Officer
Milinda Vialpando, Regulatory Project Manager
Division of Drug Oncology Products

FROM: Robert Young
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA 22 303

APPLICANT: Cephalon, Inc.

DRUG: bendamustine (Treanda)

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Treatment of patients with indolent B-cell non Hodgkin's lymphoma (NHL) who have progressed during or following treatment with rituximab or a rituximab-containing regimen.

CONSULTATION REQUEST DATE: 02/04/2008

DIVISION ACTION GOAL DATE: 09/30/2008

PDUFA DATE: 10/31/2008

I. BACKGROUND:

This investigational drug is the subject of an approved NDA. The sponsor is currently seeking an additional indication. The reviewing division identified no specific clinical investigator concerns. The larger sites were identified for inspection.

The protocols inspected include:

SDX-105-01: “A Multi-Center Phase II Study to Investigate the Safety and Activity of SDX-105 (Bendamustine) in Patients With Indolent Non-Hodgkin’s Lymphoma (NHL) who are Refractory to Rituximab.”

SDX-105-03: “Multi-Center Phase III Study to Investigate the Safety and Efficacy of TREANDA™ (Bendamustine HCl) in Patients With Indolent Non-Hodgkin’s Lymphoma (NHL) Who are Refractory to Rituximab.”

II. RESULTS (by Site):

Name of CI Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
Brad Kahl University of Wisconsin Site 062	SDX-105-03 15 subjects	Apr/May 2008	NAI
John Leonard Cornell Medical School Site 052	SDX-105-03 8 subjects	May 2008	NAI
Nancy Barlett Washington University Site 076	SCX-105-03 8 subjects	April 2008	NAI
Kristen Ganjoo Stanford University Site 061	SDX-105-03 9 subjects	May 2008	Interim classification: VAI
Bruce Cheson Georgetown University Site 005	SDX-105-01 11 subjects	April/May 2008	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;

EIR has not been received from the field and complete review of EIR is pending.

1. Brad Kahl

600 Highland Avenue
Madison, WI 53792

- a. **What was inspected:** Fifteen subject records were inspected. Source records were compared to data listings. No limitations to the inspection.

b. General observations/commentary: No significant findings. No 483 issued.

c. Assessment of data integrity: Data acceptable in support of the pending application.

2. John Leonard
520 E. 70th St.
New York, NY 10065

a. What was inspected: Five subject records were inspected. Source records were compared to data listings. No limitations to the inspection.

b. General observations/commentary: No significant findings. No 483 issued.

c. Assessment of data integrity: Data acceptable in support of the pending application

3. Nancy Bartlett
600 S. Euclid
St. Louis, MO 63110

a. What was inspected: Eight subject records were inspected. Source records were compared to data listings. No limitation to the inspection.

b. General observations/commentary: No significant findings. No 483 issued.

c. Assessment of data integrity: Data acceptable in support of the pending application.

4. Kristin Ganjoo
269 Campus Drive
Stanford, CA 94305

Note: EIR has not been received in DSI. This preliminary report is based on a written summary provided by the field inspector. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR

a. What was inspected: Seven subject records were inspected. Source documents were compared to data listings. No limitation to the inspection.

b. General observations/commentary: There were two instances where source documents could not be located - one target lesion assessment and a

cycle five CBC. There was an instance where a bone marrow was not done within 28 days of a dose.

c. **Assessment of data integrity:** Data acceptable in support of the pending application.

5. Bruce Cheson
3800 Reservoir Road, N.W.
Washington, DC 20007

a. **What was inspected:** Eight subject records were inspected. Source records were compared to data listings. There were no limitations to the inspection.

b. **General observations/commentary:** No significant findings. No 483 was issued.

c. **Assessment of data integrity:** Data acceptable in support of the pending application.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Data may be used in assessment of the pending application.

Note: EIR has not been received in DSI for Dr. (b) (4). This preliminary report is based on a written summary provided by the field inspector. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

{See appended electronic signature page}

Robert Young
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Robert Young
10/3/2008 09:12:53 AM
MEDICAL OFFICER

Tejashri Purohit-Sheth
10/3/2008 09:38:49 AM
MEDICAL OFFICER

From: Vialpando, Milinda
To: "cmarchio@cephalon.com";
CC:
Subject: FW: Responses for Treanda NDA 22-249 and 22-303
Date: Monday, June 30, 2008 2:44:25 PM
Attachments:

Carol,

Please see our responses below in red and send all comments and questions directly to me. If I am not available you can contact my Chief, Alice Kacuba at alice.kacuba@fda.hhs.gov. Our Review Team is extremely busy and your correspondence through the project manager is appreciated.

Thank You,

Milinda F. Vialpando
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products, FDA
10903 New Hampshire Avenue
Building 22, Room 2133
Silver Spring, MD 20993
Tel: 301-796-1444
Fax: 301-796-9845

From: Marchione, Carol [mailto:cmarchio@cephalon.com]
Sent: Tuesday, June 17, 2008 1:55 PM
To: Vialpando, Milinda; Kwitkowski, Virginia
Cc: Vairinhos, Franklin; Ibrahim, Amna
Subject: FDA re Treanda NDA 22-249 and 22-303

Dear Milinda and Ginny,

I am contacting you regarding a number of issues related to Treanda NDA 22-303 (for NHL) and for NDA 22-249 (for CLL). I have attempted a couple of times to contact Milinda previously but I am sure things are very busy at the Agency and our action date is in October so timing is not currently critical but I do have a several items that I would like to relay:

1. We were told by Dottie Pease before she left that a mid-review meeting for NDA 22-303 was scheduled for May. I was hoping to hear if there were any issues, concerns or insights that were discussed or if there was anything that we could help with in terms of your review. If you have had a Mid-Cycle, at present we do not have any information requests. If there are any information requests I will send them to you right away. Also, I was wondering that even though we are not on the pilot program, is it possible to share the timepoints of the Agency's internal meetings so that we can make sure that there is staff here in Cephalon to support any queries that you may have after these meetings. No, this is not practical. However, the labeling negotiations are typically the last month of the review clock.
2. We intend to file a supplement to the CLL NDA (22-249) in August for a 25 mg dosage form. This new dosage form will apply (b) (4) [redacted]. This was also suggested by the Agency at our meeting in February. It was my understanding from speaking previously with Dottie that (b) (4) [redacted]. I am hoping that this could occur following the action date for the 25 mg dosage form supplement estimated for (b) (4) [redacted]. Do you concur with this strategy? Yes, the 25 mg supplement should come into the approved NDA 22-249.

3. (b) (4) [redacted]

4. (b) (4) [redacted]

5. (b) (4) [redacted]

(b) (4)

6. (b) (4)

Please note that I will be on vacation from July 5 through July 21. If you need to contact Cephalon regarding Treanda, please call or e-mail Franklin Vairinhos at 610-727-6219 or his e-mail address in the cc block. I look forward to your responses,
Regards, Carol 610-738-6238

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/s/

Milinda Vialpando
6/30/2008 02:50:08 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-303

Cephalon, Inc.
41 Moores Road, P.O. Box 4011
Frazer, PA 19355

Attention: Carol S. Marchione
Senior Director and Group Leader,
Regulatory Affairs

Dear Ms. Marchione:

Please refer to your new drug application (NDA) dated December 28, 2007, received December 31, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Treanda (bendamustine hydrochloride) injection.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is October 31, 2008.

At this time, we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients of all ages.

If you have any questions, call Dotti Pease, Regulatory Project Manager, at (301) 796-1434.

Sincerely,
{See appended electronic signature page}
Robert L. Justice, M.D.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**

/s/

Dotti Pease
2/11/2008 09:28:34 AM
Signing for Robert Justice, M.D.