CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-249

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-249 SUPPL # HFD # 150

Trade Name TREANDA® for Injection, for intravenous infusion

Generic Name bendamustine hydrochloride

Applicant Name Cephalon, Inc.

Approval Date, If Known March 20, 2008

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES ☐	! NO ☐
		! Explain:
Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

Name of person completing form: Frank Cross
Title: Project Manager
Date: March 19, 2008

Name of Office/Division Director signing form: Robert Justice, M.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Justice
3/20/2008 10:12:25 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 22-249 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

Stamp Date: 9-20-07 **PDUFA Goal Date:** 3-20-08

HFD -150 **Trade and generic names/dosage form:** Treanda (bendamustine HCl) inj

Applicant: Cephalon **Therapeutic Class:** 5010100

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- ☑ **Yes. Please proceed to the next question.**
- ☐ **No. PREA does not apply. Skip to signature block.**

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) *previously approved* (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: CLL

Is this an orphan indication?

- ☑ **Yes. PREA does not apply. Skip to signature block.**
- ☐ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

[See appended electronic signature page]

Dotti Pease, Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE [illegible]

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- ☐ **Yes. PREA does not apply. Skip to signature block.**
- ☐ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

_____
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE

(Revised: 10/10/2006)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dotti Pease
1/25/2008 02:45:37 PM

Debarment Certification

Cephalon, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Carol S. Marchione

Carol S. Marchione
Senior Director and Group Leader
Regulatory Affairs
Cephalon, Inc.

August 27, 2007
Date

ACTION PACKAGE CHECKLIST

Application Information			
BLA # NDA # 22-249	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type	
Proprietary Name: TREANDA® Established Name: bendamustine hydrochloride Dosage Form: for injection		Applicant: Cephalon, Inc.	
RPM: Cross		Division: DDOP	Phone # 301 796-0876

NDAs: NDA Application Type: ☐ 505(b)(1) X 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Published literature on reproductive toxicity of bendamustine. Provide a brief explanation of how this product is different from the listed drug. Same compound. ☐ If no listed drug, check here and explain: **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** X Confirmed ☐ Corrected Date: 3/19/08

❖ User Fee Goal Date ❖ Action Goal Date (if different)	3-20-08
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	X Requested in AP letter ☐ Received and reviewed

❖ Application Characteristics

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

X Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☐ No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☐ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	X Yes ☐ No
• Press Office notified of action	X Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None X FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As X Other - Burst

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	X Included
• Is approval of this application blocked by any type of exclusivity?	X No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	X No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	X Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified ☐ 21 CFR 314.50(i)(1) X (ii) ☐ (iii) Note: there is published literature on reproductive toxicity of bendamustine
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	X No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	X N/A (no paragraph IV certification) ☐ Verified
• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification:	

(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (3).*

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day

period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes,**" a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	3/7/08 (P/T); 3/19/08 (CMC) 3/19/08 (Clin - DD); 3/20/08 (OD)
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	9/19/07
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	3/13/08

❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	X DMETS 3/10/08; 3/18/08 X DDMAC 3/3/08 X SEALD 2/25/08 Other reviews ☐ Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	1/25/08
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	X Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	
❖ Pediatric Page (all actions)	X Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	X Verified, statement is acceptable
❖ Postmarketing Commitment Studies	☐ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	March 19, 2008, PMC Tab
• Incoming submission documenting commitment	March 19, 2008, PMC Tab
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	Yes
❖ Internal memoranda, telecons, email, etc.	Yes
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	2/28/08
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg April 12, 2007
• EOP2 meeting *(indicate date)*	☐ No mtg May 9, 2005
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting	X No AC meeting
• Date of Meeting	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	10/10/07; 2/27/08; 3/19/08
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	X None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes X No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• ☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	2/27/08
• ☐ Review & FONSI *(indicate date of review)*	
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	10/18/07; 12/17/07; 2/6/2008

	☐ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: 3/18/08 X Acceptable ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	X Completed ☐ Requested ☐ Not yet requested ☐ Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	11/5/07; 2/27/08
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	November 28, 2007
❖ Nonclinical inspection review Summary (DSI)	☐ None requested
Clinical Information	
Clinical review(s) *(indicate date for each review)*	3/5/08, 3/18/08
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	3/5/08; 3/18/08
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	X None
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	X Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	3/5/08
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	X Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	2/29/08
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) *(indicate date for each review)*	☐ None 10/26/07; 2/19/08; 2/25/08
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 10/16/07; 11/5/07; 2/20/08; 2/22/08

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

Treanda NDA 22-249
Wrap-Up Meeting Description and Agenda
March 10, 2008

Objectives of the NDA/BLA Wrap-Up Meeting meeting are to:

- Develop a comprehensive understanding of the safety, efficacy and quality of the proposed product through presentations of key findings of all reviews, consults and inspections.
- Identify any issues that could preclude an approval action.
- Come to agreement on a preliminary decision on the regulatory action.
- Begin internal discussions regarding potential post-marketing commitments and labeling.

Attendees: Primary reviewers, team leaders, discipline division directors, OSE, and the review division DD and/or signatory authority, plus appropriate consultants (such as DDMAC, OSE, DSI, DMPQ, DMETS, CSS).

Agenda: Reviewers discuss the approvability of the application and address any outstanding critical issues that have not been resolved. Consideration should be given to critical elements such as risk management, major labeling issues, post-marketing commitments, and the need for Center-level input. At the meeting, a plan for resolution of issues is discussed. Depending on the issue, issues will be resolved either internally or with the applicant. Meeting agreements and follow-up actions are captured by the RPM.

- Primary reviewers present outstanding issues
- More detailed labeling discussion begins
- Outstanding PMC issues are discussed

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

April 3, 2008

Cephalon, Inc.
41 Moores Road
Frazer, PA 19355

Attention: Carol S. Marchione
Senior Director and Group Leader

Re: Orphan-drug designation request # 07-2448

Dear Ms. Marchione:

Reference is made to your drug bendamustine (TREANDA®) which was granted orphan-drug designation pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. 360bb) on August 17, 2007, for the treatment of patients with chronic lymphocytic leukemia. We also refer to the letter from the Office of Oncology Drug Products, Center for Drug Evaluation and Research, dated March 20, 2008, granting marketing approval of TREANDA®.

This letter is to inform you that as the first sponsor of this drug to obtain marketing approval for this indication, you are entitled to seven years of orphan-drug exclusive approval pursuant to Section 527 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360cc) for the treatment of patients with chronic lymphocytic leukemia. The exclusive period began on March 20, 2008, the date of approval of your New Drug Application (22-249), and is described under 21 CFR 316.31.

Please note that as the holder of exclusivity for TREANDA® you are required to assure the availability of sufficient quantities of this drug to meet the needs of patients. Failure to do so could result in the withdrawal of the drug's exclusive approval as stipulated under 21 CFR 316.36(b).

The entire premise of the orphan products program is based on the realization that the resources and commitment devoted to the development of drugs for "orphan" populations may not provide financial returns to their sponsors. Therefore, it is with genuine gratitude that we recognize your efforts in developing this drug.

Should you have any questions, please contact Mr. Jeff Fritsch, R.Ph., at (301) 827-0989.

Sincerely yours,

Timothy R. Coté, M.D., M.P.H.
Director, Office of Orphan Products Development

cc:
GCF-1/EDickinson
HFD-610/MHolovac
HFD-150/NDA 22-249
HFD-150/FCross/CSO
HF-35/Chron File
HF-35/OP File # 05-2448
jf 03/20/08
EXCLUSIVITY

Cephalon
deliver more>

www.cephalon.com

Cephalon, Inc.
41 Moores Road
P.O. Box 4011
Frazer, PA 19355
Phone 610-344-0200
Fax 610-344-0065

March 19, 2008

Robert Justice, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncologic Drug Products (HFD-150)
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-249
TREANDA® (bendamustine hydrochloride) for Injection
General Correspondence: Post-Marketing Commitments

Dear Dr. Justice:

Reference is made to Treanda NDA 22-249 and to an e-mail from Captain Frank H. Cross, Jr., FDA Project Manager, sent on March 19, 2008 that contained a revised list of the post-marketing commitments agreed upon by Agency personnel. Cephalon has reviewed this list (see attached) and is in agreement with all of the commitments and associated timeframes. This letter acknowledges Cephalon's commitment to conduct the studies as stated in the attached document in the timeframes stated, acknowledging that conducting some studies are predicated on the outcome of others.

If there are any questions concerning this submission, please contact me at (610) 738-6237, on my cell at (484) 802-6639 or via email at cmarchio@cephalon.com.

Sincerely,

Carol S. Marchione

Carol S. Marchione
Senior Director and Group Leader
Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY
APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Cephalon,Inc.	March 19, 2008
TELEPHONE NO. *(Include Area Code)* (610) 344-0200	FACSIMILE (FAX) Number *(Include Area Code)* (610) 738-6642
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: Cephalon, Inc. 41 Moores Road Frazer, PA 19355	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE Cephalon, Inc. 41 Moores Road Frazer, PA 19355

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 22-249

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Bendamustine hydrochloride	Unknown (Treanda® proposed)

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*: 4-{5-[Bis(2-chloroethyl)amino]-1-methyl-2-benzimidazol-2-yl} butyric acid hydrochloride
CODE NAME *(If any)*: NA

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
lyophilized solid for injection	100 mg	i.v. infusion

(PROPOSED) INDICATION(S) FOR USE: treatment of patients with Chronic Lymphocytic Leukemia (CLL)

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)*
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER OF DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Commitment to PMC

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at this site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Available upon request

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

DMF
DMF

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
	8. Clinical data section (e.g., 314.50(d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
	12. Case reports forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (l)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. Financial Information (21 CFR Part 54)
X	20. OTHER *(Specify)* General Correspondence

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Carol S. Marchione	Carol S. Marchione Senior Director and Group Leader, Regulatory Affairs	03/19/2008

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
41 Moores Road, P.O. Box 4011 Frazer, PA 19355	(610) 738-6327

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

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Please **DO NOT RETURN** this form to this address.

2 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

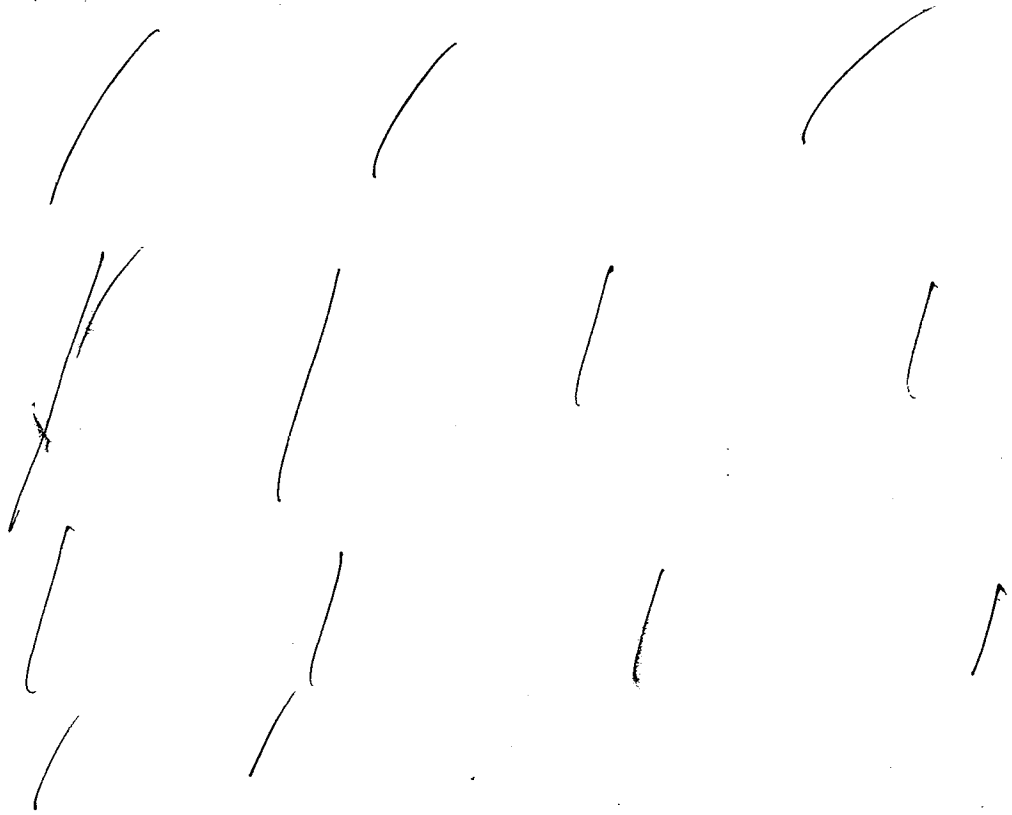
_____ Deliberative Process

Cross Jr, Frank H

From: Cross Jr, Frank H
Sent: Wednesday, March 19, 2008 6:33 PM
To: 'Marchione, Carol'
Subject: NDA 22-249, TREANDA PMCs

Hello,

Please commit to the following PMCs:



Thanks,

Frank

Frank Cross, M.A., MT (ASCP)
CAPT, USPHS Commissioned Corps
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
White Oak Building 22, Rm. 2110
10903 New Hampshire Blvd.
Silver Spring, MD 20993
Ph: 301-796-0876
Fax: 301-796-9845
e-mail: frank.crossjr@fda.hhs.gov

Treanda NDA 22-249
Wrap-Up Meeting Description and Agenda
March 10, 2008
Wrap-Up Meeting Agenda

1. Important Goal Dates

   Review Completion Goal Date according to GRMP: March 20th, 2008

   PDUFA Goal Date: March 20th, 2008

2. Discipline Specific Reviews of Application : up to 60 minutes
   - Conclusions of the studies/information submitted
   - Outstanding issues (including risk management, major labeling issues, PMC, and the need for Center-level input related to your discipline in discussion):

CMC	Ravindra Kasliwal	Up to 8 min
CMC Micro	Anastasia Lolas	Up to 3 min
DMETS	Kristina Arnwine/Tselaine Jones-Smith	Up to 5 min
Pharm Tox	Anwar Goheer	Up to 5 min
Clin Pharm	Julie Bullock	Up to 8 min
Clinical	Ryan & Kwitkowski	Up to 10 min
Stats	Shenghui Tang	Up to 5 min
DSI	Lauren Iacono-Connor	Up to 5 min

3. Discussion of Proposed Action To Be Taken -

   All

4. Labeling Discussion – Amna Ibrahim, up to 10 minutes
   - Status of labeling review
   - Open items with input needed from other reviewers
   - Discuss need for meeting and scheduling
5. Discussion of sign-off procedure and schedule – Frank Cross up to 5 minutes

Cross Jr, Frank H

From: Cross Jr, Frank H
Sent: Friday, March 07, 2008 4:02 PM
To: 'Marchione, Carol'
Subject: NDA 22-249

Hi Carol,

Please review and respond right away.

Thanks,

Frank

We have following comments concerning the vial and the carton labels. Please submit the revised labels.

- Delete — from the " — Single-Use Vial" statement. Revise it to read to read, "Single-Use Vial".
- Express the product strength as 100 mg/vial and [redacted]

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Frank Cross
3/16/2008 05:24:03 PM
CSO

Cross Jr, Frank H

From: Cross Jr, Frank H
Sent: Wednesday, March 05, 2008 9:17 AM
To: 'Marchione, Carol'
Subject: FW: Bendamustine data request (NDA 22-303)

Hi Carol,

Please provide a response.

Thanks,
Frank

It appears that the files we requested are not in the attached submission. Could you please forward the following request to the sponsor?

In your population PK report, you stated that "Using each patient's Bayesian PK parameter estimates, separate predicted concentration-time profiles for bendamustine, M4, and M3 were generated for each patient with concentrations predicted at frequent time intervals to determine estimates of exposure... The predicted concentration-time profile for each patient was used to compute AUC and C_{max} for bendamustine drug exposure and exposure of its two active metabolites, M4 and M3, for each patient." It appears that the files (control streams and datasets) used for the above mentioned analysis are not included in your submission. If you have already included these files, please help us locate the files. If you have not submitted the files, please submit them.

- All datasets should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file.
- Model codes or control streams should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

From: Cross Jr, Frank H
Sent: Tuesday, March 04, 2008 6:02 PM
To: Liu, Qi (CDER)
Cc: Bullock, Julie
Subject: FW: Bendamustine data request (NDA 22-303)

From: Marchione, Carol [mailto:cmarchio@cephalon.com]
Sent: Tuesday, March 04, 2008 1:29 PM
To: Cross Jr, Frank H
Subject: RE: Bendamustine data request (NDA 22-303)

Dear Frank,
I checked with my Clin Pharm associates who confirmed that this information was previously submitted on January 8, 2008 in the attached submission. Please let me know if the reviewer requires any additional files or explanation once they review this document. Regards, Carol

From: Cross Jr, Frank H [mailto:frank.crossjr@fda.hhs.gov]
Sent: Tuesday, March 04, 2008 9:28 AM
To: Marchione, Carol
Subject: Bendamustine data request (NDA 22-303)

Good Morning, Carol,

Please submit the program files and datasets (including the input and output datasets) that you used to compute the individual AUC and Cmax for bendamustine and its metabolites (M3 and M4):

- All datasets should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file.
- Model codes or control streams should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

Thanks,

Frank

Frank Cross, M.A., MT (ASCP),
CAPT, USPHS Commissioned Corps
Co-Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
White Oak Building 22, Rm. 2110
10903 New Hampshire Blvd.
Silver Spring, MD 20993
Ph: 301-796-0876
Fax: 301-796-9845
e-mail: frank.crossjr@fda.hhs.gov

from your system. Thank you.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Frank Cross
3/16/2008 05:27:13 PM
CSO

From: Ibrahim, Amna
Sent: Tuesday, March 04, 2008 6:12 PM
To: Marchione, Carol
Cc: Cross Jr, Frank H; Ryan, Qin
Subject: Re: Proposal for Due Diligence of Financial Disclosure for Treanda Study 02CLLIII

Carol
The form appears ok. However, we do have the following recommendations:

- The investigator should have the option to check boxes (or equivalent) in the form depending on whether they did or did not participate in any financial arrangement with the Sponsor (Ribosepharm) of the study whereby the value of compensation for conducting the study could be affected by the outcome of the study, whether they did or did not have proprietary interest in this product or significant equity interest in the Sponsor of the study, and whether they did or did not receive significant payments of other sorts.

- We recommend that you ask the investigator to respond rapidly (example in 48-72 hours). For investigators who do not respond in a timely manner, we recommend a reminder fax or telephone call.

- You should include either a certification or disclosure of information for investigators participating in foreign covered studies. Where you are unable to obtain the information despite acting with due diligence, you should submit a statement documenting your efforts to obtain the information.

- To expedite the process, we recommend that you send the cover letter and form overnight, such as by FEDEX or DHL.

Thanks
Amna

From: Marchione, Carol [mailto:cmarchio@cephalon.com]
Sent: Tuesday, March 04, 2008 4:25 PM
To: Ibrahim, Amna
Cc: Cross Jr, Frank H
Subject: Proposal for Due Diligence of Financial Disclosure for Treanda Study 02CLLIII
Importance: High

Dear Amna
To address your concerns about due diligence for financial disclosure, we are proposing the send the attached certification form to each investigator who participated in Study 02CLLL III as listed in the original NDA submission. The attached cover letter will accompany the form. It requests that the investigator fax the filled-in certification form to Cephalon no later than March 18, 2008. We will send the request by a certified letter carrier to the investigators. We will keep receipt of the letter by the investigation site on file. On March 18, we will submit all of the responses received to the Agency. Since we were not the sponsor of the study, the investigator has no contractual obligation to reply so we have no sense of the success rate but we will maintain all documentation of the request.

Does this satisfy the Agency's request for due diligence? We will be happy to adjust our plan if necessary. Please advise. Carol

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/s/

Frank Cross
3/16/2008 05:29:10 PM
CSO

Cross Jr, Frank H

From: Cross Jr, Frank H
Sent: Tuesday, March 04, 2008 5:49 PM
To: 'Marchione, Carol'
Subject: Treanda Draft Labeling

Attachments: 3 04 08.doc

Hi Carol,

Please forward the attached to your team.

The items in yellow are still being reviewed by FDA.

Items in gray need your feedback/response.

Thanks,

Frank

3 04 08.doc
(371 KB)

11 Page(s) Withheld

_____ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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/s/

Frank Cross
3/16/2008 05:30:47 PM
CSO

MEETING MINUTES

MEETING DATE: February 28, 2008 **TIME:** 9:30 a.m.
LOCATION: WO Bldg 22, Room 2201

NDA: 22-249

DRUG: TREANDA® (bendamustine hydrochloride) for Injection, for intravenous infusion

SPONSOR/APPLICANT: Cephalon, Inc.

TYPE of MEETING/TELECON: NDA Pre-Approval Safety Conference

Indication: provides for the use of TREANDA® (bendamustine hydrochloride) for Injection, for intravenous infusion, for the treatment of patients with chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established.

Members of the NDA review team and the Office of Surveillance and Epidemiology (OSE) were present for this meeting. The safety profile of TREANDA® (bendamustine hydrochloride) for Injection, for intravenous infusion for the above-referenced indication was discussed with representatives of OSE. No outstanding issues were identified and the pre-approval safety conference for this NDA was concluded.

_____
Frank Cross
Project Manager

Concurrence Chair:_____
Amna Ibrahim, M.D.
Clinical Team Leader

Attachments: None.

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/s/

Amna Ibrahim
3/21/2008 03:43:56 PM

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: February 28, 2008

TO: Dotti Pease, Regulatory Project Manager
Qin Ryan, M.D., Medical Officer

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Acting Branch Chief, Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22249

APPLICANT: Cephalon, Inc.

DRUG: Treanda (bendamustine) for Injection

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Treatment of patients with chronic lymphocytic leukemia (CLL)

CONSULTATION REQUEST DATE: October 18, 2007

DIVISION ACTION GOAL DATE: March 20, 2008

PDUFA DATE: March 20, 2008

I. BACKGROUND:

Treanda (bendamustine) is an antineoplastic agent whose clinical development began in Jena, Germany, in the early 1960s. The clinical development of this drug in the United States began in June 2003 under an IND sponsored by Salmedix, Inc., the initial licensee in the US. In June 2005, Salmedix, Inc. became a wholly owned subsidiary of Cephalon, Inc.; the NDA 22249 applicant. Bendamustine is a new molecular entity but is approved by the German health authority (most recently in July 2005) for the treatment of patients with indolent non Hodgkin's Lymphoma, chronic lymphocytic leukemia (CLL) and multiple myeloma.

Cephalon, Inc. seeks approval of Treanda (bendamustine) for the treatment of patients with CLL. This agent is a cytotoxic compound whose mechanism of action in humans has not been fully characterized. The study targeted for inspection, 02CLLIII, was carried out at 45 clinical centers in 8 countries, all of which were outside of the United States. The study enrolled the first subject on November 5, 2002, imposed a cut-off date of March 26, 2006; however, the study remains open. A total of 350 subjects were planned for enrollment. The study was not conducted under an IND.

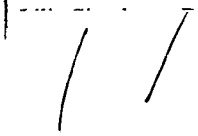
The purpose of this inspection is to validate efficacy and safety data submitted in support of NDA 22249. In addition to a sponsor inspection 4 foreign clinical investigators were inspected. The Division of Oncologic Drug Products (DODP) did not identify any specific data for which it had concerns.

Foreign sites were selected because there are no domestic sites. Noteworthy is the fact that the product division, DODP, has been informed by the sponsor that the sponsor is proposing to censor all data associated with the 2 largest enrolling sites (sites number 01 and 02). The review division, DODP, has requested that the sponsor provide justification for "throwing out" the 2 largest enrolling sites. DODP is in the process of acquiring sponsor audit and clinical monitoring reports for these 2 sites. The review division selected the 4 additional sites for inspection because they wish to determine if GCP violations have occurred in the conduct of study 02CLLIII at these additional 4 sites.

> **Protocol 02CLLIII**: "Phase III, Open-Label, Randomized, Multicenter Efficacy and Safety Study of Bendamustine Hydrochloride Versus Chlorambucil in Treatment-Naive Patients with (Binet Stage B/C) B-CLL Requiring Therapy."

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor City, State or Country	**Indication: Protocol #: and # of Subjects:**	**Insp. Date**	**Final Classification**
CI #1: Bulgaria Site Number 05	CLL: Protocol 02CLLIII: 27	TBD	Pending

CI#2:  Bulgaria Site Number 04	CLL: Protocol 02CLLIII: 14	TBD	Pending
CI #3:  Site Number 12	CLL: Protocol 02CLLIII: 18	January 14-18, 2008	Pending
CI#4:  Germany Site Number 16	CLL: Protocol 02CLLIII: 10	January 07-12, 2008	Pending
SPONSOR: Cephalon, Inc. POC: Carol Marchione Senior Director & Team Leader, Regulatory Affairs 41 Moores Road Frazer, Pennsylvania 19355	CLL: Protocol 02CLLIII	November 13-19, 2007	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI-No Response Requested= Deviations(s) from regulations.
VAI-R = Response Requested = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification based on information in 483; EIR has not been received from the field and complete review of EIR is pending.

1. **CI#1:** 

   Bulgaria
   Site Number 05

   a. **What was inspected:**

   The study records of all 27 subjects enrolled into study Protocol 02CLLIII, and under the care of Dr. —, were audited in accordance with the clinical investigator compliance program, CP 7348.811. Six subjects completed a full course of treatment

in the Bendamustine arm and 7 subjects completed a full course of treatment in the Chlorambucil arm. For all 27 subjects the record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed the date and cause of death and informed consent forms for all randomized subjects. This site did not maintain a separate screening log to identify screening failures from enrolled subjects. Also, the EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. **General observations/commentary**: The investigator was found to be adequate in the execution of the Protocol 02CLLIII. The study was found to be well controlled and well documented. No significant regulatory deviations were observed. Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. CRFs were assessed for data consistency with the source documents. SAEs were properly documented and reported. There was a minor discrepancy in the sites Chlorambucil pill accountability. No Form FDA 483 was issued.

c. **Assessment of data integrity**: The data for Dr. —— site, associated with Protocol 02CLLIII submitted to the Agency in support of NDA 22249, appear reliable based on available information. The general observations described above are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

2. **CI#2:** ——

Bulgaria
Site Number 04

a. **What was inspected**:

The study records of all 14 subjects enrolled into study Protocol 02CLLIII, and under the care of Dr —— , were audited in accordance with the clinical investigator compliance program, CP 7348.811. Five subjects completed a full course of treatment in the Bendamustine arm and 7 subjects completed a full course of treatment in the Chlorambucil arm. For these 14 subjects the record

audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed the date and cause of death and informed consent forms for all randomized subjects. This site did not maintain a separate screening log to identify screening failures from enrolled subjects. Also, the EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. **General observations/commentary**:

The investigator was found to be adequate in the execution of the Protocol 02CLLIII. The study was found to be well controlled and well documented. The protocol was very meticulously followed. No significant regulatory deviations were observed. Consistent with the routine clinical investigator compliance program assessments, the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. CRFs were assessed for data consistency with the source documents. SAEs were properly documented and reported. There was a "slight" loss in Chlorambucil tablets (less than 10%). No Form FDA 483 was issued.

c. **Assessment of data integrity**: The data for Dr —— site, associated with Protocol 02CLLIII submitted to the Agency in support of NDA 22249, appear reliable based on available information. The general observations described above are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

3. **CI#3:** ——

Germany
Site Number 12

a. **What was inspected**:

The study records of all 18 subjects enrolled into study Protocol 02CLLIII, and under the care of Dr. —— , were audited in accordance with the clinical investigator compliance program, CP 7348.811. Seven subjects completed a

full course of treatment in the Bendamustine arm and 1 subject completed a full course of treatment in the Chlorambucil arm. For these 18 subjects the record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed the date and cause of death and informed consent forms for all randomized subjects. This site did not maintain a separate screening log to identify screening failures from enrolled subjects. Also, the EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator and a facsimile copy of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. **General observations/commentary**:

The clinical investigator was generally found to be adequate in the execution Protocol 02CLLIII. The study was found to be well controlled and well documented. However, several regulatory deviations were observed. Consistent with the routine clinical investigator compliance program assessments, the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. CRFs were assessed for data consistency with the source documents. For this site there were only 2 SAEs however, both were reported late. One was for a fall, injury to the head (subject 21204), and the second was for a fungal pneumonia and pulmonary embolism (subject 21208). In addition, for 9 of the 18 subjects randomized, changes in drug dosages were made. A Form FDA 483 was issued citing 1 major observation.

Observation 1. The investigation was not conducted in accordance with the investigational plan. Specifically, the study protocol was not followed as:

- Changes in study drug dosages were made in 9 (6 in the Chlorambucil arm and 3 in the Bendamustine arm) out of 18 subjects as described below:

Subject ID Number	**Calculated Dose**	**Actual Dose Administered**	**Treatment Arm**
11202	105 mg/cycle	120 mg/cycle	Chlorambucil
21203	113 mg/cycle	160 mg/cycle	Chlorambucil
21205	112 mg/cycle	128 mg/cycle	Chlorambucil
11207	108 mg/cycle	118 mg/cycle	Chlorambucil
11208	110 mg/cycle	128 mg/cycle	Chlorambucil
11209	96 mg/cycle	216 (one cycle)	Chlorambucil
11201	205 mg/dy	190 mg/dy	Bendamustine

21201	221 mg/dy	200 mg/dy	Bendamustine
21202	221 mg/dy	190/200 for first cycle, then 210/dy for cycles 2-6	Bendamustine

- Two out of 2 Serious Adverse Events (SAEs) reports were not completed within the time periods as set forth in the protocol for the following subjects; 21204 and 21208

c. **Assessment of data integrity**: The data from Dr. site, associated with the audited Protocol, 02CLLIII, submitted to the agency in support of NDA 22249, may be considered acceptable. On February 26, 2008 Dr. Ryan, the reviewing medical officer, discussed via telecom with the DSI reviewer, Dr. Lauren Iacono-Connors, observation 1, specifically the drug dosing deviations, as described above. The drug dosing deviations described under observation 1 above were not found to be of significant concern to Dr. Ryan, with respect to the impact of these deviations on the clinical outcome of the data submitted to the agency under NDA 22249. The general observations described above are based on preliminary communication from the field investigator and a facsimile of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

4. **CI#4:**

Germany
Site Number 16

a. **What was inspected:**

The study records of all 10 subjects enrolled into study Protocol 02CLLIII, and under the responsible care of Dr. were audited in accordance with the clinical investigator compliance program, CP 7348.811. Two subjects completed a full course of treatment in the Bendamustine arm and 2 subjects completed a full course of treatment in the Chlorambucil arm. For these 10 subjects, the record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed the date and cause of death and informed consent forms for all randomized subjects. This site did not maintain a separate screening log to identify screening failures from enrolled subjects. Also, the EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator and a facsimile copy of the Form FDA 483. The EIR is currently being finalized and will be

submitted to DSI upon completion. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. **General observations/commentary**:

The clinical investigator's sub-investigator, Dr. ——— appears to have been generally in control of all aspects of study execution. The site was generally found to be adequate in the execution of Protocol 02CLLIII. However, several regulatory deviations were observed. Consistent with the routine clinical investigator compliance program assessments, the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. CRFs were assessed for data consistency with the source documents. For this site there were only 3 SAEs in 2 subjects; however, all the SAEs were reported late. One SAE was for sacral back pain and one for plural effusion for Patient 11603 ——, and 2 SAEs for allergic reaction and nausea in Patient 11602 ——. In addition, a number of study subjects were missing one or more end of treatment tests in their electronic CRF. A Form FDA 483 was issued citing 1 major observation.

Observation 1. The investigation was not conducted in accordance with the investigational plan. Specifically, the study protocol was not followed as:

- Four out of the 5 subjects in the Bendamustine arm (11603, 11605, 11602, and 21601) were given a commercially available version of the study drug instead of the study drug provided by the sponsor. Subjects 11602 and 21601 were only treated with commercially available Bendamustine and did not receive any study drug for the sponsor.

- The following study subjects were missing one or more end of treatment tests in the electronic CRF, as required in the investigational plan,

Subject Number	Missing EOT Tests
21601	Blood Chemistry
21602	ECG and Urinalysis
11602	Vitals, ECG, Blood Chemistry
11603	ECG and Urinalysis
11605	Immunoglobulin assay
21604	Vitals, ECG, Urinalysis & Immunoglobulin assay
11601	Urinalysis & Immunoglobulin assay
11604	Immunoglobulin assay
11606	ECG

- Three out of 3 initial Serious Adverse Events (SAEs) reports were not completed within the time periods as set forth in the protocol (2 SAEs for subject 11603 and 1 SAE for subject 11602.

- Three month follow-up visits following the completion of the study to verify study subject viability were not reported in the electronic CRF at the required time for two study subjects (21603 and 11601).

c. **Assessment of data integrity**: The data from Dr. [redacted] site, associated with the audited Protocol, 02CLLIII, submitted to the agency in support of NDA 22249, may be considered acceptable. The reviewing medical officer may consider the impact the above listed missing EOT tests for certain subjects and the impact these missing data may have on overall study outcome for efficacy and safety. The general observations described above are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

5. **Sponsor:** Cephalon, Inc.
   POC: Carol Marchione
   Senior Director & Team Leader, Regulatory Affairs
   41 Moores Road
   Frazer, Pennsylvania 19355

   a. **What was inspected**: The FDA field investigator reviewed study monitoring reports (Protocol 02CLLIII) for sites 01, 02, 04, 05, 12 and 16. The clinical quality assurance relevant SOPs were also assessed. In addition, CRF data versus line listing data were assessed for treatment schedule, patient disposition, investigator overall response evaluation, the independent committee for response assessment (ICRA) findings, study drug records, SAEs, death and physical exam findings. There were no limitations of inspection.

   b. **General observations/commentary**: The FDA Investigator did not issue a Form FDA 483. The audit did not identify significant errors or omissions from the data listings submitted in the NDA 22249. While the sponsor-monitor inspection was extensive there were no significant observations.

   The purpose of this inspection was to validate data submitted in support of NDA 22249. The product division, Division of Drug Oncology Products, was informed by the sponsor that they, the sponsor, proposed to censor all data associated with the 2 largest enrolling sites (sites number 01 and 02). The FDA field investigator inquired as to the basis for this proposal while conducting the sponsor inspection. Specifically, Cephalon staff, Ms. Driscoll-Alberta (Director, GCP Compliance, QA), was asked to explain why the clinical data from site 01 and 02, the highest enrolling sites in the study, were proposed to be excluded from final study analyses. Her responses are summarized below.

- **Regarding Site 01:** when Cephalon staff reviewed the clinical monitoring reports and other correspondence between the site 01 and the study sponsor (Ribosepharm), it was learned that the Ethics Committee had temporarily closed this site because the CI was not physically present at the clinical site and had not been at the site from September 2003 – June 2004. Cephalon told the FDA investigator that a record review resulted in the observations that 50% of the subjects did not meet eligibility criteria and were not evaluable (there were about 20 subjects in this category).
- **Regarding Site 02:** Cephalon staff audited 10 subjects at Site 02 and it was learned that for these subjects there was no attributable evidence that the subjects had been properly consented. Upon inquiry of the site's clinical investigators no additional comments were offered.

c. **Assessment of data integrity**: The data collected and maintained at the sponsor's site, as it pertains to the 4 clinical sites (04, 05, 12 and 16) audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810, associated with the protocol 02CLLIII are consistent with that submitted to the agency as part and in support of NDA 22249.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The study data collected by Dr — Dr. — , Dr. — , and Dr — appear reliable. The inspection of Cephalon Inc., did not identify any critical issues. Only the sponsor inspection has completed the EIR and provided that to DSI for support of the CIS. The 4 CIs final reports (EIRs) have not been completed to date. While 2 of the of the 4 clinical investigators inspected were issued Form FDA 483 inspection observations, it does not appear that the compliance deviations would significantly alter overall study outcome.

The 2 CIs that were issued Form FDA 483s appeared to have problems with protocol compliance, appropriate use of the study drug and the timely reporting of serious Adverse Events. The deliberate use of altered dosing levels in certain subjects for both the study drug and comparator drug at Dr. — , site does not appear to give the study drug a favorable advantage (personal communication with the review division medical officer, Qin Ryan). According to the final establishment inspection report for the sponsor the site deliberately altered drug dosing levels for "safety reasons."

Regarding study sites 01 and 02, the FDA inspectional findings described in this report are not sufficient to make a determination of data reliability associated with those data generated at study sites 01 and 02. The sponsor-described findings of protocol non-compliance and possible human use ethics violations at these foreign sites are very concerning. Conclusive determination of data unreliability from these sites based on inspectional findings —

Observations noted above are based in part on the preliminary communications provided the field investigators. Only the findings at the sponsor, Cephalon Inc., are based on a final EIR. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final remaining EIRs.

Follow-Up Actions: DSI will generate an inspection summary addendum if the conclusions change significantly upon receipt and review of the pending EIRs and the supporting inspection evidence and exhibits.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Acting Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations
Office of Compliance

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/s/

Lauren Iacono-Connors
2/29/2008 03:39:20 PM
UNKNOWN

Tejashri Purohit-Sheth
2/29/2008 04:21:11 PM
MEDICAL OFFICER

From: Pease, Dorothy W
Sent: Friday, February 08, 2008 6:35 AM
To: 'Marchione, Carol'
Subject: NDA 22-249 CMC requests

NDA 22249

Request for CMC information.

1. The data for drug product profile for the [redacted] appears comparable at [redacted] Therefore for the drug product [redacted] the maximum hold period (cumulative) should be [redacted] Provide amended documents that reflect this change.

2. Describe the [redacted] to assure adequate seal to maintain sterility of the vials.

3. Based on the data the acceptance criteria for the reconstitution time of the drug product should be changed to NMT [redacted]

4. The proposed limit for [redacted] in the drug product is more than then amount qualified. The batches made at [redacted] using the improved manufacturing process (using [redacted]) show a maximum amount of [redacted] in the batches. Based on the qualification level of [redacted] with an approximate 3-fold safety factor in a repeat-dose non-clinical toxicology study, the impurity limit should be reduced to ≤ [redacted]. Provide amended specifications to reflect this change.

5. You have not indicated the level at which [redacted] impurity in the drug product is qualified. Either reduce the impurity limit to [redacted] based on the available data or provide the data to qualify the proposed [redacted] limit for this impurity.

6. You have not indicated the level at which [redacted] impurity in the drug product is qualified. Either reduce the impurity limit to [redacted] based on the available data or provide the data to qualify the proposed [redacted] limit for this impurity.

7. You have not provided data for the compatibility of the constitution solution with other commonly available diluents, e [redacted]. Provide these data. [redacted]

8. Provide the impurities data, in addition to the assay values, for the constituted and diluted product in the bag. The impurities must remain within the stated limits in specifications.

The chemist is hoping for a response early next week.

Thanks

Dotti

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dotti Pease
2/8/2008 06:37:42 AM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-249 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Treanda
Established Name: bendamustine hydrochloride
Strengths: for injection 100 mg

Applicant: Cephalon, Inc.
Agent for Applicant (if applicable):

Date of Application: 9-19-07
Date of Receipt: 9-20-07
Date clock started after UN:
Date of Filing Meeting: 10-26-07
Filing Date: 11-19-07
Action Goal Date (optional): 3-20-08 User Fee Goal Date: 3-20-08

Indication(s) requested: Chronic lymphocytic leukemia

Type of Original NDA: (b)(1) ☐ (b)(2) ☒
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☐ P ☒
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.) V

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☐ Exempt (orphan, government) ☒
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☒
   This application is: All electronic ☐ Combined paper + eNDA ☒
   This application is in: NDA format ☐ CTD format ☒
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☒ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format? All except cover letter, 356H, 3542a (patent information), patent certification, debarment certification, field copy certification, 3397 (User Fee), and 3454 (financial disclosure).

   Additional comments:

3. This application is an eCTD NDA. YES ☐
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO ☒
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  YES ☐ NO ☒

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☐ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

  If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☒ NO ☐

- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 67,554

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) 9-2-04 and 5-9-05 (CMC) NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☒
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☒ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☒ YES ☐ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐

- If a parenteral product, consulted to Microbiology Team? YES ☒ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 26, 2007

NDA #: 22-249

DRUG NAMES: Treanda (bendamustine hydrochloride)

APPLICANT: Cephalon

BACKGROUND: This is a new molecular entity proposed as a lyophylized for injection formulation at 100 mg. in patients with chronic lymphocytic leukemia.

ATTENDEES: RJustice, RDagher, AIbrahim, STang, RSridhara, AGoheer, NBoocker, RHarapanhalli, SPope, LIacono-Connor, JBullock, ALolas, VKwitkowski, QRyan, RKasliwal, DPease

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	Reviewer
Medical:	Qin Ryan, M.D. Gini Kwitkowski, Senior Clinical Analyst
Secondary Medical:	Amna Ibrahim, M.D.
Statistical:	Shenghui Tang, Ph.D./Raji Sridhara, Ph.D.
Pharmacology:	Anwar Goheer, Ph.D./John Leighton, Ph.D.
Statistical Pharmacology:	
Chemistry:	Ravindra Kasliwal, Ph.D./Sarah Pope, Ph.D., PAL, ONDQA/Ravi Harapanhalli, Ph.D.
Environmental Assessment (if needed):	
Biopharmaceutical:	Julie Bullock, Ph.D./Brian Booth, Ph.D.
Microbiology, sterility:	Anastasia Lolas, Ph.D./Bryan Riley, Ph.D.
Microbiology, clinical (for antimicrobial products only):	
DSI:	Lauren Iacono-Connor
OPS:	
Regulatory Project Management:	Dotti Pease
Other Consults:	OSE – Sam Chan

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☒ NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☐ FILE ☒ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? YES ☐ NO ☒

PHARMACOLOGY/TOX N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Sterile product? YES ☒ NO ☐
  If yes, was microbiology consulted for validation of sterilization? YES ☒ NO ☐

ELECTRONIC SUBMISSION:
Any comments: not easily navigable

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☒ No filing issues have been identified.
- ☒ Issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. ☐ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5.☒ Convey document filing issues/no filing issues to applicant by Day 74.

Dotti Pease
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☒

*If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)
YES ☐ NO ☒

*If "**Yes**," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?
YES ☐ NO ☒

*If "**Yes** "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?
   YES ☐ NO ☒

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "**No**," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "**No**," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*
Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☒

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No,**" to (a) skip to question 7. Otherwise, answer part (b and (c)).*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes,**" to (c), proceed to question 7.*

***NOTE:** If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No,**" to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☐ NO ☒

*If "**No,**" skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12. NO

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☒

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☒

11. Is the application for a duplicate of a listed drug whose only difference is YES ☐ NO ☒

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO ☒

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

  YES ☒ NO ☐

  *If "**Yes**," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug* none

  Was this listed drug product(s) referenced by the applicant? (see question # 2)

  N/A YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

  N/A ☒ YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

N/A ☐ NO ☐

YES

If "**Yes**," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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/s/

Dotti Pease
1/25/2008 02:41:35 PM
CSO

From: Pease, Dorothy W
Sent: Wednesday, January 09, 2008 11:04 AM
To: 'Marchione, Carol'
Subject: Another comment from clinical pharmacology

Please submit the updated label based upon data from Studies SDX-105-02, 2006001 and legacy studies. In addition, please cite in the clinical pharmacology section which studies you used to support each claim in the labeling.

Dotti Pease
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
301 796-1434 fax 301 796-9845

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/s/

Dotti Pease
1/9/2008 11:37:13 AM
CSO

From: Pease, Dorothy W
Sent: Wednesday, January 09, 2008 6:36 AM
To: 'Marchione, Carol'
Subject: Clin Pharm request

In the clinical pharmacology summary (Appendix B, Section 6 Conclusions) it is stated that "Plasma concentration values for bendamustine in a limited number of patients in studies 98B03 (n=6) and 20BEN D1 (n=7) were obtained within the 6-month period of demonstrated stability for bendamustine, using a validated method, and with acceptable, concurrent calibration and QC results." Do you know which subjects these are so I can extract them from the data?.

In addition I am having a hard time locating the PK study reports (I found very brief clinical study summaries but that is all) for the following studies: 20BEN D1, & 20BEN03. Any guidance on where I can locate these would be appreciated.

Thanks
Dotti

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/s/

Dotti Pease
1/9/2008 11:33:21 AM
CSO

Pease, Dorothy W

From: Pease, Dorothy W
Sent: Thursday, December 20, 2007 12:51 PM
To: 'Marchione, Carol'
Subject: Treanda clin pharm request

Please submit the following datasets to support the population PK analysis (Report CP-07-002):

• All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

• Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

• A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Thanks

Dotti Pease
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
301 796-1434 fax 301 796-9845

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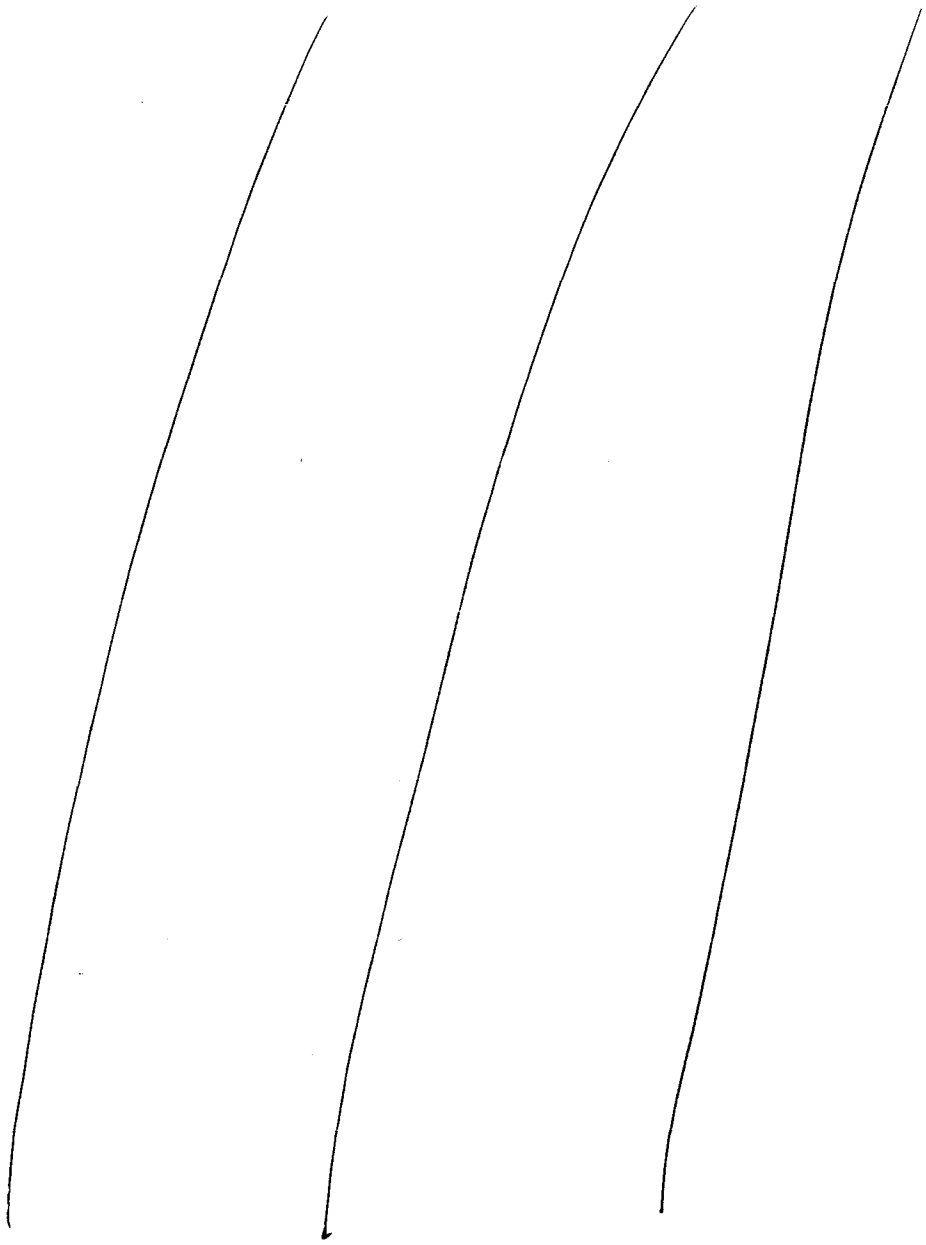
/s/

Dotti Pease
12/20/2007 01:27:42 PM
CSO

Pease, Dorothy W

From: Pease, Dorothy W
Sent: Monday, December 17, 2007 11:41 AM
To: 'Marchione, Carol'
Subject: Micro deficiencies

Below are the latest microbiology deficiencies. They would like a response within two weeks, if possible:
Deficiencies:



(C)

1 Page(s) Withheld

✓ Trade Secret / Confidential

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_____ Deliberative Process

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/s/

Dotti Pease
12/17/2007 11:50:29 AM
CSO

4 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Executive CAC
Date of Meeting: November 27, 2007

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair
Todd Bourcier, Ph.D., DMEP, Alternate Member
Chuck Resnick, Ph.D., DCRP, Alternate Member
John K. Leighton, Ph.D., DDOP, Team Leader
M. Anwar Goheer, Ph.D., DDOP, Presenting Reviewer

Author of Draft: Anwar Goheer

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 22-249
Drug Name: Treanda® (Bendamustine hydrochloride)
Sponsor: Cephalon, Inc.

Background: Bendamustine hydrochloride is a nitrogen mustard derivative, alkylating agent. It is under review for treatment of chronic lymphocytic leukemia. The proposed recommended dose is 100 mg/m^2 administered as an intravenous infusion over 30 minutes on days 1 and 2 of a 28-day cycle, up to 6 cycles.

The sponsor of this NDA (Cephalon) would like the findings of a published study [Arch Geschwulstforsch 1974; 43(1):16-21] to be included in labeling under **Carcinogenesis, Mutagenesis, Impairment of Fertility**.

Mouse Carcinogenicity Study: In the published paper [Arch Geschwulstforsch 1974; 43(1):16-21] female mice were treated orally or intraperitoneally with bendamustine hydrochloride for four consecutive days and observed until death.

Intraperitoneal injections of bendamustine for four days produced peritoneal sarcomas. **Oral administration** for four days induced mammary carcinomas and pulmonary adenomas.

Executive CAC Recommendations and Conclusions:

- The Committee noted that the full spectrum of potential carcinogenicity was not evaluated in the study. However, the Committee concurred that the following neoplasms were drug related: peritoneal sarcomas after intraperitoneal administration; pulmonary adenomas and mammary carcinomas after oral administration.

- The Committee did not concur that the ——— seen after oral administration were clearly drug related.

Abigail Jacobs, Ph.D.
Acting Chair, Executive CAC

cc: \
/Division File, DDOP
/JKLeighton, DDOP
/MAGoheer, DDOP
/DWPease, DDOP
/ASeifried, OND IO

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/s/

Abby Jacobs
11/28/2007 01:52:51 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-249

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 September 19, 2007, received September 20, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Treanda (bendamustine hydrochloride).

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 Priority. Therefore, the user fee goal date is March 20, 2008.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by February 22, 2008.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

We note the numerous requests for information already forwarded to you and your responses. One outstanding issue is the submission of the bone marrow reports, which we are expecting in the next few weeks. Additionally, please note that whether a ——— will be required ——— will be a review issue.

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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/s/

Robert Justice
11/27/2007 05:43:17 PM

Pease, Dorothy W

From: Pease, Dorothy W
Sent: Thursday, November 08, 2007 8:20 AM
To: 'Marchione, Carol'
Subject: Clin pharm request

1. In order to support the Clinical Pharmacology section of the label the pharmacokinetic final study reports and data for studies SDX-105-03 and 2006001 need to be submitted to the NDA before Dec 20, 2007. Failure to do so will require removal of the labeling sections which rely upon this data.
2. Data sets need to be provided for any of the 'legacy studies' which are used to support or confirm pharmacokinetic information in the label. In the absence of this data, phase 4 commitments will be required.

Dotti Pease
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
301 796-1434 fax 301 796-9845

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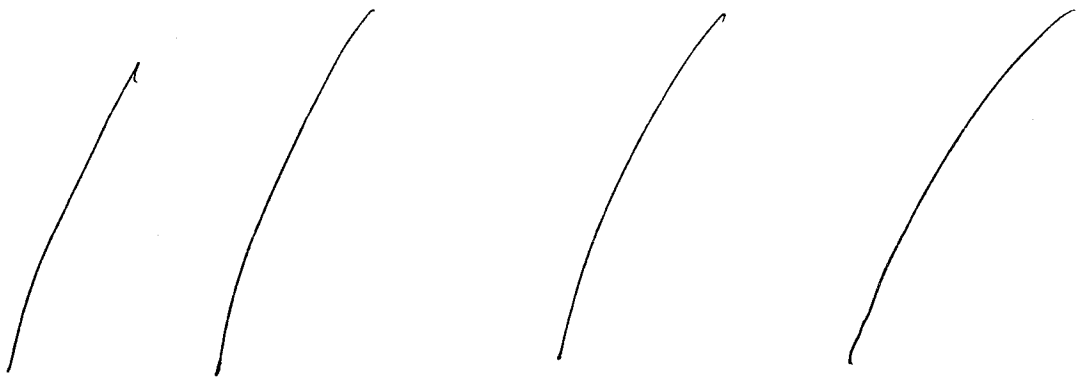
/s/

Dotti Pease
11/8/2007 08:23:13 AM
CSO

Pease, Dorothy W

From: Pease, Dorothy W
Sent: Thursday, November 08, 2007 7:42 AM
To: 'Marchione, Carol'
Subject: Request from microbiology



Thanks

Dotti Pease
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
301 796-1434 fax 301 796-9845

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/s/

Dotti Pease
11/8/2007 07:46:13 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-249

NDA ACKNOWLEDGMENT

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:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Treanda (bendamustine hydrochloride)

Date of Application: September 19, 2007

Date of Receipt: September 20, 2007

Our Reference Number: NDA 22-249

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 19, 2007 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above shown above be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

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

Sincerely,

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Dotti Pease
10/30/2007 07:32:47 AM

From: Thomas, Sharon
Sent: Monday, October 29, 2007 4:01 PM
To: 'Marchione, Carol'
Subject: NDA 22-249 Treanda in CLL

Carol,

Please see the following request below from the medical officer. Please call if you have any questions.

Thanks,
Sharon

Base on your study 02CLLIII report, 45 patients had a complete response to assigned study treatment, as detailed in the table below. Please submit these patients bone marrow pathological reports at baseline and the time of CR.

Sites	Treanda (n = 153)	Chlorambucil (n=148)	All (n = 301)
Germany	13	1	14
Bulgaria	16	2	18
Other	13	0	13
All	42	3	45

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/s/

Sharon Thomas
10/29/2007 03:04:36 PM
CSO

Pease, Dorothy W

From: Johnson, J. Lloyd
Sent: Tuesday, October 23, 2007 9:06 AM
To: Pease, Dorothy W
Cc: Iacono-Connor, Lauren
Subject: Treanda(bendamustine)/22-249/Cephalon/DDOP (Ryan) - Pease

Dotti,

Please note that Lauren Iacono-Connor has been assigned as the DSI reviewer for this NDA.

Please include her on all relevant NDA meetings for this application requiring DSI participation.

Thanks,
Lloyd

Pease, Dorothy W

From: Kwitkowski, Virginia
Sent: Thursday, October 18, 2007 2:59 PM
To: 'cmarchio@cephalon.com'
Cc: Ibrahim, Amna; Pease, Dorothy W; Thomas, Sharon; Ryan, Qin
Subject: NDA 22-249 Bendamustine

Dear Carol,

I have a few questions for your team pertaining to the application and Study 02CLLIII:

1) Please provide me with the location of the MedDRA hierarchichal terms "HLGT" and "HLT" for the adverse events in the submission. The Adverse Event dataset provided only contains the MedDRA verbatim term, SOC, and LLT.

2) Please provide clarification of what modifications were made to the MedDRA SOC and HLT as mentioned in Table 36, Section 2.7.4, Summary of Clinical Safety.

3) Please provide complete chemistry and hematology datasets for all patients (n=296). I joined the **D_LABC1.xpt** and **D_LABC2.xpt** datasets and only obtained records on 160 patients. Likewise, I joined the **D_LABH1.xpt** to **D_LABH2.xpt** to **D_LAB H3.xpt** and only obtained records on 114 patients.

4) Please provide the randomized treatment group for patient 27402. This patient has the treatment group missing in the **D_RANDOM.xpt** dataset.

Please let me know how soon we can expect to receive this information from you.

Thank you,

Virginia (Gini) E. Kwitkowski
Senior Clinical Analyst

Division of Drug Oncology Products
Office of Oncology Drug Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

10903 New Hampshire Avenue
Bld 22, Rm 2161, Mailstop 2105
Silver Spring, MD
20993-0002

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/s/

Dotti Pease
10/19/2007 08:25:13 AM
CSO

DSI CONSULT: Request for Clinical Inspections

Date: October 16, 2007

To: Leslie Ball, M.D., Branch Chief, GCP2, HFD-47

Through: Robert Justice, M.D.
Director, Division of Drug Oncology Products

cc: Gary Della'Zanna, D.O, Director, Division of Scientific Investigations, HFD-45
J. Lloyd Johnson, Division of Scientific Investigations, HFD-47

From: Dotti Pease, Chief, Project Management Staff, HFD-150
Division of Drug Oncology Products

Subject: **Request for Clinical Site Inspections**
NDA 22-249
Cephalon, Inc.
Treanda (bendamustine) for Injection

Protocol/Site Identification:

A single randomized study, 02CLLIII, has been submitted to support the approval of Treanda in patients with CLL. As discussed with you, the following sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Site number	Investigator and affiliation	Number of patients enrolled
05	Bulgaria	26
12	Germany	18
04	Bulgaria	14
16	Germany	10

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) February 20, 2008. We intend to issue an action letter on this application by (division action goal date) March 20, 2008. The PDUFA due date for this application is March 20, 2008.

Should you require any additional information, please contact Dotti Pease.

Robert Justice, M.D., Division Director (for foreign inspection requests only)

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/s/

Robert Justice
10/18/2007 03:31:05 PM

Pease, Dorothy W

From: Goheer, M A
Sent: Thursday, October 18, 2007 3:04 PM
To: Ibrahim, Amna; Pease, Dorothy W
Cc: Leighton, John K; Goheer, M A
Subject: FW: NDA 22,249, labeling

We are taking this NDA to Exec CAC meeting on November 27, 2007.
Thanks
Anwar & John

From: Goheer, M A
Sent: Thursday, October 18, 2007 2:33 PM
To: Seifried, Adele S
Cc: Leighton, John K; Goheer, M A
Subject: RE: NDA 22,249, labeling

Information needed to schedule an Exec CAC meeting

1. For final studies:

- IND or NDA number: NDA 22-249
- Name of drug: TREANDA (Bendamustine hydrochloride)
- Sponsor: Cephalon
- Number of studies: 1 published paper (Güttner J, Bruns G, Jungstand W. [Oncogenicity of gamma-(1-methyl-5-bis-(betachloroethyl)-aminobenzimidazolyl-(2))-butyric acid hydrochloride (cytostasan) in mice. Arch Geschwulstforsch 1974;43(1):16-21).
- Your supervisor: John Leighton
- Your project manager: Dorothy W. Pease
- To which specific submission I should link the minutes (particularly for an IND): IND 67,554, NDA 22-249
- Date you would like to meet: November 27, 2007
- Due date: Priority GRMP NDA

Please let me know if you need more information.
Thanks

From: Goheer, M A
Sent: Thursday, October 18, 2007 1:52 PM
To: Seifried, Adele S
Cc: Goheer, M A
Subject: RE: NDA 22,249, labeling

I will be in touch after talking to John.
Thanks

From: Seifried, Adele S
Sent: Thursday, October 18, 2007 1:46 PM
To: Goheer, M A
Subject: FW: NDA 22,249, labeling

To recap, 10/30 and 11/6 are very bad days; 11/13 or 11/20 would be possible with David, but not Abby; 11/27 would have Abby, but not David. Here's what I need to schedule, and just let me know which dates you decide on -- Thanks, Adele

Information needed to schedule an Exec CAC meeting

1. For final studies:

- IND or NDA number:
- Name of drug:
- Sponsor:
- Number of studies:
- Your supervisor:
- Your project manager:
- To which specific submission I should link the minutes (particularly for an IND):
- Date you would like to meet:
- Due date:

From: Jacobson-Kram, David
Sent: Thursday, October 18, 2007 1:29 PM
To: Goheer, M A
Cc: Leighton, John K; Seifried, Adele S
Subject: RE: NDA 22,249, labeling

Please provide Adele with copies of the relevant documents and schedule a date for discussion.
Tx

David Jacobson-Kram, Ph.D., DABT
Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-0175
Fax: 301-796-9856
email: note new address david.jacobsonkram@fda.hhs.gov

From: Goheer, M A
Sent: Thursday, October 18, 2007 11:40 AM
To: Jacobson-Kram, David
Cc: Leighton, John K; Goheer, M A
Subject: RE: NDA 22,249, labeling

Thank you very much for your prompt response. The reference language is from a published paper by "Güttner J, Bruns G, Jungstand W. [Oncogenicity of gamma-(1-methyl-5-bis-(betachloroethyl)-

aminobenzimidazolyl-(2))-butyric acid hydrochloride (cytostasan) in mice. Arch Geschwulstforsch 1974;43(1):16-21.

Looking forward to hearing from eCAC.

Anwar

From: Jacobson-Kram, David
Sent: Thursday, October 18, 2007 11:07 AM
To: Goheer, M A
Cc: Leighton, John K
Subject: RE: NDA 22,249, labeling

I would ask the eCAC to comment of the quality of the studies. I think that could be pivotal in deciding when to include in labeling.

David Jacobson-Kram, Ph.D., DABT
Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-0175
Fax: 301-796-9856
email: note new address david.jacobsonkram@fda.hhs.gov

From: Goheer, M A
Sent: Thursday, October 18, 2007 9:14 AM
To: Jacobson-Kram, David
Cc: Leighton, John K; Goheer, M A
Subject: NDA 22,249, labeling

This NDA in CTD format has been selected as our division's pilot GRMP NDA.

On page 6 of 8, the sponsor has proposed the following language.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

standard carcinogenicity study in female mice treated orally (187.5 mg/m2) or intraperitoneally (37.5 and 75 mg/m2) with bendamustine hydrochloride for four consecutive days

; pulmonary adenomas, and mammary carcinoma (oral route)

1) Should this be in the labeling?
2) Do we need this to take to CAC? There was no previous concurrence on dose. Our recommendation would be no, but we are looking for concurrence.

Thanks

Pease, Dorothy W

From: Pease, Dorothy W
Sent: Tuesday, October 16, 2007 11:54 AM
To: 'Marchione, Carol'
Subject: Request from medical officer re: Treanda

Please submit your full QC review report/record for study 02CLLIII sites 01, 02, 04, 05, 12, 26, and 41.

Dotti Pease
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
301 796-1434 fax 301 796-9845

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/s/

Dotti Pease
10/17/2007 06:44:32 AM
CSO

Pease, Dorothy W

From: Pease, Dorothy W
Sent: Tuesday, October 16, 2007 6:36 AM
To: Thompson, Elizabeth
Cc: CDER SEALD Labeling
Subject: RE: PLR labeling and SEALD review

- Are you the RPM for this submission? Yes
- What is the complete trade name and generic name? As noted in COMIS, Treanda (bendamustine hydrochloride)
- Receipt date: As noted in COMIS, 9-20-07
- Is this a resubmission? If so, is it exempt from PLR? No
- PDUFA- associated dates (filing, mid-cycle and goal date):
    1. Filing Meeting: 10-26-07
    2. Mid-cycle Meeting: 12-3-07
    3. Labeling Meetings: tbd
    4. PDUFA goal date: 3-20-08
    5. Division's internal planned action date (not GRMP date): 3-20-08

Submitted label in PLR format: YES/NO (if yes, provide electronic and/or EDR link): yes \\CDSESUB1\NONECTD\N22249\N_000\2007-09-19

bmitted SPL: YES/NO: yes

From: Thompson, Elizabeth
Sent: Sunday, October 07, 2007 8:22 AM
To: Pease, Dorothy W
Cc: CDER SEALD Labeling
Subject: PLR labeling and SEALD review

Dear Dotti:

According to COMIS, you have an application (NDA 22-249) that was submitted to the Agency. I am contacting you from the SEALD-Labeling team to verify and offer assistance with any PLR-SPL issues.

For our tracking purposes, please provide and/or verify the following information:

- Are you the RPM for this submission?
- What is the complete trade name and generic name?
- Receipt date:
- Is this a resubmission? If so, is it exempt from PLR?
- PDUFA- associated dates (filing, mid-cycle and goal date):
    1. Filing Meeting:
    2. Mid-cycle Meeting:

Pease, Dorothy W

From: Chan, Samuel
Sent: Tuesday, October 09, 2007 2:08 PM
To: Pease, Dorothy W
Subject: RE: Treanda NDA 22-249 tradename consult

It looks like this submission only requires tradename and labeling (container and carton) reviews. I didn't see any risk management plan or PPI (Medguide). So I don't think you need to send me a separate consult. If you find any specific safety issues of this application in the future that you want OSE feedback, please then send us another safety consul. Thanks.

Sam

From: Pease, Dorothy W
Sent: Friday, October 05, 2007 9:46 AM
To: Chan, Samuel
Subject: Treanda NDA 22-249 tradename consult

I forgot your request to separate out the tradename consult from the rest of the OSE consult. Do you want me to do a separate one for tradename?

Thanks

Dotti

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR SEALD CONSULTATION

TO *(Division/Office)*:
Study Endpoints and Label Development Team (SEALD)
CDER/OND-IO White Oak Bldg 22, Mail Drop 6411

FROM *(Division/Office)*: Dotti Pease, PM, OODP, DDOP, Rm. 2204, 301-796-1434

DATE of REQUEST	NDA/BLA/IND NO.	SERIAL NO/SUPPL. NO	TYPE OF DOCUMENT	DATE OF DOCUMENT
Oct. 2, 2007	NDA 22-249		Orig. NDA	Sept. 20, 2007

NAME OF DRUG	MEETING DATES FOR SUBMISSION	CLASSIFICATION OF DRUG	REQUESTED COMPLETION DATE
Treanda (bendamustine hydrochloride)	Internal: Filing 10-26-07 Sponsor: Presentation 10-1-07	1 P V	Feb. 20, 2008

NAME OF SPONSOR or INVESTIGATOR (for investigator InitiatedINDs): Cephalon Inc.

DRUG DEVELOPMENT PHASE & MILESTONE

- ☐ pre-IND/pre-BBIND
- ☐ PHASE II
- ☐ PHASE III
- ☐ PRE-NDA/BLA MEETING
- ☐ NDA/BLA/sNDA/SBLA REVIEW
- X NDA/BLA SAFETY/EFFICACY UPDATE
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ NDA/BLA/sNDA/SBLA RESUBMISSION REVIEW
- ☐ ADVISORY COMMITTEE MEETING
- ☐ LABELING (INITIAL OR REVISION)
- ☐ ADVERTISING REVIEW
- ☐ OTHER (Specify)

STUDY ENDPOINT OR LABELING To BE REVIEWED

STUDY ENDPOINT REVIEW

- ☐ TYPE A MEETING PACKAGE
  - ☐ CLINICAL HOLD/DISPUTE RESOLUTION
  - ☐ SPA RESPONSE
- ☐ TYPE B MEETING PACKAGE
  - ☐ PRE-IND MEETING
  - ☐ END OF PHASE II/Pre-PHASE III
  - ☐ PRE-NDA/BLA
- ☐ TYPE C MEETING PACKAGE
- ☐ SPECIAL PROTOCOL ASSESSMENT REVIEW
- ☐ STANDARD PROTCOL REVIEW
- ☐ PROGRESS REPORT
- ☐ STATISTICAL ANALYSIS PLAN REVIEW
- ☐ ENDPOINT DEVELOPMENT/VALIDATION DOSSIER
- ☐ NDA / BLA REVIEW
- ☐ AC MEETING

LABELING REVIEW

- X PROPOSED LABELING
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ DRUG ADVERTISING
- ☐ OTHER (SPECIFY):

CONSULT REVIEW REQUESTED

Consult requested for labeling review for new NDA for CLL in PLR format .

Submission available in EDR

Thanks

Dotti

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Dotti Pease, Project Manager	☐ INTEROFFICE MAIL ☐ HAND-CARRIED X E-MAIL
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

- receipt date: 9-20-07
- PDUFA- associated dates (filing, mid-cycle and goal date):
  1. Filing Meeting - 10-26-07
  2. Mid-cycle Meeting – 12-3-07
  3. Labeling Meetings – nto be scheduled
  4. PDUFA goal date – 3-20-08
  5. Internal Division goal date – 3-20-08
- Submitted product label in PLR format (electronic and/or EDR link): \\CDSESUB1\NONECT\N22249_000\2007-9-19
- Submitted SPL: yes

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Office of Surveillance and Epidemology (OSE), Attention: Samuel Chan			FROM *(Name, Office/Division, and Phone Number of Requestor)*: Dotti Pease, PM, OODP/DDOP, 301-796-1434	
DATE 10-2-07	IND NO.	NDA NO. 222-249	TYPE OF DOCUMENT orig NDA	DATE OF DOCUMENT 9-20-07
NAME OF DRUG Treanda (bendamustine hydrochloride)	PRIORITY CONSIDERATION P		CLASSIFICATION OF DRUG 1 P V	DESIRED COMPLETION DATE February 20, 2008

NAME OF FIRM: Cephalon Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Consult for new NDA. Available in EDR. PDUFA Due Date (PRIORITY) is March 20, 2008. Filing meeting scheduled for Oct. 26, 2007. Consult needed for final labeling review and Tradename (not previously reviewed). There is no proposed Risk Management Plan to my knowledge.

Proposed name *	Treanda
Established name*	bendamustine hydrochloride
Indication of use *	chronic lymphocytic leukemia
Dosage forms*	lyophilized solid for injection
Strength*	100 mg
Usual dose*	IV infusion over 30 min. 100 mg/m2
Dosing Frequency*	Day 1 and 2 of 28 day cycle, up to 6 cycles
Prescribing population	oncologists
Packaging information (if injectable)	100 mg/20 mL single-use vial
Route of administration	IV
Any unique product characteristics for the drug	

Major adverse events that may have been identified that can result form a medication error
Labels and Labeling
Carton container

Thanks
Dotti

SIGNATURE OF REQUESTOR Dotti Pease	METHOD OF DELIVERY (Check one) ☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Dotti Pease
10/2/2007 09:21:56 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: DDMAC
'ention: Joe Grillo, Pharm D

FROM *(Name, Office/Division, and Phone Number of Requestor)* Division of Drug Oncology Products
Dotti Pease, PM, 301-796-1434

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
October 2, 2007		22-249	Orig NDA	Sept. 20, 2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATIONOF DRUG	DESIRED COMPLETION DATE
Treanda (bendamustine hychloride)	Priority	1 P V	February 20, 2008

NAME OF FIRM: Cephalon Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☒ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ 'ROTOCOL REVIEW
- ☐ 'THER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Consult requested for new NDA. Please review labeling, attend relevant meetings and review any advertising materials that may be submitted.
Filing meeting scheduled for Oct. 26. PDUFA due date is March 20, 2008.
Submission available in EDR.

Thanks
Dotti

'ATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Dotti Pease, PM	☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Pease, Dorothy W

Subject:	INT MTG filing/Treanda(bendamustine)/22-249/Cephalon/DDOP (Ryan) - Pease
Location:	CDER OODP MEETING CALENDAR; CDER WO 2201 conf rm Bldg22
Start:	Fri 10/26/2007 3:00 PM
End:	Fri 10/26/2007 4:00 PM
Show Time As:	Tentative
Recurrence:	(none)
Meeting Status:	Not yet responded
Required Attendees:	Pease, Dorothy W; Justice, Robert; Dagher, Ramzi; Ibrahim, Amna; Ryan, Qin; Sridhara, Rajeshwari; Tang, Shenghui; Pope, Sarah; Sarker, Haripada; Leighton, John K; Goheer, M A; Booth, Brian P
Optional Attendees:	Grillo, Joseph; Chan, Samuel; Johnson, J. Lloyd; CDER 150 Calendar; Pazdur, Richard

OPTIONAL ATTENDEES: Johnson, Chan, Grillo

PRODUCT: Treanda (bendamustine - AMD3100)
INDICATION: chronic lymphocytic lymphoma
PURPOSE: Discuss filing of new NDA and timelines for this pilot NDA
MO: Ryan

INTERNAL ONLY: Friday, Oct. 26, 2007 3:00-4:00 Rm 2201

1: Pease

Pease, Dorothy W

Subject:	NDA Presentation/Treanda/IND 67,554/Cephalon/DDOP (Ryan/Thomas-PM)
Location:	CDER 150 Calendar; CDER OODP MEETING CALENDAR; CDER WO 1315 conf rm Bldg22 - AR
Start:	Mon 10/1/2007 2:00 PM
End:	Mon 10/1/2007 3:30 PM
Recurrence:	(none)
Meeting Status:	Accepted
Required Attendees:	Thomas, Sharon; Justice, Robert; Farrell, Ann T; Ibrahim, Amna; Ryan, Qin; Goheer, M A; Leighton, John K; Booth, Brian P; Sridhara, Rajeshwari; Jiang, Xiaoping (Janet); Madabushi, Rajnikanth
Optional Attendees:	Patel, Hasmukh B; Pawar, Vinayak; Jenney, Susan; Pazdur, Richard; Weiss, Karen; Grillo, Joseph; Oh, Kathy; Johnson, J. Lloyd; Ning, Yang-Min (Max); Chan, Samuel; Pope, Sarah; Harapanhalli, Ravi S; Mcfadden, Emily

Sponsor: Cephalon, Inc.

Product: Treanda (bendamustine hydrochloride) injection

Indication: Treatment of patients with chronic lymphocytic leukemia (CLL)

MO: Qin Ryan, MD

Sponsor Presentation: October 1, 2007, 2:00 pm - 3:30 pm, WO 1315

Slides: Not available at this time.

If you have any questions, please contact Sharon Thomas at 301-796-1994.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Office of Microbiology
Attention: David Hussong, Ph.D.

FROM *(Name, Office/Division, and Phone Number of Requestor)*:
Karl Stiller, ONDQA x6-1993 for Sarah Pope x6-1436

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
September 28, 2007		22-249	Original application (in EDR)	September 19, 2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
TREANDA			January 21, 2008

NAME OF FIRM: CEPHALON INC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☒ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
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IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Please review the application for micro issues. This application was selected for the Division of Drug Oncology Products' GRMP Pilot.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Karl Stiller	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Karl Stiller
9/28/2007 02:28:03 PM

USER FEE PAYMENT & PDUFA/FDAMA VALIDATION SHEET

Must be completed for ALL original NDAs, efficacy supplements and initial rolling review submissions

NDA # 22-249 SUPP TYPE & # N-000 Division 150 UFID # 3007617

Applicant Name: Cephalon Inc. Drug Name: Treanda

For assistance in filling out this form see the Document Processing Manual for complete instructions and examples.

1. Was a Cover Sheet submitted?
   ☒ Yes ☐ No

2. Firm in Arrears?
   ☐ Yes ☒ No

3. Bundling Policy Applied Appropriately? Refer to Draft "Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees" http://www.fda.gov/cder/guidance
   ☐ Yes ☐ No (explain in comments)

4. Administrative Split? (list all NDA#s and Divisions)

   NDA #/Doc Type Div. Fee? (Y/N)

   _____

   _____

   _____

5. Type 6?
   ☐ Yes ☒ No

   Type 6 to which other application?

   NDA # _____ Supp Type &# _____

6. Clinical Data Required for Approval? (Check one)
   ☒ Yes*

   ☐ Yes, by reference to another application

   NDA # _____ Supp Type & # _____

   ☒ No

   * Yes if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., adding an adverse reaction, contraindication or warning to the labeling).

7. 505(b)(2) application? (NDA original applications only) Refer to Draft "Guidance for Industry Applications Covered by Section 505(b)(2)" http://www.fda.gov/cder/guidance
   ☐ Yes ☒ No ☐ To be determined

8. Subpart H (Accelerated Approval/Restricted Distribution)?
   ☐ Yes ☒ No ☐ To be determined

9. Exclusion from fees? (Circle the appropriate exclusion. For questions, contact User Fee staff)

   List of exclusions:

   2 – No fee - administrative split
   4 – No fee - 505b2
   7 – Supplement fee - administrative split
   9 – No fee Subpart H supplement– confirmatory study
   11 – No fee Orphan Exception
   13 – No fee State/Federal exemption from fees

10. Waiver Granted?
    ☐ Yes (letter enclosed) ☐ No

    Select Waiver Type below: Letter Date: _____

    ☐ Small Business ☐ Barrier-to-Innovation
    ☐ Public Health ☐ Other (explain)

11. If required, was the appropriate fee paid?
    ☐ Yes ☐ No

12. Application Review Priority
    ☒ Priority ☐ Standard ☐ To be determined

13. Fast Track/Rolling Review Presubmission?
    ☐ Yes ☐ No

Comments

Dufour 9-27-07
PM Signature/Date

This form is the initial data extraction of information for both User Fee payment and PDUFA/FDAMA data elements. The information entered may be subject to change due to communication with the User Fee staff. This form will not reflect those changes. Please return this form to your document room for processing.

CC: original archival file
HFD-007

Processor Name & Date _____

QC Name & Date _____

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

August 17, 2007

Cephalon, Inc.
41 Moores Road
Frazier, Pennsylvania 19355

Attention: Carol S. Marchione
Senior Director and Group Leader

Re: Designation request #07-2448

Dear Ms. Marchione:

Reference is made to your request for orphan-drug designation submitted June 19, 2007, of bendamustine (trade name: Treanda®) for "treatment of B-cell chronic lymphocytic leukemia (CLL)." Please also refer to our letter of June 20, 2007, and to the August 1, 2007, telecon with Mr. Peter Vaccari of this Office to amend the indication to "treatment of CLL."

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your request for orphan-drug designation of bendamustine is granted for *treatment of chronic lymphocyticleukemia (CLL).* Please be advised that it is the active moiety of the drug and not the formulation of the drug that is designated.

Please note that if the above drug receives marketing approval for an indication broader than what is designated, it may not be entitled to exclusive marketing rights under section 527 (21 U.S.C. 360cc). Therefore, prior to final marketing approval, we request that you compare the drug's designated orphan indication with the proposed marketing indication, and submit additional information to amend the orphan-drug designation if warranted.

Please submit to the Office of Orphan Products Development a brief progress report of drug development within 14 months after this date and annually thereafter until marketing approval (*see* 21 C.F.R. 316.30). Finally, please notify this Office within 30 days of a marketing application submission for the drug's designated use.

If you need further assistance in the clinical development of your drug, please feel free to contact Peter L. Vaccari, R.Ph., RAC, at 301-827-3666. Please refer to this letter as official notification. Congratulations on obtaining your orphan-drug designation.

Sincerely yours,

Debra Y. Lewis, O.D., M.B.A.
Acting Director
Office of Orphan Products Development

INDUSTRY MEETING MINUTES

TELECON DATE: April 12, 2007 **TIME:** 2:00 pm **LOCATION:** 2201

APPLICATION: IND 67,554 **TYPE OF MEETING:** EOP 2

DRUG NAME: Treanda® (bendamustine hydrochloride)

SPONSOR/APPLICANT: Cephalon, Inc.

PROPOSED INDICATION: Treanda® (bendamustine hydrochloride) is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL).

Meeting Request Submission Received Date: January 12, 2007
Briefing Document Submission Date: March 12, 2007
Meeting Granted Fax: January 25, 2007

FDA ATTENDEES:

Robert Justice, M.D., Division Director, DDOP
Ann Farrell, M.D., Acting Deputy Director, DDOP
Amna Ibrahim M.D., Acting Medical Team Leader, DDOP *(Chair)*
Qin Ryan, M.D., Medical Reviewer, DDOP
Shenghui Tang, Ph.D., Statistical Reviewer, DBI
Brian Booth, Ph.D., Clinical Pharmacology Team Leader, DCP5
Roshni Ramchandani, Ph.D., Clinical Pharmacology Reviewer, DCP5
M A Goheer, Ph.D. Pharmacology/Toxicology Reviewer, DDOP
Sharon Thomas, Consumer Safety Officer *(Facilitator)*

SPONSOR ATTENDEES:

Brad Barnes, Ph.D., Sr. Director, Drug Safety
Peter Brown, D. Phil., Vice President, Clinical Research, Oncology
Mona Darwish, Ph.D., Sr. Director, Clinical Pharmacology
Eric Floyd, Ph.D., Vice-President, Worldwide Regulatory Affairs
Carol Marchione, Sr. Director and Group Leader, Regulatory Affairs
Phil Robertson, Ph.D., Sr. Director, Drug Disposition
Elizabeth Barrett, Vice-President, Oncology Business Unit
Srdjan Stankovic, MD, MSPH Vice President, Worldwide Clinical Research
Lothar Tremmel, Ph.D. Sr. Director, Biometrics

Consultant

BACKGROUND:

In September 2004, Salmedix met with the FDA to discuss its registration strategy for bendamustine [redacted] as first-line treatment for patients with, CLL. The FDA confirmed in the EOP 2 meeting minutes that the design of the Ribosepharm study 02CLLIII would be considered acceptable to demonstrate the efficacy of bendamustine as first-line treatment, providing results were statistically and clinically significant under an appropriate statistical analysis plan (SAP).

In August 2005, the sponsorship of the IND was transferred from Salmedix to Cephalon, Inc. On March 15, 2006, Cephalon submitted a SAP in follow-up to comments from the FDA after the EOP 2 meeting. This SAP reflected Cephalon proposal for analysis of the data from Ribosepharm study 02CLLIII. In July 2006, subsequent to the Cephalon submission, the FDA provided comments on this SAP. Cephalon has since revised the SAP, and on February 5, 2007, Cephalon submitted a revised SAP.

The purpose of this meeting is to discuss the proposed registration strategy for Treanda. The Division comments were sent to the sponsor on April 9, 2007. The sponsor decided to proceed with the scheduled industry meeting for clarification. The discussion points are indicated in italics.

QUESTIONS for DISCUSSION with FDA RESPONSE AND DECISIONS REACHED:

1. Does the FDA concur that the single pivotal study, study 02CLLIII, is adequate to support the registration of bendamustine for the proposed indication?

   FDA Response: This will be a review issue for the NDA. For a single randomized trial to support an NDA, the trial should be well designed, well conducted, internally consistent and provide statistically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform.

   We have reservations about the adaptive strategy used. Please submit all versions of the protocol, SAP and all DSMB deliberations with your NDA.

   Sponsor: FDA made reference to the adaptive design. Since filing the briefing package, we have conducted further analysis of the data and we believe that a review of this analysis would benefit the Agency in determining the adequacy of the adaptive design.

   DISCUSSION:

   The sponsor will provide a signed memo from the head of the DSMB that explains the two interim analyses. The sponsor will also provide a chronology of the SAP and protocol amendments as well as the different versions.

   The sponsor will also provide sensitivity analyses to address potential bias.

2. On 17 July 2006, the FDA provided comments on the Cephalon statistical analysis plan (SAP) for study 02CLLIII, which was submitted on 15 March 2006. This briefing document contains responses to these comments along with a revised SAP, which will serve as the basis of the analyses to be included in the NDA. Does the Agency concur that the responses and revised SAP are adequate to support the analysis of study 02CLLIII?

   FDA Response: We have serious concerns regarding the study integrity and potential bias introduced by the adaptive design. We note that you have revised your SAP multiple times. The acceptability of the SAP will be a review issue for the NDA.

   For the PFS primary analysis, patients who change therapy before progression should be censored at the last assessment. Patients with two or more missing assessments immediately prior to the next visit with a documented progression should be censored at the last assessment with documentation of no progression.

   DISCUSSION: There was no discussion.

3. The FDA has recommended an independent review committee for this study. Ribosepharm (Astellas licensee) did institute an independent review committee for this study and Cephalon has provided the charter in this briefing document. Does the FDA agree that this independent review process is adequate?

   FDA Response: Since the study has been completed and study results have been reported, the adequacy of the radiology charter will be a review issue.

   Sponsor: FDA made reference to the radiology charter. We wanted to review the impact of the clinically meaningful data that supports the outcome of the study in view that no radiology data were collected, as per protocol.

   DISCUSSION:

   The sponsor clarified that the IRC did not review radiology studies since these are not standard practice in CLL treatment and research. However, they reviewed in a blinded manner bone marrow, CBC, and physical examinations performed by the investigator. The FDA commented that the adequacy of these will be a review issue.

4. Would the totality of the proposed safety data be adequate for registration of bendamustine for the approved indication?

   FDA Response: The safety sample size and profile appear to be acceptable for review. However, the adequacy of the safety data will be a review issue that depends on both the study data and support provided by other studies and post marketing data.

   DISCUSSION: There was no discussion.

5. Treatment with bendamustine has been shown to have a low risk for arrhythmogenic potential (QT prolongation) in vitro and in nonclinical safety studies. The potential for this effect has not yet been evaluated in a clinical study. Due to the nature of the targeted indication and the lack of a class effect, is it acceptable to provide an evaluation of this potential in a clinical study following approval of bendamustine for the proposed indication?

   FDA Response: The risk of QT prolongation should be addressed. Please provide the in vitro and non-clinical data regarding the risk for QT prolongation. You should propose a plan as soon as possible to evaluate the risk of QT prolongation in a clinical trial.

   Sponsor: Cephalon wants to review plans to address QT prolongation in a future clinical trial.

   DISCUSSION:

   The sponsor commits to provide details and timing of a study protocol to further define the effect of bendamustine on QT interval.

6. Does the FDA concur that bendamustine fulfils the requirements for a priority review?

   FDA Response: This will be determined at the time of NDA filing.

   DISCUSSION: There was no discussion.

7. Does the FDA concur that the available pharmacokinetic data from patients with NHL are adequate to support a marketing application for the proposed CLL indication?

   FDA Response:

   - **It appears that your planned submission will include PK data on bendamustine in 10 NHL patients, which is not adequate from the clinical pharmacology perspective. Also, it appears that you are not planning to submit the results of your population PK and exposure-response analyses, which includes rich (n=10) and sparse (n=88) PK data in NHL patients, until after the NDA submission. We strongly recommend that you include these data and the results of your analyses in your planned NDA submission.**
   - **We further recommend that you submit the analysis plan as soon as possible for your population PK and exposure-response analysis.**

   Sponsor: Cephalon would like to review our plans and timing for submitting PK data in the initial NDA and subsequent filings in order to respond to FDA requests.

   DISCUSSION:

The sponsor will provide population PK and PK-PD analysis plan. The sponsor agreed to submit the results as soon as they are complete.

8. Does the FDA concur that the safety pharmacology and toxicology data presented in this briefing document, with the tables included in this section, are adequate to support registration of bendamustine for the proposed indication?

FDA Response: The dosing cycle in the non-clinical toxicology studies should approximate the planned clinical regimen. Completed and ongoing toxicity studies described in your package appear adequate to support NDA filing for the proposed indication.

DISCUSSION: There was no discussion.

ADDITIONAL COMMENTS

1. **We recommend that you submit the PK data from your five phase 1 studies, and also please clarify the GLP deviations and what impact this would have on the interpretation of the results.**

DISCUSSION:

The sponsor commits to provide the legacy studies and the interpretation of their adequacy.

2. **The following clinical pharmacology issues will need to be addressed:**
   - **Information on ADME of bendamustine in humans, which would be important in determining the need for studies in renal and/or hepatically-impaired patients.**
   - **Information on dose-proportionality of the PK of bendamustine.**
   - **The need for drug-drug interaction studies with inhibitors/inducers would be determined based on the ADME data and knowledge of the fraction of bendamustine metabolized, as well as any information obtained from your population PK analysis.**
   - **The need for drug-drug interaction studies with CYP substrates, which would be determined based on the expected peak concentration of drug in patients relative to the Ki estimates obtained in your in vitro CYP inhibition studies. If the ratio of the drug concentration to Ki is less than 0.1, drug-drug interaction studies may not be necessary. Also, we recommend that you conduct *in vitro* studies to determine if bendamustine and its active metabolite(s) are substrates/inhibitors of P-glycoprotein. Please refer to the guidance at http://www.fda.gov/cder/guidance/6695dft.pdf for more information.**

DISCUSSION: ***There was no discussion.***

ADDITIONAL COMMENTS (REGULATORY)

NDA/sNDA Presentations to CDER's Division of Oncology

The Center for Drug Evaluation and Research's Division of Oncology Drug Products implemented an initiative in which we request an NDA/sNDA applicant to present their NDA/sNDA to Division personnel shortly after NDA/sNDA submission and before the expected NDA/sNDA filing date. This initiative allows the applicant to present an overview of the entire NDA/sNDA to the review team and interested Division personnel.

These presentations are generally expected to last one hour followed by a half-hour question and answer session. The applicant, not consultants, should present important information on each technical aspect (i.e., clinical, statistical, CMC, pre-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics) of the NDA/sNDA. In addition to providing an overview of the NDA/sNDA, the applicant should present their reasons for why the Division or the Office of Drug Evaluation I should approve their NDA/sNDA.

Please contact your Project Manager shortly after NDA/sNDA submission to schedule a date for your presentation. Alternatively, you may provide available dates in the cover letter of your NDA/sNDA and we will try to accommodate them.

SUBMISSION OF CLINICAL TRIALS TO NIH PUBLIC ACCESS DATA BASE

Section 113 of the Food and Drug Modernization Act (Modernization Act) amends 42 U.S.C. 282 and requires the establishment of a public resource for information on studies of drugs for serious or life-threatening diseases conducted under FDA's Investigational New Drug (IND) regulations (21 CFR part 312). The National Institutes of Health (NIH) through its National Library of Medicine (NLM), and with input from the FDA and others, developed the Clinical Trials Data Bank, as required by the Modernization Act.

FDA has made available a final guidance to implement Section 113 of the Modernization Act. The guidance describes the type of information to submit and how to submit information to the Clinical Trials Data Bank. The guidance entitled "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions" was made available on March 18, 2002. It is accessible through the Internet at http://www.fda.gov/cder/guidance/4856fnl.htm

The clinical trial information for the Clinical Trials Data Bank should include the purpose of the trial, the patient eligibility criteria, the location of the trial sites and, a contact for patients wanting to enroll in the trial. The data fields and their definitions are available in the Protocol

Registration System at http://prsinfo.clinicaltrials.gov/. Protocols listed in this system by will be made available to the public on the Internet at http://clinicaltrials.gov.

If you have any questions, contact Theresa Toigo at (301) 827-4460 or 113trials@oc.fda.gov.

FINANCIAL DISCLOSURE FINAL RULE

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 "*Guidance for Industry: Financial Disclosure By Clinical Investigators*" (posted on the Internet 3/27/2001) at http://www.fda.gov/oc/guidance/financialdis.html.

PEDIATRIC RESEARCH EQUITY ACT (PREA)

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 encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

PEDIATRIC EXCLUSIVITY

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

DEMOGRAPHICS

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.

CATEGORY		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG
Gender	Males		All Females		Females >50	
Age:	0-≤1 Mo.		>1 Mo.-≤ 2Year		>2-<12	
	12-16		17-64		≥65	
Race:	White		Black		Asian	
	Other					

CHEMISTRY

Prior to initiating pivotal clinical studies, we request a complete, updated submission of chemistry, manufacturing and controls (CMC). Please refer to the appropriate CDER guidelines for assistance in preparing this submission. At the time of this submission, we strongly urge you to request a meeting to discuss CMC issues, e.g., impurity profile, stability protocols, approaches to specifications, and attributes, packages, etc.

QT Evaluation

In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Please plan to address this issue early in development.

Office of Surveillance and Epidemiology (OSE)

Comments to be included in the pre-NDA meeting minutes

- If the sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then the Sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).

- For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:

  -Premarketing Risk Assessment: http://www.fda.gov/cder/guidance/6357fnl.htm

-Development and Use of Risk Minimization Action Plans:
http://www.fda.gov/cder/guidance/6358fnl.htm>

-Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment:
http://www.fda.gov/cder/guidance/6359OCC.htm

- If there is any information on product medication errors from the premarketing clinical experience, OSE requests that this information be submitted with the NDA/BLA application.
- The sponsor is encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.

ACTION ITEMS: None

Sharon Thomas
Project Manager

Concurrence Chair:
Amna Ibrahim, M.D.
Acting Medical Team Leader, DDOP

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amna Ibrahim
5/12/2007 08:07:57 AM

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

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Pages (including cover): 5		**Date:**	June 3, 2005
Re:	IND 67,554 for SDX-105		

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Kim,

Attached are the FDA internal meeting minutes in response to the meeting request dated March 16, 2005.

Please contact me should you have any questions or concerns.

Sincerely,

Sheila Ryan
Project Manager

TELECON MINUTES

TELECON DATE: May 9, 2005

IND: IND 67,554 **Meeting Request Submission Date:** March 16, 2005 (sn050)
FDA Response Date: March 21, 2005
Briefing Document Submission Date: April 11, 2005 (sn051)

DRUG: Bendamustine HCl (SDX-105) for injection

SPONSOR: Salmedix, Inc.

TYPE of MEETING:

1. Type B: End of Phase 2/Chemistry, Manufacturing, and Controls
2. Proposed Indication [redacted]

FDA PARTICIPANTS:

Nallaperumal Chidambaram, Ph.D.	-	Chemistry Team Leader
Haripada Sarker, Ph.D.	-	Chemistry Reviewer
Sheila Ryan, Pharm.D.	-	Regulatory Project Manager, DODP

INDUSTRY PARTICIPANTS:

C. Kim Litner	-	Director, Regulatory Affairs

MEETING OBJECTIVE:

To reach agreement on the specifications, analytical methods, and stability protocol design that will be used to support a new drug application.

BACKGROUND:

Bendamustine HCl (SDX-105) for injection is an anti-tumor agent that has both a nitrogen mustard group and a purine-like benzimidazole ring. Pre-clinical and clinical studies suggest that the mechanism of action may be distinguishable from other standard nitrogen mustard compounds. Bendamustine HCl for injection is marketed in Germany under the name Ribomustin®. Currently, Salmedix is conducting two Phase 2 clinical trials of bendamustine HCl for injection and plans to initiate a pivotal Phase 3 trial in mid 2005. The proposed indication is for use [redacted]

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/s/

Nallaperumal Chidambaram
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/s/

Sheila Ryan
6/3/05 10:05:00 AM