

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207953Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 207953

SUPPL #

HFD # 107

Trade Name Yondelis

Generic Name trabectedin

Applicant Name Janssen Products, LP

Approval Date, If Known October 23, 2015

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) (1)

b) 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.

N/A

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:

N/A

c) Did the applicant request exclusivity?

YES NO

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

JRD is requesting 5 years of New Chemical Entity (NCE) exclusivity for JNJ-17027907 (trabectedin). JRD certifies that JNJ-17027907 (trabectedin) has not previously been approved under section 505(b) of the Federal Food, Drug and Cosmetic Act.

JRD is requesting 7 years of Orphan Drug exclusivity.

d) 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?

N/A

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:

Investigation #2
!
! YES
! NO
! 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: Anuja Patel, MPH
Title: Senior Regulatory Health Project Manager
Date: September 25, 2015

Name of Office/Division Director signing form: Patricia Keegan, M.D.
Title: Division Director, Division of Oncology Products 2, Office of Hematology and Oncology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/

ANUJA PATEL
09/25/2015

PATRICIA KEEGAN
09/25/2015

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed):
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):						
		minimum	maximum		Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	wk. mo.	wk. mo.		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed):

***** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population		minimum	maximum				
<input type="checkbox"/>	Neonate	wk. mo.	wk. mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy):							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason:

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum		maximum		PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	wk.	mo.	wk.	mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.		16 yr. 11 mo.		Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum		maximum	
<input type="checkbox"/>	Neonate	wk.	mo.	wk.	mo.
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.		16 yr. 11 mo.	

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	wk. mo.	wk. mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Anuja Patel, Regulatory Project Manager

(Revised: 6/2008)

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/s/

ANUJA PATEL
08/17/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 19, 2015
From: Anuja Patel Senior Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 207953: Sponsor Teleconference to Discuss Janssen Adverse Events Issues Related to Labeling Amendment received October 19, 2015

Janssen Products, LP Attendees:

Barbara Kolb, North America Regulatory Head, Oncology
Sandra, Rattray, PhD, VP, Global Regulatory Affairs, Oncology
Trilok Parekh, PhD, Compound Development Team Leader
Roland Knoblauch, MD, PhD, Clinical Development Leader
Sharon McCarthy, Clinical Project Scientist
Loreta Marquez, MD, Global Medical Safety Leader
Hemal Morjaria, Global Regulatory Leader, Oncology
Barbara Kolb, North America Regulatory Head, Oncology
Ronald Szumigala, MS, North America Regulatory Leader
Cynthia Chianese, Global Labeling Product Leader

FDA Attendees:

Marc Theoret, Clinical Team Leader, DOP2
Dow-Chung Chi, Clinical Reviewer, DOP2
Monica Hughes, Chief, Project Management Staff, DOP2
Anuja Patel, Senior Regulatory Health Project Manager, DOP2
Idara Udoh, Senior Regulatory Health Project Manager, DOP2

Discussion:

During this teleconference, FDA informed Janssen that the Clinical team would be re-running analysis regarding splitting and dose-modifications for certain adverse events associated with trabectedin. FDA explained that the dose modification increases in a way that the current labeling would be misleading. FDA will forward patient IDs for Janssen review, and requests that Janssen confirm whether the assessments are accurate.

FDA also addressed a typographical error in Section 2.2 where the term “intravenous” should be corrected to “intravenously.” Janssen agreed to the correction proposed by FDA for Section 2.2.

FDA requested a 24-hour turnaround for the information including a response document with a justification in support of Janssen’s proposed modification to the label.

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ANUJA PATEL
10/30/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 15, 2015
From: Anuja Patel, Senior Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 207953: Sponsor Teleconference to Discuss Janssen Labeling Amendment Received October 14, 2015

Janssen Products, LP Attendees:

Sandra Rattray, Ph.D., Vice President, Global Regulatory Affairs, Oncology
Craig Tendler, M.D., Vice President, Late Development and Global Market Affairs
Trilok Parekh, Ph.D., Compound Development Team Leader
Roland Knoblauch, M.D., Ph.D., Clinical Development Leader
Sharon McCarthy, Clinical Project Scientist
Loreta Marquez, M.D., Global Medical Safety Leader
Hemal Morjaria, Global Regulatory Leader, Oncology
Barbara Kolb, North America Regulatory Head, Oncology
Ronald Szumigala, M.S., North America Regulatory Leader
Cynthia Chianese, Global Labeling Product Leader
Sudhakar Rao, Ph.D., Biostatistics

FDA Attendees:

Patricia Keegan, Director, Division of Oncology Products 2 (DOP2)
Marc Theoret, Clinical Team Leader, DOP2
Dow-Chung Chi, Clinical Reviewer, DOP2
Anuja Patel, Senior Regulatory Health Project Manager, DOP2
Idara Udoh, Senior Regulatory Health Project Manager, DOP2

Discussion:

During this teleconference, FDA and Janssen reviewed recent revisions in the Package Insert (PI) and Patient Package Insert (PPI), received October 14, 2015. FDA proposed new revisions in Sections 2.1, Section 2.3, and Section 5.3 to address the effect of dexamethasone and risk of hepatotoxicity.

FDA and Janssen discussed edits to the PI in the following sections, and Janssen accepted all changes:

- Section 2.1 Recommended Dose and Schedule
- Section 2.3 Dose Modifications
- Section 5.3 Hepatotoxicity
- Section 6.1 Adverse Reactions in Clinical Trials
- Section 14 Clinical Studies

FDA and Janssen discussed edits to terminology used in the PPI, and Janssen accepted all changes.

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/s/

ANUJA PATEL
10/30/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 18, 2015
From: Anuja Patel, MPH, Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 207953 (trabectedin): Internal Labeling Meeting

FDA reviewed and discussed Janssen proposed revisions (without Sections 5 and 6), submitted July 31, 2015.

Attendees: Anuja Patel, Dow- Chung Chi, Amy Barone, riram Subramaniam, Hong Zhao, Patricia Keegan, Nazia Fatima

Discussion: The team discussed the following:

Section 2 Dosage and Administration
Section 5 Warnings and Precautions (5.1)
Section 12.1 Mechanism of Action
Section 14 Clinical Studies

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/s/

ANUJA PATEL
10/29/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 4, 2015
From: Anuja Patel, MPH, Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 207953 (trabectedin): Internal Labeling Meeting

FDA reviewed and discussed Janssen proposed revisions (without Sections 5 and 6), submitted July 31, 2015.

Attendees: Anuja Patel, Dow- Chung Chi, Patricia Keegan, Olen Stephens, Nazia Fatima, Naomi Redd, Sharon Mills, Huanyu Chen, Dubravka Kufrin

Discussion: The team discussed the following sections:

Section 1 Indications and Usage
Section 2 Dosage and Administration
Section 7 Drug Interactions
Section 8 Use in Specific Populations
Section 10 Overdosage
Section 11 Description
Section 12 Clinical Pharmacology
Section 14 Clinical Studies

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/s/

ANUJA PATEL
10/29/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 31, 2015

From: Anuja Patel, MPH, Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 207953 (trabectedin): Internal Labeling Meeting

FDA reviewed and discussed Janssen proposed labeling revisions to Section 5, submitted February 27, 2015 following clinical review of the major amendment.

Attendees: Anuja Patel, Dow- Chung Chi, Patricia Keegan, Sharon Mills, Idara Udoh

Discussion: The team discussed the following sections:

Section 5 Warnings and Precautions

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/s/

ANUJA PATEL
10/29/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 27, 2015

From: Anuja Patel, MPH, Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 207953 (trabectedin): Internal Labeling Meeting

FDA reviewed and discussed Janssen proposed labeling revisions to Section 5, submitted February 27, 2015 following clinical review of the major amendment.

Attendees: Anuja Patel, Dow- Chung Chi, Patricia Keegan, Sharon Mills, Idara Udoh

Discussion: The team discussed the following sections:

Section 6 Adverse Reactions

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/s/

ANUJA PATEL
10/29/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 30, 2015

From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 207953 (trabectedin)- Sponsor Teleconference- OSI/DOP 2

Janssen Attendees:

Erik Poulsen, Director Regulatory Affairs
Barb Kolb, North American Oncology Regulatory Affairs Therapeutic Area Lead
Hemal Morjaria, Global Regulatory Leader
Craig Tendler, VP, Late Development & Medical Affairs
Loreta Marquez, Medical Safety Officer
Trilok Parekh, Compound Development Team Leader
Roland Knoblauch, Clinical Leader
Nushmia Khokhar, Lead Study Physician
Leah Bednarek, Lead Statistical Programmer
Youn Park-Choi, Statistical Leader
Dawn Wydner, Senior Director, Regulatory Compliance
Nicole Chieffo, Clinical Operations Head, Central Trial Coordination - Oncology

FDA Attendees:

Anuja Patel, Senior RPM
Monica Hughes, CPMS
Leah Her, RPM
Marc Theoret, Clinical TL
Amy Barone, Clinical Reviewer
Dow-Chung Chi, Clinical Reviewer
Patricia Keegan, Director, DOP 2
Lauren Iaconno-Connor, OSI

Background:

During the OSI inspection, it was discovered that the eCFRs provided by Janssen for OSI review contained additional or corrected safety data (AEs and SAEs) when compared to the data listings provided in the original application for at least one of the five sites audited. Form FDA 483 issued to Janssen on March 26, 2015. FDA inspector found during the inspection that the eCFRs provided by Janssen for FDA review contained additional or corrected safety data (AEs and SAEs) when compared to the data listings provided in the original application for at least one of the five sites audited. The FDA field investigator added the observation to the 483 as a clear compliance violation in that they failed to ensure that sites followed the investigational plan with respect to data management. In doing so, the firms limited oversight for this site, and perhaps others, resulted in an incomplete representation of data submitted to the original application.

At the inspection close-out meeting, the 483 items were discussed

On April 17, 2015, Janssen submitted updated safety datasets with a database cutoff date of July 10, 2014 as part of its 120-Day Safety Update (NDA 207953, SDN22) and an updated Clinical Study Report submitted on March 24, 2015 (NDA 207953, SDN17). Comparison of the ae.xpt dataset from the Interim Analysis with a database cutoff date of September 16, 2013, (November 24, 2014, NDA 207953, SDN 01) with the ae.xpt dataset submitted as part of the 120-Day Safety Update, using an imposed cutoff date of September 16, 2013. This modification of the 120DSU dataset was performed so that it would have the same cutoff date as the Interim Analysis dataset. Comparison of the two datasets revealed several discrepancies, as a result of retroactive modification of historical adverse events data.

Discussion:

- Janssen provided preliminary response to the 483 that was issued on March 26, 2015.
- Janssen provided the attached document in response to Observation 1 contained in FDA Form 483 Inspectional Findings. Included is an analysis demonstrating the completeness of the interim analysis database forming the basis of the NDA filed on 24 November 2014.
- The clinical team leader informed Janssen that the clinical team will have to further review the character of the safety update and will followup up accordingly with Janssen.

Attachments: Janssen's email received March 27, 2015 containing response to 483.

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ANUJA PATEL
10/29/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 17, 2015

From: Anuja Patel, MPH, Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 207953 (trabectedin): Internal Labeling Meeting #5

FDA reviewed and discussed Janssen proposed labeling revisions, submitted February 27, 2015 in response to filing letter.

Attendees: Anuja Patel, Marc Theoret, Dow Chung Chi, Amy Barone, Patricia Keegan, Marybeth Toscano, Sriram Subramaniam, Jeanne Fourie Zirkelbach

Discussion: The team discussed the carton and container labeling and the following sections of the PI:

Section 2 Dosage and Administration

Section 7 Drug Interactions

Section 12 Clinical Pharmacology

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/s/

ANUJA PATEL
10/29/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 15, 2015
From: Anuja Patel, MPH, Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 207953 (trabectedin): Internal Labeling Meeting #3

FDA reviewed and discussed Janssen proposed labeling revisions, submitted February 27, 2015 in response to filing letter.

Attendees: Anuja Patel, Marc Theoret, Olen Stephens, Sriram Subramaniam, Patricia Keegan, Otto Townshend, Sharon Mills, Jeanne Fourie Zirkelbach, Latonia Ford, Nazia Fatima

Discussion: The team discussed the following sections:

Section 2: Dosage and Administration

Section 7: Drug Interactions

Section 8:

8.5 Geriatric Use,

8.6 Hepatic Impairment,

8.7 Renal Impairment

Section 12

12.2 Pharmacodynamics and 12.3 Pharmacokinetics

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/s/

ANUJA PATEL
10/29/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 13, 2015
From: Anuja Patel, MPH, Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 207953 (trabectedin): Internal Labeling Meeting #2

FDA reviewed and discussed Janssen proposed labeling revisions, submitted February 27, 2015 in response to filing letter.

Attendees: Anuja Patel, Marc Theoret, Dow- Chung Chi, Patricia Keegan, Amy Barone, Huanyu Chen, Kun He

Discussion: The team discussed the following sections:

Section 1: Indications and Usage
Section 14: Clinical Studies

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/s/

ANUJA PATEL
10/29/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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Center for Drug Evaluation and Research

Memorandum

Date: April 13, 2015
From: Anuja Patel, MPH, Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 207953 (trabectedin): Internal Labeling Meeting #1

FDA reviewed and discussed Janssen proposed labeling revisions, submitted February 27, 2015 in response to filing letter.

Attendees: Anuja Patel, Marc Theoret, Dow- Chung Chi, Whitney Helms, Patricia Keegan, Dubravka Kufirin, Latonia Ford, Carrie Ceresa, Sharon Mills, Denise Picc-Branco

Discussion: The team discussed the following sections:

Section 1: Indications and Usage
Section 8: Use in Specific Population (specifically Sections 8.1, 8.2, 8.3, 8.4)
Section 12.1 Mechanism of Action
Section 13: Nonclinical Toxicology

Action Item: Nonclinical Information Request for Section 13.1 (Nonclinical)

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/s/

ANUJA PATEL
10/29/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 13, 2015
From: Anuja Patel, MPH, Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 207953 (trabectedin): Memo to File- Internal Filter Discussion with OPQ

Attendees:

Patricia Keegan, Marc Theoret, Monica Hughes, Anuja Patel, Amy Barone, Rabiya Laiq, Olen Stephens, Erika Pfeiler, Otto Townshend, Stephen Langille

Background:

The CMC review is complete at this time except for the facility inspections and a rehash of the in-line filter issue. On May 13, 2015, Office of Product Quality held a 1 hour internal meeting to discuss DMEPA and OPQ final recommendations regarding their filter review.

DMEPA looked into other precedence of using in-line filters to mitigate the risk of microbial growth. Based on DMEPA finding, they have amended their review and are recommending to further stress the importance of following strict aseptic technique during preparation of Yondelis and to strengthen language requiring the use of an in-line filter during administration of Yondelis. To address this risk to patients, the review team plans to recommend the use of a 0.2 micron in-line filter during the 24-hour infusion of Yondelis.

Discussion Points:

DMEPA Key points:

- Stress importance of following strict aseptic technique.
- In-line filter and infusion tubing should be attached during preparation under aseptic conditions (this addresses the risk of contamination and in-line filter not being attached by the nurse just prior to infusion).

OPQ Key Point:

- Root cause
- Propose options such as combined vials for future considerations (e.g. manufacturer site changes and equipment changes)
- Possible reformulation (add antimicrobial preservatives, etc)

Following the internal meeting, OPQ held a teleconference with Janssen to discuss further.

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/s/

ANUJA PATEL
10/27/2015

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA# 207953
Product Name: Yondelis (trabectedin)

PMR/PMC Description: Submit integrated safety analyses and supporting data from an adequate number of clinical trial(s) to characterize the risk of cardiomyopathy and its sequelae in patients receiving trabectedin; to identify risk factors for development of these sequelae; and to support labeling instructions for dose modification and monitoring. The design of the trial should include a patient population with previous exposure to anthracyclines and have sufficient cardiac monitoring to achieve these objectives.

PMR/PMC Schedule Milestones:

Final Analysis Plan Submission Date:	<u>March 2016</u>
Study/Clinical Trial Completion Date::	<u>July 2018</u>
Final Report Submission Date:	<u>November 2018</u>
Interim Report Submission Date:	<u>n/a</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Metastatic soft tissue sarcoma is a life threatening condition with historical median survival times of 8 to 13 months and with less than 10% of patients surviving beyond five years. Approximately 50% of patients will present with or develop metastatic disease and despite chemotherapy. There are few effective treatments for metastatic sarcoma in the second or third line setting: doxorubicin, ifosfamide, gemcitabine, dacarbazine, and pazopanib.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Review Issue: In the review of the NDA 207953, there was insufficient data to provide evidence-based recommendations for the dose modification and safety monitoring for trabectedin-related cardiomyopathy.

Goals:

- Define and characterize risk of trabectedin-related cardiomyopathy and its sequelae
- Provide evidence-based recommendations for the dose modification and safety monitoring for cardiomyopathy in the labeling for trabectedin

○

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Randomized, controlled clinical trial(s) to characterize the risk of trabectedin-related cardiomyopathy and its sequelae in a study population with adequate exposure to anthracyclines. The design of the trial should incorporate adequate safety monitoring for and assessments of cardiomyopathy, including, but not limited to left ventricular ejection fraction assessments and clinical assessments for symptoms related to cardiomyopathy. Rules for dose modification, dose interruption, and discontinuation should be delineated clearly in the protocol. The data generated from this clinical trial should support recommendations for dose modification and safety monitoring for trabectedin-related cardiomyopathy.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
Refer to Question 4 above.

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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/s/

DOW-CHUNG CHI
10/23/2015

MARC R THEORET
10/23/2015

JEFFERY L SUMMERS
10/23/2015

Patel, Anuja

From: Patel, Anuja
Sent: Thursday, October 22, 2015 1:40 PM
To: 'Kolb, Barbara [JRDUS]'
Subject: FDA Labeling Modification to 10.20.15 Amendment- NDA 207953 YONDELIS
Attachments: draft-labeling-text-tracked-changes-word.doc.docx

Importance: High

Dear Ms. Kolb,

Please find attached FDA modified labeling in response to your October 20, 2015 amendment. A response is requested by 4 PM, EST today.

Please confirm receipt.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
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10903 New Hampshire Avenue
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/s/

ANUJA PATEL
10/22/2015

Patel, Anuja

From: Patel, Anuja
Sent: Tuesday, October 20, 2015 6:53 AM
To: 'Kolb, Barbara [JRDUS]'
Subject: FDA Information Request- Re: 10.19.15 Teleconference-NDA 207953 YONDELIS
Attachments: NDA 207953_Revised_Dose Modifications_WarningsPrecautions_IDList_101915.pdf

Importance: High

Dear Ms. Kolb,

We refer to your amended labeling received on October 18, 2015. We further refer to the teleconference held October 20, 2015 notifying you of this forthcoming information request upon our review of the current version of the labeling..

Our clinical team has the following information request and requests a response by 8 AM, EST October 21, 2015 or sooner.

Please send the attached updated list of Patient IDs with the following comments:

1. Please update Section 6.1 of labeling with revised incidences of adverse reactions leading to dose modifications of Yondelis, as follows:
 - Neutropenia leading to dose reductions: 8%
 - Neutropenia leading to dose interruptions: 31%
 - Thrombocytopenia leading to discontinuation: (b) (4)%
 - Thrombocytopenia leading to dose reductions: 4.2%
 - Thrombocytopenia leading to dose interruptions: 15%
 - Anemia leading to dose interruption: (b) (4)%

Patient IDs are provided in the attached document to support the above incidence values. Confirm whether Janssen accepts these revised incidence values otherwise provide justification with supporting information to support different incidence values.

2. Revise Section 5.1 of labeling (revisions bolded and underlined):

From

“The median time to the first occurrence of Grade 3 or 4 neutropenia was 16 days (range: 8 days to 9.7 months). The median time to complete resolution of neutropenia was (b) (4) days (range (b) (4) days to (b) (4) months)”

To

“The median time to the first occurrence of Grade 3 or 4 neutropenia was 16 days (range: 8 days to 9.7 months). The median time to complete resolution of neutropenia was **13** days (range: **3** days to **2.3** months).”

The revised duration of neutropenia is based on resolution of these Grade 3 or 4 cases based on laboratory values. Patient IDs and supporting information are provided in the attached document.

Please confirm receipt of this email and the attachment.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
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Silver Spring, MD 20993
☎ 301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

PT = thrombocytopenia + PLT count decreased

AEACN = drug withdrawn

13/378 = 3.5%

ET743SAR3007-001008-000399
ET743SAR3007-001013-000456
ET743SAR3007-001023-000485
ET743SAR3007-001028-000405
ET743SAR3007-001031-000510
ET743SAR3007-001033-000421
ET743SAR3007-001047-000444
ET743SAR3007-001053-000683
ET743SAR3007-001073-000122
ET743SAR3007-001075-000204
ET743SAR3007-001105-000603
ET743SAR3007-001117-000322
ET743SAR3007-001128-000452

PT = neutropenia + neutrophil count decreased + febrile neutropenia

AEACN = dose reduced

30/378 = 8%

ET743SAR3007-001001-000197
ET743SAR3007-001004-000321
ET743SAR3007-001005-000245
ET743SAR3007-001009-000081
ET743SAR3007-001009-000623
ET743SAR3007-001013-000289
ET743SAR3007-001013-000377
ET743SAR3007-001024-000479
ET743SAR3007-001025-000342
ET743SAR3007-001033-000030
ET743SAR3007-001033-000042
ET743SAR3007-001033-000120
ET743SAR3007-001033-000305
ET743SAR3007-001033-000395
ET743SAR3007-001033-000653
ET743SAR3007-001056-000135
ET743SAR3007-001062-000477
ET743SAR3007-001075-000207
ET743SAR3007-001082-000295
ET743SAR3007-001085-000363
ET743SAR3007-055006-000495
ET743SAR3007-055006-000573
ET743SAR3007-055007-000594
ET743SAR3007-055007-000637
ET743SAR3007-055008-000656
ET743SAR3007-055009-000668
ET743SAR3007-061001-000053
ET743SAR3007-061001-000087
ET743SAR3007-061003-000110
ET743SAR3007-061004-000648

PT = neutropenia + neutrophil count decreased + febrile neutropenia

AEACN = drug interrupted

118 / 378 = 31%

ET743SAR3007-001001-000022
ET743SAR3007-001001-000161
ET743SAR3007-001001-000195
ET743SAR3007-001001-000345
ET743SAR3007-001002-000036
ET743SAR3007-001002-000256
ET743SAR3007-001002-000403
ET743SAR3007-001002-000404
ET743SAR3007-001004-000321
ET743SAR3007-001004-000410
ET743SAR3007-001004-000501
ET743SAR3007-001004-000582
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ET743SAR3007-001015-000089
ET743SAR3007-001018-000351
ET743SAR3007-001020-000571
ET743SAR3007-001023-000331
ET743SAR3007-001023-000436
ET743SAR3007-001023-000540
ET743SAR3007-001023-000593
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ET743SAR3007-001024-000165
ET743SAR3007-001024-000459
ET743SAR3007-001025-000147
ET743SAR3007-001027-000003
ET743SAR3007-001028-000055
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ET743SAR3007-001098-000203
ET743SAR3007-001101-000432
ET743SAR3007-001101-000517
ET743SAR3007-001101-000559
ET743SAR3007-001102-000695
ET743SAR3007-001103-000208
ET743SAR3007-001105-000497
ET743SAR3007-001105-000513
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ET743SAR3007-001140-000516
ET743SAR3007-055005-000579
ET743SAR3007-055006-000573
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ET743SAR3007-055009-000649
ET743SAR3007-055009-000668

ET743SAR3007-061001-000053
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ET743SAR3007-061001-000523
ET743SAR3007-061002-000045
ET743SAR3007-061003-000110
ET743SAR3007-061004-000300
ET743SAR3007-061004-000648
ET743SAR3007-064002-000471

PT = thrombocytopenia + PLT count decreased

AEACN = dose reduced

16/378 = 4.2%

ET743SAR3007-001001-000178
ET743SAR3007-001002-000036
ET743SAR3007-001004-000501
ET743SAR3007-001007-000021
ET743SAR3007-001012-000312
ET743SAR3007-001028-000252
ET743SAR3007-001031-000470
ET743SAR3007-001062-000346
ET743SAR3007-001082-000295
ET743SAR3007-001082-000430
ET743SAR3007-001101-000517
ET743SAR3007-001105-000497
ET743SAR3007-001105-000603
ET743SAR3007-055007-000637
ET743SAR3007-055008-000656
ET743SAR3007-055009-000668

PT = thrombocytopenia + PLT count decreased

AEACN = drug interrupted

56/378 = 15%

ET743SAR3007-001001-000178
ET743SAR3007-001001-000345
ET743SAR3007-001002-000036
ET743SAR3007-001004-000501
ET743SAR3007-001005-000245
ET743SAR3007-001007-000021
ET743SAR3007-001009-000265
ET743SAR3007-001009-000623
ET743SAR3007-001013-000255
ET743SAR3007-001018-000351
ET743SAR3007-001021-000064
ET743SAR3007-001023-000485
ET743SAR3007-001024-000472
ET743SAR3007-001028-000055
ET743SAR3007-001028-000085
ET743SAR3007-001028-000101
ET743SAR3007-001028-000139
ET743SAR3007-001028-000252
ET743SAR3007-001028-000405
ET743SAR3007-001031-000470
ET743SAR3007-001031-000532

ET743SAR3007-001033-000297
ET743SAR3007-001033-000421
ET743SAR3007-001033-000653
ET743SAR3007-001047-000444
ET743SAR3007-001056-000134
ET743SAR3007-001056-000527
ET743SAR3007-001057-000140
ET743SAR3007-001057-000386
ET743SAR3007-001062-000346
ET743SAR3007-001062-000477
ET743SAR3007-001067-000115
ET743SAR3007-001079-000119
ET743SAR3007-001079-000206
ET743SAR3007-001079-000539
ET743SAR3007-001082-000097
ET743SAR3007-001082-000282
ET743SAR3007-001082-000295
ET743SAR3007-001082-000430
ET743SAR3007-001098-000125
ET743SAR3007-001101-000517
ET743SAR3007-001102-000142
ET743SAR3007-001105-000497
ET743SAR3007-001105-000603
ET743SAR3007-001105-000693
ET743SAR3007-001117-000322
ET743SAR3007-001128-000452
ET743SAR3007-001140-000516
ET743SAR3007-055006-000495
ET743SAR3007-055006-000573
ET743SAR3007-055007-000594
ET743SAR3007-055007-000637
ET743SAR3007-055008-000656
ET743SAR3007-055009-000649
ET743SAR3007-055009-000668
ET743SAR3007-061001-000087

PT = anemia, red blood cell count decreased, hemaglobin decreased, hematocrit decreased

AEACN = dose interruption

11/378 = 2.9%

ET743SAR3007-001001-000307
ET743SAR3007-001028-000139
ET743SAR3007-001053-000683
ET743SAR3007-001057-000140
ET743SAR3007-001059-000148
ET743SAR3007-001075-000618
ET743SAR3007-001082-000097
ET743SAR3007-001082-000097
ET743SAR3007-001098-000203
ET743SAR3007-001102-000695
ET743SAR3007-001105-000693

Patient Listing of time to first G3-4 neutropenic event and time to recovery from that event.

USUBJID (ADY)	Time to first G3-4 (ADY)	Time to Recovery
ET743SAR3007-001001-000022	15	21
ET743SAR3007-001001-000178	15	28
ET743SAR3007-001001-000197	15	14
ET743SAR3007-001001-000345	254	14
ET743SAR3007-001001-000358	37	6
ET743SAR3007-001001-000466	148	7
ET743SAR3007-001002-000036	15	14
ET743SAR3007-001002-000256	15	11
ET743SAR3007-001004-000066	15	7
ET743SAR3007-001004-000098	15	11
ET743SAR3007-001004-000286	15	11
ET743SAR3007-001004-000321	15	12
ET743SAR3007-001004-000407	36	7
ET743SAR3007-001004-000410	15	14
ET743SAR3007-001004-000501	15	12
ET743SAR3007-001004-000582	15	69
ET743SAR3007-001005-000244	36	7
ET743SAR3007-001005-000245	14	28
ET743SAR3007-001007-000021	36	18
ET743SAR3007-001008-000074	68	17
ET743SAR3007-001008-000332	20	7
ET743SAR3007-001008-000399	8	5
ET743SAR3007-001008-000565	35	7
ET743SAR3007-001009-000081	15	36
ET743SAR3007-001009-000265	16	20
ET743SAR3007-001009-000623	15	21
ET743SAR3007-001012-000312	15	14
ET743SAR3007-001012-000327	91	7
ET743SAR3007-001013-000289	36	13
ET743SAR3007-001013-000377	9	62
ET743SAR3007-001013-000438	57	7
ET743SAR3007-001013-000456	13	6
ET743SAR3007-001013-000515	37	6
ET743SAR3007-001015-000060	14	14
ET743SAR3007-001015-000543	15	7
ET743SAR3007-001018-000351	115	5
ET743SAR3007-001020-000223	107	8
ET743SAR3007-001020-000571	37	31
ET743SAR3007-001021-000011	36	6
ET743SAR3007-001022-000292	29	31
ET743SAR3007-001023-000485	20	16
ET743SAR3007-001023-000540	294	14
ET743SAR3007-001024-000041	58	12
ET743SAR3007-001024-000165	36	14
ET743SAR3007-001024-000177	55	9
ET743SAR3007-001024-000472	71	21
ET743SAR3007-001024-000479	15	15
ET743SAR3007-001024-000529	246	7
ET743SAR3007-001025-000147	16	41
ET743SAR3007-001027-000003	15	14
ET743SAR3007-001028-000055	15	19

ET743SAR3007-001028-000085	93	19
ET743SAR3007-001028-000106	66	6
ET743SAR3007-001028-000124	30	5
ET743SAR3007-001028-000252	15	14
ET743SAR3007-001028-000426	14	15
ET743SAR3007-001028-000600	26	3
ET743SAR3007-001031-000279	21	6
ET743SAR3007-001033-000030	22	7
ET743SAR3007-001033-000042	15	14
ET743SAR3007-001033-000062	148	7
ET743SAR3007-001033-000120	20	9
ET743SAR3007-001033-000183	8	48
ET743SAR3007-001033-000214	15	9
ET743SAR3007-001033-000297	99	5
ET743SAR3007-001033-000305	15	13
ET743SAR3007-001033-000319	15	14
ET743SAR3007-001033-000371	15	14
ET743SAR3007-001033-000395	15	11
ET743SAR3007-001033-000491	15	12
ET743SAR3007-001033-000653	16	5
ET743SAR3007-001041-000612	85	11
ET743SAR3007-001046-000576	36	6
ET743SAR3007-001047-000444	57	6
ET743SAR3007-001050-000094	13	9
ET743SAR3007-001053-000014	15	10
ET743SAR3007-001053-000016	69	9
ET743SAR3007-001053-000029	16	6
ET743SAR3007-001053-000232	12	13
ET743SAR3007-001053-000602	15	7
ET743SAR3007-001053-000683	73	13
ET743SAR3007-001054-000468	20	14
ET743SAR3007-001055-000202	15	16
ET743SAR3007-001055-000205	36	42
ET743SAR3007-001056-000134	15	14
ET743SAR3007-001056-000135	78	14
ET743SAR3007-001056-000225	49	7
ET743SAR3007-001056-000527	43	13
ET743SAR3007-001057-000099	15	21
ET743SAR3007-001057-000140	15	28
ET743SAR3007-001057-000386	36	19
ET743SAR3007-001059-000148	22	7
ET743SAR3007-001059-000329	36	42
ET743SAR3007-001059-000375	57	12
ET743SAR3007-001059-000638	36	14
ET743SAR3007-001061-000308	64	14
ET743SAR3007-001062-000346	16	12
ET743SAR3007-001062-000431	15	26
ET743SAR3007-001062-000477	36	7
ET743SAR3007-001062-000631	15	14
ET743SAR3007-001064-000686	14	21
ET743SAR3007-001066-000613	15	13
ET743SAR3007-001073-000122	29	14
ET743SAR3007-001073-000382	9	24
ET743SAR3007-001074-000469	38	9
ET743SAR3007-001075-000207	14	21
ET743SAR3007-001075-000618	9	34

ET743SAR3007-001079-000539	261	14
ET743SAR3007-001081-000209	8	5
ET743SAR3007-001081-000415	57	5
ET743SAR3007-001082-000097	16	20
ET743SAR3007-001082-000282	15	20
ET743SAR3007-001082-000295	14	29
ET743SAR3007-001085-000076	58	5
ET743SAR3007-001085-000363	15	14
ET743SAR3007-001090-000156	15	7
ET743SAR3007-001096-000143	15	22
ET743SAR3007-001098-000203	22	7
ET743SAR3007-001100-000169	15	14
ET743SAR3007-001101-000432	14	14
ET743SAR3007-001101-000517	15	14
ET743SAR3007-001101-000559	91	8
ET743SAR3007-001102-000142	36	7
ET743SAR3007-001102-000451	15	7
ET743SAR3007-001103-000482	15	12
ET743SAR3007-001105-000497	14	35
ET743SAR3007-001105-000513	22	7
ET743SAR3007-001117-000322	13	8
ET743SAR3007-001121-000641	59	12
ET743SAR3007-001121-000661	123	11
ET743SAR3007-001124-000566	30	25
ET743SAR3007-001128-000452	15	13
ET743SAR3007-001128-000666	36	13
ET743SAR3007-001140-000514	8	21
ET743SAR3007-055006-000573	15	42
ET743SAR3007-055007-000594	16	5
ET743SAR3007-055007-000637	15	14
ET743SAR3007-055008-000656	14	7
ET743SAR3007-055009-000505	15	14
ET743SAR3007-055009-000649	14	16
ET743SAR3007-055009-000668	19	5
ET743SAR3007-061001-000053	22	6
ET743SAR3007-061001-000087	16	6
ET743SAR3007-061002-000045	13	16
ET743SAR3007-061003-000110	15	14
ET743SAR3007-061004-000300	64	14
ET743SAR3007-061004-000648	15	28
ET743SAR3007-064002-000471	38	13

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/s/

ANUJA PATEL
10/20/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 27, 2015
From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 207953 (trabectedin)- Sponsor Teleconference- Clarifications re: April 25, 2015 Information Request letter

Janssen Attendees:

Erik Poulsen, Director Regulatory Affairs
Barb Kolb, North American Oncology Regulatory Affairs Therapeutic Area Lead
Hemal Morjaria, Global Regulatory Leader
Julie Brennan, Regulatory Scientist
Loreta Marquez, Medical Safety Officer
Trilok Parekh, Compound Development Team Leader
Roland Knoblauch, Clinical Leader
Nushmia Khokhar, Lead Study Physician, SAR-3007
Youn Park-Choi, Statistical Leader
Craig Tendler, VP, Late Development & Medical Affairs
Susan Wendel, Director, CMC Leader
Dawn Krach, Director, CMC Regulatory Affairs
Chi Keung, Clinical Pharmacology Leader
Sandra Rattray, VP, Regulatory Affairs Oncology
Dawn Wydner, Sr. Director, Bioresearch Quality and Compliance (BRQC) Regulatory Compliance
Pamela Paul-McNeil, Sr. Director, Quality Monitoring & Compliance

FDA Attendees:

Marc Theoret, CDTL
Anuja Patel, RPM
Dow-Chung Chi, Medical Officer, Safety
Amy Barone, Medical Officer, Efficacy

Purpose:

The purpose of this teleconference is to clarify any questions Janssen has on the April 25, 2015 letter. Janssen's response is due formally to the NDA on April 30, 2015.

Background:

On March 30, 2015 a teleconference was held between the Division of Oncology Products 2 (DOP2), Division of Clinical Compliance Evaluation (DCCE), and representatives from Janssen Research & Development, LLC (Janssen) regarding a 483 that issued. On April 3, 2015, FDA issued an information request letter concerning the preliminary inspection observations from the sponsor inspection associated with this application that was conducted from March 16-26, 2015. Janssen submitted their response to our letter formally to the NDA on April 17, 2015.

Midcycle Communication meeting (teleconference) was held on April 23, 2015, between

representatives of the Food and Drug Administration (FDA) and Janssen during which we discussed major clinical review issues. An Information Request letter was issued on April 25, 2015 containing the following comments.

Discussion During Teleconference:

1. Submit a detailed summary of the procedures followed to assure data integrity in the original NDA submission (NDA 207953, SDN 1, submitted on 11/24/2014) and in the 120-day safety update (datasets submitted to NDA 207953, SDN 22, dated 4/17/2015). In your response include details of the timelines and procedures related to the preparation of the primary data submitted for FDA review (i.e., case report forms and primary source documents) including data cutoff date, data cleaning process, and database lock for the datasets provided in the original NDA submission and in the 120-Day Safety Update.

Discussion during teleconference: Janssen acknowledged FDA comment and no discussion occurred.

2. Submit a comprehensive analysis of the differences between the datasets containing safety information submitted in the original NDA and those submitted in the 120-day safety update using the safety clinical data cut-off date of September 16, 2013. This analysis should include a summary of the differences between the two datasets at the patient level by treatment group and at the adverse event level by treatment group. For example, if the 120-day update AE.xpt dataset contained 100 adverse event line listings with an adverse event start date that had been revised from that recorded in the Original Submission AE.xpt dataset, provide a tabular summary that lists the total number of patients (and proportion of the safety population) and the number of patients (and proportion) by treatment arm affected by the revision. Provide a similar tabular listing based on the total number of adverse event line listings affected by the revision (total and by treatment arm).

Discussion during teleconference: Janssen stated that the PROC conducted was uninformative and proposed that they focus their comparisons on those datasets directly entered by site. Please refer to the 2 tables sent via email on April 27, 2015 (attached). FDA requested clarification on the structure of the database, specifically if there was a unique identifier to link the Adverse Events (AEs between the datasets included in the original NDA submissions and the (INSERT date) submission. Janssen stated that there was no unique identifier.

FDA requested that in Janssen's response to the April 25, 2015 information request letter that that Janssen include narrative on how Janssen went about identifying change in variable i.e. AE onset.

FDA also requested additional line summaries for the following listings: dictionary terms and verbatim, in addition to AE, include reasons (ie hospitalization, life-threatening, deaths) that identified the SAE.

FDA further referenced the tables provided via email on April 27, 2015, and stated that Janssen should include numbers as well as percentages. Janssen acknowledged FDA

request.

3. Submit a discussion of the root causes, at the level of the individual study site, leading to the inaccuracies/incompleteness of the datasets submitted in the original NDA and the corrective measures implemented at each of the sites to address the aforementioned root causes.

Discussion during teleconference: Janssen acknowledged FDA comment and no discussion occurred.

4. Submit a detailed summary of the remaining items/issues (e.g., data entry backlog) outstanding at the time of database lock (i.e., the finalized datasets) for the datasets and case report forms (CRFs) submitted in the original NDA and for the 120-day safety update datasets.

Discussion during teleconference: Janssen acknowledged FDA comment and no discussion occurred.

5. Submit a listing of the 11 sites that had a data entry backlog which required issue escalation and remediation plans as documented in the site monitor reports. In addition, provide the number of subjects enrolled and treated at each site, and the number of subjects that were affected by this data entry backlog. If tables presenting data are included in the response to this Information Request, provide the data in these tables in .xpt or .xls format to facilitate analysis as well as in a word or Adobe (.pdf) file.

Discussion during teleconference: Janssen clarified that 11 sites did not have data entry backlog. Only one site (out of 13) had backlog. Many of the sites had 5 or less at time of NDA cutoff. Janssen proposed to target 10% of sites (9 of highest enrolling that represent 40% of patients). Of those 9 sites, 2 sites had inspections.

FDA inquired on the process for confirming no data entry backlog. Janssen responded and stated that initial investigation was based on site monitoring reports. "Escalation" was part of protocol deviation process. The escalation would be entered into Clinical Trial Management system separately from the monitor report and followup would occur following the time it was escalated.

6. Submit your audit plan to assure the data integrity of the datasets submitted for the 120-day safety update. At a minimum, your audit plan should include a focused re-verification visit at the 11 sites that were previously identified as having data entry backlogs. A sample of the high-enrolling sites that are not already included in the 11 sites should also be included in the audit plan.

Discussion during teleconference: This item was not discussed due to time. FDA instructed Janssen to submit their proposal as discussed during the teleconference formally to the NDA as an amendment.

7. Submit a thoughtful and integrated analysis of the results from the aforementioned information requests (Comments 1-6 above) to support your conclusions regarding the data integrity of the 120-day safety update and the benefit:risk of trabectedin for the proposed indication based on the updated safety information.

Discussion during teleconference: Janssen acknowledged FDA comment and no discussion occurred.

Post Action Follow up: On April 27, 2015, Janssen formally submitted their email sent April 27, 2015 containing the proposed tables for discussion during the teleconference. In the April 27, 2015 amendment, Janssen also included their proposal for the content of their amendment in response to the April 25, 2015 Information Request letter. The amendment was forwarded to the review team and is under review.

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/s/

ANUJA PATEL
10/20/2015

Face to Face Mid-Cycle Internal Meeting

March 30, 2015

NDA: 207953- Type 1 New Molecular Entity
eCTD submission: SDN 001

Product: trabectedin, powder for reconstitution, 1 mg, intravenous
Proposed Proprietary Name: YONDELIS
Submission Date: November 24, 2014
Received Date: November 24, 2014
Applicant: Janssen Products, LP (Janssen)

Proposed Indication:



Attendees Present: Richard Pazdur, Tamy Kim, Patricia Keegan, Monica Hughes, Anuja Patel, Marc Theoret, Amy Barone, Dow-Chung Chi, Kun He, Huanyu Chen, Hong Zhao, Sriram Subramaniam, Whitney Helms, Dubravka Kufrin, Olen Stephens, William Adams, Charles Jewell, Erica Pfeiler, Lauren Iacono-Connor, Latonia Ford, Nazia Fatima, Mona Patel, Naomi Redd, Carrie Ceresa, Sharon Mills, Barbara Fuller

Discussion During Meeting:

1. **Slides were presented by the following disciplines (in order):**
 - Regulatory Intro- Anuja Patel (CPMS: Monica Hughes)
 - Clinical and Statistical, Efficacy & Safety- Amy Barone (Efficacy) and Dow-Chung Chi (Safety) (CDTL: Marc Theoret)
 - Clinical Pharmacology- Sriram Subramaniam (TL: Hong Zhao)
 - Pharm/Tox Review- Dubravka Kufrin (TL: Whitney Helms)
 - Chemistry, Manufacturing and Control (CMC), Microbiology, and Biopharmaceutics- Olen Stevens
 - Manufacturing Facility Inspection Update
 - Office of Scientific Investigation- 483 issued

2. **Clinical**
 - OSI findings and issuance of a Form 483 to Sponsor – data integrity issues and potential impact on the interpretation of the safety information in the submission of the original NDA.

 - Benefit-Risk Overview (summarized from Clinical):



Clinical Benefit Analysis

	Evidence
Clinically meaningful?	- Rare disease with unmet medical need - PFS improvement of 3 months is accepted by community as meaningful (ETOC, ODAC)
Statistically persuasive?	- Substantial improvement in PFS - Trend towards improvement in OS - Primary endpoint not achieved statically
Free from bias?	- rPFS confirmed by audit - Internal consistency - Balanced randomization
Risk-benefit profile?	- Manageable toxicity
Uncertainties	- Lack of reproducibility in upfront setting in similar but not identical populations ₄₂

Action Item for Clinical:

- *Information Request*-Ask Janssen to comment on where the 24-hour infusion was primarily given (inpatient vs. outpatient).
- *Information Request*-Given that the challenge studies demonstrate that the product supports microbial growth, ask Janssen to comment on the post-marketing experience of infusion-related infection.

3. Nonclinical

- All studies required to support the approval of trabectedin (b) (4) [redacted]; only one additional study was included in the current package -- a study of placental transfer of ET-743 in rats
- No new unique issues have been identified in the current application; issues raised in the previous application have been addressed and thus we concur with the previous determination that there are no additional nonclinical studies required to support the approval of trabectedin
- Nonclinical recommends a warning for pregnancy
- No PMR/PMCs are currently being considered

4. Clinical Pharmacology

- What is an appropriate dose in patients taking a strong CYP3A4 inhibitor or inducer?
 - Study OVC-1003 (Ketoconazole)
Ketoconazole: ↑ C_{max} by 21% and AUC_{last} by 66%
Recommendation: Under discussion.
 - Study OVC-1002 (Rifampin)
Rifampin: ↓ C_{max} by 22% and AUC_{last} by 31%
Recommendation: Avoid strong CYP3A4 inducers.
- Hepatic Impairment
 - Planned Study Completion: 01/28/15
 - To be submitted as a PMR by 09/30/15
 - Hepatic impairment study will be reviewed as a PMR

5. CMC

- There were no pending approvability issues from CMC
- Inspection of drug substance manufacturing site (b) (4) is pending (planned for (b) (4)); no facilities need to be inspected for rug product
- Challenge studies demonstrate that Janssen's reconstituted and diluted drug product supports microbial growth. The review team is considering options to mitigate the risk posed by the potential for microbial growth in a clinical setting.
- Three options are available to mitigate the risk of microbial bioburden
 - 1) (b) (4)
 - 2) Labeling: change out bag every 8 hours (would potentially work for in-patient setting only)
 - 3) Labeling: **recommend** use of in-line filter

6. Discussion of PMCs/PMRs

- Clinical- review ongoing
- Nonclinical- No PMR and No PMCs at this time
- Clinical Pharmacology - A PMR for ongoing Hepatic Impairment study ET743-OVC-1004, "An Open-Label, Multicenter, Pharmacokinetic Study of Trabectedin in Subjects with Advanced Malignancies and Hepatic Dysfunction." The study is planned for completion on 28 January 2015. The clinical study report will be submitted to FDA by 30 September 2015.
- CMC- There was a discussion of the possibility (b) (4) this proposal required further discussion in OPQ.

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/s/

ANUJA PATEL
10/19/2015

**Internal Monthly Meeting Summary
February 19, 2015**

NDA: 207953- Type 1 New Molecular Entity
eCTD submission: SDN 001

Product: trabectedin, powder for reconstitution, 1 mg, intravenous
Proposed Proprietary Name: YONDELIS
Submission Date: November 24, 2014
Received Date: November 24, 2014
Applicant: Janssen Products, LP (Janssen)

Proposed Indication:

(b) (4)

Current Review Team for NDA (b) (4)
*Attendees marked with **

(b) (4)

Discussion Items:

1. Discuss status of Information Requests and responses received

Discussion During Meeting: OPQ informed DOP 2 that the Drug Substance, Drug Product, and Process reviews have been completed. OPQ is preparing an information request on compatibility data (b) (4)

(b) (4) This item will be further discussed during labeling negotiations. There were no other information requests or updates from the other disciplines. Pharm/Tox provided their update via e-mail on February 20, 2015, and stated that a short review will be conducted for one new study that has been submitted with this application and has not been reviewed previously. All other P/T studies have been reviewed previously, and it is our plan to use that review as a basis for our edits of the label. There are no other noteworthy changes for this NDA,

Post Meeting Followup: The information request was issued via email on February 19, 2015 by Rabiya Laiq.

2. OPQ Update regarding Inspections

Discussion During Meeting: All facilities, including testing sites, are currently approved; however FDA will be inspecting the API manufacturing site (b) (4)

(b) (4) Inspection is anticipated for late April due to challenges regarding VISA.

3. OSI Update

Discussion During Meeting: Inspection assignments were issued in early December 2014. OSI is targeting a completed CIS/Primary Review on or before anticipated primary review due date of April 26, 2015.

Planned inspections:	Scheduled dates for inspection	Status	Preliminary Outcome	Site Number
Janssen R&D	Planned for Mid-March	Field Assignment Issued Jan 27th	N/A	N/A
CI: Scott Schuetze (Detroit)	Planned for Mid-March	Field Assignment Issued Jan 23rd	N/A	1033
CI: Shreyaskumar Patel (Dallas)	Pending	Field Assignment Issued Jan 23rd	N/A	1028
CI: George Demetri (Boston)	Pending	Field Assignment Issued Jan 23rd	N/A	1001

4. Dates Milestone Letters Must Issue- Revised since the Filing Meeting as dates generated by Panorama were incorrect

Milestone	Priority Review 6-month planned review (PDUFA 8 Month Review)
Application Received	Monday, November 24, 2014
Acknowledgment Letter	Issued December 7, 2014

Planning/Filing Meeting	Planning Meeting held Thursday, December 11, 2014 Filing meeting held Thursday, January 8, 2015
Application Orientation Meeting	Held January 16, 2015
Filing Day 60 Review Designation (Day 60)	Issued Friday, January 24, 2015 (PDUFA Goal: January 23, 2015)
Deficiencies Identified Letter (74 Day Letter)	Issued Friday, February 5, 2015
Midcycle Meeting	Scheduled for Monday, March 30, 2015 <i>(not communicated to Applicant as of 2/19/15)</i>
Hold Mid-Cycle Communication with Applicant (2 weeks after Midcycle)	Scheduled for Thursday, April 23, 2015 <i>(not communicated to Applicant as of 2/19/15)</i>
Send proposed labeling/PMR/PMC/REMS to applicant	Tuesday, April 28, 2015 (per Priority Designation letter)
Internal Late Cycle Meeting	Scheduled for Monday, May 4, 2015
Hold Wrap-Up meeting, including Safety Discussion	<i>To be Scheduled same week as LCM</i>
Late Cycle Meeting (LCM) with Applicant	<i>To be Scheduled same week as wrap up</i>
<u>Review Target Due Dates:</u> <i>Primary Review Due</i>	Friday, May 1, 2015
<i>Secondary Review Due</i>	Tuesday, May 5, 2015
<i>Issue Disciplinary Review Letters, as needed</i>	Friday, May 8, 2015
<i>CDTL Review Due</i>	Friday, May 8, 2015
<i>Division Director Review Due</i>	Tuesday, May 19, 2015
<i>Office Director Review Due/Sign-Off</i>	Friday, May 29, 2015
FINAL Action Letter Due	6 Month Planned AGD: Friday, May 29, 2015 8 Month PDUFA GOAL: Friday, July 24, 2015

Discussion During Meeting: CPMS and RPM to ask CDER whether due date for Primary Reviews in Panorama are calculated based on Day 60 being the start date for review or if calculated by date of receipt. The Desk Reference Guide is unclear on this. RPM will update team at next monthly meeting in March.

5. Upcoming Meetings:
 - a. **Internal Mid-Cycle Meeting:** Monday, March 30, 2015

- b. **Mid-Cycle Communication with Applicant:** Thursday, April 23, 2015
- c. **Internal Labeling Meetings**
 - Labeling meeting #1: (Clinical, Maternal Health Team, Nonclinical)
12 Noon – 1 PM, Monday, April 13, 2015
 - Labeling Meeting #2: (Clinical, Stats)
2 PM – 3 PM, Monday, April 13, 2015
 - Labeling Meeting #3: (Clinical, Clinical Pharmacology)
Wednesday, April 15, 2015
 - Labeling Meeting #4: (Clinical, OPQ, DMEPA, OSE)
Thursday, April 16, 2015
 - Labeling Meeting #5: (Clinical, OPDP, Patient Labeling)
Friday, April 17, 2015
** send SCL to Applicant and OPDP/Patient Labeling after this meeting
 - Labeling Meeting #6:
Monday, May 11, 2015
** discuss Applicants counterproposal and due date for OPDP/Patient Labeling Review
- d. **Monthly Team Meeting- next one is Thursday, March 19, 2015**
- e. **Internal Meeting for Late Cycle- scheduled Monday, May 4, 2015**

Discussion During Meeting: No discussion occurred

- 6. Miscellaneous Items
 - Press Release and Burst Planned-
Draft PR and Burst due to Press office 2 months prior to AGD
 - No ODAC
 - Competing Products List/SGEs:
 - Competing Products list under CDTL review and will be sent to DACCM this week (RPM will CC: Diane Spillman and Clinical team)
 - Dr. Ephraim Casper- Divisional Assignment form sent to DACCM 2/17/15
 - Dr. Angela Myers- Patient Rep- OHCA contacted and confirmed 12/18/14; Divisional Assignment form sent to DACCM 2/17/15
 - Any additional SGEs to be contacted and forwarded to DACCM?

Discussion During Meeting: Clinical is trying to contact one other SGE. No discussion occurred

- 7. Other Issues/Concerns
 - PMR and PMC Identified should be communicated ASAP to CDTL and RPM

Discussion During Meeting: The review team acknowledged and no discussion occurred

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/s/

ANUJA PATEL
10/18/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 9, 2015
From: Anuja Patel, MPH, Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 207953: Sponsor Tcon to discuss FDA Snapshot Website

Janssen Attendees:

Erik Poulsen, Director Regulatory Affairs
Barb Kolb, North American Oncology Regulatory Affairs Therapeutic Area Lead
Hemal Morjaria, Global Regulatory Leader
Loreta Marquez, Medical Safety Officer
Trilok Parekh, Compound Development Team Leader
Roland Knoblauch, Clinical Leader
Nushmia Khokhar, Lead Study Physician, SAR-3007
Leah Bednarek, Lead Statistical Programmer
Youn Choi-Park, Statistical Leader

FDA Attendees:

Anuja Patel, Monica Hughes, Marc Theoret, Huanyu Chen, Kun He, Amy Barone, Naomi Lowy (PASE)

Background:

On February 25, 2015, FDA sent an information request via email requesting information intended to populate the FDA Drug Trails Snapshot Website for their NDA 207953. Janssen requested a teleconference to discuss the requested information.

From: Poulsen, Erik [JRDUS] [mailto:epoulse@ITS.JNJ.com]
Sent: Thursday, February 26, 2015 1:14 PM
To: Patel, Anuja
Subject: Follow-up regarding FDA Request for Information: Drug Trials Snapshot on FDA Website- NDA 207953- Janssen (trabectedin)

Hella Anuja,

Thank you again for providing me a copy of the Drug Trial Snapshot information request. I am providing this email following a team discussion so that for completeness, I can provide how we are already working towards addressing the request. We respectfully request any comments the FDA may have so that we may remain on track to develop supporting outputs and SAS programs by the requested date of 13 March 2015.

In addition I also added a few policy-related questions in terms of the process of ultimately populating the corresponding website. Any insight when time would be greatly appreciated so I can provide that context to the team as well to ensure we provide the

FDA with most robust information possible to support this new process.

Specifically, with respect to tables 1 through 6.3, we would like to clarify our intent on addressing the provided templates based on the NDA data package submitted.

Efficacy Tables 1 through 3:

- Pivotal trial SAR-3007 with the single (trabectedin) treatment arm will be used to reflect the NDA's pivotal trial
- Table 2.1 will be used for Baseline Demographics – Table 2.2 is not applicable
- Based on the data forming the basis of the NDA (results at the time of the interim analysis for overall survival), a version of Table 3 will be created for both the primary endpoint (OS) and final analysis of the major secondary endpoint (PFS), to include the corresponding hazard ratio and its 95% confidence interval

Safety Tables 4 through 6.3

- The integrated soft tissue sarcoma (STS) analysis set (as defined in the Summary of Clinical Safety) will be used. All subjects in this pooled dataset have STS. Subjects treated at the proposed dose of 1.5 mg/m² q3wk; 24 hr regimen which will serve as the *Treatment* arm column in tables and Dacarbazine treated subjects from SAR-3007 will serve as the *Comparator* arm
- Table 5.2 is not applicable
- For Table 4, footnote "1" (stating (b) (4)) is inconsistent with the proposed table shell columns provided by FDA. Janssen proposes to follow the table shell by including subjects in the STS analysis set in the *New Drug* column and the Dacarbazine treated patients from SAR-3007 in the *Active Control* column
- For Tables 5.1, 6.1, and 6.3, to remain consistent with that submitted in the NDA, Janssen proposes to use the strata of "< 18 years" and "≥18 – <65 years" in place of the FDA-specified strata using 17 years of age. Note that there is only a single patient < 18 years old in the STS analysis set
- Table 6.3 will be generated based on a subgroup analysis by age for TEAE of special grouping

General Questions

- In the information request there is reference to provision of *descriptions of the analyses used to generate the data*. I assume this to mean we should provide textual context for each table provided? Would this context then be used to help populate the actual website content/wording?
- Following on the above, any context you can provide on the process of ultimately finalizing website through collaboration etc. would be greatly appreciated

Hopefully the above is helpful and as always, if easier to speak by phone just let me know.

Thanks again,
Erik

Discussion:

- Janssen provided the tables above via email and asked FDA if they had any questions on the proposed table format. FDA stated that they had no questions at this time however Janssen should submit proposed tables to the NDA for further review. The overall process of how the sponsor can expect to go from provision of tables to resultant/finalized website text was outlined by PASE, Naomi Lowy.

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/s/

ANUJA PATEL
10/18/2015

**Internal Monthly Meeting Summary
March 19, 2015**

NDA: 207953- Type 1 New Molecular Entity
eCTD submission: SDN 001

Product: trabectedin, powder for reconstitution, 1 mg, intravenous
Proposed Proprietary Name: YONDELIS
Submission Date: November 24, 2014
Received Date: November 24, 2014
Applicant: Janssen Products, LP (Janssen)

Attendees:

Monica Hughes, M.S., CPMS, DOP2
Anuja Patel, M.P.H., Senior Regulatory Health Project Manager
Marc Theoret., Clinical Team Leader, CDTL
Amy Barone, Medical Officer, Efficacy
Dow-Chung Chi, M.D., Medical Officer, Safety
Kun He, Ph.D., Statistics, Team Leader (TL)
Huanyu Chen, Ph.D. Statistics Reviewer
Hong Zhao, Ph.D., Clinical Pharmacology (TL)
Sriram Subramaniam, Pharm, D., Clinical Pharmacology
Whitney Helms, Ph.D., Non-Clinical (TL)
Dubravka Kufirin, Non-Clinical Reviewer
Olen Stephens, Ph.D., ONDQA Application Team Lead (ATL)
William Adams, Ph.D., Drug Product (DP) Product Quality Reviewer, ONDQA
Charles Jewell., Drug Substance (DS) Quality Reviewer, ONDQA
Carrie Ceresa, Maternal Health and Pediatric Reviewer

Discussion Summary

1. Discuss status of Information Requests and responses received

- Are there any outstanding responses (OND/OPQ) that we are waiting for from Applicant?
 - *Janssen's response to the 05 March 2015 information request received today, March 19, 2015*
- Are there any issues with the amendments received in response to our information requests?

Discussion: OPQ discussed concerns micro had with regards to the filter and stated review was ongoing. An internal meeting was scheduled for April 20, 2015 to discuss concerns and OPQ agreed to inviting the clinical team at the meeting.

2. OPQ Update regarding Inspections and DMEPA question regarding compatibility

- *OPQ to have internal meeting to address compatibility and will update DMEPA and DOP 2 review team via email following the meeting.*

Discussion: No further discussions.

3. OSI Update

- *Inspection assignments were issued in early December 2014. OSI is targeting a completed CIS/Primary Review on or before anticipated primary review due date of April 26, 2015.*

Discussion: No further discussions.

4. Review Timeline Update- *Per CDER feedback received, we will be reverting back to the Panorama generated timeline (used during the filing meeting) where primary reviews will be due approximately 3 months prior to PDUFA action. **All primary reviews will be due Friday April 24, 2015 (Actual: Saturday, April 26, 2015).***

8 Month PDUFA Goal: Friday, July 24, 2015

6 Month AGD: Friday, May 29, 2015

Discussion: No further discussions.

5. Upcoming Meetings:

- a. **Internal Mid-Cycle Meeting:** Monday, March 30, 2015
**TL/OPQ cleared slides due 1 week prior to Midcycle (March 23) to RPM (CC: CDTL).*
- b. **Mid-Cycle Communication with Applicant: confirmed for Thursday, April 23, 2015**
**** Midcycle Communication Agenda due 2 days prior to Midcycle Communication: April 20, 2015**
- c. **Internal Labeling Meetings**
 - Labeling meeting #1: (Clinical, Maternal Health Team, Nonclinical)
12 Noon – 1 PM, Monday, April 13, 2015
 - Labeling Meeting #2: (Clinical, Stats, DMEPA)
2 PM – 3 PM, Monday, April 13, 2015
 - Labeling Meeting #3: (Clinical, Clinical Pharmacology)
Wednesday, April 15, 2015
 - Labeling Meeting #4: (Clinical, OPQ, DMEPA, OSE)
Thursday, April 16, 2015
 - Labeling Meeting #5: (Clinical, OPDP, Patient Labeling)
Friday, April 17, 2015
*** send SCL to Applicant and OPDP/Patient Labeling after this meeting*
 - Labeling Meeting #6:
Monday, May 11, 2015
*** discuss Applicants counterproposal and due date for OPDP/Patient Labeling Review*
- d. **Internal Meeting for Late Cycle Meeting (LCM):** scheduled Monday, May 4, 2015
**** Briefing Document for Late Cycle due 2 days prior to LCM to Applicant: May 8, 2015**

- e. **Internal Wrap Up Meeting:** scheduled Monday, May 11, 2015
- f. **Late Cycle Communication with Applicant: confirmed for May 13, 2015**

Discussion: The above dates were discussed and the team acknowledged. No further discussions.

6. Miscellaneous Items

- Press Release and Burst Planned-
 - *Draft PR due to Press Office now per OHOP policy. Agreement to send labeling submitted by applicant to Press Office now?*
- No ODAC
- Divisional Assignments (SGE Update):
 - Dr. Ephraim Casper- Divisional Assignment form sent to DACCM 2/17/15
 - Dr. Angela Myers- Patient Rep- OHCA contacted and confirmed 12/18/14

Discussion: RPM inquired whether additional SGEs were identified and clinical stated that no additional SGEs have been identified.

7. PMR/PMC Updates (any PMR/PMC should be communicated ASAP to RPM and CDTL)

- Clinical
- Nonclinical
- Clinical Pharmacology
- CMC

Discussion: No further discussions as reviews were ongoing and no PMR/PMCs were identified at the time of the meeting.

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/s/

ANUJA PATEL
10/18/2015

Patel, Anuja

From: Patel, Anuja
Sent: Friday, October 16, 2015 4:36 PM
To: 'Kolb, Barbara [JRDUS]'
Subject: FDA Response to email---Courtesy Copy: FDA Revised Labeling following tcon held 10.15.15- NDA 207953 YONDELIS
Importance: High

Dear Ms. Kolb,

We refer to your amendment received October 15, 2015 and to your email below indicating that an additional revision was noted by Janssen in Section 14. The clinical team agrees to the proposed revisions in your email below.

In addition, we have the following additional edits to the Package Insert in response to your October 15, 2015 amendment:

1. Refer to the Highlights section of the PI. Highlights did not have information about not breastfeeding while taking Yondelis. FDA proposes to add the language noted below in pink:

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use YONDELIS® safely and effectively. See full prescribing information for YONDELIS.

YONDELIS (trabectedin) for injection, for intravenous use

Initial U.S. Approval: -2015

INDICATIONS AND USAGE

YONDELIS is an alkylating drug indicated for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen (1)

DOSAGE AND ADMINISTRATION

- Administer at 1.5 mg/m² body surface area as a 24-hour intravenous infusion, every 3 weeks through a central venous line (2.1, 2.5)
- Premedication: dexamethasone 20 mg IV, 30 min before each infusion (2.2)

DOSAGE FORMS AND STRENGTHS

For injection: 1 mg sterile lyophilized powder in a single-dose vial (3)

CONTRAINDICATIONS

Known hypersensitivity to trabectedin (4)

WARNINGS AND PRECAUTIONS

- **Neutropenic sepsis:** Severe, and fatal, neutropenic sepsis may occur. Monitor neutrophil count during treatment. Withhold YONDELIS for Grade 2 or greater neutropenia (5.1)

- **Rhabdomyolysis:** Rhabdomyolysis may occur; withhold YONDELIS for severe or life-threatening increases in creatine kinase level (5.2)
- **Hepatotoxicity:** Hepatotoxicity may occur. Monitor and delay and/or reduce dose if needed. (5.3)
- **Cardiomyopathy:** Severe and fatal cardiomyopathy can occur. Withhold YONDELIS in patients with left ventricular dysfunction (5.4)
- **Embryofetal toxicity:** Can cause fetal harm. Advise of potential risk to a fetus and use effective contraception (5.6, 8.1, 8.3)

ADVERSE REACTIONS

The most common (≥20%) adverse reactions reported are nausea, fatigue, vomiting, constipation, decreased appetite, diarrhea, peripheral edema, dyspnea, headache, increases in AST or ALT, increased alkaline phosphatase, hypoalbuminemia, increased creatinine, increased creatine phosphokinase, anemia, neutropenia, and thrombocytopenia (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-526-7736 (1-800-JANSSEN) or FDA at 1-800-FD 1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CYP3A inhibitors: Avoid concomitant strong CYP3A inhibitors. (7.1)
- CYP3A inducers: Avoid concomitant strong CYP3A inducers. (7.2)

USE IN SPECIFIC POPULATIONS

- **Lactation:** Breastfeeding not recommended (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling

Revised: 10/2

2. The letter “S” in subtitle Risk Summary under section 8.1 Pregnancy was not capitalized. Please capitalize “s” in Risk Summary.

Please submit amended labeling incorporating all revisions above by close of business today. Please confirm receipt.

Thank you!
Anuja

From: Kolb, Barbara [JRDUS] [mailto:BKolb@its.jnj.com]

Sent: Friday, October 16, 2015 2:25 PM

To: Patel, Anuja

Subject: Fwd: Rev. Courtesy Copy: FDA Revised Labeling following tcon held 10.15.15- NDA 207953 YONDELIS

Dear Anuja: Per my voice mail to you today, we have found a further correction to the label that was not picked up in previous versions of the section 14 clinical studies section. Please see below.

A revised label will be dispatched this evening.

Please call me at [REDACTED] ^{(b) (6)} to confirm process.

Thanks and best regards,

Barbara

Sent from my iPhone

Rev. Courtesy Copy: FDA Revised Labeling following tcon held 10.15.15- NDA 207953 YONDELIS

Current Text:

14 CLINICAL STUDIES

The clinical efficacy and safety of YONDELIS in patients with metastatic or recurrent leiomyosarcoma or liposarcoma were demonstrated in Trial 1, a randomized (2:1), open-label, active-controlled trial comparing treatment with YONDELIS 1.5 mg/m² as a 24-hour continuous intravenous infusion once every 3 weeks to dacarbazine 1000 mg/m² intravenous infusion (20 to 120 minutes) once every 3 weeks. Treatment continued in both arms until disease progression or unacceptable toxicity; all patients in the YONDELIS arm were required to receive dexamethasone 20 mg intravenous injection prior to each YONDELIS infusion. Patients were required to have unresectable, locally advanced or metastatic leiomyosarcoma [REDACTED] ^{(b) (4)} or liposarcoma and previous treatment with an anthracycline- and ifosfamide-containing regimen or an anthracycline-containing regimen and one additional cytotoxic chemotherapy regimen. Randomization was stratified by subtype of soft tissue sarcoma (leiomyosarcoma vs. liposarcoma), ECOG performance status (0 vs. 1), and number of prior chemotherapy regimens (1 vs. ≥2). The efficacy outcome measures were investigator-assessed progression-free survival (PFS) according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1), overall survival (OS), objective response rate (ORR), and duration of response (DOR). Patients in the dacarbazine arm were not offered YONDELIS at the time of disease progression.

Revised text:(revision in red)

14 CLINICAL STUDIES

The clinical efficacy and safety of YONDELIS in patients with metastatic or recurrent leiomyosarcoma or liposarcoma were demonstrated in Trial 1, a randomized (2:1), open-label, active-controlled trial comparing treatment with YONDELIS 1.5 mg/m² as a 24-hour continuous intravenous infusion once every 3 weeks to dacarbazine 1000 mg/m² intravenous infusion (20 to 120 minutes) once every 3 weeks. Treatment continued in both arms until disease progression or unacceptable toxicity; all patients in the YONDELIS arm were required to receive dexamethasone 20 mg intravenous injection prior to each YONDELIS infusion. Patients were required to have unresectable, locally advanced or metastatic leiomyosarcoma [REDACTED] (b) (4) or liposarcoma (dedifferentiated, myxoid round cell, or pleomorphic) and previous treatment with an anthracycline- and ifosfamide-containing regimen or an anthracycline-containing regimen and one additional cytotoxic chemotherapy regimen. Randomization was stratified by subtype of soft tissue sarcoma (leiomyosarcoma vs. liposarcoma), ECOG performance status (0 vs. 1), and number of prior chemotherapy regimens (1 vs. ≥2). The efficacy outcome measures were investigator-assessed progression-free survival (PFS) according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1), overall survival (OS), objective response rate (ORR), and duration of response (DOR). Patients in the dacarbazine arm were not offered YONDELIS at the time of disease progression.

Begin forwarded message:

From: "Patel, Anuja" <Anuja.Patel@fda.hhs.gov>

Date: October 16, 2015 at 8:00:39 AM CDT

To: "Kolb, Barbara [JRDUS]" <BKolb@its.jnj.com>

Subject: RE: Rev. Courtesy Copy: FDA Revised Labeling following tcon held 10.15.15- NDA 207953 YONDELIS

Hi Barbara,

I am confirming receipt of your email and the formal amendment thru the gateway.

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/s/

ANUJA PATEL
10/16/2015

Patel, Anuja

From: Patel, Anuja
Sent: Thursday, October 15, 2015 12:45 PM
To: 'Kolb, Barbara [JRDUS]'
Subject: FDA Modified labeling in response to 10.14.15 Amendment- For Tcon 10/15/15 at 2:00 PM, EST- NDA 207953 YONDELIS (trabectedin)
Attachments: draft-labeling-text-tracked-changes-word to Janssen pre tcon 10 15 15.doc
Importance: High

Dear Ms. Kolb,

Please find attached FDA modified labeling in response to your labeling submitted and received on October 14, 2015. We will be referring to the attached label during today's teleconference and in addition the clinical team would like to discuss your response concerning the hepatoprotective effect of dexamethasone.

Please confirm receipt of this email.

Thank you!
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎ 301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

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ANUJA PATEL
10/15/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 15, 2015

From: Anuja Patel, M.P.H., Senior Regulatory Health Project Manager,
DOP2/OHOP/CDER/FDA

Janssen Products, L.P.
c/o Janssen Research & Development, LLC
Attention: Barbara G. Kolb
Senior Director, Global Regulatory Affairs, North America Regional Lead, Oncology
920 U.S. Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Kolb,

We refer to your October 14, 2015, amendment to NDA 207953 containing your revised package insert (PI) and Patient Package Insert (PPI) labeling in response to FDA labeling modifications to the PI and PPI sent via e-mail on October 13, 2015.

We also refer to our email communication sent October 15, 2015, containing our revisions to your October 14, 2015 amendment which was later discussed during the teleconference held on October 15, 2015.

Please find attached FDA's final proposed labeling based on the discussions during the teleconference, inclusive of the package insert (PI) and Patient Package Insert (PPI).

If you are in final agreement with the draft labeling then formally submit a response by 2:00 PM, EST, October 16, 2015. In addition to submitting your response to the NDA, please email me a copy of your submission.

Please let me know if you have any questions.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Attachments: FDA Modified labeling following October 15, 2015 teleconference

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/s/

ANUJA PATEL
10/15/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 15, 2015
From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 207953- Clinical PMR Comments in response to September 30, 2015 amendment

Janssen Products, L.P.
c/o Janssen Research & Development, LLC
Attention: Barbara Kolb
Director, Global Regulatory Affairs
920 U.S. Route 202, P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Kolb:

Please refer to your New Drug Application (NDA) dated November 24, 2014, received November 24, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Yondelis (trabectedin), for injection, for intravenous use, 1 mg sterile lyophilized powder.

We refer to our September 16, 2015 electronic mail (e-mail) communication containing clinical PMR communication regarding risk of cardiomyopathy and to your amendment dated and received September 30, 2015 containing your response to our communication.

Your proposed milestone dates in your September 30, 2015 submission were as follows:

PMR/PMC Schedule Milestones:

Final Protocol Amendment Submission Date: March 2016
Study/Clinical Trial Completion Date (Cut-off date for Cardiac Analysis Report): July 2018
Interim Report (Cardiac Analysis) Submission Date: November 2017
Final Report (Cardiac Analysis) Submission Date: November 2018

We have the following response to your September 30, 2015 submission:

- An interim report is not needed; therefore, the agreed milestone dates are as follows:

PMR/PMC Schedule Milestones:

Final Analysis Plan Submission Date: March 2016
Study/Clinical Trial Completion Date (Cut-off date for Cardiac Analysis Report): July 2018
Final Report (Cardiac Analysis) Submission Date: November 2018

If you have any questions, please feel free to contact me.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ANUJA PATEL
10/15/2015

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 207953, Yondelis (trabectedin)
Product Name: _____

PMR/PMC Description: Submit the final report of the completed clinical pharmacokinetic trial to determine an appropriate dose of Yondelis in patients with hepatic impairment in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>Submitted</u>
	Study/Trial Completion:	<u>Completed</u>
	Final Report Submission:	<u>01/28/2016</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Trabectedin is extensively metabolized in liver by CYP3A4. Patients with hepatic impairment may have higher trabectedin exposures than patients with normal hepatic function, which may lead to increased toxicity.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the clinical pharmacokinetic trial is to determine appropriate Yondelis dose in patients with moderate to severe hepatic impairment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A clinical pharmacokinetic trial to determine an appropriate dose of Yondelis in patients with varying degrees of hepatic impairment in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for NDAs)

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/s/

SRIRAM SUBRAMANIAM
10/14/2015

HONG ZHAO
10/14/2015
I concur.

JEFFERY L SUMMERS
10/20/2015

Udoh, Idara

From: Udoh, Idara
Sent: Tuesday, October 13, 2015 12:06 PM
To: 'bkolb@its.jnj.com'
Cc: Patel, Anuja
Subject: FDA Modified Package Insert/Labeling and Preliminary Comments to Patient Package Insert: NDA 207953/Trabectedin/Janssen Products LP
Attachments: FDA 10.13.15 Modifications To Rcvd Janssen Labeling_Package Insert_NDA 207953.doc; Patient Package Insert (Yondelis)_ NDA 207953.docx

Good afternoon, Ms. Kolb. I hope this message finds you well.

On behalf of Anuja Patel, we refer to your amendment received October 2, 2015, following the teleconference that was held on the same day October 2, 2015, containing your revised draft labeling .

Please find attached FDA's modified labeling to the Package Insert in response to the October 2, 2015 amendment . Additionally, we are attaching preliminary comments to the Patient Package Insert, reviewed by FDA's Office of Prescription Drug Promotion (OPDP) and Division of Medical Policy (DMPP) Program's Patient Labeling Team. Word versions are being provided to assist you in your response.

A response is requested by 9AM, Wednesday, October 14, 2015.

Please confirm receipt and feel free to contact me if you have any questions.

Best,

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER
U.S. Food and Drug Administration
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WO Building 22, Room 2365
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/s/

IDARA UDOH
10/13/2015

Wrap Up Meeting Agenda
October 5, 2015

Application Number: NDA 207953
Product Name: trabectedin
Proposed Indication: for the treatment of patients with unresectable or metastatic
(b) (4) liposarcoma or
leiomyosarcoma, who (b) (4) received (b) (4) prior
anthracycline-containing regimen

Sponsor/Applicant Name: Janssen Products, L.P.

Attendees: Patricia Keegan, Anuja Patel, Marc Theoret, Dow Chung Chi, Amy Barone, Latonia Ford, Otto Townsend, Lauren Iacono-Connor, Whitney Helms, Dubravka Kufirin, Hong Zhao, Steven Kinsley, Idara Udoh, Sharon Mills, Miriam Dinatale, Mona Patel, Nazia Fatima, Afrouz Nayernama, Tracy Salaam, Peter Waldron, Sriram Subramaniam

Overview: Important Review Goal Dates

Milestone	Priority Review	Comments
<u>Pending Reviews:</u>		
<i>CDTL Review Due</i>	Wednesday, September 30, 2015	<i>Pending</i>
<i>Division Director Review Due</i>	Wednesday, October 14, 2015	<i>Pending</i>
<i>Office Director Review Due/Sign-Off</i>	Monday, October 19, 2015	<i>Pending</i>
Compile and circulate Action Letter and Action Package	Monday, September 28, 2015	<i>Circulating</i>
FINAL Action Letter Due	PDUFA Goal: Saturday, October 24, 2015 Planned Early Action: week of October 19	<i>Circulating, pending Clinical PMR agreement and then to SRT review/clearance</i>

PDUFA GOAL: Saturday, October 24, 2015

Discussion: RHPM informed the review team that planned early action was for October 19, 2015 pending the status for the clinical review, final labeling agreement, agreement on clinical PMR, and HHS clearance of Press Release and Information Advisory.

Discussion During Meeting:

1. Discipline Specific Reviews of Application

a. CMC: review complete in Panorama

- Please confirm that we waived inspections at 2 of the 5 facilities (the summary in Panorama is not clear on this point).

Discussion: OPQ confirmed that one of the sites (drug substitute site, named (b) (4)) was inspected and approved for this application. All others have been waived.

b. Non-Clinical: review complete in DARRTs 7.2.15

- The non-clinical review indicates that pharm/tox studies were compromised because of adherence of product to delivery materials. Does CMC think we should strengthen the direction for biocompatibility in the D&A section to ensure only biocompatible products are used in preparation?

Discussion: Question arose on whether FDA should clarify that applicant should not use products not already identified as biocompatible with tubing in bag. Division Director requested additional information from Pharm/Tox review team and Product Quality team to find out what the tubing is made of, and then proposed to modify the pertinent section of the Package Insert to the following: 1) stating “use only” for particular tubing type that are biocompatible; 2) and allude to (or state directly) what tubing types should not be used.

***Post meeting followup:** OPQ Application Team Leader, Olen Stephen, provided an email update to DOP 2 on October 6, 2015 after discussing with Product Substance Reviewer and Pharm/Tox teams. The labeling submitted formally to the NDA on October 2, 2015 was modified accordingly.*

c. Clinical Pharmacology: Sriram Subramaniam: review complete in DARRTs 5.15.15; ***PMR/PMC template finalized pending SRT clearance then needs to be uploaded in DARRTS***

- The clin pharm review states that the basis for dexamethasone premedication was to **intentionally** decrease exposure to reduce hepatotoxicity; the review further states this was established in a clinical study. Does the clinical review team agree that this intervention mitigates the severity of hepatotoxicity and if so, should this be clarified in the W&P section of product labeling, so that prescribers understand the importance of this.

Discussion: Clinical team will review the clinical study reports for the dexamethasone study 10-99, which is a study in soft tissue sarcoma. The clinical pharmacology team stated that they would review dose modification of the

package insert (PI) and propose a modification to the PI to address dosing in patients with hepatic impairment and to clarify our clinical pharmacology recommendations with regard to the concomitant use of strong CYP3A inhibitors and strong CYP3A inducers with YONDELIS.

***Post Meeting follow-up:** Clinical Pharmacology uploaded an addendum to their review in DARRTS to address comments above and proposed modification to the current labeling submitted October 2, 2015. The proposed modification was sent to Division Director for review and concurrence via email on October 6, 2015.*

d. Clinical:

- Dow Chung-Chi (Safety) and Amy Barone (Efficacy): **review pending**
- CDTL review **pending; PMR template pending agreement on PMR and SRT clearance then needs to be uploaded in DARRTS**

Discussion: Clinical informed the team that their review will be completed by October 7, 2015. RHPM asked whether clinical had an opportunity to review the amendment that came in on September 30, 2015, containing Janssen's proposal for study to fulfill the PMR regarding cardiac myopathy.

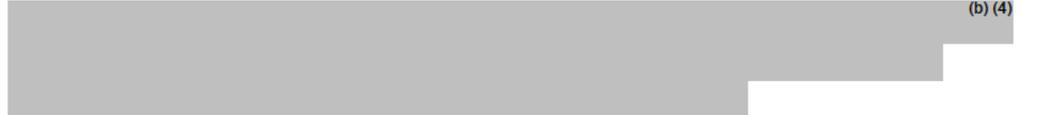
(b) (4)



(b) (4)



(b) (4)



e. Statistics: Huanyu Chen: review **complete** in DARRTs 7.23.15

Discussion: No discussion occurred.

f. OSI (OSI inspection update): Lauren Iacono-Connor: review **complete** in DARRTs 5.26.15

Discussion: No discussion occurred.

2. **Status of Consults**

a. Pediatric and Maternal Health:

- Carrie Ceresa: review complete in DARRTs 4.22.15

Discussion: No discussion occurred.

b. DRISK: Mona Patel: review complete in DARRTs 5.15.15

- Do we need an updated DRISK memo based on safety data submitted in the major amendment?

Discussion: DRISK reviewer stated that no addendum is needed because

c. Patient Labeling Team: Sharon Mills: review complete in DARRTs 9.30.15

Discussion: No discussion occurred.

d. OPDP: Nazia Fatima: review complete in DARRTs 9.30.15

Discussion: No discussion occurred.

e. DMEPA: Otto Townsend: review complete in DARRTs 3.27.15 and 9.11.15

Discussion: No discussion occurred.

f. PERC: Exempt- Orphan Designated

Discussion: No discussion occurred.

3. **Discussion of SGE Teleconference:** *Clinical to update team on discussion with Patient Representative, Dr. Angela Myers*

Discussion: Clinical informed the review team that, Dr. Myers was in agreement with FDA's labeling recommendations and stated that the benefits outweigh the risks associated with the drug.

4. **Labeling Discussion: CDTL and discipline reviewers will lead discussion of any major issues.**

a. Status of labeling review of Janssen's labeling received 10.2.15 (SDN 43)

- Should the D&A section denote that the recommended dose is in patients with bilirubin within normal limits and that there is no recommended dose in patients with abnormal hepatic function?

Discussion: The labeling was under Division Director's review. When review is completed Dr. Keegan will notify RHPM.

- b. Tentative Internal meeting scheduled following wrap up meeting; labelling planned to be sent to applicant with our counterproposal

Discussion: RHPM informed the review team that a internal meeting was scheduled for October 7, 2015 for clinical team only. The purpose of the email is to address any comments from Division Director on the forthcoming revisions to the labeling submitted October 2, 2015

5. Discussion of Status of Postmarketing Requirements

- 1 Clinical PMR: update requested from clinical
- 1 Clinical Pharmacology PMR- Language agreed upon and template to be sent to SRT along with approval letter once clinical PMR finalized

Discussion: Refer to Clinical discussion.

6. Discussion of Late Cycle Meeting- minutes with CDTL for signoff; Due

7. Other activities under NDA:

- Draft Press Release/Information Advisory- Division cleared and sent to Press Office 9.30.15 for OHOP/CDER/HHS clearance

Discussion: RHPM to follow-up with Press Office to get status of press release. Draft letter to be sent to SRT along with templates, with notice that clinical review is in draft.

- Draft (b) (4) – under review with Dr. Chi (refer to email 10.2.15 7:19 AM)

Additional discussion:

Dr. Keegan reminded the group that one of the purposes of the wrap up meeting is for DOP2 clinical review to provide DPV with issues to look out for as it may pertain to application under discussion. DPV representative stated that cardiomyopathy is an issue, since they don't know what the appropriate dose should be to determine any potential abnormalities. DPV also indicated that they have completed a review for DOP1 and can forward to clinical so that they have a sense of what sort of issues DPV considers significant.

All attendees were in agreement to approve the application. RHPM to send out yes/no voting email.

RHPM to send out meeting participation email to capture remote access (phone) attendees.

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/s/

ANUJA PATEL
10/09/2015

Patel, Anuja

From: Patel, Anuja
Sent: Friday, October 02, 2015 8:01 AM
To: 'Kolb, Barbara [JRDUS]'
Subject: FDA Modified Labeling for 10.2.15 Teleconference at 8:30 AM- NDA 207953 YONDELIS
Attachments: NDA 207953 Labeling Draft post-LCM for tcon 10 2 15 .docx

Importance: High

Dear Ms. Kolb,

Please find attached labeling for the tcon scheduled at 8:30 AM EST today, October 2, 2015.

Please note that review by upper management is ongoing and additional edits may be forthcoming following the labeling meeting. In addition, edits to the Patient Labeling have not been provided as review is ongoing.

Please confirm receipt.

Thank you!
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
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/s/

ANUJA PATEL
10/02/2015

Patel, Anuja

From: Kolb, Barbara [JRDUS] <BKolb@its.jnj.com>
Sent: Friday, October 02, 2015 12:15 PM
To: Patel, Anuja
Subject: RE: FDA Response to Action Items from 10.2.15 Teleconference at 8:30 AM- NDA 207953 YONDELIS

Dear Anuja,

We are confirming receipt of this email and will include additional information, as appropriate, in the draft label and response document to be submitted to you this afternoon (by 4:30pm).

Kind regards,
Barbara

From: Patel, Anuja [<mailto:Anuja.Patel@fda.hhs.gov>]
Sent: Friday, October 02, 2015 11:57 AM
To: Kolb, Barbara [JRDUS]
Cc: Udoh, Idara
Subject: FDA Response to Action Items from 10.2.15 Teleconference at 8:30 AM- NDA 207953 YONDELIS
Importance: High

Dear Ms. Kolb,

Reference is made to our October 2, 2015 email communication containing revised labeling that was discussed during the teleconference today at 8:30 AM, EST. The purpose of this email communication is to follow-up on action items identified during the teleconference.

We have the following responses:

1. Action Item: Section 14: Table 4: FDA to confirm numbers for Components of PFS Events:

FDA response: FDA agrees with the numbers (see below table)

Table 4: Efficacy Results for Trial 1

Efficacy endpoint	YONDELIS N=345	Dacarbazine N=173
Progression-free survival		
PFS Events, n (%)	217 (63%)	112 (65%)
Disease progression	204 (59%)	109 (63%)
Death	13 (4%)	3 (2%)

2. Action Item: FDA to provide Pt ID numbers for the 3 cardiac related deaths

FDA response: The Patient IDs for the 3 Cardiac-Related Deaths are: ET743SAR3007-001013-000456, ET743SAR3007-001028-000096, ET743SAR3007-001033-000371

3. Action Item: FDA to identify case regarding listing “fatal anaphylaxis” under Section 6.1

FDA response: FDA refers to Janssen’s September 23, 2015 amendment containing “Response Document”. Reference is made to Allergic reaction, fatal. Case 20111104702.

FDA requests that Janssen confirm that this case did not occur under IND 050286, or another clinical trial

Please confirm receipt of this email.

Thank you!
Anuja

From: Patel, Anuja
Sent: Friday, October 02, 2015 9:04 AM
To: 'Kolb, Barbara [JRDUS]'
Subject: RE: FDA Modified Labeling for 10.2.15 Teleconference at 8:30 AM- NDA 207953 YONDELIS
Importance: High

Dear Ms. Kolb,

Please find the following Patient ID numbers for renal failure as discussed during the tcon today under Section 5.2.

ET743SAR3007-001008-000332
ET743SAR3007-001009-000357
ET743SAR3007-001009-000623
ET743SAR3007-001020-000223
ET743SAR3007-001028-000106
ET743SAR3007-001033-000549
ET743SAR3007-001050-000073
ET743SAR3007-001054-000468
ET743SAR3007-001064-000685
ET743SAR3007-001090-000156
ET743SAR3007-001105-000513

Please confirm receipt.

Thank you!
Anuja

From: Patel, Anuja
Sent: Friday, October 02, 2015 8:01 AM
To: 'Kolb, Barbara [JRDUS]'
Subject: FDA Modified Labeling for 10.2.15 Teleconference at 8:30 AM- NDA 207953 YONDELIS
Importance: High

Dear Ms. Kolb,

Please find attached labeling for the tcon scheduled at 8:30 AM EST today, October 2, 2015.

Please note that review by upper management is ongoing and additional edits may be forthcoming following the labeling meeting. In addition, edits to the Patient Labeling have not been provided as review is ongoing.

Please confirm receipt.

Thank you!

Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
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anuja.patel@fda.hhs.gov (email)

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/s/

ANUJA PATEL
10/02/2015

**Initial Planning Meeting Summary
December 11, 2014**

NDA: 207953- Type 1 New Molecular Entity
eCTD submission: SDN 001

Product: trabectedin, powder for reconstitution, 1 mg, intravenous
Proposed Proprietary Name: YONDELIS
Submission Date: November 24, 2014
Received Date: November 24, 2014
Applicant: Janssen Products, LP (Janssen)

Proposed Indication:

(b) (4)

Current Review Team for NDA (b) (4)

***denotes attendee**

(b) (4)

Regulatory Background

Trabectedin, an antineoplastic agent, was granted marketing authorization (MA) under “exceptional circumstances” by the EMA in 2007 for the treatment of patients with STS who have progressed after both anthracycline and ifosamide treatment or for whom these treatments are unsuitable, under Study ET743-ST5-201 which FDA considered to be exploratory give limitations in design and conduct. As of July 10, 2014, trabectedin is approved for the treatment of STS in 75 countries.

(b) (4)

The current NDA submission (NDA 207953) (b) (4) contains multiple study reports that were provided in NDA (b) (4)

A pre-NDA (Type B) clinical meeting was held October 17, 2014, between FDA and Janssen to discuss the format and content of NDA 207953 based on progression-free survival (PFS), overall response rate (ORR) and duration of response results from Study ET743-SAR-3007 entitled, “ A Randomized Controlled Study of Yondelis (trabectein) or Dacarbazine for the Treatment of Advanced Liposarcoma or Leimyosarcoma.” Meeting Minutes issued on November 16, 2014.

Summary of Regulatory History- Trabectedin for Study ET743-SAR-3007 under IND 50286 (Please refer to DARRTS for entire regulatory history for drug product)

October 21, 2010 Type C Meeting	Meeting Minutes issued November 30, 2010	Discuss design of Phase 3 Study ET743-SAR-3007; discussion on restricting enrollment of patients with L-sarcoma to the currently active expanded access protocol, ET743-SAR-3002, in order to optimize recruitment of eligible patients to the ET743-SAR-3007.
Type C WRO submitted April 9, 2013	WRO Final Written Response issued June 7, 2013	To discuss the progression-free survival (PFS) and response rate (RR) data from Study ET743-SAR-3007 as a basis for possible accelerated approval. FDA advised

		Janssen to conduct independent analysis of tumor-based assessments by IRC or Janssen may propose detailed auditing plan
January 9, 2014 Amendment	Janssen submitted interim results for OS, PFS, and response rates from Study ET743-SAR-3007	February 18, 2014 FDA notified Janssen via e-mail that auditing plan was acceptable and stated that whether the proposal may introduce potential bias will be determined upon review of the NDA submission
March 19, 2014 Amendment	Janssen submitted Addendum to original Statistical Analysis Plan (SAP) dated October 22, 2013	SAP and audit plan modified to state symptomatic deterioration, in the absence of radiographic evidence of progression, will not be considered disease progression event
July 7, 2014 Type C meeting	Meeting Minutes issued July 21, 2014	To discuss the audit results of the investigator-assessed PFS endpoint for Study ET743-SAR-3007 as assessed by IRC
October 17, 2014 Type B Pre NDA Teleconference	Meeting Minutes issued on November 16, 2014	To discuss the format and content of NDA 207953 based on progression-free survival (PFS), overall response rate (ORR) and duration of response results from Study ET743-SAR-3007

*A standard **reminder** that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss.

Discussion Items:

1. **Review Status:**

- a. Priority Review Requested
- b. Exclusivity Request- Claiming (b) (4)
7 years Orphan Drug marketing Exclusivity; Orphan Drug Designation Granted for treatment of STS \
- c. Environmental Assessments; Categorical Exclusion requested
- d. The clinical development of trabectedin (b) (4) is under IND 050286 (b) (4)
- e. Proprietary Name Review – **not included in NDA submission**

- f. OSI Site Data for Study ET743-SAR-3007 submitted?
- g. Other items for Discussion

DISCUSSION DURING MEETING: *The team discussed the submission and determined that based on the evidence of increased effectiveness in the second-line treatment of liposarcoma, a serious condition for which there is no available therapy a priority review designation may be granted and therefore agreed to grant 8 month priority review (PDUFA User Fee Goal Date: July 24, 2015). The priority designation request was still under review following the planning meeting.*

OSE RPM informed the team that they contacted the Applicants with regards to the lack of request for Proprietary Name Review. The applicant subsequently submitted an amendment on December 16, 2015 requesting Proprietary Name review.

OSI informed the team that they are still reviewing the submission for site data and will follow-up with RPM should there be any issues.

2. Review and determination of consult and additional reviewers needed for application.

DISCUSSION DURING MEETING: *The following update was provided by the RPM:*

- *Patient Package Insert included with application therefore a Patient Labeling Consult to be uploaded in DARRTs – uploaded January 30, 2015*
- *OPDP (former DDMAC) consult to be uploaded in DARRTs - consult uploaded January 20, 2015*
- *OSE Consult for DMEPA/DRISK to be uploaded in DARRTs- consult uploaded February 2, 2015*
- *OSI Inspections Consult to be uploaded in DARRTs: uploaded in DARRTs January 27, 2015 ; OSI informed the review team that they are still reviewing the data and will update the clinical team with any issues.*
- *QT-IRT Consult to be submitted- uploaded in DARRTs January 20, 2015*
- *The Pediatric Page was prepared and sent via email communication to PERC on August 17, 2015*
- *Maternal Heal Consult will be needed for labeling review- consult uploaded February 2, 2015*
- *Micro Consult and Facility Consults to be uploaded by Teicher Agosto*
- *Patient Representative and Special Government Employees (SGE) were determined to be needed to assist with this application review, therefore a request for Divisional Assignments will be requested in order to review product labeling and respond to specific questions from the Division. RPM and Medical Officer will contact OHCA for suitable Patient Representative.*

4. Internal Team Meetings:

- **Filing Meeting:** *Scheduled for Thursday, January 8, 2015*
- **Mid-Cycle Meeting:** *to be scheduled*

- **Wrap- Up Meeting:** *to be scheduled*

DISCUSSION DURING MEETING: *The review team discussed and identified that Clinical, Statistics, Product Quality, and Clinical Pharmacology disciplines will present at the Midcycle Meeting. OPQ RPBM (Rabiya Laiq) will consolidate their slides and send to OND RPM to forward to CDTL for review.*

Slides will be sent to CDTL no later than 1 week prior to Internal Midcycle

5. Labeling Meetings & Labeling submitted in the application included:

- Draft PI Labeling (tracked changes in Word);
- Carton/Container: Vial label (1 mg strength), Carton Label (1 mg strength)
- Patient Package Insert

DISCUSSION DURING MEETING: *The review team discussed and agreed to begin scheduling labeling 2-3 weeks after the Internal Mid-cycle meeting. The team agreed to scheduling 7 labeling meetings for this application. CDTL prepared the following table with the breakdown of labeling sections by discipline and in discussion order for each meeting.*

Discipline	Label Section
Clinical, Maternal Health Team, Nonclinical	8.1, 8.2, 8.3, 8.4, 12.1, 13
Clinical, Statistics	1, 14
Clinical Pharmacology, Clinical	2, 7, 8.5, 8.6, 8.7, 12.2, 12.3
CMC, DMEPA, Clinical	3, 6, 11, 16
Clinical	2 (Dose Modifications), 4, 5, 17

6. Team Meetings and PMR/PMC Working Meetings:

DISCUSSION DURING MEETING: *The team agreed to scheduling monthly team meetings and a separate PMR/PMC meeting will be scheduled ad hoc as soon as safety issues are identified. OPQ will be setting up OPQ internal meetings and will invite OND RPM as fyi. The clinical pharmacology team identified a PMR for hepatic impairment in the pNDA meeting minutes.*

7. **Applicant Orientation Presentation:** scheduled for January 16, 2015

DISCUSSION DURING MEETING: *No further discussion occurred.*

6. **ODAC Not Needed:**

DISCUSSION DURING MEETING: *The review team discussed and determined that ODAC will not be needed for the following reasons:*

- *This drug/biologic is not first in its class;*
- *The clinical study design was acceptable;*
- *The application did not raise significant safety or efficacy issues; and*
- *The application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease*

The team agreed to identifying 3 SGEs including a patient representative. Clinical team will identify the SGEs and contact them initially and follow with an email to the RPM. RPM will submit the names to DACCM as they SGEs are identified and accepted assignments pending COI clearance.

7. **ONDQA Discussion**

DISCUSSION DURING MEETING: *OPQ RBPM, Rabiya Laiq, will assist with the following consults via Panorama:*

- a. *Establishment (EES)/ Coordinate Inspections- Rabiya working on issues with Panorama team*
- b. *Microbiology- already assigned to Erika Pfeiler in Panorama*
- c. *Biopharmaceuticals- already assigned to Okpo Eradiri in Panorama*

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/s/

ANUJA PATEL
10/02/2015

MEMORANDUM OF INTERNAL MEETING MINUTES

MEETING DATE: October 1, 2015
TIME: 8:00 AM to 8:30 AM
LOCATION: Teleconference, WO 22, RM 2327
APPLICATION: NDA 207953
DRUG NAME: trabectedin
TYPE OF MEETING: Teleconference with Special Government Employee (SGE), Dr. Angela Myers, cleared for participation by CDER's Division of Advisory Committee and Consultant Management (DACCM).

FDA ATTENDEES:

Dow Chung Chi-Medical Officer for Safety
Anuja Patel- Senior Regulatory Health Project Manager
Marc Theoret- Clinical Disciplinary Team Leader
Amy Barone- Medical Officer for Efficacy

EXTERNAL CONSTITUENT ATTENDEES:

Dr. Angela Myers (Patient Representative)

BACKGROUND: Dr. Myers agreed to serve and was cleared as an SGE for this new molecular entity (NME) application. Prior to this teleconference, background materials and draft product labeling were provided to Dr. Myers, along with three specific division questions for Dr. Myers to address during this teleconference. Those materials are attached to this document.

DISCUSSION POINTS:

In this application, Janssen seeks the approval of YONDELIS (trabectedin). (b) (4)

Discussion:

Prior to discussing the questions, FDA asked Dr. Myers if she needed clarification on any of the reading materials provided with the background and she stated that she had no clarification questions.

FDA Questions for Discussion During Teleconference:

1. Is the risk:benefit profile of Yondelis favorable (b) (4)
? ?
2. Does the attached draft label adequately reflect the risks and benefits of Yondelis (b) (4)
? ?
3. Is improvement in progression-free survival clinically meaningful (b) (4)
? ?

DISCUSSION DURING TELECONFERENCE:

Dr. Myers noted that the side effects with trabectedin appeared to be greater than with dacarbazine, but stated that overall benefit outweighed the risks for trabectedin.

With regards to the draft labeling:

- Dr. Myers asked whether LVEF risk would be included in the label. Dr. Myers expressed the concern that the rate of cardiomyopathy observed with trabectedin is reflective of the patient population (age underlined cardiac risk factors and in prior anthracycline exposure) under study rather than a treatment effect based upon the lack of information regarding the control arm in the labeling.
- Dr. Myers expressed concern in regards to the clinical significance of anemia given that the between group difference in the incidence of Grade 3-4 anemia was not as large as was the difference in all grades anemia.
- Dr. Myers requested clarification on Efficacy Results for Trial 1, regarding the PFS events. FDA clarified that the components (Disease Progression and Death) of the composite endpoint, PFS, were not available at the time that the labeling (dated September 17, 2015) was provided to her for review. FDA confirmed that this information would be included in the final label.

In terms of the clinical meaningfulness of progression free survival [REDACTED] (b) (4)
[REDACTED] Dr. Myers stated that trabectedin provides an option for patients with “bad disease” where the mortality is high. She stated that an improvement in median progression free survival of 3 months compared to another drug is meaningful to the patient. “A lot can be done in 3 months.”

FDA inquired whether Dr. Myers had any additional comments to provide with regards to this application. Dr. Myers had no further comments.

ATTACHMENTS: Background information provided to Dr. Myers via a password protected file, secure email communication on September 18, 2015.

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20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ANUJA PATEL
10/01/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 25, 2015
From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 207953- Clinical Pharmacology PMR Communication

Janssen Products, L.P.
c/o Janssen Research & Development, LLC
Attention: Barbara Kolb
Director, Global Regulatory Affairs
920 U.S. Route 202, P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Kolb:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Yondelis (trabectedin).

We refer to our September 16, 2015 electronic mail communication containing clinical post-marketing requirement (PMR) communication and acknowledge receipt of your amendment dated and received September 21, 2015 containing your response.

Please refer to our Late Cycle Meeting Background package that issued September 24, 2015 for the forthcoming Late Cycle Meeting scheduled for September 28, 2015.

In addition, we refer to your email communication sent September 25, 2015 referring to the pre-NDA meeting minutes issued on November 16, 2014 and following up on the discussion regarding the hepatic impairment study. Below please find additional proposed clinical pharmacology PMR to be discussed during the September 28, 2015, Late Cycle Meeting.

PMRs Subject to the Reporting Requirements Under Section 506B

CLINICAL PHARMACOLOGY

Complete the ongoing clinical pharmacokinetic trial to determine an appropriate dose of Yondelis in patients with moderate to severe hepatic impairment in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

PMR/PMC Schedule

Milestones:

Final Protocol Submission Date:	_____
Study/Clinical Trial Completion Date:	_____
Final Report Submission Date:	_____
Other:	_____

Provide your agreement and your proposed scheduled milestone dates to this proposal. We remind you to use due diligence in proposing timelines for completion of this trial.

In addition, please note that final language will be included in the action letter. We are requesting that you respond to our proposal by close of business on **Thursday, October 1, 2015** or sooner.

Please note that additional post-marketing requirement (PMR) and post-marketing commitment (PMC) proposals may be forthcoming while your application is under review.

Please let me know if you have any questions.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9022
Fax: 301-796-9849

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/s/

ANUJA PATEL
09/25/2015

Patel, Anuja

From: Patel, Anuja
Sent: Friday, September 25, 2015 10:00 AM
To: 'Kolb, Barbara [JRDUS]'
Subject: FDA Response: hepatic impairment study timeline discussions

Dear Ms. Kolb,

I will be sending you a PMR communication today regarding hepatic impairment study. In addition, we will also be adding as a discussion item during the Late Cycle Meeting.

Please confirm receipt.

Thank you!
Anuja

From: Kolb, Barbara [JRDUS] [<mailto:BKolb@its.jnj.com>]
Sent: Friday, September 25, 2015 9:57 AM
To: Patel, Anuja
Cc: Kolb, Barbara [JRDUS]
Subject: hepatic impairment study timeline discussions

Dear Anuja,

In follow up to our discussion this morning, and after review of the Late Cycle Meeting agenda, I would like to confirm with you the following regarding the Hepatic Impairment Study Discussion which has taken place to date (and previous attachments).

Due to the extension of the PDUFA review, we would like to confirm a revised date for submission of the Hepatic Impairment Study Report of January 30, 2015.

Should this be added to the Late Cycle Meeting Agenda?

Kind regards,
Barbara

Background:

See question 8 of pre-NDA minutes for hepatic impairment study discussion.

Discussion during the meeting: FDA asked Janssen if the final study report of the PK data is currently available; Janssen stated that the final study report would not be available at the time of the NDA submission. Instead, Janssen proposed to submit the final study report at the 120-day safety update. FDA stated that this was not acceptable based on the requirement to have a complete application in the original submission. FDA stated that Janssen should propose a postmarketing requirement (PMR) that describes the goals of the study and the study design as well as milestones for study completion and submission of the final study report.

From 02 Feb 2015 Response (Seq 11) to IR rec'd 20 Jan:

In the proposed wording below, a description for this hepatic impairment study as a PMR along with the corresponding study completion date and timeline for submission of the final clinical study report is provided:

To complete clinical trial ET743-OVC-1004 entitled “An Open-Label, Multicenter, Pharmacokinetic Study of Trabectedin in Subjects with Advanced Malignancies and Hepatic Dysfunction”, to evaluate the pharmacokinetics of trabectedin in patients with hepatic impairment. The study is planned for completion on 28 January 2015. **The clinical study report will be submitted to FDA by 30 September 2015.**

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ANUJA PATEL
09/25/2015

Patel, Anuja

From: Patel, Anuja
Sent: Thursday, September 17, 2015 3:19 PM
To: 'Kolb, Barbara [JRDUS]'
Cc: Udoh, Idara
Subject: RE: Yondelis container label question

Dear Ms. Kolb,

We refer to your September 17, 2015, email communication in response to our carton and container comments sent via email on September 16, 2015. Our product quality team has reviewed your email and attachment referenced in your email sent September 17, 2015 and agree with your proposed changes.

Please confirm receipt and reference this email communication and your September 17, 2015 communication in the cover letter of your forthcoming amendment.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎ 301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

From: Kolb, Barbara [JRDUS] [<mailto:BKolb@its.jnj.com>]
Sent: Thursday, September 17, 2015 2:46 PM
To: Patel, Anuja
Cc: Kolb, Barbara [JRDUS]
Subject: Yondelis container label question
Importance: High

Dear Anuja,
RE: YONDELIS carton and vial labeling:

We are working on a revised mock up for the draft container label. As you'll see (attached) "single dose" now appears on the principal display panel. However, I noticed another mention of (b) (4) which I've annotated on the attached. I think this also needs to be changed to "Contains 1 single dose vial." To be consistent throughout the label.

Do you agree this instance should be change in the mockup for response tomorrow?

Thanks,

Barbara

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/s/

ANUJA PATEL
09/18/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 17, 2015
From: Anuja Patel, M.P.H., Senior Regulatory Health Project Manager,
DOP2/OHOP/CDER/FDA
Subject: NDA 207953/ trabectedin/ Janssen Products, L.P.
FDA modifications to Janssen labeling amendment received July 31, 2015

Janssen Products, L.P.
c/o Janssen Research & Development, LLC
Attention: Barbara G. Kolb
Senior Director, Global Regulatory Affairs, North America Regional Lead, Oncology
920 U.S. Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Kolb,

We refer to your July 31, 2015, amendment to NDA 207953 containing your revised package insert (PI) labeling in response to FDA preliminary comments sent July 27, 2015.

Please find attached additional FDA's modifications to the package insert (PI), including Sections 5 and 6 of the PI, contained in your amendment submitted on July 31, 2015. Please provide a response to FDA's proposed changes by close of business on **September 22, 2015**. In addition to submitting your response to the NDA, please email me a MS Word labeling in both clean and redlined versions (showing track changes).

Please note these are our preliminary comments, this labeling is currently being reviewed by our counterparts in Office of Prescription Drug Promotion (OPDP) and the Patient Labeling Team (PLT) and additional comments will follow.

Where you agree with FDA's proposed edits, please accept the tracked change to aid in reviewability. Please include a comment (cite "From Janssen" in the comment field) stating your agreement.

For those edits which you do not agree, provide your proposed modifications and a comment (cite "From Janssen" in the comment field) that includes justification for your proposal.

Please feel free to contact me if you have any questions.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products

Attachments:

FDA Additional edits to Janssen July 31, 2015 Amendment with Sections 5 and 6

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ANUJA PATEL
09/17/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 16, 2015
From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 207953- Clinical PMR Communication

Janssen Products, L.P.
 c/o Janssen Research & Development, LLC
 Attention: Barbara Kolb
 Director, Global Regulatory Affairs
 920 U.S. Route 202, P.O. Box 300
 Raritan, NJ 08869-0602

Dear Ms. Kolb:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for “Yondelis (trabectedin), powder for reconstitution, 1 mg.”

Please note that additional post-marketing requirement (PMR) and post-marketing commitment (PMC) proposals may be forthcoming while your application is under review. Provide your agreement and your proposed scheduled milestone dates to the below proposal. We remind you to use due diligence in proposing timelines for completion of these trials.

In addition, please note that final language will be included in the action letter. We are requesting that you respond to our proposal by close of business on Monday, September 21, 2015.

PMRs Subject to the Reporting Requirements Under Section 506B

CLINICAL

Submit integrated safety analyses and supporting data from an adequate number of clinical trial(s) to characterize the risk of cardiomyopathy and its sequelae in patients receiving trabectedin; to identify risk factors for development of these sequelae; and to support labeling instructions for dose modification and monitoring. The design of the trial should include a patient population with previous exposure to anthracyclines and have sufficient cardiac monitoring to achieve these objectives.

PMR/PMC Schedule
 Milestones:

Final Protocol Submission Date:	
Study/Clinical Trial Completion Date:	
Final Report Submission Date:	
Interim Report Submission Date:	

Please note for any multi-study PMC/PMR, results from each study are to be submitted as an individual clinical study report (CSR) to the NDA or BLA as soon as possible after study completion. The cover letter for these individual CSRs should identify the submission as **PMC/PMR CORRESPONDENCE – PARTIAL RESPONSE** in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the approval letter, as well as the date of the approval letter.

The PMC/PMR final study report (FSR) submission intended to fulfill the PMC/PMR should include submission of the last remaining CSR and all previously submitted individual CSRs. The FSR should also contain an integrated analysis and thoughtful discussion across all studies regarding how these data support the fulfillment of the PMC/PMR. The cover letter should state the contents of the submission.

Furthermore, if a PMC/PMR requests, as a milestone, the submission of individual study reports as interim components of a multi-study PMC/PMR, the cover letter should identify the submission as **PMC/PMR CORRESPONDENCE – INTERIM STUDY REPORT** in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the final action letter, as well as the date of the final action letter.

If you have any questions, please feel free to contact me.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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ANUJA PATEL
09/16/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 16, 2015

From: Anuja Patel, M.P.H., Senior Regulatory Health Project Manager,
DOP2/OHOP/CDER/FDA

Subject: NDA 207953/ trabectedin/ Janssen Products, L.P.
FDA edits to Janssen Carton and Container labeling amendment received
September 4, 2015

Janssen Products, L.P.
c/o Janssen Research & Development, LLC
Attention: Barbara G. Kolb
Senior Director, Global Regulatory Affairs, North America Regional Lead, Oncology
920 U.S. Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Kolb,

We refer to your September 4, 2015 amendment to NDA 207953 containing your revised carton/container labeling and responses to FDA preliminary carton and container comments sent September 1, 2015.

Please find attached additional FDA's modifications to your September 4, 2015, amendment.

Provide a response to FDA's proposed changes by 3 PM, EST, September 18, 2015. In addition to formally submitting your response to the NDA, please email me a copy of your responses to our comments and questions below as well as the revised carton and container labeling.

FDA comments on the Container (vial) Labeling 1 mg, received September 4, 2015:

(b) (4)

1. **FDA Response to Comments 2, 4, and 9 of Janssen September 4, 2015 Submission:**

FDA acknowledges that more than one vial is required to achieve a therapeutic dose.

(b) (4)

[Redacted]

(b) (4)

Therefore, the term [Redacted] should be replaced with “single dose” in the package insert, carton, and container labels.

2. **FDA Response to Comment #7 of Janssen’s September 4, 2015 Submission:**

FDA agrees that the quantitative contents of the vial may appear only on the carton due to space constraints and that there is no room on the current vial label.

FDA Comment on Carton Labeling received September 4, 2015

(b) (4)

3. Please refer to FDA comments 1 and 2 above for revision to the carton labeling.

Please feel free to contact me if you have any questions.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products

Enclosures: Janssen Response Document received September 4, 2015

Janssen Research & Development, LLC

BACKGROUND

Reference is made to our New Drug Application for trabectedin for injection, 1 mg (NDA 207953) submitted on 24 November 2014 to the Division of Oncology Products 2 (DOP2). Reference is also made to the Agency's 01 September 2015 memo (Reference ID: 3814302) regarding FDA preliminary comments on our proposed carton and container labeling submitted 24 November 2014 (Sequence No. 0000). The comment/response table below details Janssen's responses to each of the Agency's numbered comments.

Please also note that in an effort to ensure the quantity of trabectedin in this vial may be easily identified, and to ensure the quantity of trabectedin in this vial may be easily differentiated from other vial quantities that are currently recorded in the local labels (e.g. Summary of Product Characteristics) and the published literature, Janssen proposes the addition of a green band behind the text "1 mg per vial" that appears beneath the text "for Injection".

FDA Comments on Container Labeling	Janssen Responses
<p>Comment #1: Revise the dosage form (b) (4) to “for Injection”</p>	<p>Agreed.</p>
<p>Comment #2: Revise the statement, (b) (4) to “Single Dose”</p>	<p>(b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p>
<p>Comment #3: (b) (4)</p> <p>(b) (4)</p> <p>The graphic (b) (4)</p> <p>(b) (4) looks like the letter, “Y,”</p> <p>(b) (4) We recommend deletion of this interfering graphic, or that it be decreased in its size and be relocated.</p>	<p>Agreed. Revised to smaller font (4) and moved towards right.</p>
<p>Comment #4: Since the proposed product is a dry powder, express the strength in terms of the total amount of drug per vial as follows: XX mg/vial or XX mg per vial</p>	<p>Agreed. Revised to state “1 mg per vial”.</p>
<p>Comment #5: To better organize information on the container label and to limit the need to rotate the vial when reading important safety information, consider the following:</p> <p>a. Change the orientation of the statements, “Cytotoxic. Store unopened vials in a refrigerator at...” (b) (4) to vertical and relocate above (to the left of) the barcode.</p> <p>b. Relocate the manufacturer statements and logo (b) (4) (b) (4) to the right side of the label such that it appears between the barcode and the space reserved for the lot number and expiration date. This format is similar to the format on the back panel of the carton labeling.</p> <p>c. Relocate the cautionary statements, “Single Dose” (refer to comment 2) and “Discard any unused portion” (b) (4) (b) (4) to the lower portion of the PDP.</p>	<p>(b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p>
<p>Comment #6: Add the following statement such that it follows the statements in Comment 5.a, “Reconstitute each vial with 20 mL Sterile</p>	<p>Agreed.</p>

FDA Comments on Container Labeling	Janssen Responses
Water for Injection, USP. Resulting solution contains 0.05 mg trabectedin per mL.”	
<p>Comment #7: (b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p>	<p>(b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p>

FDA Comments on Carton Labeling	Janssen Responses
<p>Comment #8: Revise the dosage form (b) (4) to “for Injection”</p>	<p>Agreed.</p>
<p>Comment #9: Revise the statement, (b) (4) to “Single Dose”</p>	<p>Janssen respectfully proposes (b) (4)</p> <p>(b) (4)</p>
<p>Comment #10: (b) (4)</p> <p>(b) (4)</p> <p>(b) (4) The graphic (b) (4)</p> <p>(b) (4)</p> <p>(b) (4) looks like the letter, “Y,” (b) (4)</p> <p>(b) (4) We recommend deletion of this interfering graphic, or that it be decreased in its size and be relocated.</p>	<p>Agreed. Revised to smaller font and moved towards right.</p>
<p>Comment #11: Since the proposed product is a dry powder, express the strength in terms of the total amount of drug per vial as follows: XX mg/vial or XX mg per vial</p>	<p>Agreed. Revised to state “1 mg per vial”.</p>
<p>Comment #12: Current labeling on the principal display panel (PDP) contains the following (b) (4)</p> <p>(b) (4)</p> <p>Change the statement to, “Reconstitute before further dilution.” And</p>	<p>Agreed.</p>

FDA Comments on Carton Labeling	Janssen Responses
relocate this statement such that it is immediately before the statement, "For Intravenous Infusion Only".	
Comment #13: On the rear panel, change the following statement, [REDACTED] (b) (4) to read, "Reconstitute each vial with 20 mL Sterile Water for Injection, USP. Resulting solution contains 0.05 mg trabectedin per mL."	Agreed.

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/s/

ANUJA PATEL
09/16/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 21, 2015
From: Idara Udoh, M.S., Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 207953 Trabectedin Teleconference

Janssen R&D Development LLC Attendees

Craig Tendler, M.D., Vice President, Late Development and Global Market Affairs
Roland Knoblauch, M.D., Ph.D., Clinical Development Leader
Loreta Marquez, M.D., Global Medical Safety Leader
Nushmia Khokhar, M.D., Clinical Development Lead
Sharon McCarthy, Clinical Project Scientist
Trilok Parekh, Ph.D., Compound Development Team Leader
Kathy Wu, M.Ed., Clinical Team Programming
Ronald Szumigala, M.S., North America Regulatory Leader
Barbara Kolb, M.B.A., North America Regulatory Head, Oncology
Elise Mazzola, M.P.H., North America Regulatory Affairs

FDA Attendees:

Patricia Keegan, M.D., Division Director, CDER/OHOP/DOP 2
Dow-Chung Chi, M.D., Clinical Reviewer, CDER/OHOP/DOP 2
Monica Hughes, Chief, Project Management Staff, CDER/OHOP/DOP 2
Anuja Patel, Sr. Regulatory Project Manager, CDER/OHOP/DOP 2
Idara Udoh, Sr. Regulatory Project Manager, CDER/OHOP/DOP 2

Purpose: The purpose of this teleconference is to 1) discuss Janssen Research and Development, LLC's safety data submitted under the NDA with regards to cardiac-related adverse events (AE), and 2) request additional safety data regarding cardiac-related AEs that may have been collected during the Treatment Phase or the Follow-Up Phase of study ET743-SAR-3007.

To facilitate the discussion, FDA provided a table of patients generated from queries of the adverse event datasets using an SMQ (narrow), the Sponsor's provided case definition for cardiac-related AEs, and cardiomyopathy-related Preferred Terms (PT). This table was sent via email prior to the teleconference on August 21, 2015.

FDA informed Janssen that review of patients with cardiac-related AE uncovered missing safety data, including assessments of left ventricular ejection fraction (LVEF), case narratives, AE attribution, and other cardiac-related PT's for this list of patients.

During the discussion on the Sponsor's protocol and procedures for capturing LVEF data in the study, Janssen informed FDA that the eCRF did not allow for unscheduled LVEF assessments.

Missing End-of-Treatment (EOT) LVEF for the study included continued active treatment, withdrawal of consent, refusal of LVEF, decline in medical condition, hospice, and early death. Janssen agreed to attempt to obtain the missing LVEF assessment data for the list of 23 patients.

FDA also requested additional case narratives for patients 000062 and 000486 and to provide assessments of the cardiac-related AEs for these patients.

Janssen mentioned that since its statistician was currently away, they would be able to submit the requested data by Tuesday, August 25, 2015. FDA approved of this timeline and reminded Janssen that the information was needed to conclude the safety labeling review. Any additional questions should be forwarded to the RHPM, in the interim.

Post Teleconference Action Item:

A complete response to the questions raised by the SMQ Inquiry of safety data was formally submitted and received August 25, 2015.

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/s/

IDARA UDOH
09/15/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 1, 2015
From: Anuja Patel, M.P.H., Senior Regulatory Health Project Manager,
DOP2/OHOP/CDER/FDA
Subject: NDA 207953/ trabectedin/ Janssen Products, L.P.
FDA Preliminary edits to Carton and Container labeling

Janssen Products, L.P.
c/o Janssen Research & Development, LLC
Attention: Barbara G. Kolb
Senior Director, Global Regulatory Affairs, North America Regional Lead, Oncology
920 U.S. Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Kolb,

Please find attached FDA's preliminary comments to your carton and container labeling submitted on November 24, 2014.

Attached is our preliminary comments on your proposed carton and container labeling.

Provide a response to FDA's proposed changes by close of business on September 8, 2015. In addition to formally submitting your response to the NDA, please email me a copy of your responses to our comments and questions below as well as the revised carton and container labeling.

Comments:

1. Revise the dosage form [redacted] (b) (4) to “for Injection”).
2. Revise the statement, [redacted] (b) (4) to “Single Dose”.
3. [redacted] (b) (4)
[redacted] (b) (4) The graphic [redacted] (b) (4)
[redacted] (b) (4) looks like the letter, “Y,” [redacted] (b) (4)
[redacted] (b) (4) We recommend deletion of this interfering graphic, or that it be decreased in its size and be relocated.
4. Since the proposed product is a dry powder, express the strength in terms of the total amount of drug per vial as follows:¹
XX mg/vial or XX mg per vial
5. To better organize information on the container label and to limit the need to rotate the vial when reading important safety information, consider the following:
 - a. Change the orientation of the statements, “Cytotoxic. Store unopened vials in a refrigerator at...” [redacted] (b) (4) to vertical and relocate above (to the left of) the barcode.
 - b. Relocate the manufacturer statements and logo [redacted] (b) (4) [redacted] to the right side of the label such that it appears between the barcode and the space reserved for the lot number and expiration date. This format is similar to the format on the back panel of the carton labeling.
 - c. Relocate the cautionary statements, “Single Dose” (refer to comment 2) and “Discard any unused portion” [redacted] (b) (4) to the lower portion of the PDP.
6. Add the following statement such that it follows the statements in Comment 5.a,
“Reconstitute each vial with 20 mL Sterile Water for Injection, USP. Resulting solution

¹ Guidance for Industry: Safety considerations for container labels and carton labeling design to minimize medication errors (Draft Guidance). April 2013.

contains 0.05 mg trabectedin per mL.”

7.

(b) (4)

A large rectangular area of the document is redacted with a solid grey fill, obscuring the text that would follow the number 7.

For example (please note this example FOR ILLUSTRATION PURPOSES ONLY that is provided to clarify recommendations 5.a to 5.c, but does not reflect all of our recommendations):

(b) (4)

A very large rectangular area of the document is redacted with a solid grey fill, covering the majority of the page's content below the example text.

Carton Labeling

(b) (4)

8. Revise the dosage form (b) (4) to “for Injection”).
9. Revise the statement, (b) (4) to “Single Dose”.
10. (b) (4)
The graphic (b) (4)
looks like the letter, “Y,” (b) (4)
We recommend deletion of this interfering graphic, or that it be decreased in its size and be relocated.
11. Since the proposed product is a dry powder, express the strength in terms of the total amount of drug per vial as follows:²
XX mg/vial or XX mg per vial
12. Current labeling on the principal display panel (PDP) contains the following (b) (4)
Change the statement to, “Reconstitute before further dilution.” and relocate this statement such that it is immediately before the statement, “For Intravenous Infusion Only”.

² Guidance for Industry: Safety considerations for container labels and carton labeling design to minimize medication errors (Draft Guidance). April 2013.

13. On the rear panel, change the following statement, [REDACTED] (b) (4)
[REDACTED] to read, “Reconstitute each vial with 20 mL Sterile
Water for Injection, USP. Resulting solution contains 0.05 mg trabectedin per mL.”

Please feel free to contact me if you have any questions.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products

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/s/

ANUJA PATEL
09/01/2015

Patel, Anuja

From: Patel, Anuja
Sent: Friday, August 21, 2015 9:18 AM
To: 'Kolb, Barbara [JRDUS]'
Subject: RE: Table for Discussion during tcon- NDA 207953 trabectedin (Yondelis)

Dear Ms. Kolb,

Please see below breakdown of the table.

1. Table: Summary of patients with cardiac-related AE.
 - Column A-C: list of patients identified by various means
 - Column D: compiled list of patients
 - Column E –G: LVEF values for baseline, post-treatment (i.e., end of study), and LLN for the screening test)
 - Column H: whether subject narrative was provided (blank means no)
 - Column I – K: reason for inclusion of subject narrative (death, SAE, or tx discontinuation)
 - Column L: Cardiac related PT's reported for each patient

Please confirm receipt.

Thank you.
Anuja

From: Patel, Anuja
Sent: Friday, August 21, 2015 9:07 AM
To: 'Kolb, Barbara [JRDUS]'
Subject: Table for Discussion during tcon- NDA 207953 trabectedin (Yondelis)
Importance: High

Hi Ms. Kolb,

Please find attached table for discussion during the meeting.

Please confirm receipt.

Regards,
Anuja

	A	B	C	D	E	F	G	H	I	J	K	L
1	NDA 207953											
2	SAR3007											
3	Cardiomyopathy Analysis											
4	120 Safety Data											
5												
6												
7												
8	Patient Listing											
9	SMQ-Narrow: Cardiac Failure (21)	Cardiac-Related AE (from Janssen) (57)	Cardiomyopathy-related PT (from FDA) (20)	Complied List of Patients	Baseline LVEF	Post LVEF	Normal cutoff for Screening	Subject Narrative Provided	AEDeath	SAE	AE discount	Cardiac-Related PT reported
10	ET743SAR3007-001001-000178	ET743SAR3007-001001-000178	ET743SAR3007-001001-000178	ET743SAR3007-001001-000178	59		50	178		Y	Y	Cardiac failure congestive Ejection fraction decreased
11		ET743SAR3007-001001-000307		ET743SAR3007-001001-000307	63	65	50	307		Y		Tachycardia
12		ET743SAR3007-001004-000098		ET743SAR3007-001004-000098	47		45	98		Y		Atrial flutter Electrocardiogram QT prolonged Sinus tachycardia
13		ET743SAR3007-001004-000407		ET743SAR3007-001004-000407	55	60	55	407		Y		Sinus tachycardia
14		ET743SAR3007-001005-000238		ET743SAR3007-001005-000238	60	55	55	238		Y	Y	Tachycardia
15		ET743SAR3007-001005-000244		ET743SAR3007-001005-000244	60	55	50	244		Y		Tachycardia
16		ET743SAR3007-001005-000660		ET743SAR3007-001005-000660	67		50	660		Y		Palpitations
17	ET743SAR3007-001008-000074	ET743SAR3007-001008-000074	ET743SAR3007-001008-000074	ET743SAR3007-001008-000074	37		50	74		Y		Cardiac failure congestive
18		ET743SAR3007-001008-000565		ET743SAR3007-001008-000565	60	60	50	565		Y		Atrial fibrilla ion Palpitations
19	ET743SAR3007-001009-000623	ET743SAR3007-001009-000623	ET743SAR3007-001009-000623	ET743SAR3007-001009-000623	57		50	623		Y	Y	Cardiac failure congestive Pericardial effusion
20		ET743SAR3007-001011-000507		ET743SAR3007-001011-000507	60		55	507		Y		Tachycardia
21		ET743SAR3007-001012-000107		ET743SAR3007-001012-000107	67	71	50	107		Y		Tachycardia
22		ET743SAR3007-001012-000312		ET743SAR3007-001012-000312	60	60	50	312		Y		Sinus tachycardia
23		ET743SAR3007-001013-000456		ET743SAR3007-001013-000456	50		50	456	Y	Y	Y	Cardiac arrest
24		ET743SAR3007-001014-000034		ET743SAR3007-001014-000034	69		50	34		Y		Sinus tachycardia
25		ET743SAR3007-001015-000543		ET743SAR3007-001015-000543	56	54	50					Tachycardia
26	ET743SAR3007-001020-000365	ET743SAR3007-001020-000365	ET743SAR3007-001020-000365	ET743SAR3007-001020-000365	60	34	50	365		Y	Y	Cardiac failure congestive Cardiomyopathy Ejection frac ion
27		ET743SAR3007-001020-000571		ET743SAR3007-001020-000571	60	64	50	571		Y	Y	Tachycardia
28		ET743SAR3007-001021-000064		ET743SAR3007-001021-000064	55		50	64		Y		Tachycardia
29	ET743SAR3007-001023-000540	ET743SAR3007-001023-000540	ET743SAR3007-001023-000540	ET743SAR3007-001023-000540	55	35	55	540		Y	Y	Ejection fraction decreased
30		ET743SAR3007-001023-000550		ET743SAR3007-001023-000550	55		55					Palpitations
31	ET743SAR3007-001023-000593	ET743SAR3007-001023-000593	ET743SAR3007-001023-000593	ET743SAR3007-001023-000593	40		50	593		Y	Y	Cardiac failure acute Cardiac failure conges ive Ejection fraction

	A	B	C	D	E	F	G	H	I	J	K	L
32	SMQ-Narrow: Cardiac Failure (21)	Cardiac-Related AE (from Janssen) (57)	Cardiomyopathy-related PT (from FDA) (20)	Complied List of Patients	Baseline LVEF	Post LVEF	Normal cutoff for Screening	Subject Narrative Provided	AEDeath	SAE	AE discont	Cardiac-Related PT reported
33		ET743SAR3007-001024-000037		ET743SAR3007-001024-000037	59	53	50	37		Y		Palpitations
34		ET743SAR3007-001024-000369		ET743SAR3007-001024-000369	71		50	369		Y		Tachycardia
35		ET743SAR3007-001024-000472		ET743SAR3007-001024-000472	69		50	472		Y	Y	Tachycardia
36		ET743SAR3007-001027-000676	ET743SAR3007-001027-000676	ET743SAR3007-001027-000676	60		50	676		Y		Bradycardia Right ventricular dysfunction
37		ET743SAR3007-001028-000096		ET743SAR3007-001028-000096	32		50	96	Y	Y		Cardiac arrest
38	ET743SAR3007-001028-000139	ET743SAR3007-001028-000139	ET743SAR3007-001028-000139	ET743SAR3007-001028-000139	65	59	50	139		Y	Y	Ejection fraction decreased Pericardial effusion
39		ET743SAR3007-001031-000320		ET743SAR3007-001031-000320	55		50	320		Y		Tachycardia
40		ET743SAR3007-001033-000040		ET743SAR3007-001033-000040	73		50	40		Y	Y	Tachycardia
41	ET743SAR3007-001033-000062	ET743SAR3007-001033-000062	ET743SAR3007-001033-000062	ET743SAR3007-001033-000062	74	58	50	62			Y	Ejection fraction decreased Palpitations
42		ET743SAR3007-001033-000183		ET743SAR3007-001033-000183	67		50	183		Y	Y	Sinus tachycardia
43		ET743SAR3007-001033-000334		ET743SAR3007-001033-000334	67	69	50					Heart rate increased
44	ET743SAR3007-001033-000371	ET743SAR3007-001033-000371	ET743SAR3007-001033-000371	ET743SAR3007-001033-000371	50	20	55	371	Y	Y		Ejection fraction decreased
45	ET743SAR3007-001036-000313	ET743SAR3007-001036-000313	ET743SAR3007-001036-000313	ET743SAR3007-001036-000313	45	15	50	313		Y	Y	Cardiac failure Ejection fraction decreased Palpitations Sinus tachycardia
46		ET743SAR3007-001041-000519		ET743SAR3007-001041-000519	59	57	55	519		Y		Sinus tachycardia
47		ET743SAR3007-001041-000606		ET743SAR3007-001041-000606	65			606	Y	Y	Y	Cardiac arrest
48	ET743SAR3007-001057-000454	ET743SAR3007-001057-000454	ET743SAR3007-001057-000454	ET743SAR3007-001057-000454	56	37	50	454		Y		Diastolic dysfunction Diastolic dysfunction Ejection fraction decreased
49		ET743SAR3007-001061-000308		ET743SAR3007-001061-000308	55	45	50	308		Y		Atrial flutter
50	ET743SAR3007-001064-000186	ET743SAR3007-001064-000186	ET743SAR3007-001064-000186	ET743SAR3007-001064-000186	47	27	50	186		Y	Y	Atrial fibrillation Cardiac failure Cardiomyopathy Ejection fraction decreased Pericardial effusion Sinus tachycardia
51	ET743SAR3007-001064-000296	ET743SAR3007-001064-000296	ET743SAR3007-001064-000296	ET743SAR3007-001064-000296	55	25	50	296		Y	Y	Ejection fraction decreased Electrocardiogram QT prolonged Palpitations Sinus tachycardia Tachycardia
52		ET743SAR3007-001064-000685		ET743SAR3007-001064-000685	60		50	685	Y	Y	Y	Atrial fibrillation
53		ET743SAR3007-001064-000686		ET743SAR3007-001064-000686	55	60	50	686		Y		Cardiac murmur
54	ET743SAR3007-001079-000206	ET743SAR3007-001079-000206	ET743SAR3007-001079-000206	ET743SAR3007-001079-000206	61	45	55	206		Y		Ejection fraction decreased
55	ET743SAR3007-001079-000406	ET743SAR3007-001079-000406	ET743SAR3007-001079-000406	ET743SAR3007-001079-000406	68	54	55	406		Y		Ejection fraction decreased

	A	B	C	D	E	F	G	H	I	J	K	L
56	ET743SAR3007-001082-000131	ET743SAR3007-001082-000131	ET743SAR3007-001082-000131	ET743SAR3007-001082-000131	54	20	50	131		Y	Y	Atrial fibrillation Cardiac failure congestive Heart rate increased
57	SMQ-Narrow: Cardiac Failure (21)	Cardiac-Related AE (from Janssen) (57)	Cardiomyopathy-related PT (from FDA) (20)	Complied List of Patients	Baseline LVEF	Post LVEF	Normal cutoff for Screening	Subject Narrative Provided	AE Death	SAE	AE discount	Cardiac-Related PT reported
58	ET743SAR3007-001082-000295	ET743SAR3007-001082-000295	ET743SAR3007-001082-000295	ET743SAR3007-001082-000295	50	45	50	295		Y	Y	Atrial flutter Cardiac failure congestive
59		ET743SAR3007-001096-000143		ET743SAR3007-001096-000143	50	44	50	143		Y		Cardiac disorder
60		ET743SAR3007-001105-000497		ET743SAR3007-001105-000497	60	50	50					Arrhythmia Tachycardia
61		ET743SAR3007-001105-000513	ET743SAR3007-001105-000513	ET743SAR3007-001105-000513	60		60	513		Y	Y	Cardiomyopathy
62		ET743SAR3007-001105-000693		ET743SAR3007-001105-000693	55		50					Arrhythmia
63	ET743SAR3007-001110-000486			ET743SAR3007-001110-000486	71	44	50					
64	ET743SAR3007-001110-000522	ET743SAR3007-001110-000522	ET743SAR3007-001110-000522	ET743SAR3007-001110-000522	60	50	50	522		Y	Y	Cardiac failure congestive
65	ET743SAR3007-001128-000666	ET743SAR3007-001128-000666		ET743SAR3007-001128-000666	66	56	50	666		Y	Y	Cardiac murmur Tachycardia
66	ET743SAR3007-055006-000495			ET743SAR3007-055006-000495	68	56	50	495		Y		
67		ET743SAR3007-055007-000594		ET743SAR3007-055007-000594	59	63	55	594			Y	Extrasystoles
68		ET743SAR3007-061001-000087		ET743SAR3007-061001-000087	58		50	87		Y		Sinus tachycardia Tachycardia
69		ET743SAR3007-064001-000367		ET743SAR3007-064001-000367	60		50	367		Y	Y	Tachycardia
70		ET743SAR3007-064002-000589		ET743SAR3007-064002-000589	31		50					Atrial thrombosis

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/s/

ANUJA PATEL
08/21/2015

Patel, Anuja

From: Patel, Anuja
Sent: Monday, August 10, 2015 2:59 PM
To: 'Kolb, Barbara [JRDUS]'
Subject: New Statistical Information Request: NDA 207953 trabectedin/YONDELIS
Importance: High

Dear Ms. Kolb,

We refer to our August 5, 2015 email communications containing a clinical information request regarding verification of overall response rate (ORR) datasets and to your amendment received August 7, 2015 containing your response to our email communication.

We have the following statistical information request:

Variables AVAL (duration of response in month) and CNSR (censored for DOR) should be re-derived based on the dates of confirmed response, PD, death, new anticancer therapy, last adequate disease assessment, disposition, and clinical data cut-off. In the submitted SAS programs (ORR_confirmation_sensitivity 1 and ORR_confirmation_sensitivity 2) dated 06 August 2015, variables AVAL and CNSR were carried from unconfirmed ORR.

- 1. Please provide all related analysis data(s) and updated SAS programs with AVAL and CNSR derivations. ORR and DoR results should be summarized in the Tables1 and 2.**
- 2. Please provide all related documents, dataset(s), and SAS code to support the updates for the following patients/records in the sensitivity analysis 2.**

(b) (4)

Please formally submit your response to this information request no later than close of business Wednesday, August 12, 2015.

Please confirm receipt and feel free to contact me if you have any questions.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
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anuja.patel@fda.hhs.gov (email)

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/s/

ANUJA PATEL
08/10/2015

Patel, Anuja

From: Patel, Anuja
Sent: Thursday, August 06, 2015 4:19 PM
To: 'Kolb, Barbara [JRDUS]'
Subject: FDA Clarification to August 5, 2015 Clinical Information Request- Verification of ORR results in July 31, 2015 submission/ NDA 207953

Importance: High

Dear Ms. Kolb,

Thank you for your email dated August 5, 2015 in response to our August 5, 2015 information request.

We would like to clarify that you should use the same RECIST criteria v1.1 that was used to define the initial response in protocol ET743-SAR-3007.

We further refer you to the publication (EUROPEAN JOURNAL OF CANCER 45 (2 0 0 9) 2 2 8 –2 4 7) describing RECIST v1.1, which states on page 235: “Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.”

Please formally submit your response to our August 5, 2015 information request no later than close of business Monday, August 10, 2015.

Please confirm receipt.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
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anuja.patel@fda.hhs.gov (email)

From: Kolb, Barbara [JRDUS] [<mailto:BKolb@its.jnj.com>]
Sent: Wednesday, August 05, 2015 1:57 PM
To: Patel, Anuja
Cc: Kolb, Barbara [JRDUS]
Subject: RE: New Clinical Information Request- Verification of ORR results in July 31, 2015 submission/ NDA 207953

Dear Anuja,

I am confirming receipt of this information request. However, we would like to clarify with the review team that ET743-SAR-3007, per protocol, was conducted according to RECIST v1.1, which does not require confirmatory scans for partial or complete responses for randomized studies. As a result, we have not carried out any analyses according to RECIST 1.0 criteria (which required confirmatory scans). This information request will therefore require new analyses and programming which we will include in our response.

We note the due date requested for a formal submission to the NDA.

If you have any questions, please feel free to contact me at (908) 432-0544.

Best regards,
Barbara

From: Patel, Anuja [<mailto:Anuja.Patel@fda.hhs.gov>]
Sent: Wednesday, August 05, 2015 11:32 AM
To: Kolb, Barbara [JRDUS]
Subject: New Clinical Information Request- Verification of ORR results in July 31, 2015 submission/ NDA 207953
Importance: High

Dear Ms. Kolb,

We refer to your July 31, 2015 submission containing your revised labeling in response to our July 27, 2015 email communication. We have the following new clinical information request from our clinical team:

- **The submitted data (RS) and SAS programs do not provide sufficient information to verify the objective response rates and duration of responses that have been confirmed on a subsequent tumor assessment (i.e., repeat tumor response evaluation performed at least 4 weeks after the initial evaluation demonstrating a response). Please provide all related dataset(s) and SAS code to verify the confirmed ORR results provided in your July 31, 2015, submission of draft labeling.**

A response is requested **by Noon Friday, August 7, 2015** followed by a formal submission to your NDA.

Please confirm receipt of this email.

Take care,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
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/s/

ANUJA PATEL
08/06/2015

Patel, Anuja

From: Patel, Anuja
Sent: Wednesday, August 05, 2015 11:32 AM
To: 'Kolb, Barbara [JRDUS]'
Subject: New Clinical Information Request- Verification of ORR results in July 31, 2015 submission/ NDA 207953

Importance: High

Dear Ms. Kolb,

We refer to your July 31, 2015 submission containing your revised labeling in response to our July 27, 2015 email communication. We have the following new clinical information request from our clinical team:

- **The submitted data (RS) and SAS programs do not provide sufficient information to verify the objective response rates and duration of responses that have been confirmed on a subsequent tumor assessment (i.e., repeat tumor response evaluation performed at least 4 weeks after the initial evaluation demonstrating a response). Please provide all related dataset(s) and SAS code to verify the confirmed ORR results provided in your July 31, 2015, submission of draft labeling.**

A response is requested **by Noon Friday, August 7, 2015** followed by a formal submission to your NDA.

Please confirm receipt of this email.

Take care,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
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/s/

ANUJA PATEL
08/05/2015

Patel, Anuja

From: Patel, Anuja
Sent: Monday, August 03, 2015 2:25 PM
To: 'Kolb, Barbara [JRDUS]'
Subject: Clinical Information Request- Section 5.1 and 5.2 of labeling/ NDA 207953

Importance: High

Dear Ms. Kolb,

We refer to your NDA 207953 that is currently under our review. Our clinical team has the following request for information with a formal response due by 2 PM, EST, Wednesday, August 5, 2015, or sooner.

- 1. Provide the criteria that were used in the definition and grading of febrile neutropenia. Specifically, what vital signs, laboratory data, and microbiology data as well as any other criteria that were used in this case definition. Additionally, provide an adverse event-level listing of each case of febrile neutropenia, reported in trial 3007 (18 cases in each arm of Trial 3007) and the details of the criteria that were met to identify each of these cases. Apply this definition to the raw data to ensure that there are no additional cases that were not reported in the adverse events datasets.**
- 2. Provide the criteria that were used in the definition and grading of the Preferred Terms used in the definition of “neutropenic-selected infections”. Specifically, what vital signs, laboratory data, and microbiology data as well as any other criteria that were used in this case definition. Additionally, provide a listing of each case of neutropenic-selected infection and details of the criteria that were met to identify each of these cases.**

Please confirm receipt of this email and please email me a courtesy copy of your response once it has been formally submitted to the NDA.

Thank you,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
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/s/

ANUJA PATEL
08/03/2015

Patel, Anuja

From: Kolb, Barbara [JRDUS] <BKolb@its.jnj.com>
Sent: Thursday, July 09, 2015 3:29 PM
To: Patel, Anuja
Cc: Kolb, Barbara [JRDUS]
Subject: RE: FDA Comment Re: June 25, 201 Janssen Email and Draft Labeling for NDA 207953/ trabectedin

Dear Anuja,

Janssen is appreciative of the Agency's preliminary feedback to the draft labeling for NDA 207953 at your convenience. Please let me know when we might expect these preliminary comments and the plan for FDA's feedback on Sections 2, 5, and 6.

Kind regards,
Barbara

From: Patel, Anuja [<mailto:Anuja.Patel@fda.hhs.gov>]
Sent: Thursday, July 09, 2015 1:37 PM
To: Kolb, Barbara [JRDUS]
Subject: FDA Comment Re: June 25, 201 Janssen Email and Draft Labeling for NDA 207953/ trabectedin
Importance: High

Dear Ms. Kolb,

We refer to your email sent June 25, 2015, containing a CSR addendum and requesting verbal guidance to confirm your formal submission to the NDA currently under our review. As communicated to you via phone today, your email communication from June 25, 2015 inter is being discussed internally and I will try to have an update for you on Monday, July 14, 2015.

We also refer to the draft labeling formally submitted February 27, 2015 to your NDA and have the following comment and request for response:

- With regards to the labeling, the review team is proposing the possibility of sending you our preliminary edits to the package insert in the absence of Sections 2, 5, and 6 since we are still reviewing your June 11 and 16, 2015 amendments. While a determination has not yet been made at the time of this communication, would you mind letting me know if Janssen would be open to our proposal so that we can plan accordingly?

Kindly respond by close of business today.

Thank you!
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎ 301.796.9022 (phone)
301.796.9849 (fax)

From: Kolb, Barbara [JRDUS]
Sent: Thursday, June 25, 2015 2:46 PM
To: Anuja.Patel@fda.hhs.gov
Cc: Varney, Deanne; Kolb, Barbara [JRDUS]
Subject: trabectedin NDA 207953

Dear Anuja:

In accordance with the protocol, all protocol-specified analyses are completed for Study ET743-SAR-3007. Janssen Research & Development, LLC (JRD) is preparing an addendum to the ET743-SAR-3007 Clinical Study Report (CSR) submitted with NDA 207953 (24 Nov 2014; Seq. No. 0000). The ET743-SAR-3007 CSR included in the NDA presented data from the interim analysis (IA) with a clinical cut-off of 16 Sept 2013; the CSR addendum will include the final analysis of overall survival (OS) and safety data at a clinical cut-off 5 Jan 2015.

- Final Analysis of OS Report previously submitted to the FDA (24 Mar 2015; Seq. No. 0017), and now part of the CSR addendum.
- At the time of the Clinical cutoff (CCO) for the 120-day safety update (10 July 2014) submitted to FDA (24 Mar 2015; Seq. No. 0017), 19 (5.0%) subjects were ongoing on trabectedin treatment and 6 (3.5%) on dacarbazine treatment. At the CCO for the Final analysis, 8 subjects were ongoing on trabectedin treatment and 2 subjects on dacarbazine treatment.
- The data in the Final OS CSR addendum represents an additional 6 months of safety data since 120-Day Safety Update. Overall, the final safety profile with the inclusion of the additional exposure data are consistent with the data provided in the 120-Day Safety Update.

Given your verbal guidance to confirm submissions to the active NDA under review, Janssen would like to confirm with FDA the appropriate time to submit this CSR addendum.

Thank you for your assistance,

Barbara

Barbara Gerard Kolb

Senior Director, Global Regulatory Affairs
North America Regional Lead, Oncology
Janssen Research and Development, LLC

Tel: 908-218-6379

Cell: (b) (6)

Barbara Gerard Kolb

Senior Director, Global Regulatory Affairs
North America Regional Lead, Oncology

Janssen Research and Development, LLC

Tel: 908-218-6379

Cell: [REDACTED] (b) (6)

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/s/

ANUJA PATEL
07/27/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 27, 2015
From: Anuja Patel, M.P.H., Senior Regulatory Health Project Manager,
DOP2/OHOP/CDER/FDA
Subject: FDA Preliminary edits to Package Insert (PI) received February 27, 2015-
NDA 207953/ trabectedin/ Janssen Products, L.P.

Janssen Products, L.P.
c/o Janssen Research & Development, LLC
Attention: Barbara G. Kolb
Senior Director, Global Regulatory Affairs, North America Regional Lead, Oncology
920 U.S. Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Kolb,

Please find attached FDA's proposed modifications to the package insert (PI) contained in your amendment submitted on February 27, 2015. Please provide a response to FDA's proposed changes by close of business on **August 3, 2015**. In addition to submitting your response to the NDA, please email me MS Word labeling in both clean and redlined versions (showing track changes).

Please note these are our preliminary comments, this labeling is currently being reviewed by our counterparts in Office of Prescription Drug Promotion (OPDP) and the Patient Labeling Team (PLT) and additional comments will follow.

Where you agree with FDA's proposed edits, please accept the tracked change to aid in reviewability. Please include a comment (cite "From Janssen" in the comment field) stating your agreement.

For those edits which you do not agree, provide your proposed modifications and a comment (cite "From Janssen" in the comment field) that includes justification for your proposal.

In addition, we have the following comment from our clinical team:

- We refer to our July 9, 2015, e-mail communication containing our proposal to send you FDA preliminary edits to your PI labeling submitted February 27, 2015, without sections 2, 5, and 6. We acknowledge receipt of your July 9, 2015, email communication agreeing with our proposal.
- Please note that the attached labeling includes our proposed revisions to section 2; however, we have not included revisions to Sections 5 and 6 as we are reviewing your April 17 and 27, 2015 major amendment.

Please feel free to contact me if you have any questions.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products

Attachments:

FDA Additional edits to Janssen February 27, 2015 Amendment

26 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ANUJA PATEL
07/27/2015

Patel, Anuja

From: Patel, Anuja
Sent: Wednesday, June 10, 2015 2:54 PM
To: 'Kolb, Barbara [JRDUS]'
Subject: FDA Request for Response: Audit Results- NDA 207953- trabectedin

Importance: High

Dear Ms. Kolb,

We refer to your April 30, 2015, submission containing your response to our April 25, 2015, Information Request letter. Specifically, we refer to Item 6 of our letter where we requested the following:

- “Submit your audit plan to assure the data integrity of the datasets submitted for the 120- day safety update. At a minimum, your audit plan should include a focused re-verification visit at the 11 sites that were previously identified as having data entry backlogs. A sample of the high-enrolling sites that are not already included in the 11 sites should also be included in the audit plan”.

We have the following request for response:

- **In your April 30, 2015, response Janssen stated that Janssen has initiated the focused re-verification visits and Janssen plans to have the visits completed by the end of May 2015. Please provide an update as to when you will be submitting the results from this audit. Kindly respond by close of business today.**

Kindly acknowledge receipt. Please note that I will be out of the office June 11 and June 12 but will be checking email intermittently.

Thank you,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎ 301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

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/s/

ANUJA PATEL
06/10/2015

Patel, Anuja

From: Patel, Anuja
Sent: Tuesday, June 02, 2015 7:02 AM
To: 'Kolb, Barbara [JRDUS]'
Cc: Brennan, Julie [JRDUS] (JBrenna6@its.jnj.com)
Subject: Request for Form 356 h: New Authorized POC for NDA 207953- Janssen - trabectedin

Importance: High

Hello Ms. Kolb,

Please refer to my email sent June 2, 2015 regarding your June 1, 2015 submission. Form 356 h that was submitted currently states Erik Poulsen in Box 32. Please submit a revised Form 356 H with your name in Box 32 along with your address and contact information in Box 37.

Please acknowledge receipt.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎ 301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

From: Patel, Anuja
Sent: Tuesday, June 02, 2015 6:45 AM
To: Kolb, Barbara [JRDUS]
Cc: Brennan, Julie [JRDUS] (JBrenna6@its.jnj.com)
Subject: New Authorized POC for NDA 207953- Janssen - trabectedin
Importance: High

Dear Ms. Kolb,

I am confirming receipt of your correspondence dated and received June 1, 2015 identifying you as the new point of contact for all communications related to NDA 207953. In addition, I acknowledge that Ms. Julie Brennan is the alternate point of contact.

Please feel free to contact me if you have any questions. I am in the office Monday through Friday from 6:30 AM, EST through 2:30 PM, EST. Please note I will be out of the office June 11 and June 12 [REDACTED] (b) (6) [REDACTED] and will have out of office coverage.

Take care,

Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
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/s/

ANUJA PATEL
06/02/2015



NDA 207953

MID-CYCLE COMMUNICATION

Janssen Products, L.P.
c/o Janssen Research & Development, LLC
Attention: Erik Poulsen, M.S.
Director, Global Regulatory Affairs
920 U.S. Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Mr. Poulsen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for trabectedin for injection, 1 mg.

We also refer to the teleconference between representatives of your firm and the FDA on April 23, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: Thursday, April 23, 2015

Application Number: NDA 207953

Product Name: trabectedin

Indication:



Applicant Name: Janssen Products, LP

Meeting Chair: Marc Theoret

Meeting Recorder: Anuja Patel

FDA ATTENDEES

Richard Pazdur, Director, Office of Hematology and Oncology Products

Patricia Keegan, Director, Division of Oncology Products 2 (DOP2)

Monica Hughes, Chief, Project Management Staff, DOP2

Anuja Patel, Senior Regulatory Health Project Manager (SRPM)

Marc Theoret, Clinical Team Leader (CDTL)

Amy Barone, Medical Officer, Efficacy Reviewer, DOP 2

Dow-Chung Chi, Medical Officer, Efficacy Reviewer, DOP 2

Kun He, Statistical Team Leader (TL)

Huanyu (Jade) Chen, Statistics Reviewer

Hong Zhao, Clinical Pharmacology (TL)

Sriram Subramaniam, Clinical Pharmacology Reviewer

Whitney Helms, Non-Clinical (TL)

Dubravka Kufrin, Non-Clinical Reviewer

Olen Stephens, Application Team Lead (ATL), Office of Product Quality (OPQ)

William Adams, Drug Product Reviewer, OPQ

Rabiya Laiq, Regulatory Business Process Manager (RBPM), OPQ

Latonia Ford, Safety RPM, Office of Surveillance and Epidemiology (OSE)

Marybeth Toscano, Labeling Reviewer, Office of Prescription Drug Promotion (OPDP)

Naomi Redd, DRISK Reviewer (TL), Division of Risk Management (DRISK)

Mona Patel, DRISK Reviewer

Carrie Ceresa, Maternal Health Medical Officer, Division of Pediatric and Maternal Health (DPMH)

Tamara Johnson, Acting TL, DPMH
Lori Gorski, SRPM, DPMH
Sharon Mills, Senior Patient Labeling Reviewer, Office of Medical Policy (OMP)
Tracy Salaam, Safety Evaluator (TL), Division of Pharmacovigilance II (DPV II), OSE
Otto Townsend, Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)
Afrouz Nayerma, Safety Evaluator, DPV II, OSE
Lauren Iaconno-Connor, Office of Scientific Investigations
Azada Hafiz, Operations Research Analyst, Office of Strategic Programs

EASTERN RESEARCH GROUP ATTENDEES

Patrick Zhou

APPLICANT ATTENDEES

Erik Poulsen, Director Regulatory Affairs
Barb Kolb, North American Oncology Regulatory Affairs Therapeutic Area Lead
Hemal Morjaria, Global Regulatory Leader
Julie Brennan, Regulatory Scientist
Loreta Marquez, Medical Safety Officer
Trilok Parekh, Compound Development Team Leader
Roland Knoblauch, Clinical Leader
Nushmia Khokhar, Lead Study Physician, SAR-3007
Youn Park-Choi, Statistical Leader
Craig Tendler, Vice President (VP), Late Development & Medical Affairs
Susan Wendel, Director, Chemistry, Manufacturing, and Control (CMC) Leader
Dawn Kracht, Director, CMC Regulatory Affairs
Chi Keung, Clinical Pharmacology Leader
Sandra Rattray, VP, Regulatory Affairs Oncology
Dawn Wydner, Sr. Director, Bioresearch Quality and Compliance (BRQC) Regulatory Compliance
Pamela Paul-McNeil, Sr. Director, Quality Monitoring & Compliance

Ana Belen Irigaray Huarte, PharmaMar
Sonia Vela Herrero, PharmaMar

INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If

you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

SIGNIFICANT ISSUES

Clinical:

- a. OSI findings and issuance of a Form 483 to Sponsor – data integrity issues and potential impact on the interpretation of the safety information in the submission of the original NDA.

Discussion during Teleconference: FDA and Janssen discussed findings from the Division of Clinical Compliance Evaluation and referred to the April 3, 2015, information request letter concerning the preliminary inspection observations from the sponsor inspection associated with this application that was conducted on March 16-26, 2015. FDA discussed the preliminary, high-level findings in the comparison of adverse events datasets (ae.xpt) from the Interim Analysis (IA) with a clinical cutoff date (CCO) of 9/16/2013 and the 120-Day Safety Update with a CCO of 7/10/2014. These findings included differences uncovered in any variable between the adverse events datasets as well as differences found in serious adverse events based on analyses of adverse events with a start date of 9/16/2013 or earlier. FDA expressed concern over data integrity issues and the potential impact on the interpretation of the safety information in the submission of the original NDA.

FDA also discussed with Janssen the list of sites that had a data entry backlog at the time of the CCO of 9/16/2013 as well as the status of the backlog at the time of the CCO of 7/10/2014. A preliminary discussion was held regarding the list of sites that should undergo an audit to verify the quality of the data.

FDA acknowledged the April 17, 2015, submission to the NDA in response to the April 3, 2015, Information Request letter. The submission contained Janssen's responses and the datasets associated with the 120-Day Safety Update (CCO: July 10, 2014). FDA stated that an information request to Janssen would be forthcoming concerning data integrity issues and the potential impact on the interpretation of the safety information in the NDA.

Nonclinical:

- b. There were no issues nonclinical identified at this time of our review.

Discussion during Teleconference: Janssen acknowledged FDA's comment and did not have any additional questions. No additional discussion occurred.

- c. There are no Post-marketing Requirement (PMR)/ Post-marketing Commitments (PMCs) identified at this time of our review.

Discussion during Teleconference: Janssen acknowledged FDA's comment and did not have any additional questions. No additional discussion occurred.

Clinical Pharmacology:

- d. No issues identified at this time

Discussion during Teleconference: Janssen acknowledged FDA's comment and did not have any additional questions. No additional discussion occurred.

Chemistry, Manufacturing, and Control:

- e. Challenge studies demonstrate your reconstituted and diluted drug product supports microbial growth. The review team is considering options to mitigate the risk posed by the potential for microbial growth in a clinical setting.

Discussion during Teleconference: Janssen acknowledged FDA's comment and did not have any additional questions. No additional discussion occurred.

INFORMATION REQUESTS

The following requests for additional information were discussed during the teleconference:

- a. Provide details regarding clinical setting under which subjects were treated in ET743-SAR-3007. For example, discuss whether treatment (study or control) was administered as outpatient or inpatient for each cycle of treatment. Discuss any changes in clinical settings that occurred for each subject and discuss the reasons for these changes that were made.
- b. Provide a thoughtful assessment of the safety of trabectedin with respect to adverse events related to infectious complications seen in the Global Clinical Experience of trabectedin.

A response to the above clinical information request is due formally to your NDA by May 15, 2015.

MAJOR SAFETY CONCERNS/RISK MANAGEMENT

- a. There is a planned PMR for ongoing Hepatic Impairment study ET743-OVC-1004. The study is planned for completion on 28 January 2015. The clinical study report will be submitted to FDA by 30 September 2015.

Discussion during Teleconference: Janssen acknowledged FDA's comment and confirmed that Janssen will be able to submit the final study report by 30 September 2015. No additional discussion occurred.

ADVISORY COMMITTEE MEETING

There are no plans for an Advisory Committee Meeting at this time.

Discussion During Meeting: FDA stated that a Special Government Employee (SGE) with expertise in the clinical management of advanced soft tissue sarcoma will perform additional review of specific aspects of the trabectedin application. No additional discussion occurred.

LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

- Late-Cycle Meeting with Applicant: Wednesday, May 13, 2015
- Background for Late Cycle to Applicant: planned for May 11, 2015
- Proposed labeling and any post marketing commitment requests to Applicant: planned for April 28, 2015

Discussion During Meeting: FDA informed Janssen that the above projected milestone date(s) would potentially be delayed based on the April 17, 2015, submission to the NDA. Revised milestone date(s) would be communicated to Janssen at a later date.

POST MEETING FOLLOWUP

On May 1, 2015, FDA issued a Review Extension-Major Amendment letter informing the Applicant that the goal date was extended by 3 months. In addition, it was stated in the letter that the dates listed above for the projected milestones will change and those new dates will be communicated to Janssen in a separate communication.

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/s/

ANUJA PATEL
05/11/2015



NDA 207953

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Janssen Products, L.P.
c/o Janssen Research & Development, LLC
Attention: Erik Poulsen, M.S.
Director, Global Regulatory Affairs
920 U.S. Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Mr. Poulsen:

Please refer to your New Drug Application (NDA) dated November 24, 2014, received November 24, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for trabectedin for injection, 1 mg.

On April 17 and 27, 2015, we received formal amendments to your application. Together, these submissions constitute a major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is October 24, 2015.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by July 29, 2015.

Furthermore, the face-to-face late cycle communication meeting currently scheduled for May 13, 2015, will be rescheduled to a later date and will be communicated to you in a separate communication from your Regulatory Health Project Manager.

If you have any questions, call Ms. Anuja Patel, Senior Regulatory Project Manager, at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

PATRICIA KEEGAN
05/01/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 29, 2015
From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 207953- Clinical Response to April 27, 2015 Amendment (Seq 0023) and Clarification of FDA Comments 2, 5, and 6 of the April 25, 2015 Information Request letter

Janssen Products, L.P.
c/o Janssen Research & Development, LLC
Attention: Erik Poulsen, M.S.
Director, Global Regulatory Affairs
920 U.S. Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Mr. Poulsen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for “Yondelis (trabectedin), powder for reconstitution, 1 mg.”

We refer to our April 25, 2015, Information Request letter and to the teleconference held on April 27, 2015, between the clinical review team of the Division of Oncology Products 2, and representatives from Janssen Products, L.P. to discuss Janssen’s request for clarification regarding items 2, 5, and 6 of the April 25, 2015, letter.

We acknowledge receipt of your April 27, 2015, amendment containing your proposed tables for inclusion in your forthcoming amendment in response to our April 25, 2015 letter.

We have the following response to your proposed tables submitted in your amendment and requests for clarification for items 2, 5, and 6:

Clinical:

FDA April 25, 2015, Information Request Item 2:

Submit a comprehensive analysis of the differences between the datasets containing safety information submitted in the original NDA and those submitted in the 120-day safety update using the safety clinical data cut-off date of September 16, 2013. This analysis should include a summary of the differences between the two datasets at the patient level by treatment group and at the adverse event level by treatment group. For example, if the 120-day update AE.xpt dataset contained 100 adverse event line listings with an adverse event start date that had been revised from that recorded in the Original Submission AE.xpt dataset, provide a tabular summary that lists the total number of patients (and proportion of the safety population) and the number of patients (and

proportion) by treatment arm affected by the revision. Provide a similar tabular listing based on the total number of adverse event line listings affected by the revision (total and by treatment arm).

Janssen's Proposal submitted April 27, 2015, in response to the Information

Request:

Below is a summary of Janssen's understanding regarding the output formats for Information Request Question 2, as discussed with the FDA review team. Janssen agreed to also provide a description of how the output for the tables below is generated.

Proposed Output For Analysis - AEs



(b) (4)

Proposed Output for AE Analysis by Subjects

(b) (4)



FDA Response to Janssen's April 27, 2015 Amendment:

We request the following modifications to the proposed tables:

- Provide the Variable Name(s) associated with each line entry where applicable.
- Add a line item for Modified AE (coded). This line should capture any modifications that were made to the AEDECOD that is derived from AETERM.
- The "End date" analyses should include separate line entries for the following:
 - AE listings where an AE end date had been recorded in the AE.xpt original NDA submission dataset and was revised to a different date in AE.xpt dataset for the 120-day safety update
 - AE listings with an AE End date that is different in the AE.xpt 120-day safety update dataset for any reason (e.g., no AE end date recorded in the original NDA submission AE.xpt dataset but an AE end date is recorded in the 120-day safety update AE.xpt dataset)
- Clarify that Toxicity means Toxicity Grade

As discussed during the April 25, 2015, teleconference, we request that you provide a detailed description of the methodology used in the analysis of each variable.

FDA April 25, 2015, Information Request Item 5:

Submit a listing of the 11 sites that had a data entry backlog which required issue escalation and remediation plans as documented in the site monitor reports. In addition, provide the number of subjects enrolled and treated at each site, and the number of subjects that were affected by this data entry backlog. If tables presenting data are included in the response to this Information Request, provide the data in these tables in .xpt or .xls format to facilitate analysis as well as in a word or Adobe (.pdf) file.

FDA Response to Janssen's April 27, 2015, Amendment:

Please see response under Item 6.

FDA April 25, 2015, Information Request Item 6:

Submit your audit plan to assure the data integrity of the datasets submitted for the 120-day safety update. At a minimum, your audit plan should include a focused re-verification visit at the 11 sites that were previously identified as having data entry backlogs. A sample of the high-enrolling sites that are not already included in the 11 sites should also be included in the audit plan.

Janssen's Proposal submitted April 27, 2015 in response to the Information Request:

Below is a summary of Janssen's understanding of our discussion with FDA regarding Information Request Questions 5 and 6.

Janssen clarified that the 11 previously identified sites were escalated during study conduct for specific AE data entry delays noted by site monitors and did not represent sites with data entry backlogs. Furthermore, many of those 11 sites enrolled 5 or less subjects at the time of the CCO for the IA. Our proposal for an audit plan is to conduct re-verification visits at the top 9 high enrolling sites (10% of sites, 202 of 495 [41%])

subjects treated at CCO for IA). Of the 9 sites, sites 1001 and 1033 were already inspected by the FDA and no data related issues were identified. Therefore, Janssen proposes to not conduct re-verification visits at these 2 sites. Of the 7 remaining sites, Janssen R&D has already conducted re-verification visits at 3 of these sites (1008, 1013 and 1028; up to CCO for interim analysis). Thus, additional focused re-verification visits are proposed for the 4 remaining sites (1024, 1031, 1082 and 1009, up to the cut off for the 120-date safety update.

Janssen respectfully requests confirmation that this audit plan is acceptable, so that we may move forward with implementation.

Site #	Total Treated IA	Randomized Total
1028*	37	38
1013*	25	25
1008*	16	16
1001^	27	29
1033^	23	24
1024	22	22
1031	26	28
1082	12	14
1009	14	14
Total	202	210

*Re-verification visits completed.

^Inspected by FDA.

FDA Response to Janssen's April 27, 2015 Amendment:

The list of additional sites that will undergo a Reverification Visit (1024, 1031, 1082, 1009) up to the clinical cutoff date (CCO) for the 120-day safety update (7/10/2014) is acceptable. However, we request that the reverification process be completed up to the CCO for the 120-day safety update (7/10/2014) for all sites with 20 or more treated patients. This includes the following additional sites: 1033, 1001, 1013, and 1028.

Note that the adequacy of the proposed Audit Plan will be determined within the context of your responses to Items 1 and 6 in the April 25, 2015, information request letter. Your response(s) should contain the details of the auditing process that will be performed during the reverification visits.

As communicated to you in our April 25, 2015, letter, a response is due formally to your NDA no later than, **April 30, 2015**. Please email me a courtesy copy of your cover letter once it has been submitted through the gateway.

If you have any questions, please feel free to contact me.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ANUJA PATEL
04/29/2015



NDA 207953

INFORMATION REQUEST

Janssen Products, L.P.
c/o Janssen Research & Development, LLC
Attention: Erik Poulsen, M.S., Director, Global Regulatory Affairs
920 U.S. Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Dr. Poulsen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for trabectedin for injection, 1 mg.

We refer to our March 30, 2015, teleconference between the Division of Oncology Products 2 (DOP2), Division of Clinical Compliance Evaluation (DCCE), and representatives from Janssen Research & Development, LLC (Janssen) and to our April 3, 2015, information request letter concerning the preliminary inspection observations from the sponsor inspection associated with this application that was conducted from March 16-26, 2015.

We acknowledge receipt of your April 17, 2015, submission in response to our information request—your submission is currently under review.

We also refer to the April 23, 2015, Mid-cycle Communication meeting (teleconference) between representatives of the Food and Drug Administration (FDA) and Janssen during which we discussed major clinical review issues.

We have the following requests for additional information with a response due formally to your NDA no later than 12 Noon, EST, **Thursday, April 30, 2015**:

1. Submit a detailed summary of the procedures followed to assure data integrity in the original NDA submission (NDA 207953, SDN 1, submitted on 11/24/2014) and in the 120-day safety update (datasets submitted to NDA 207953, SDN 22, dated 4/17/2015). In your response include details of the timelines and procedures related to the preparation of the primary data submitted for FDA review (i.e., case report forms and primary source documents) including data cutoff date, data cleaning process, and database lock for the datasets provided in the original NDA submission and in the 120-Day Safety Update.

2. Submit a comprehensive analysis of the differences between the datasets containing safety information submitted in the original NDA and those submitted in the 120-day safety update using the safety clinical data cut-off date of September 16, 2013. This analysis should include a summary of the differences between the two datasets at the patient level by treatment group and at the adverse event level by treatment group. For example, if the 120-day update AE.xpt dataset contained 100 adverse event line listings with an adverse event start date that had been revised from that recorded in the Original Submission AE.xpt dataset, provide a tabular summary that lists the total number of patients (and proportion of the safety population) and the number of patients (and proportion) by treatment arm affected by the revision. Provide a similar tabular listing based on the total number of adverse event line listings affected by the revision (total and by treatment arm).
3. Submit a discussion of the root causes, at the level of the individual study site, leading to the inaccuracies/incompleteness of the datasets submitted in the original NDA and the corrective measures implemented at each of the sites to address the aforementioned root causes.
4. Submit a detailed summary of the remaining items/issues (e.g., data entry backlog) outstanding at the time of database lock (i.e., the finalized datasets) for the datasets and case report forms (CRFs) submitted in the original NDA and for the 120-day safety update datasets.
5. Submit a listing of the 11 sites that had a data entry backlog which required issue escalation and remediation plans as documented in the site monitor reports. In addition, provide the number of subjects enrolled and treated at each site, and the number of subjects that were affected by this data entry backlog. If tables presenting data are included in the response to this Information Request, provide the data in these tables in .xpt or .xls format to facilitate analysis as well as in a word or Adobe (.pdf) file.
6. Submit your audit plan to assure the data integrity of the datasets submitted for the 120-day safety update. At a minimum, your audit plan should include a focused re-verification visit at the 11 sites that were previously identified as having data entry backlogs. A sample of the high-enrolling sites that are not already included in the 11 sites should also be included in the audit plan.
7. Submit a thoughtful and integrated analysis of the results from the aforementioned information requests (Comments 1-6 above) to support your conclusions regarding the data integrity of the 120-day safety update and the benefit:risk of trabectedin for the proposed indication based on the updated safety information.

If you have any questions, please contact Ms. Anuja Patel, Senior Regulatory Project Manager, at (301) 796-9022. If you would like to further discuss the content of your response to this letter via teleconference on Monday, April 27, 2015, please contact Ms. Patel.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

PATRICIA KEEGAN
04/25/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 21, 2015
From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 207953- Midcycle Communication Meeting (Teleconference) Agenda

Janssen Products, L.P.
c/o Janssen Research & Development, LLC
Attention: Erik Poulsen, M.S.
Director, Global Regulatory Affairs
920 U.S. Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Mr. Poulsen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for “Yondelis (trabectedin), powder for reconstitution, 1 mg.”

Please find attached our agenda for the Midcycle Communication Meeting (teleconference), scheduled for Thursday, April 23, 2015, from 12:00 P.M. to 1:00 P.M., EST. Please provide a dial in number with at least 10 ports in case we have reviewers dialing in.

If you have any questions, please feel free to contact me.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Midcycle Communication Meeting- Agenda

Sponsor Mid-Cycle Communication Meeting Agenda
April 23, 2015
NDA 207953

Application: NDA 207953- Type 1 New Molecular Entity

Product: trabectedin, powder for reconstitution, 1 mg, intravenous
Proposed Proprietary Name: YONDELIS
Sponsor: Janssen Products, LP
Proposed Indication:  (b) (4)

Date: Thursday, April 23, 2015
Time: 12:00 PM – 1:00 PM, EST
Location: Teleconference

Introduction:

We are providing these comments to you before we complete our review of the entire application to give you **preliminary** notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

Topics for Discussion:

1. **Introductions by DOP 2 RPM, Anuja Patel**
2. **Significant Review Issues Identified by FDA**

Clinical:

- a. OSI findings and issuance of a Form 483 to Sponsor – data integrity issues and potential impact on the interpretation of the safety information in the submission of the original NDA.

Nonclinical:

- a. No issues identified at this time
- b. No PMR/PMCs identified at this time

Sponsor Mid-Cycle Communication Meeting Agenda
April 23, 2015
NDA 207953

Clinical Pharmacology:

- a. No issues identified at this time

Chemistry, Manufacturing, and Control:

- a. Challenge studies demonstrate your reconstituted and diluted drug product supports microbial growth. The review team is considering options to mitigate the risk posed by the potential for microbial growth in a clinical setting.

3. New or Pending Information Requests

Clinical:

- a. For clarification, please comment on where the 24-hour infusion was primarily given (inpatient vs. outpatient).
- b. Given that the challenge studies demonstrate that the product supports microbial growth, please comment on the post-marketing experience of infusion-related infection.

Clinical Pharmacology:

- a. No new or pending information requests at this time.

Chemistry, Manufacturing, and Control:

- a. No new or pending information requests at this time.

4. Major Safety Concerns/ Risk Management Update

- a. A PMR for ongoing Hepatic Impairment study ET743-OVC-1004, “An Open-Label, Multicenter, Pharmacokinetic Study of Trabectedin in Subjects with Advanced Malignancies and Hepatic Dysfunction” The study is planned for completion on 28 January 2015. The clinical study report will be submitted to FDA by 30 September 2015.

5. Advisory Committee Meeting Plans

- a. No AC meeting planned; however, SGE(s) with an expertise in the proposed indication will be consulted with regard to aspects of the trabectedin application.

6. Proposed Date and Format for Late-Cycle Meeting/Other Projected Milestones

- Late-Cycle Meeting with Applicant: Wednesday, May 13, 2015
- Background for Late Cycle to Applicant: planned for May 11, 2015
- Proposed labeling and any post marketing commitment requests to Applicant: planned for April 28, 2015

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/s/

ANUJA PATEL
04/21/2015

From: Laiq, Rabiya
To: "Poulsen, Erik [JRDU5]"
Cc: Patel, Anuja
Subject: NDA 207953 Information Request 4
Date: Wednesday, April 15, 2015 3:46:00 PM

Dear Mr. Poulsen,

We have the following information request.

Please refer to your New Drug Application (NDA 207953) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Yondelis (trabectedin) powder for reconstitution 1mg IV.

We also refer to your submission dated November 24, 2014.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests.

1. Regarding NDA section 3.2.P.4.1, revise the procedure for accepting each lot of each excipient to include at least a test for identity. (b) (4)

[Redacted]

2. Regarding the drug product specification in NDA section 3.2.P.5.1:

(a) Revise the proposed criterion for Appearance of Reconstituted Solution (b) (4)

[Redacted]

(b) For the test for unit dose uniformity, describe the sampling strategy with regards to sample size, and when samples are collected, and where the sample is collected.

3. The validation study for selectivity on method DS-TMD-16274 performed (b) (4) and transferred to Baxter Oncology does not include a forced degradation component, thus has not been established to be stability-indicating. Provide forced degradation data using method DS-TMD-16274. If this information is not available, provide a commitment to provide the forced degradation data and anticipated time frame when this data will be submitted to the NDA.

Additionally, we have the following advice (b) (4)

[Redacted]

[Redacted] (b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted text block]

(b) (4)

We request a prompt written response in order to continue our evaluation of your NDA by April 21, 2015. Please let me know if you have any questions.

Kindly confirm receipt of this email.

Best wishes,
Rabiya Laiq

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-6153
Email: rabiya.laiq@fda.hhs.gov





NDA 207953

INFORMATION REQUEST

Janssen Products, L.P.
C/o Janssen Research & Development, LLC
Attention: Erik Poulsen, M.S., Director, Global Regulatory Affairs
920 U.S. Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Dr. Poulsen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for trabectedin for injection, 1 mg.

We also refer to the March 30, 2015, teleconference between the Division of Oncology Products 2 (DOP 2), Office of Scientific Investigations (OSI), and representatives from Janssen Research & Development, LLC (Janssen) to discuss the findings from the recent OSI inspection.

1. Based upon FDA OSI site inspection observations of the Sponsor/Monitor, the Clinical Study Report and datasets submitted to the original NDA did not contain adverse events (AE), including serious adverse events, from one of the five sites reviewed. Submit your plan for determining whether missing AE data was a wide-spread issue that would call into question the data integrity of this application. As part of this plan or as a separate submission if available earlier, provide the following information:
 - a. Details concerning the site monitoring performed during Trial ET743-SAR-3007
 - b. Summary of the deficiencies that led to missing data from Site 001013
 - c. Audit plan, including a detailed analysis of the site monitoring reports for all study sites, to identify all sites with potential missing adverse event data or adverse event data that was misclassified (e.g., serious, Grade 3-4, drug-related, leading to treatment discontinuation, leading to death) in the eCRFs and datasets in the original NDA submission.

Whether the extent of the missing and misclassified data, including AE data from Site 001013 and any other affected sites, requires corrected datasets, clearly identifying the new information, will be a review issue. Additionally, if the missing information is substantial, you may need to repeat the sponsor safety analyses.

2. Submit a patient-level, tabular listing of the subject IDs and the details of the changes for all adverse events that were added, removed, or reclassified (e.g., serious, Grade 3-4, drug-related, leading to treatment discontinuation, leading to death) from time of initial submission to the time of the new analysis provided in Tables 1-5 of the Document JNJ-17027907-AAA (preliminary response to Form 483 inspectional findings), dated 3/29/2015.
3. Submit the SDTM and ADaM datasets and any supporting files for the 120-day safety update.

If you have any questions, please contact Ms. Anuja Patel, Senior Regulatory Project Manager, at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

PATRICIA KEEGAN
04/03/2015

Patel, Anuja

From: Poulsen, Erik [JRDUS] <epoulse@ITS.JNJ.com>
Sent: Thursday, March 26, 2015 1:16 PM
To: Patel, Anuja
Subject: RE: Filing Review Day 74 Letter- Yondelis NDA 207953
Attachments: emfinfo.txt

Thanks for confirming

From: Patel, Anuja [<mailto:Anuja.Patel@fda.hhs.gov>]
Sent: Thursday, March 26, 2015 9:22 AM
To: Poulsen, Erik [JRDUS]
Subject: RE: Filing Review Day 74 Letter- Yondelis NDA 207953
Importance: High

Dear Mr. Poulsen,

In response to your email communication sent March 26, 2015, regarding the scheduled date for the FDA Internal Midcycle Meeting. The meeting is scheduled for March 30, 2015.

Regards,
Anuja

Anuja Patel, MPH
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎ 301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

From: Poulsen, Erik [JRDUS] [<mailto:epoulse@ITS.JNJ.com>]
Sent: Thursday, March 26, 2015 10:53 AM
To: Patel, Anuja
Subject: RE: Filing Review Day 74 Letter- Yondelis NDA 207953

Hello Anuja,

If you don't mind, can you remind me, or update me if changed, as to when FDA's internal mid-cycle meeting is planned to occur?

Best Regards
Erik

From: Patel, Anuja [<mailto:Anuja.Patel@fda.hhs.gov>]
Sent: Friday, February 06, 2015 1:01 PM
To: Poulsen, Erik [JRDUS]
Subject: Filing Review Day 74 Letter- Yondelis NDA 207953
Importance: High

Dear Mr. Poulsen,

Please find attached a courtesy copy of our Day 74 letter with our general edits for the package insert. The formal letter will be sent to you via postal mail.

Please acknowledge receipt.

Also, I will be out of the office for the rest of the day (b) (6) but I should be in the office on Monday.

Take care,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎ 301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

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/s/

ANUJA PATEL
03/26/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 24, 2015
From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 207953- Statistical Information Requests

Janssen Products, L.P.
c/o Janssen Research & Development, LLC
Attention: Erik Poulsen, M.S.
Director, Global Regulatory Affairs
920 U.S. Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Mr. Poulsen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for “Yondelis (trabectedin), powder for reconstitution, 1 mg.”

We have the following statistical request for information and request your response:

1. Please clarify the algorithm to derive censoring variable CNSR for DoR. The statistical reviewer could not verify CSR Table 36 (25 events). Please update the ADTTE dataset, if variable CNSR is incorrect.

```
data RSDURM ; /*duration of response*/  
    set adam.adtte (where=(PARAMCD="RSDURM"));  
run;  
proc freq data=RSDURM; table cnsr; run;
```

The FREQ Procedure

	Censor				
		Cumulative	Cumulative		
CNSR	Frequency	Percent	Frequency	Percent	

Frequency Missing = 46

A response is requested via email by **10:00 AM, EST, Thursday, April 2, 2015** followed by a formal submission to the NDA by close of business, April 2, 2015. Please email me and Ms. Gina Davis, who is covering for me between April 1 and April 3, 2015, a courtesy copy of your cover letter once it has been submitted through the gateway.

NDA 207953

Page 2

If you have any questions, please feel free to contact me.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ANUJA PATEL
03/24/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 23, 2015
From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 207953- Statistical Information Requests

Janssen Products, L.P.
c/o Janssen Research & Development, LLC
Attention: Erik Poulsen, M.S.
Director, Global Regulatory Affairs
920 U.S. Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Mr. Poulsen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for “Yondelis (trabectedin), powder for reconstitution, 1 mg.”

We have the following statistical request for information and request your response:

- 1. The statistical reviewer could not verify the derivation on Line of prior chemotherapy. Please provide comment or modified SAS program, if Janssen does not agree. Please note lines of prior chemotherapy in CSR Table 10 and Table 15 are inconsistent.**

```
proc sort data=adam.adcm out=_adcm ;
  by usubjid ; run;
proc sort data= adcm out=_adcm1 nodupkey;
  by usubjid;
  where upcase(cmcat) = 'PREVIOUS THERAPY' and CMOCCUR eq 'Y';
run;

data prthpy1;
  length prthpyfl $3. ;
  merge demo(in=a) _adcm1(in=b);
  by usubjid;
  if a;
  if (upcase(cmcat) eq 'PREVIOUS THERAPY' and CMOCCUR eq 'Y')
  then prthpyfl='YES' ;
  else prthpyfl='NO';
  if b then one=1;
;
run;
proc freq data= prthpy1;
  tables (prthpyfl cmlnchpy) *trt01p/missing nopercnt norow; ;
run;
```

Table of CMLNCHPY by TRT01P

CMLNCHPY(Line of Chemotherapy)
TRT01P(Planned Treatment for Period 1)

Frequency Col Pct	Dacarbaz ine	Trabecte din	Total
First Line	164 94.80	328 95.07	492
Fourth Line	0 0.00	1 0.29	1
Second Line	7 4.05	14 4.06	21
Third Line	2 1.16	2 0.58	4
Total		173	345 518

2. Please provide a summary of stratification factors' misclassification between CRF and IVRS.

3. The statistical reviewer could not verify CSR Table 13. Please provide comment or modified SAS program, if Janssen does not agree.

```

Data demo; set adam.adsl
proc sort data=demo out=demo; by usubjid; run;

data ds; set adam.adds (where=(paramcd='TDISC')); run;
proc sort data=ds; by usubjid; run;

data adsls; merge ds demo; by usubjid; run;

proc freq data=adsls; tables DSTERM *arm/missing nopercnt norow;
where dsterm ne " " ; run;
    
```

	Trabectedin (N=345)	Dacarbazine (N=173)
Treatment discontinued	247 (72%)	148 (86%)
ADVERSE EVENT	35 (14%)	13 (9%)
ALTERNATIVE ANTI-CANCER THERAPY	1 (<1%)	0
DEATH	9 (4%)	1 (<1%)
DISEASE PROGRESSION	186 (75%)	106 (72%)
WITHDRAWS CONSENT	13 (5%)	25 (17%)
Others	3 (<1%)	3 (2%)

4. Provide the meaning of adsl.evalfl .

Table of EVALFL by TRT01P

EVALFL(Evaluable Subject Flag)		TRT01P(Planned Treatment for Period 1)		Total
Frequency				
Col	Pct	Dacarbaz ine	Trabecte din	
N		47	54	101
		27.17	15.65	
Y		126	291	417
		72.83	84.35	
Total		173	345	518

A response to the items is requested via email by **10:00 AM, EST, Tuesday, March 24, 2015**, followed by a formal submission to the NDA by close of business, March 24, 2015. Please email me a courtesy copy of your cover letter once it has been submitted through the gateway.

If you have any questions, please feel free to contact me.

Regards,

Anuja Patel, M.P.H.
 Senior Regulatory Health Project Manager
 Division of Oncology Products 2
 Office of Hematology and Oncology Products
 Center for Drug Evaluation and Research

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/s/

ANUJA PATEL
03/23/2015

Patel, Anuja

From: Patel, Anuja
Sent: Monday, March 09, 2015 11:52 AM
To: 'Poulsen, Erik [JRDUS]'
Subject: FDA IR/Attendees List: SPON TCON 09 March 2015 Re: FDA Drug Snap Shot

Importance: High

Hello Mr. Poulsen,

We refer to the teleconference held today, March 9, 2015, to discuss any questions Janssen had regarding FDA information request sent via e-mail on February 25, 2015, containing FDA request for tables for the Drug Trials Snapshot. We also refer to your email sent March 9, 2015 containing list of Janssen attendees for the teleconference and request for list of FDA attendees that attended.

The following are the FDA attendees:

Marc Theoret, Clinical TL
Amy Barone, Clinical MO
Monica Hughes, CPMS
Anuja Patel, Sr. RPM
Huanyu Chen, Stats Reviewer
Kun He, Stats TL
Naomi Lowy Professional Affairs & Stakeholders Engagement (PASE)

Please note, we have an additional information request from PASE that was sent to me following our teleconference:

- **Regarding the tables for efficacy and safety by subgroup: the denominator used for each calculation should be the total number of subjects in that particular subgroup. For instance, for efficacy in males, the calculation should be # of males who achieved the primary endpoint/total number of males.**

Please feel free to contact me if you have any further clarifying questions. Please acknowledge receipt.

Thank you,
Anuja

Anuja Patel, MPH
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎ 301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

From: Poulsen, Erik [JRDUS] [<mailto:epoulse@ITS.JNJ.com>]
Sent: Monday, March 09, 2015 10:30 AM
To: Patel, Anuja
Subject: RE: Janssen Attendees from 09 March 2015 call

I mistyped Youn's name sorry. Her last name is Choi Park, not Park Choi.

From: Poulsen, Erik [JRDUS]
Sent: Monday, March 09, 2015 6:52 AM
To: Anuja.Patel@fda.hhs.gov
Subject: Janssen Attendees from 09 March 2015 call

Hello Anuja,

Thank you again for allowing us the time to better understand the process. Below are those who were on the line from Janssen.

If you don't mind, can you please email me those from FDA who were online?

Erik Poulsen	Director Regulatory Affairs
Barb Kolb	North American Oncology Regulatory Affairs Therapeutic Area Lead
Hemal Morjaria	Global Regulatory Leader
Loreta Marquez	Medical Safety Officer
Trilok Parekh	Compound Development Team Leader
Roland Knoblauch	Clinical Leader
Nushmia Khokhar	Lead Study Physician, SAR-3007
Leah Bednarek	Lead Statistical Programmer
Youn Park-Choi	Statistical Leader

Regards,
Erik

Director, Regulatory Affairs
Janssen Research and Development, LLC
Tel: 805-205-5602

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/s/

ANUJA PATEL
03/09/2015

Laiq, Rabiya

From: Laiq, Rabiya
Sent: Thursday, March 05, 2015 11:16 AM
To: 'Poulsen, Erik [JRDUS]'
Cc: Tran-Zwanetz, Catherine; Patel, Anuja
Subject: NDA 207953 Information Request 3

Dear Mr. Poulsen,

We have the following information request.

Please refer to your New Drug Application (NDA 207953) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Yondelis (trabectedin) powder for reconstitution 1mg IV.

We also refer to your submission dated November 24, 2014.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests.

1. Provide the yields for all drug product unit operations and compare it against the theoretical and acceptable yields. Provide representative information for each batch size (b) (4)
2. We note that in your Module 3.2.P.3.4 (b) (4)
(b) (4)
(b) (4) We also note (b) (4)
(b) (4) Please explain this discrepancy.

We request a prompt written response in order to continue our evaluation of your NDA by March 19, 2015. Please let me know if you have any questions.

Best wishes,
Rabiya Laiq

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-6153
Email: rabiya.laiq@fda.hhs.gov





DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 25, 2015
From: Anuja Patel, RPM, DOP2/OHOP/CDER/FDA
Subject: Request for Information Intended to Populate the FDA Drug Trials Snapshot Website for: NDA 207953 trabectedin

Janssen Products, L.P.
c/o Janssen Research & Development, LLC
Attention: Erik Poulsen, M.S.
Director, Global Regulatory Affairs
920 U.S. Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Mr. Poulsen,

We are requesting your assistance in populating the attached tables for your New Molecular Entity, trabectedin, that is currently under review in the Division. This information will be posted publically, if approved, at the FDA drug snapshot website:
<http://www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm>

We are requesting this information to allow for greater transparency by providing information to the public about participation in clinical trials for newly approved drugs and biologics.

The website will include information on the trial design, the results of efficacy and safety trials, and whether there were any differences in efficacy and side effects among sex, race, and age subgroups. The information posted on the FDA drug snapshot website will be published approximately 30 days after drug/biologic approval and is not intended to replace or replicate the package insert (PI), which is intended for health care practitioners, and will contain the following:

- Information written in consumer-friendly language
- Information that focuses on subgroup data and analyses
- Links to the PI for the product and to the FDA reviews at Drugs@FDA

Therefore, we are requesting that you complete the attached tables as well as provide your data, descriptions of the analyses used to generate the data, and any programs used to generate or analyze the data, if these are not already in the NDA 207953 submission.

We are requesting that you submit this information no later than March 13, 2015.

Thank you in advance for your cooperation.

Please let me know if you have any questions.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products

Attachments: Proposed Shell Tables for Completion

PROPOSED SHELL TABLES

Table 1. Listing of Clinical Trials for the Efficacy Analysis

Study ID	No. of patients enrolled in the Drug X Arm	No. of patients enrolled in the Comparator Arm

Table 2.1 Baseline Demographics, Single or Pooled Pivotal Efficacy Trials

Demographic Parameters	Comparator/ Control (n=) n (%)	Treatment Group(s) (n=)		Total (n=) n (%)
		Treatment arm #1 (n=) n (%)	Treatment arm #2 (n=) n (%)	
Sex				
Male				
Female				
Age				
Mean years (SD)				
Median (years)				
Min, max (years)				
Age Group				
<17 years				
≥17 - <65 years				
≥65 years				
≥75 years				
Race				
White				
Black or African American				
Asian				
American Indian or Alaska Native				
Native Hawaiian or Other Pacific Islander				
Other				
Ethnicity				
Hispanic or Latino				
Not Hispanic or Latino				
Region				
United States				
Rest of the World				
Canada				
South America				
Europe				
Asia				
Africa				

Source: list datasets or other sources of information

Table 2.2 Baseline Demographics, Multiple Pivotal Efficacy Trials

Demographic Parameters	Trial #1 (N=)		Trial #2 (N=)		Total (n=) n (%)
	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	
Sex					
Male					
Female					
Age					
Mean years (SD)					
Median (years)					
Min, max (years)					
Age Group					
<17 years					
≥17 - <65 years					
≥65 years					
≥75 years					
Race					
White					
Black or African American					
Asian					
American Indian or Alaska Native					
Native Hawaiian or Other Pacific Islander					
Other					
Ethnicity					
Hispanic or Latino					
Not Hispanic or Latino					
Region					
United States					
Rest of the World					
Canada					
South America					
Europe					
Asia					
Africa					

Source: list datasets or other sources of information

Table 3 Subgroup Analysis of Primary Endpoint, Pivotal Efficacy Trials

Demographic Subgroup	Trial #1 (N=)			Trial #2 (N=)		
	Comparat or/control (n=) n (%)	Treatme nt arm (n=) n (%)	Differenc e (95% CI)	Comparat or/control (n=) n (%)	Treatme nt arm (n=) n (%)	Differen ce (95% CI)
Overall Response/All patients						
Sex						
Male						
Female						
Age Group						
<17 years						
≥17 - <65 years						
≥65 years						
≥75 years						
Race						
White						
Black or African American						
Asian						
American Indian or Alaska Native						
Native Hawaiian or Other Pacific Islander						
Other						
Ethnicity						
Hispanic or Latino						
Not Hispanic or Latino						
Region						
United States						
Rest of the World						
Canada						
South America						
Europe						
Asia						
Africa						

Source: list datasets or other sources of information

Table 4 Safety Population, Size and Denominators

Safety Database for the Study Drug ¹ Individuals exposed to the study drug in this development program for the indication under review N= (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	New Drug (n=)	Active Control (n=)	Placebo (n=)
Normal Volunteers			
Controlled trials conducted for this indication ²			
All other than controlled trials conducted for this indication ³			
Controlled trials conducted for other indications ⁴			

¹ *study drug* means the drug being considered for approval; do not include comparator arm drugs, placebo, or vehicle control in this table

² to be used in product's labeling

³ if placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm

⁴ include n in this column only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review. Consider n=0 in this column if no patients treated for other indication(s) were included in this safety database.

**Table 5.1 Baseline Demographics, Safety Population, Single or Pooled Trials
(If efficacy population = safety population, refer to Table 2.1 or 2.2)**

Demographic Parameters	Comparator/ Control (n=) n (%)	Treatment Group(s) (n=)		Total (n=) n (%)
		Treatment arm #1 (n=) n (%)	Treatment arm #2 (n=) n (%)	
Sex				
Male				
Female				
Age				
Mean years (SD)				
Median (years)				
Min, max (years)				
Age Group				
<17 years				
≥17 - <65 years				
≥65 years				
≥75 years				
Race				
White				
Black or African American				
Asian				
American Indian or Alaska Native				
Native Hawaiian or Other Pacific Islander				
Other				
Ethnicity				
Hispanic or Latino				
Not Hispanic or Latino				
Region				
United States				
Rest of the World				
Canada				
South America				
Europe				
Asia				
Africa				

Source: list datasets or other sources of information

Table 5.2 Baseline Demographics, Safety Population, Multiple Trials

Demographic Parameters	Trial #1 (N=)		Trial #2 (N=)		Total (n=) n (%)
	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	
Sex					
Male					
Female					
Age					
Mean years (SD)					
Median (years)					
Min, max (years)					
Age Group					
<17 years					
≥17 - <65 years					
≥65 years					
≥75 years					
Race					
White					
Black or African American					
Asian					
American Indian or Alaska Native					
Native Hawaiian or Other Pacific Islander					
Other					
Ethnicity					
Hispanic or Latino					
Not Hispanic or Latino					
Region					
United States					
Rest of the World					
Canada					
South America					
Europe					
Asia					
Africa					

Source: list datasets or other sources of information

Table 6.1 Subgroup Analysis of TEAEs, Safety Population

Demographic Subgroup	Comparator/Control		Treatment		Relative Risk	95% CI	
	n (%)	Total, N	n (%)	Total, N		LL	UL
Any TEAEs							
Sex							
Male							
Female							
Age Group							
<17 years							
≥17 - <65 years							
≥65 years							
≥75 years							
Race							
White							
Black or African American							
Asian							
American Indian or Alaska Native							
Native Hawaiian or Other Pacific Islander							
Other							
Ethnicity							
Hispanic or Latino							
Not Hispanic or Latino							
Region							
United States							
Rest of the World							
Canada							
South America							
Europe							
Asia							
Africa							

Source: list datasets or other sources of information

**Table 6.2 Subgroup Analysis by Sex of Common AEs, Safety Population
(Events ≥ 2% of drug-treated subjects and more frequent than placebo)¹**

MedDRA System Organ Class Preferred Term	Male (N=)		Female (N=)	
	Compara tor/Contr ol (n=) n (%)	Total Drug X (n=) n (%)	Compara tor/Contr ol (n=) n (%)	Total Drug X (n=) n (%)
Gastrointestinal disorders				
Nausea				
Vomiting				
Diarrhea				
Abdominal pain				
General disorders/administration site conditions				
Fatigue				
Edema peripheral				
Infections and Infestations				
Influenza				
Urinary tract infection				
Injury, poisoning and procedural complications				
Fall				
Contusion				
Investigations				
Weight increased				
Blood CPK increased				
Musculoskeletal & connective tissue disorders				
Arthralgia				
Nervous system disorders				
Dizziness				
Headache				
Psychiatric disorders				
Depression				
Insomnia				
Respiratory, thoracic & mediastinal disorders				
Cough				
Skin & subcutaneous tissue disorders				
Rash				
Pruritus				

Source: list datasets or other sources of information

Example of an application-specific adverse event

Table 6.3 Subgroup Analysis by Age of Dizziness/Gait Disturbance Adverse Events, Safety Population*

MedDRA Preferred Term	Age ≥17-<65 years (N=)		Age ≥65 years (N=)	
	Comparat or/Contro l (n=) n (%)	Total Drug X (n=) n (%)	Comparat or/Contro l (n=) n (%)	Total Drug X (n=) n (%)
Dizziness				
Ataxia				
Vertigo				
Balance disorder				
Gait disturbance				
Coordination abnormal				
Cerebellar syndrome				
Cerebellar ataxia				
Vestibular ataxia				
Vestibular disorder				
Total				

*Pediatric subjects were not included in the safety population

Source: list datasets or other sources of information

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/s/

ANUJA PATEL
02/25/2015

Laiq, Rabiya

From: Laiq, Rabiya
Sent: Thursday, February 19, 2015 1:25 PM
To: 'Poulsen, Erik [JRDUS]'
Cc: Tran-Zwanetz, Catherine; Patel, Anuja
Subject: NDA 207953 CMC Information Request 2

Dear Mr. Poulsen,

We have the following information request.

Please refer to your New Drug Application (NDA 207953) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Yondelis (trabectedin) powder for reconstitution 1mg IV.

We also refer to your submission dated November 24, 2014.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests.

1. In NDA section 3.2.P.4, specify the tests performed on each lot of each excipient for acceptance.
2. In NDA section 3.2.P.5:
 - (a) Describe the sample scheme and method of analysis for the uniformity of dosage units test.
 - (b) For method DS-TMD-16274, describe sample preparation procedure for uniformity of dosage unit testing and provide copies of example HPLCs for blank 1, blank 2, reference standard, test sample and reporting level solution.
 - (c) Explain [REDACTED] (b) (4).
 - (d) Explain the need [REDACTED] (b) (4) for the commercial batches and [REDACTED] (b) (4) for the clinical batches. The stability data shows [REDACTED] (b) (4).
 - (e) The method validation studies for the bacterial endotoxins test and the HPLC method DS-TMD-16274 were not performed at the site of use, Baxter Oncology. Provide the results from method validation studies for the current versions of these two methods performed at Baxter Oncology.
 - (f) Specify when the validation study for the sterility method was performed. The submitted report does not include the signature page.
3. For NDA section 3.2.P.7, specify the tests that are performed on each lot of each primary and secondary packaging component for acceptance.

We request a prompt written response in order to continue our evaluation of your NDA by March 5, 2015. Please let me know if you have any questions.

Best wishes,
Rabiya Laiq

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-6153
Email: rabiya.laiq@fda.hhs.gov





DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

NDA 207953

Janssen Products, LP
c/o Janssen Research & Development, LLC
920 US Route 202
PO Box 300
Raritan, NJ 08869-0602

ATTENTION: Erik Poulsen, MS
Director, Global Regulatory Affairs

Dear Mr. Poulsen:

Please refer to your New Drug Application (NDA) dated and received November 24, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trabectedin for Injection, 1 mg/vial.

We also refer to your correspondence, dated and received December 16, 2014, requesting review of your proposed proprietary name, Yondelis. We have completed our review of the proposed proprietary name, Yondelis and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your December 16, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Latonia Ford, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4901. For any other information regarding this application contact, Anuja Patel, Regulatory Project Manager in the Office of New Drugs, at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
02/09/2015



NDA 207953

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Janssen Products, L.P.
c/o Janssen Research & Development, LLC
Attention: Erik Poulsen, M.S.
Director, Global Regulatory Affairs
920 U.S. Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Mr. Poulsen:

Please refer to your New Drug Application (NDA) dated November 24, 2014, received November 24, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for trabectedin for injection, 1 mg.

We also refer to your amendments December 11, 16 (2), and 18, 2014; January 21, 23, 27 (2), 28, and 30, 2015; and February 2, 2015.

We also refer to our January 24, 2015, Priority Review Designation letter in which we informed you that the review classification for this application is **Priority**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is July 24, 2015.

In addition, the planned date for our internal mid-cycle review meeting is **March 19, 2015**. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

Clinical Pharmacology:

We reiterate our comments previously conveyed to you on January 20, 2015:

1. Submit to the NDA a description of the proposed hepatic impairment study as postmarketing requirement (PMR), including your proposed timelines for completion of the and submission of the final study reports, as requested during the pre-NDA meeting held on October 17, 2014.

2. Submit to the NDA the study report for Study 10045020 entitled “A phase I and pharmacokinetic study to assess the tolerability of ET-743 administered as a continuous intravenous infusion over 24 hours every 21 days in patients with soft tissue sarcoma,” and the related concentration time and derived pharmacokinetic (PK) parameter datasets as SAS transport files (*.xpt) with description of each data item (in a define.pdf file).

We acknowledge your January 29, 2015, e-mail communication and your subsequent February 2, 2015, submission containing your response to comment 1 above and a request for an extension to provide your response to comment 2 above. We also refer to our January 29, 2015, e-mail communication in which we granted you an extension for your response until February 18, 2015, based on the justification you provided.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments:

3. Use either underlining or italics (but not both) for subheadings and headings. Use a consistent approach (e.g., italics for subheadings and underlining for headings) throughout the labeling.
4. Please refer to the attached labeling for additional FDA comments and FDA proposed revisions.

We request that you resubmit labeling (in both clean and redlined (track-changes shown) Microsoft Word format) that addresses the labeling issues identified above and in the attached labeling by **February 27, 2015**. The resubmitted labeling will be used for further labeling

discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Ms. Anuja Patel, Senior Regulatory Project Manager, at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure: FDA comments/proposed revisions to labeling

29 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

PATRICIA KEEGAN
02/05/2015

Patel, Anuja

From: Patel, Anuja
Sent: Thursday, January 29, 2015 1:18 PM
To: 'Poulsen, Erik [JRDUS]'
Subject: RE: Extension Requested <<RE: Clinical Pharmacology Information Request- NDA 207953 Yondelis>>

Dear Mr. Poulsen,

The clinical pharmacology team will grant you your requested extension to February 18, 2015.

Regards,
Anuja

From: Poulsen, Erik [JRDUS] [<mailto:epoulse@ITS.JNJ.com>]
Sent: Thursday, January 29, 2015 12:51 PM
To: Patel, Anuja
Subject: Extension Requested <<RE: Clinical Pharmacology Information Request- NDA 207953 Yondelis>>

Hello Anuja,

Per our discussion this morning, I wanted to follow-up via email per your request to do so. Based on the below, we are respectfully requesting an extension (Feb 18) to address item #2 from the clinical pharmacology information request.

Study 10045020 is a Japanese study sponsored by Taiho Pharmaceutical Co., where PharmaMar (JRD commercial partner) is our contact with the sponsor. As I mentioned, the CSR is in the process of being translated from its current Japanese version, via an external vendor, and would be available for submission to FDA 18 February 2015. The requested datasets are in the process of being made submission-ready and will also be available for submission on 18 February 2015.

Please let us know if this acceptable and thank you for your help.

Regards
Erik

From: Patel, Anuja [<mailto:Anuja.Patel@fda.hhs.gov>]
Sent: Tuesday, January 20, 2015 6:00 AM
To: Poulsen, Erik [JRDUS]
Subject: Clinical Pharmacology Information Request- NDA 207953 Yondelis
Importance: High

Dear Mr. Poulsen,

It was a pleasure meeting you and your team at the Application Orientation meeting. Please find attached clinical pharmacology information request with a response due February 2, 2015.

Please confirm receipt.

Thank you,
Anuja

Anuja Patel, MPH
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎ 301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

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/s/

ANUJA PATEL
02/02/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Memorandum

DATE: January 23, 2015

FROM: Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research

SUBJECT: Review Designation Memo for trabectedin (NDA 207953) for the proposed indication: [REDACTED] (b) (4)

TO: NDA 207953

The review status of this file submitted as an NDA efficacy supplement is designated:

Standard (12 Months) Priority 8 Months

In the original BLA submission, Janssen is requesting priority review designation based on the results of Study ET743-SAR-3007, supported by the results of Study ET743-ST5-201. Both of these randomized trials investigated the activity of the trabectedin at a dose of 1.5 mg/m² as a 24-hour infusion administered every 21 days in patients with liposarcoma or leiomyosarcoma (L-type sarcoma) who have received prior chemotherapy, including an anthracycline, defined as: an anthracycline and ifosfamide containing regimen or an anthracycline containing regimen and one additional cytotoxic chemotherapy regimen.

In the major efficacy trial, Study ET743-SAR-3007, there were 518 patients enrolled and randomized (2:1) to trabectedin or dacarbazine. The majority (73%) of patients had a leiomyosarcoma and the remaining patients (27%) had a liposarcoma. The majority of patients received 2 prior lines of chemotherapy. Janssen reported that at the final analysis of progression-free survival (PFS), there was a significant improvement for patients randomized to trabectedin as compared to dacarbazine [HR 0.55 (0.44, 0.70); p<0.001]; the median PFS was 4.2 months in the trabectedin arm and 1.5 months in the dacarbazine

arm. Janssen further noted that at an interim analysis of overall survival did not show a significant difference between treatment arms [HR 0.87 (95% CI: 0.64, 1.18); p=0.37] and there was no significant difference in overall response rate between arms.

ASSESSMENT OF REQUEST

In evaluating the applicant's request for priority review designation, I considered the results from the Study ET743-SAR-3007, Janssen's justification for the request, and the following FDA Guidance and MAPP:

- CDER MAPP 6020.3, Priority Review Policy (version 2)
- Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014)

As stated in these FDA documents, an application for a drug will receive priority review designation if it is for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. In addition, specific statutory provisions provide for priority review for certain applications.

On a case-by-case basis, FDA determines at the time of NDA, BLA, or efficacy supplement filing whether the proposed drug would be a *significant improvement* in the safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition. Significant improvement may be illustrated by the following examples:

- Evidence of increased effectiveness in treatment, prevention, or diagnosis of a condition
- Elimination or substantial reduction of a treatment-limiting adverse reaction
- Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes
- Evidence of safety and effectiveness in a new subpopulation

Assessment:

This NDA was not submitted under the statutory provisions where priority review designation is mandatory.

Metastatic or unresectable soft tissue sarcoma, of which leiomyosarcoma and liposarcoma are histologically distinct subtypes, is serious condition. The American Cancer Society cites 5-year survival rates of 16% for Stage IV soft tissue sarcoma.

Pazopanib is the only one drug that is FDA- approved for the second-line treatment of soft tissue sarcoma. However pazopanib is not indicated for the treatment of patients with liposarcoma, based on lack of clinical experience in this sarcoma subtype since patients with liposarcoma were not enrolled in the trial demonstrating the efficacy of pazopanib. Approval of pazopanib was based on a statistically significant and clinically important increase in PFS.

The results of Study ET743-SAR-3007 demonstrated a statistically robust and clinically important improvement in progression-free survival, with a 3-month increase in median PFS of 3 months and relative improvement in the immediate risk of progression or death of 45% (HR 0.55) for patients in the trabectedin arm as compared to those receiving dacarbazine. This treatment effect on PFS was present in the randomized subgroups of patients with leiomyosarcoma and liposarcoma. While Study ET743-SAR-3007 did not demonstrate evidence of increased effectiveness over available therapy (pazopanib) in patients with leiomyosarcoma, the results of Study ET743-SAR-3007 provide evidence of increased effectiveness in the treatment of liposarcoma, for which there is no available therapy.

RECOMMENDATION: This application is designated priority review based on the evidence of increased effectiveness in the second-line treatment of liposarcoma, a serious condition for which there is no available therapy.

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

PATRICIA KEEGAN
01/24/2015



NDA 207953

PRIORITY REVIEW DESIGNATION

Janssen Products, L.P.
c/o Janssen Research & Development, LLC
Attention: Erik Poulsen, M.S.
Director, Global Regulatory Affairs
920 U.S. Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Mr. Poulsen:

Please refer to your New Drug Application (NDA) dated November 24, 2014, received November 24, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for trabectedin for injection, 1 mg.

We also refer to your submissions dated December 11, 2014; December 16 (2), and 18, 2014; January 21, 2015; and January 23, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is July 24, 2015.

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 requirement/commitment requests by April 28, 2015.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before February 6, 2015.

If you have any questions, call Anuja Patel, Senior Regulatory Project Manager, at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

PATRICIA KEEGAN
01/24/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 20, 2015
From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 207953- Clinical Pharmacology Information Requests

Janssen Products, L.P.
c/o Janssen Research & Development, LLC
Attention: Erik Poulsen, M.S.
Director, Global Regulatory Affairs
920 U.S. Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Mr. Poulsen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for “Yondelis (trabectedin), powder for reconstitution, 1 mg.”

We have the following clinical pharmacology request for information:

1. Submit to the NDA a description of the proposed hepatic impairment study as post marketing requirement (PMR), including your proposed timelines for completion of the study and submission of the final study reports, as requested during the pre-NDA meeting held in October 17, 2014.
2. Submit to the NDA the study report for Study 10045020, and the related concentration-time and derived pharmacokinetic (PK) parameter datasets as SAS transport files (*.xpt) with description of each data item (in a define.pdf file).

A response to the items above is due formally to your NDA no later than Monday, February 2, 2015. Please email me a courtesy copy of your cover letter once it has been submitted through the gateway.

If you have any questions, please feel free to contact me.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ANUJA PATEL
01/20/2015



NDA 207953

Janssen Products, L.P.
c/o Janssen Reserch & Development, LLC
Attention: Erik Poulsen, M.S.
Director, Global Regulatory Affairs
920 U.S. Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Mr. Poulsen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for “Yondelis (trabectedin), powder for reconstitution, 1 mg.”

We also refer to your November 24, 2014, correspondence requesting an application orientation meeting to discuss Yondelis (trabectedin). Based on the statement of purpose, objectives, and proposed agenda, we will consider this an informal type C meeting. Meeting minutes will not be issued.

The meeting is scheduled as follows:

Date: Friday, January 16, 2014
Time: ~1:00 PM– 2:00 PM, EST
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 2205
Silver Spring, Maryland 20903

Please e-mail Anuja Patel a list of your meeting participants so that their names can be entered into our LobbyGuard system.

Please e-mail and electronic copy of your slides by 2:00 PM, EST., Wednesday, January 14, 2014 and submit 40 desk copies of your slides to Anuja Patel at the following address no later than close of business, January 14, 2014:

Anuja Patel
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 2365
10903 New Hampshire Avenue
Silver Spring, Maryland
*Use zip code **20903** if shipping via United States Postal Service (USPS).*
*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

If you have any questions, please call me at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ANUJA PATEL
12/17/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 15, 2014
From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 207953: Division of Risk Management Information Request (DRISK)

Janssen Products, L.P.
c/o Janssen Research & Development, LLC
Attention: Erik Poulsen, M.S.
Director, Global Regulatory Affairs
920 U.S. Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Mr. Poulsen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Yondelis (trabectedin).

We refer to your submission dated and received November 24, 2014 containing your NDA application. The Division of Risk Management (DRISK) has the following comment and request for information:

- DRISK notes that a risk management plan was not submitted with this application. Please formally submit by 4:30, P.M., EST. close of business, Wednesday, December 17, 2014, as an amendment to your NDA application, a copy of your most recent EU Risk Management plan and a U.S. risk management plan if you have one available.

If you have any questions, please feel free to contact me.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9022
Email: Anuja.Patel@fda.hhs.gov

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/s/

ANUJA PATEL
12/15/2014



NDA 207953

NDA ACKNOWLEDGMENT

Janssen Products, L.P.
c/o Janssen Reserch & Development, LLC
Attention: Erik Poulsen, M.S.
Director, Global Regulatory Affairs
920 U.S. Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Mr. Poulsen:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Yondelis (trabectedin), powder for reconstitution, 1 mg

Date of Application: November 24, 2014

Date of Receipt: November 24, 2014

Our Reference Number: NDA 207953

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 January 23, 2015, 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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. 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 conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should 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 Oncology Products 2
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/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ANUJA PATEL
12/07/2014



IND 50286

MEETING MINUTES

Janssen Research and Development, LLC
Attention: Erik Poulsen, MS
Director, Global Regulatory Affairs
920 Route 202, PO Box 300
Raritan, NJ 08869

Dear Mr. Poulsen:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for trabectedin.

We also refer to the teleconference between representatives of your firm and the FDA on October 17, 2014. The purpose of the meeting was to obtain the Division's input on the proposed format and content of the planned New Drug Application (NDA) submission based on progression-free survival (PFS), overall response rate (ORR) and duration of response results from randomized Study ET743-SAR-3007 at the time of the overall survival (OS) interim analysis.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding the meeting outcomes.

If you have any questions, call me at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:

Meeting Minutes

CR letter for NDA (b) (4)

OSI Attachments I and II



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA
Meeting Date and Time: October 17, 2014
Meeting Location: CDER WO 22 - Room 1313
Application Number: IND 50286
Product Name: Trabectedin
Indication: (b) (4)
Sponsor/Applicant Name: Janssen Research and Development, LLC

FDA ATENDEES

Division of Oncology Products 2, (DOP 2)

Patricia Keegan, M.D., Director, DOP 2
Marc Theoret, M.D., Medical Team Lead, DOP 2
Jennie Chang, Pharm.D., Senior Clinical Analyst, DOP 2
Gina Davis, M.T., Regulatory Project Manager, DOP 2

Division of Hematology Oncology Toxicology (DHOT)

Whitney Helms, Ph.D., Supervisor, DHOT
Dubravka Kufin, Ph.D., Toxicology Reviewer

Division of Clinical Pharmacology V (DCP V)

Hong Zhao, Ph.D., Acting Division Director, DCP V

Division of Biostatistics V (DB V)

Kun He, Ph.D., Statistics Team Lead, DB V
Huanyu Chen, Ph.D., Statistics Reviewer, DB V

Division of New Drug Quality Assessment (DNDQA)

Ali Al Hakim, Ph.D., CMC Division Director, DNDQA

Office of Pharmaceutical Science – New Drug Microbiology Staff

John W. Metcalfe, Ph.D., Senior Review Microbiologist

SPONSOR ATTENDEES

Nushmia Khokhar, Janssen R&D, LLC Director, Study Physician
Roland Knoblauch, Janssen R&D, LLC Senior Director, Clinical Leader
Trilok Parekh, Janssen R&D, LLC Senior Director, Compound Development
Team Leader
Craig Tendler, Janssen R&D, LLC Vice President, Late Development and
Medical Affairs
Youn Choi Park, Janssen R&D, LLC Director, Statistical Leader
Susan Wendel, Janssen R&D, LLC Director, CMC Leader
Dawn Kracht, Janssen R&D, LLC Director, CMC Regulatory Affairs
Hemal Morjaria, Janssen R&D, LLC Senior Director, Global Regulatory
Leader
Barbara Kolb, Janssen R&D, LLC Senior Director, Regulatory Affairs North
America Oncology Therapeutic Area Leader
Ana Irigaray, PharmaMar, SA Regulatory Affairs Director
Antonio Nieto, PharmaMar, SA BioStatistics Manager

(b) (4)

Peter Lebowitz, Janssen R&D, LLC, Global Therapeutic Head, Oncology
Chi (Anther) Keung, Janssen R&D, LLC, Clinical Pharmacology Leader

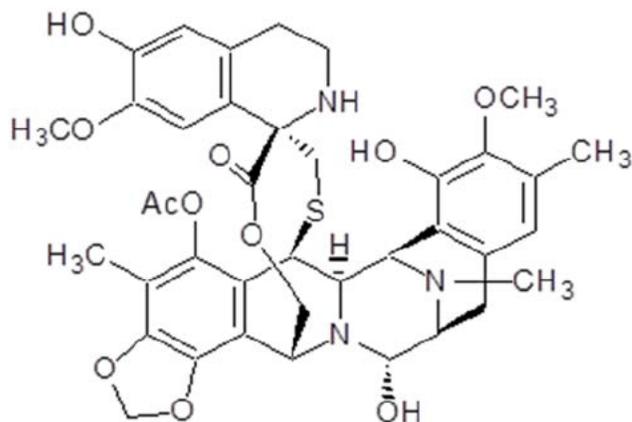
1.0 BACKGROUND

Proposed Indication

(b) (4)

Chemical Name and Structure

(1'R,6R,6aR,7R,13S,14S,16R)-5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-spiro[6,16-(epithiopropoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one. The structure of trabectedin is illustrated below:



Janssen states that in clinical studies, trabectedin was administered via a central venous catheter at a dose of 1.5 mg/m² as a 24-hour intravenous (IV) infusion once every 3 weeks (q 3wk; 24-h). Patients were pretreated with 20 mg of dexamethasone IV (or an equivalent IV corticosteroid) 30 minutes prior to trabectedin administration.

Regulatory History

On July 16, 2014, Janssen Research and Development, LLC (Janssen) submitted a pre-NDA meeting request under IND 50286 to discuss the content and format for the proposed New Drug Application (NDA) for trabectedin. The proposed NDA, based on the progression-free survival (PFS) and overall survival (OS) results from Study ET743-SAR-3007, “A Randomized Controlled Study of Yondelis (trabectedin) or Dacarbazine for the Treatment of Advanced Liposarcoma or Leiomyosarcoma.”

Study ET743-SAR-3007 is a randomized, open-label, multicenter, active-controlled trial that enrolled 570 patients with unresectable, locally advanced or metastatic lipo- or leiomyosarcoma who have been previously treated with an anthracycline regimen.

IND 50286 [REDACTED] (b) (4)

The regulatory history regarding development of trabectedin [REDACTED] (b) (4) under IND 50286 is summarized, as follows:

On October 18, 2000, FDA held a Type B, End-of-Phase 2 (EOP2) meeting with the sponsor (PharmaMar) to discuss the development program of trabectedin [REDACTED] (b) (4)

[REDACTED] Key agreements and comments at the meeting were as follows:

- FDA did not agree with a proposed primary endpoint [REDACTED] (b) (4)

- FDA stated that the primary endpoint of the trial should be overall survival based on the proposal that the study would provide the data for full approval.

On March 5, 2002, FDA held an EOP2 meeting with PharmaMar to discuss a proposed trial. (b) (4)

[Redacted]

were as follows:

Key agreements and comments at the meeting

[Redacted] (b) (4)

On May 21, 2004, FDA held an EOP2 meeting with the new sponsor (Johnson & Johnson) to discuss development of trabectedin for the indication treatment of patients with locally advanced or metastatic liposarcoma or leiomyosarcoma. Specifically, the proposal to submit the ORR results from Trial ET743-STS-201, an activity-estimating trial investigating two dosage regimens of trabectedin (0.58 mg/m² administered as a 3-hour infusion every week for 3 out of 4 weeks and 1.5 mg/m² administered as a 24-hour infusion every 3 weeks) (b) (4)

[Redacted]

[REDACTED] (b) (4)

On March 10, 2005, FDA held a pre-NDA meeting with Johnson & Johnson to discuss the organization, content, and format of an NDA for the proposed indication [REDACTED] (b) (4)

[REDACTED] A separate pre-NDA meeting was held on March 15, 2005, to discuss CMC and Nonclinical sections of an NDA.

On November 4, 2005, FDA held a Type A meeting with Johnson & Johnson to discuss a proposal to perform [REDACTED] (b) (4) analysis of Trial ET743-STS-201, which was recommended by an independent data monitoring committee (IDMC), and to discuss and reach agreement on the proposed NDA strategy including statistical analysis and submission of the ET743-STS-201 trial data. FDA did not agree to a modification [REDACTED] (b) (4)

On December 15, 2005, FDA issued a Special Protocol Assessment – No Agreement letter for a protocol [REDACTED] (b) (4) titled [REDACTED] (b) (4)

[REDACTED] FDA did not agree that the proposed [REDACTED] (b) (4) was acceptable for full approval [REDACTED] (b) (4)

On April 14, 2006, FDA held a Type A meeting with Johnson & Johnson to reach agreement on a revision to the data acquisition process for the final analysis of the primary endpoint [REDACTED] (b) (4) for Trial ET743-STS-201. FDA did not agree [REDACTED] (b) (4)

[REDACTED] FDA stated that a confirmatory study would likely be required given the problems identified.

On October 5, 2006, Johnson & Johnson submitted a meeting request to discuss their development program for trabectedin [REDACTED] (b) (4). FDA granted a Type A meeting on October 19, 2006. Johnson & Johnson cancelled the meeting on November 6, 2006.

On November 23, 2010, FDA held a Type C meeting with Johnson & Johnson to discuss clinical development plan for treatment of locally advanced, unresectable, or metastatic L-sarcoma (liposarcoma and leiomyosarcoma), specifically to address the design of the proposed Phase 3 study ET743-SAR-3007, a randomized, open-label, active-controlled, parallel-group, multicenter study comparing the safety and efficacy of trabectedin with dacarbazine in adults with unresectable, locally advanced or metastatic L-sarcoma who were previously treated with anthracyclines and ifosfamide. The proposed primary endpoint of the trial was OS. Key agreements and comments at this meeting were as follows:

- FDA agreed with the proposed superiority design with OS as the primary endpoint.
- Johnson & Johnson clarified that patients with refractory disease on previous regimens would be eligible for the proposed trial. The Sponsor stated that patients will not be allowed to cross over to the trabectedin arm.
- FDA agreed with DTIC as an acceptable comparator arm
- FDA agreed with Johnson & Johnson's plan to collect pathology samples from all randomized subjects and that a pathology report indicating a diagnosis of leiomyosarcoma or liposarcoma was acceptable for randomization. However, FDA stated that Johnson & Johnson must demonstrate an improvement in OS in the intent-to-treat (ITT) population.
- FDA agreed with Johnson & Johnson's proposal to limit enrollment of an expanded access protocol (ET743-SAR-3002; submitted to IND 50286 on August 1, 2005) to patients with non-L-type sarcoma in order to not impede the clinical development of trabectedin for the proposed indication; however, FDA recommended that Johnson & Johnson consider continuing the EAP for patients ineligible for the proposed clinical trial
- FDA did not agree that the studies supported the proposed (b) (4)
[REDACTED]
[REDACTED] this information would be reviewed during the trial and at the time of the submission of the NDA.
- FDA recommended revising the proposed eligibility criterion for age (b) (4)
[REDACTED] to greater than 15 years of age.

According to the pre-NDA meeting briefing document, during a pre-IND/EOP2 meeting on July 23, 2012, (b) (4) Dr. Richard Pazdur proposed that Janssen R&D share the mature PFS and response rate (RR) results from the ET743-SAR-3007 study with FDA as a basis for possible accelerated approval.

In a Type C, Written Responses Only, meeting minutes memorandum dated June 7, 2013, FDA recommended that if Janssen (formerly Johnson & Johnson) sought approval based on an analysis of PFS and ORR in an open-label trial, then an independent analysis of tumor-based assessments to determine tumor response should be conducted by an independent radiologic review committee (IRC) blinded to treatment assignment. Alternatively, FDA stated that Janssen may propose a detailed auditing plan that includes a strategy to detect potential assessment bias

and minimize selection bias; the auditing plan should include the percentage of patients to be audited, the method used to identify the subset of images to be audited, the method for comparing the PFS/ORR results obtained by local review with the PFS/ORR results of the audit, and the criteria for determining whether all images need to be audited. Janssen proposed a mechanism by which the IDMC could recommend that clinically compelling PFS and RR results, available at the time of the protocol-specified interim analysis for OS, be discussed with FDA. Janssen also proposed to crossover patients randomized to the dacarbazine arm if an NDA based on PFS is submitted. FDA stated that crossover might jeopardize the ability to demonstrate clinical benefit based on effect on overall survival in the event that the treatment effect on PFS is not of sufficient magnitude to be considered evidence of clinical benefit; however, FDA stated that the proposal may be reconsidered when summary results for the final analysis of PFS, ORR, and response duration are available.

On January 9, 2014, Janssen submitted interim results for OS, PFS, and response rates from Study ET743-SAR-3007, accompanied by a proposed auditing plan for the PFS endpoint to assess for bias in this open-label trial. Janssen proposed to carry out an independent central review using all available scans from sites that enrolled nine or more subjects into the trial at the time of the interim analysis of OS. Janssen stated that 19 sites met this criterion, consisting of approximately 60% of the patients enrolled on the trial at the time of the interim analysis of OS. FDA notified Janssen on February 18, 2014, that the auditing plan was acceptable and stated that whether the proposal may introduce potential bias will be determined upon review of the NDA submission. FDA further requested that Janssen provide analyses of centers with < 9 patients (unaudited subset) versus ≥ 9 patients (audited subset) to show that the patients in the two groups are comparable. The proposed audit plan was limited to radiographic PFS (rPFS).

On March 17, 2014, Janssen submitted an addendum to the original statistical analysis plan (SAP) dated October 22, 2013, to implement the audit plan and describe the analysis methods for comparisons between radiological PFS (rPFS) based on investigator's radiologic assessments and rPFS based on independent radiologic review using the audit methodology by Dodd et al¹. The SAP and audit plan were modified to state that symptomatic deterioration, in the absence of radiographic evidence of progression, will not be considered a disease progression event.

On July 7, 2014, FDA held a Type C meeting with Janssen to discuss the audit results of the investigator-assessed PFS endpoint for Study ET743-SAR-3007 as assessed by independent radiologic review. FDA agreed that the results of the independent audit of investigator-assessed PFS appeared consistent with the results of the primary analysis of PFS; however, a determination that an independent audit sufficiently evaluates introduction of bias in an investigator-assessed PFS analysis would be made during review of an NDA submission. The FDA also stated that the PFS effect was similar in magnitude to a recent approval for treatment of STS and agreed that the result may support accelerated approval; however, whether a 2.7-month median improvement in PFS in the trabectedin arm over the dacarbazine arm will support a finding of effectiveness for trabectedin and demonstrate a positive benefit: risk assessment will be a review issue after the NDA submission. Furthermore, FDA stated that the acceptability of

¹ Dodd LE, Korn EL, Freidlin B, Gray R, Bhattacharya S. An audit strategy for progression-free survival. *Biometrics* 2011;67:1092-9.

PFS to serve as direct evidence of clinical benefit or evidence that is reasonably likely to predict clinical benefit depends on whether FDA concludes that the improvement in PFS is clinically meaningful, statistically persuasive, free from bias, and supports an acceptable risk-benefit profile.

NDA [REDACTED] (b) (4)

On November 19, 2008, Johnson & Johnson Pharmaceutical Research & Development L.L.C., on behalf of Ortho Biotech Products, L.P., submitted New Drug Application (NDA) [REDACTED] (b) (4) for YONDELIS® (trabectedin) [REDACTED] (b) (4)

(b) (4)

On April 29, 2011, the Applicant requested to withdraw NDA (b) (4), and FDA acknowledged the request on May 6, 2011.

Foreign Marketing Status

Trabectedin was granted marketing authorization (MA) under “exceptional circumstances” by the EMA in 2007 for the treatment of patients with soft tissue sarcomas who have progressed after both anthracycline and ifosfamide treatment or for whom these treatments are unsuitable. Authorization under “exceptional circumstances” was based primarily on results in patients with liposarcoma or leiomyosarcoma enrolled in protocol ET743-STS-201. The FDA considered this an exploratory study given limitations in design and conduct. As of July 10, 2014, trabectedin is approved for the treatment of STS in 75 countries.

In October 2009, the European Commission granted approval for trabectedin in combination with pegylated liposomal doxorubicin (PLD) for the treatment of patients with relapsed platinum sensitive ovarian cancer. As of July 10, 2014, trabectedin is approved for the treatment of patients with relapsed platinum sensitive ovarian cancer in 68 countries.

Clinical Data

Phase 1 Clinical Studies

Per Janssen, 23 phase 1 studies of trabectedin have been completed (see Table 1). Janssen states that clinical study reports for these studies will be included in the NDA submission.

Table 1. List of Completed Phase 1 Studies

Study Type/ Study Number	Trabectedin Intravenous Regimen		
	Dose	Schedule	No. of Treated Subjects ^a
(b) (4)			

Phase 2 Clinical Studies

Table 2 outlines 23 completed Phase 2 studies that evaluated trabectedin administered as a single agent or in combination using various treatment dosing/schedules. Three dosage regimens of trabectedin were selected for further evaluation in Phase 2 studies on the basis of the findings in the Phase 1 studies:

- 1.3 mg/m² administered as a 3 hour intravenous infusion once every 3 weeks (Day 1 of 21-day cycle).
- 1.5 mg/m² administered as a 24 hour intravenous infusion every 3 weeks (Day 1 of 21-day cycle).

Note: this is the dosing regimen registered in the European Union and other countries where trabectedin is approved for STS, and is the dosing regimen in Study ET743-SAR-3007.

- 0.58 mg/m² administered as a 3 hour intravenous infusion every week for 3 weeks followed by 1 week of rest (Days 1, 8, and 15 of 28-day cycle).

Table 2. List of Phase 2 Studies

Study Type/ Study Number	Trabectedin Intravenous Regimen		
	Dose	Schedule	No. of Treated Subjects ^a
(b) (4)			

Study ET743-SAR-3007

Study ET743-SAR-3007, “A Randomized Controlled Study of Yondelis (trabectedin) or Dacarbazine for the Treatment of Advanced Liposarcoma or Leiomyosarcoma”, is an ongoing randomized, open-label, multicenter, active-controlled, trial in patients with unresectable, locally advanced or metastatic L-type sarcoma (liposarcoma or leiomyosarcoma) who were previously treated with either:

- an anthracycline and ifosfamide containing regimen
- an anthracycline containing regimen and one additional cytotoxic chemotherapy regimen.

The primary endpoint of the study is OS. PFS, TTP, ORR, and clinical benefit rate (CBR) are secondary endpoints. Randomization is stratified by number of lines of prior chemotherapy (one vs. two or more), performance status (ECOG PS 0 vs. 1), and L-type sarcoma subtype (liposarcoma vs. leiomyosarcoma).

Eligible patients were randomly assigned in a 2:1 ratio to one of two treatment arms:

- Trabectedin: 1.5 mg/m² administered as a 24-h IV infusion q3wk
- Dacarbazine: 1 g/m² administered as a 20-120 minute IV infusion q3wk

Patients randomized to the dacarbazine treatment group were not permitted to receive trabectedin following disease progression. Patients who discontinued treatment were to be followed for documentation of subsequent anticancer therapy and survival status.

Assuming that the median OS is 10 months in the dacarbazine arm and 13.5 months in the experimental arm, 376 events from 570 patients are needed to detect a hazard ratio of 0.74 with 80% power at an overall two-sided alpha level of 0.05. The protocol specifies an interim analysis of OS when approximately 188 (50%) deaths have been observed. The final OS analysis will occur following the clinical cutoff of 376 death events. The O’Brien-Fleming boundary method is utilized with respective alpha allocation of 0.003; the alpha allocation for the final analysis is 0.047. The unstratified log-rank test will be used to evaluate OS.

The secondary endpoints are PFS and ORR. PFS is defined as the time between randomization and disease progression (either radiographic progression or clinical progression) or death regardless of the cause of death, whichever occurs first. The final PFS analysis was planned to be conducted at the time of the interim OS analysis. Assuming that the median PFS is 2.5 months in the dacarbazine arm and 3.75 months in the trabectedin arm, a total of 331 PFS events from 500 patients are projected to detect a hazard ratio of 0.667 with at least 90% power at an overall two-sided alpha level of 0.05. The analysis methods used to evaluate PFS are similar to those used to evaluate OS. Radiographic assessment of disease is performed by the investigator every 6 weeks for the first 36 weeks on study and every 9 weeks thereafter according to RECIST version 1.1

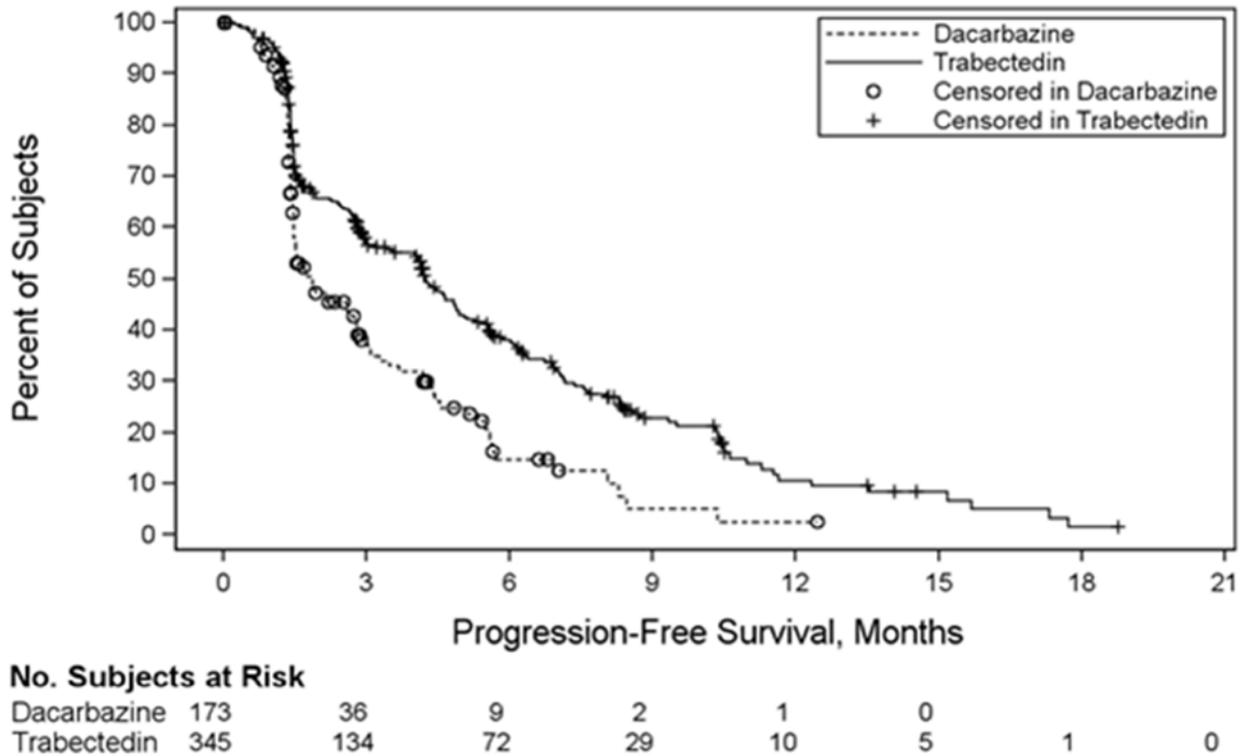
The secondary endpoints of PFS, TTP, ORR, and duration of response (DOR), will be based on investigator assessment, as no central independent review of radiographic imaging was prespecified.

Hochberg test procedure is proposed to adjust for multiplicity in testing the secondary endpoints of PFS, TTP, ORR, and clinical benefit rate.

Results

According to the meeting briefing document, the median PFS as determined by the investigator, was 4.21 months [95% confidence interval (CI): 2.99, 4.83 months] in the trabectedin group, and 1.54 months (95% CI: 1.48, 2.60 months) in the dacarbazine group [hazard ratio (HR): 0.55, 95% CI: 0.436, 0.696; $p < 0.0001$]. The subgroup analyses of PFS showed a consistent pattern in the HR favoring the trabectedin group. By stratified analysis, the HR was 0.551 (95% CI: 0.435, 0.699; $p < 0.0001$) and was similar to the unstratified analysis of PFS. The HR results by radiographic assessment (rPFS) by investigator was 0.569 (95% CI: 0.446, 0.724; $p < 0.001$). The rPFS results are shown below:

Figure 1. Kaplan-Meier Curve of Radiographic Progression-Free Survival



Additionally, the audit demonstrated an independent radiologic review assessed PFS HR of 0.582 (95% CI: 0.367, 0.803). A summary of the PFS results are displayed below in Table 1:

Table 1: Summary of PFS and rPFS Results

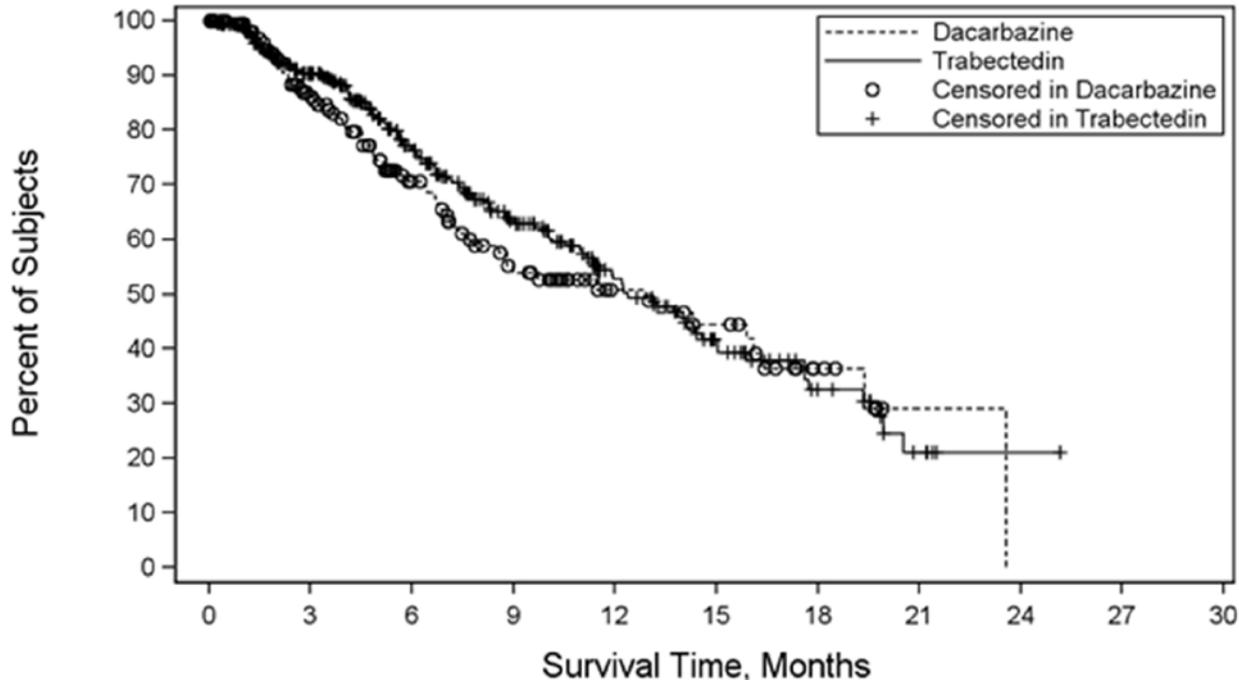
	PFS-INV (N=518)	rPFS-INV (N=518)	rPFS-INV (audited subset) (N=304)	rPFS-INV (unaudited subset) (N=214)	rPFS-IR (audited) (N=304)	rPFS-IR overall estimate (Dodd Method) (N=304,214)
HR	0.550	0.569	0.582	0.543	0.549	0.536
95% CI	(0.436, 0.696)	(0.446, 0.724)	(0.427, 0.793)	(0.367, 0.803)	(0.399, 0.754)	(0.407, 0.705)

CI=confidence interval; HR=hazard ratio; IR=independent review; INV=investigator assessed; PFS=progression-free survival; rPFS=radiographic progression-free survival

For response rate, no subject in either treatment group achieved a complete response (CR). A higher proportion of subjects in the trabectedin group (34 subjects; 9.9%) achieved a partial response (PR) compared with the dacarbazine group (12 subjects; 6.9%).

The primary efficacy analysis of OS is planned at the time of 376 observed death events. A summary of the OS data at the time of the interim analysis (16 September 2013), triggered by 50% OS events (188 events). Study ET743-SAR-3007 is ongoing and will continue until the protocol-specified 376 death events are reached. At the time of the interim analysis (16 September 2013), 189 subjects died [126 subjects (36.5%) in the trabectedin group and 63 subjects (36.4%) in the dacarbazine group]. The HR was 0.872 (95% CI: 0.644, 1.181; p=0.3741). The Kaplan Meier plots of OS by treatment arm are presented below:

Figure 2. Kaplan Meier Curve of Overall Survival



No. Subjects at Risk

Dacarbazine	173	113	69	43	25	19	7	1	0	0
Trabectedin	345	251	166	107	63	35	16	5	1	0

2.0 OBJECTIVES

- The purpose of this meeting is to obtain the Division’s input on the proposed content and format and of the planned electronic common technical document (eCTD) for the new drug application (NDA).
- To reach agreement on the proposed NDA based on progression-free survival (PFS), overall response rate (ORR), duration of response (DOR), and clinical benefit rate (CBR) results from the randomized study ET743-SAR-3007 at the time of the overall survival (OS) interim analysis

3.0 SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSE

Clinical/Statistical

1. Janssen R&D proposes to submit a Summary of Clinical Efficacy that includes:
 - Efficacy data from the pivotal Phase 3 study, ET743-SAR-3007, by study treatment (trabectedin 1.5 mg/m² as a 24-h IV infusion once every 3 wks (q 3wk;

24-h) as compared with dacarbazine 1 g/m² as a 20-120 minute IV infusion once every 3 weeks (q 3wk)).

- Efficacy data from a supportive randomized single-agent Phase 2 study, ET743-STS-201, by study treatment (trabectedin 1.5 mg/m² q 3wk; 24-h or 0.58 mg/m² as a 3-h IV infusion once weekly for 3 weeks (q wk; 3-h)).
- Efficacy data from 3 initial single-arm Phase 2 studies in advanced, treatment refractory STS (ET-B-005-98, ET-B-008-98, and ET-B-017-99) where trabectedin was administered according to the same q 3wk regimen of 1.5 mg/m² over 24 h. Efficacy data from these 5 studies will not be integrated and will be presented separately by study as the populations and prior treatment requirements differed across the studies.

Does the Agency agree with this proposal?

FDA response: No, FDA does not agree with Janssen R&D's proposal. In addition to presenting the data from the five studies separately, the NDA should contain: (1) an integrated (side-by-side) analyses of the data from these studies according to dose and schedule and (2) a thoughtful discussion of the results with the summaries of efficacy and safety to support the conclusion that the data from Study ET743-SAR-3007 represents substantial evidence of a trabectedin treatment effect that is reasonably likely to predict clinical benefit should be included. According to Table 3, there are other phase 2 studies (ET-B-016-99, ET-B-028-06, ET-B-010-99, ET-B-022-00, and ET-B-023-00) that evaluated the effect of trabectedin in patients with STS. Please include these studies in your analyses, in the aforementioned format.

Janssen's October 17, 2014 electronic (email) communication: JRD acknowledges and agrees with the Agency's feedback for sub-points one and two.

Our rationale for inclusion of studies in the SCE was as follows: advanced STS (excluding GIST), relapsed after front-line treatment (usually containing an anthracycline), and a trabectedin dosing regimen consistent with the pivotal study (1.5mg/m² infused over 24 hours q 3 wk). Based on these criteria, the following studies were included: SAR-3007, STS-201 and three single-arm Phase 2 studies: ET-B-005-98, ET-B-008-98, and ET-B-017-99.

(b) (4)

Study No.	Dosing Schedule	Study population
ET-B-016-99	q 3 wk; 24-h (1.5 mg/m ²)	First line
ET-B-028-06	q 3 wk; 24-h (1.5 mg/m ²)	Neoadjuvant
ET-B-010-99	q 3 wk; 3-h (1.65, 1.5 and 1.3 mg/m²)	Relapsed
ET-B-022-00	q 3 wk; 3-h (1.65, 1.5 and 1.3 mg/m²)	Relapsed
ET-B-023-00	q 3 wk; 3-h (1.65, 1.5 and 1.3 mg/m²)	Relapsed

(b) (4)

It should be noted that these studies will be integrated in the SCS and an individual CSR will be provided for each in Module 5.

Discussion during the meeting: FDA clarified that the ISE should contain adequate and well-controlled studies, whether positive or negative, in support of the overall discussion of a treatment effect of trabectedin. FDA stated that submission of individual CSRs for the five trials referenced in the response to question # 1 is acceptable in lieu of inclusion of the integrated study report inclusive of these studies in the ISE. JRD clarified that single arm trials in a relatively small number of patients were conducted under Study ET-B-010-99. JRD agreed to provide the information noted in points one and two in FDA's response to question # 1.

2. In addition to the safety data from Study ET743-SAR-3007, Janssen R&D is proposing to include safety data from the following two integrated safety analysis sets in the Summary of Clinical Safety:
 - Safety data from 24 studies; a Phase 3 Study ET743-SAR-3007 up to the interim analysis (cutoff date of 16 September 2013) plus the safety data from 23 previously completed Phase 2 single-agent studies in various tumor types. This data integration will include the combined safety data from 1,681 subjects who received trabectedin when administered either once every 3 weeks as a 24-h IV infusion (q 3 wk; 24-h), once every 3 weeks as a 3-h IV infusion (q 3 wk; 3-h), or once weekly as a 3-h IV infusion (q wk; 3-h).

- Safety data for the subset of subjects (n=865 subjects) from the integrated analysis set above who had a diagnosis of STS.

Does the Agency agree with the proposed integrated safety analysis sets?

FDA response: Yes; however, an additional safety analysis for patients who were treated at the proposed dosing regimen, 1.5 mg/m² as a 24-h IV infusion q 3 wk, and the stand-alone safety analysis for patients in Study ET743-SAR-3007 should also be presented separately as this will constitute the primary safety population for the NDA submission.

A safety analysis for events of special interest consisting of sepsis, pneumonitis, rhabdomyolysis, hepatitis, and other relevant adverse events identified by Janssen R&D should be provided. Include a list of MedDRA Preferred Terms mapped to the HLT, HLGT, and SOC for these events of special interest.

Please confirm that a Summary of Clinical Safety will also be included to summarize the safety experience of trabectedin, separately from the integrated summary of safety.

Janssen's October 17, 2014 electronic (email) communication: In order to facilitate the comparison of safety between ET743-SAR-3007 and the integrated data sets, JRD had planned to sequentially present within each section of the SCS the results for each of the datasets, as follows:

Study ET743-SAR-3007 safety analysis set

Safety Profile; All Treated Subjects (Study ET743-SAR-3007)

	Dacarbazine (N=155) n (%)	Trabectedin (N=340) n (%)
Treatment-emergent adverse events (TEAEs)	152 (98.1%)	337 (99.1%)
Drug-related	132 (85.2%)	322 (94.7%)
Grade 3-4 TEAEs	80 (51.6%)	259 (76.2%)
Drug-related	57 (36.8%)	220 (64.7%)
Serious TEAEs	44 (28.4%)	124 (36.5%)
Drug-related	17 (11.0%)	64 (18.8%)
Grade 3-4	39 (25.2%)	107 (31.5%)
TEAE leading to treatment termination	34 (21.9%)	62 (18.2%)
Drug-related	12 (7.7%)	36 (10.6%)
TEAE leading to death	4 (2.6%)	22 (6.5%)
Drug-related	0	7 (2.1%)
Deaths within 30 days of last dose	3 (1.9%)	22 (6.5%)
Due to TEAE	0	11 (3.2%)
Due to progressive disease	3 (1.9%)	11 (3.2%)
Due to other	0	0

Note: Percentages calculated with the number of subjects treated in each treatment group as denominator.

Integrated STS safety analysis set

Safety Profile; All Treated Subjects (Trabectedin – Integrated Phase 2 and 3 STS Studies)

	q 3 wk; 24-h (1.5 mg/m ²)	q wk; 3-h (0.58 mg/m ²)	q 3 wk; 3-h (1.3 mg/m ²)	Total
Total treated subjects	717	130	18	865
Treatment-emergent adverse events (TEAEs)	711 (99.2%)	130 (100.0%)	16 (88.9%)	857 (99.1%)
Drug-related	664 (92.6%)	116 (89.2%)	14 (77.8%)	794 (91.8%)
Grade 3-4 TEAEs	481 (67.1%)	84 (64.6%)	8 (44.4%)	573 (66.2%)
Drug-related Grade 3-4	385 (53.7%)	54 (41.5%)	3 (16.7%)	442 (51.1%)
Serious TEAEs*	216 (35.0%)	41 (31.5%)	7 (38.9%)	264 (34.5%)
Drug-related	95 (15.4%)	8 (6.2%)	1 (5.6%)	104 (13.6%)
Grade 3-4	184 (29.8%)	34 (26.2%)	5 (27.8%)	223 (29.1%)
Drug-related Grade 3-4	82 (13.3%)	8 (6.2%)	1 (5.6%)	91 (11.9%)
Treatment termination due to AE	65 (9.1%)	10 (7.7%)	2 (11.1%)	77 (8.9%)
Death due to AE	32 (4.5%)	6 (4.6%)	1 (5.6%)	39 (4.5%)
Within 30 days of last dose	24 (3.3%)	6 (4.6%)	1 (5.6%)	31 (3.6%)
Within 60 days of first dose	22 (3.1%)	4 (3.1%)	1 (5.6%)	27 (3.1%)
Death due to drug-related TEAE	15 (2.1%)	3 (2.3%)	0	18 (2.1%)

Note: Percentages calculated with the number of subjects in each group as denominator.

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

Note: All adverse events including unknown toxicity grade are used in the analysis.

Note: *Data from Study ET-B-005 with 99 treated STS subjects on q3wk; 24-h regimen (1.5 mg/m²) were excluded because serious TEAE information was not collected in the case report form. Therefore, 618 subjects for q 3wk; 24-h and 766 subjects for Total are used as denominator for percentage calculation.

Integrated STS and other solid tumors safety analysis set

Safety Profile; All Treated Subjects (Trabectedin – Integrated Phase 2 & Phase 3 Studies)

	q 3 wk; 24-h (1.5 mg/m ²)	q wk; 3-h (0.58 mg/m ²)	q 3 wk; 3-h (1.3 mg/m ²)	Total
Total treated subjects	944	337	400	1681
Treatment-emergent adverse events(TEAEs)	933 (98.8%)	336 (99.7%)	390 (97.5%)	1659 (98.7%)
Drug-related	873 (92.5%)	307 (91.1%)	354 (88.5%)	1534 (91.3%)
Grade 3-4 TEAEs	600 (63.6%)	209 (62.0%)	239 (59.8%)	1048 (62.3%)
Drug-related Grade 3-4	469 (49.7%)	128 (38.0%)	169 (42.3%)	766 (45.6%)
Serious TEAEs*	280 (34.2%)	103 (30.6%)	118 (29.5%)	501 (32.2%)
Drug-related	122 (14.9%)	34 (10.1%)	58 (14.5%)	214 (13.8%)
Grade 3-4	241 (29.5%)	83 (24.6%)	103 (25.8%)	427 (27.5%)
Drug-related Grade 3-4	108 (13.2%)	24 (7.1%)	55 (13.8%)	187 (12.0%)
Treatment termination due to AE	89 (9.4%)	34 (10.1%)	35 (8.8%)	158 (9.4%)
Death due to AE	36 (3.8%)	9 (2.7%)	11 (2.8%)	56 (3.3%)
Within 30 days of last dose	24 (2.5%)	9 (2.7%)	8 (2.0%)	41 (2.4%)
Within 60 days of first dose	24 (2.5%)	6 (1.8%)	10 (2.5%)	40 (2.4%)
Death due to drug-related TEAE	15 (1.6%)	4 (1.2%)	4 (1.0%)	23 (1.4%)

Note: Percentages calculated with the number of subjects in each group as denominator.

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

Note: All adverse events including unknown toxicity grade are used in the analysis.

Note: *Data from Study ET-B-005 with 126 treated subjects on q 3 wk; 24-h regimen (1.5 mg/m²) were excluded because serious TEAE information was not collected in the case report form. Therefore, 818 subjects for q 3 wk; 24-h and 1555 subjects for Total are used as denominator for percentage calculation.

It is JRD's view that the current presentation as described above allows for assessment of ET743-SAR-3007 against the prior experience with subjects treated at 1.5 mg/m² as a 24-h IV infusion q 3 weeks, and will help evaluate the consistency of the trabectedin safety profile at the recommended dose regimen.

In preparation of the upcoming NDA filing, changes to the above proposed format at this time will significantly delay the submission timelines.

Is this data presentation acceptable for the SCS?

With respect to adverse events of special interest, JRD acknowledges and agrees with the Agency proposal, but would like to seek clarification why the Agency has identified pneumonitis as an event of special interest.

JRD also confirms that a Summary of Clinical Safety (SCS) document will be included.

Discussion during the meeting: Janssen stated that the data requested by FDA was included in an alternative format as shown in the three tables in Janssen's response above ("Study ET743-SAR-3007 safety analysis set", "Integrated STS safety analysis set", and "Integrated STS and other solid tumors safety analysis set"). FDA stated that the proposed format is acceptable provided there is an integration of the data in the narrative format in the ISS. Janssen agreed.

Janssen clarified that there were four cases of pneumonitis in the integrated STS and other solid tumors safety analysis set. In Study ET743-SAR-3007, one case of pneumonitis was reported in each arm. FDA agreed that pneumonitis does not need to be included in the analysis of adverse events of special interest in the ISS; however, FDA stated that it may request additional information on pneumonitis events during the NDA review.

3. Safety narratives for Study ET743-SAR-3007 will be provided for the subjects who meet the following criteria.
 - Criterion 1: Deaths for reasons other than disease progression that occurred within 30 days of the last dose of study medication.
 - Criterion 2: Drug-related treatment-emergent serious adverse event(s).
 - Criterion 3: Drug-related treatment-emergent adverse events that led to discontinuation of study treatment.

Note: A brief description of subjects meeting the laboratory criteria for Hy's Law will be included in the clinical study report.

Does the Agency agree?

FDA response: No, safety narratives should be provided for treatment-emergent adverse events regardless of attribution. Additionally, FDA may request that Janssen R&D submit additional listings, narratives, and case report forms during the review of the NDA.

For the Hy's Law cases, provide a detailed analysis of the cases with regard to demographics, time-to-onset, liver enzymes tests, dose and duration of treatment, and outcome. Additionally, provide a graphical display of the time course of liver tests and enzyme elevations. The case narratives should be included in this section separately.

Janssen's October 17, 2014 electronic (email) communication: JRD acknowledges the Agency's response and will include narratives for all treatment emergent serious adverse events and all treatment-emergent adverse events that led to discontinuation of study treatment.

For patients who met Lab criteria for Hy's law, JRD acknowledges and accepts the Agency's proposal.

Discussion during the meeting: FDA acknowledged Janssen's proposal and no discussion occurred.

4. As per the discussion with the Agency on 7 July 2014, Janssen R&D conducted a survival update as of 10 July 2014 for all subjects on Study ET743-SAR-3007, with the data summarized below (Section 12.3.3.2). Janssen R&D proposes to submit a separate report for this survival update in Module 5 of the NDA submission and discuss these results in the Clinical Overview in Module 2.5.

Does the Agency agree with this proposal?

FDA response: Yes; additionally, the final OS results should be included in the 120-day safety update as the final number of OS results is expected in December 2014 (refer to meeting minutes dated July 21, 2014).

Janssen's October 17, 2014 electronic (email) communication: JRD acknowledges the Agency's response. JRD anticipates the number of survival events needed for the final OS analysis in January 2015. If so, JRD can provide a report on the final OS results at the time of the 120-day safety update.

Discussion during the meeting: FDA acknowledged Janssen's proposal and no discussion occurred.

5. In accordance with previous Agency communications (7 June 2013 written responses to Janssen R&D's 8 May 2013 Type C meeting briefing document), Janssen R&D had agreed to continue Study ET743-SAR-3007 per protocol, consistent with Food and Drug Administration's (FDA's) suggestion, and to revisit the question of offering subjects randomized to the dacarbazine group the option to cross over to the trabectedin group should the study results demonstrate clinical benefit. We now believe that the current ET743-SAR-3007 study results support a favorable benefit-risk profile for patients with relapsed leiomyosarcoma or liposarcoma (L-type STS) and that implementing a cross over amendment at the time of an NDA submission in November 2014 would have minimal impact on the outcome of the final OS analysis as greater than 85% of the protocol-specified number of death events will have occurred. Therefore, Janssen R&D is requesting the Agency's agreement to allow subjects randomized to the dacarbazine group an option to cross over to receive treatment with trabectedin and to amend the ongoing expanded access program protocol to include subjects in line with the proposed indication.

Does the agency agree?

FDA response: Yes. FDA recognizes that if no effect in OS is observed in the trabectedin arm, then the lack of treatment effect is attributable to trabectedin and has not been confounded by patients in the dacarbazine arm crossing over to receive trabectedin.

Janssen's October 17, 2014 electronic (email) communication: JRD acknowledges the Agency's response. JRD plans to expand the EAP program to include L-type sarcoma patients.

Study SAR-3007 will be amended to include an Optional Extension Phase (OEP). All patients randomized to the dacarbazine arm, who are either actively receiving study treatment or are in the follow-up phase, will have an option to receive treatment with trabectedin as per the treating physician's discretion. Those patients will be treated under an OEP, during which patients will continue to be followed for survival as per the protocol, until required number of events are achieved for final OS analysis. All patients in OEP will be treated as per the protocol and serious adverse event data will be reported to the Agency. The sponsor will submit an amended protocol for SAR-3007 for the Agency's information.

Discussion during the meeting: FDA acknowledged Janssen's proposal and no discussion occurred.

6. The 120-day safety update will provide an update of Study ET743-SAR-3007 safety data with a clinical cutoff date of 10 July 2014.

Does the Agency agree?

FDA response: Yes, please focus the update on new serious adverse events and deaths within 30 days of treatment discontinuation.

Janssen's October 17, 2014 electronic (email) communication: JRD acknowledges the Agency's request and agrees with the proposed approach.

Discussion during the meeting: FDA acknowledged Janssen's proposal and no discussion occurred.

7. Cumulative integrated postmarketing and compassionate use experience safety data will be provided for the duration between the international first market launch date (11 October 2007) to the cutoff date of 10 July 2014.

Does the Agency agree that this is acceptable?

FDA response: Yes, the proposal to submit cumulative integrated postmarketing and compassionate use experience safety data is acceptable. FDA notes that the limitations of this data will be considered in determining which, if any data, would be appropriate for inclusion of product labeling.

Janssen's October 17, 2014 electronic (email) communication: JRD acknowledges the Agency's response and has no further comments.

Discussion during the meeting: FDA acknowledged Janssen's proposal and no discussion occurred.

8. Study ET743-OVC-1004, a hepatic impairment study, was initiated in May of 2010

[REDACTED] (b) (4)

the clinical study report will not be available at the time of the NDA submission.

[REDACTED] (b) (4)

Does the Agency agree?

FDA response: FDA agrees with the proposal to submit a clinical study report including all available data [REDACTED] (b) (4) at the time of NDA submission. The adequacy of the data will be evaluated at the time of NDA review. If Janssen does not plan to submit the final report for the hepatic impairment study at the time of NDA submission, Janssen should propose the hepatic impairment study as a postmarketing requirement (PMR), including major milestones (e.g., study completion date, submission of final study report), for FDA review at the time of NDA submission.

Janssen's October 17, 2014 electronic (email) communication: JRD will submit a preliminary safety summary with PK-data of ET743-OVC-1004 at the time of the NDA submission [REDACTED] (b) (4)

[REDACTED]

Discussion during the meeting: FDA asked Janssen if the final study report of the PK data is currently available; Janssen stated that the final study report would not be

available at the time of the NDA submission. Instead, Janssen proposed [REDACTED] (b) (4) [REDACTED] FDA stated that this was not acceptable based on the requirement to have a complete application in the original submission. FDA stated that Janssen should propose a postmarketing requirement (PMR) that describes the goals of the study and the study design as well as milestones for study completion and submission of the final study report.

9. Janssen R&D proposes to submit the following electronic datasets and electronic case report (eCRFs):
- Clinical datasets, including independent radiology review data from the agreed upon audit plan, in study data tabulation model (SDTM) format and the analysis datasets for Study ET743-SAR-3007 along with the appropriate supporting documentation.
 - Analysis datasets for the integrated safety data along with supporting documentation.
 - All subject eCRFs only for Study ET743-SAR-3007.

Does the Agency agree with this plan?

FDA response: Yes, additionally, confirm that the documentation under the audit review will also be submitted. Alternatively, provide the documentation for the audit review upon request. A copy of the independent review charter, the annotated CRFs for investigators and independent radiology review should be included in the NDA submission. Please verify that the CRFs are correctly annotated with the dataset names and variables. Please also provide the .pdf and .xml format for the SDTM datasets and confirm that the hyperlinks for the Define files are working.

Janssen's October 17, 2014 electronic (email) communication: JRD acknowledges the Agency's response and will include the documentation of audit review datasets (raw data from independent radiology review, SDTM, and analysis datasets). JRD also acknowledges the additional requests and will address them in the NDA.

Discussion during the meeting: FDA acknowledged Janssen's proposal and no discussion occurred.

Regulatory

10. Janssen R&D plans to provide Financial Disclosure information for investigators who participated in the pivotal study ET743-SAR-3007 and the key supportive study ET743-ST5-201.

Does the Agency agree with this plan?

FDA response: Yes, additionally, include the following information with the Financial Disclosure Form:

- A list of clinical investigators.
- The number of investigators who are sponsor employees (including both full-time and part-time employees).
- The number of investigators with disclosable financial interests/arrangements.
 - If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):
 - Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study.
 - Significant payments of other sorts.
 - Proprietary interest in the product tested held by investigator.
 - Significant equity interest held by investigator in sponsor of covered study.
- Details of the disclosable financial interests/arrangements.
- A description of the steps taken to minimize potential bias.
- The number of investigators with certification of due diligence (Form FDA 3454, box 3), and include the reason in an attachment.
- A narrative discussion on whether Janssen has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators. Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data?
 - If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data).
 - If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements).

Janssen's October 17, 2014 electronic (email) communication: JRD acknowledges the Agency's response and plans to provide the requested information in the NDA submission. No further discussion required.

Discussion during the meeting: FDA acknowledged Janssen's proposal and no discussion occurred.

11. Janssen R&D proposes to submit published references cited in the Summary of Clinical Efficacy, Summary of Clinical Safety, and Clinical Overview. Janssen R&D proposes not to submit references listed in clinical study reports and protocols, however any reference will be provided upon request.

Does the Agency agree with this plan?

FDA response: Yes, Janssen's plan not to submit the references cited in the clinical study reports unless requested by the FDA, is acceptable.

Janssen's October 17, 2014 electronic (email) communication: JRD acknowledges the Agency's comments, with no further discussion required.

Discussion during the meeting: FDA acknowledged Janssen's proposal and no discussion occurred.

12. Janssen R&D proposes to submit the clinical reports in Module 5 for 23 completed Phase 1 (Table 2), 23 completed Phase 2 (Table 3), and 2 Phase 3 studies (reports ET743-SAR-3007 [REDACTED] (b) (4)).

Does the Agency agree with this plan?

FDA response: Refer to FDA's responses to the STS studies in Question 1 regarding the need to submit additional STS studies.

Janssen's October 17, 2014 electronic (email) communication: JRD acknowledged the Agency's response and accordingly, all CSRs of completed studies (including the ones mentioned in Question 1) will be included in Module 5.

Discussion during the meeting: FDA acknowledged Janssen's proposal and no discussion occurred.

Chemistry Manufacturing Controls

13. At the Type C meeting on 23 November 2010, Janssen R&D shared with the Agency results of the post-penetration hold time studies for trabectedin. As discussed in the meeting (FDA minutes issued 30 November 2010), Janssen R&D prospectively collected information regarding infection/sepsis in Study ET743-SAR-3007 as a risk minimization assessment, in light of the post-penetration hold-time study results. The company position is that [REDACTED] (b) (4) but it has not been tested in the clinic and available clinical data from Study ET743-SAR-3007, supported by the compassionate use/expanded access program (>3,500 subjects) and the postmarketing experience (>34,000 patients) reveal no clinical cases of bacteremia associated with the 24-h infusion. Collectively, the safety data from both the clinical and postmarketing databases demonstrate the 24-h trabectedin infusion schedule to be safe and does not warrant the addition of an in-line filter at this time.

Does the Agency agree?

FDA response: FDA disagrees with the assertion that patients who receive microbiologically contaminated intravenous infusions would experience adverse events immediately. In fact, some microbiological adverse events may not be apparent in the

subject for multiple days or weeks after intravenous injection. As such, microbiological product contamination may have been the reason that some patients in Study ET743-SAR-3007 experienced sepsis or septic shock.

Janssen has indicated that the microbiological challenge studies demonstrate (b) (4)

(b) (4); however, Janssen has not provided these data to the Agency. Consequently, FDA has not been able to complete a thorough review of the microbial challenge data, and therefore, FDA does not know the (b) (4) product's ability to support microbial growth. (b) (4)

Please clarify whether Janssen intends to seek approval (b) (4) in the planned NDA.

FDA believes that an in-line filter would mitigate patient exposure to microbiological cells from a contaminated bag (b) (4)

The NDA submission should include the methods used and the raw data from the microbiological challenge studies, including the actual microbial counts at each sampling point, as well as graphs demonstrating the microbiological growth curves for each challenge organism and storage condition.

Janssen's October 17, 2014 electronic (email) communication: We appreciate the Agency's position and response. As agreed in the 23 Nov 2010 Type C meeting, a separate eCRF page was incorporated to collect data for any cases of sepsis related events in the pivotal study ET743-SAR3007.

A total of 10 patients (3%) had sepsis/septic shock. Seven were neutropenic sepsis and all cases were >7 days from the date of infusion. Most cases were related with clinical scenarios suggesting sources of infection some compatible with sites of disease progression (2 patients with obstructive uropathy due to disease with bilateral stents, 1 with infected tumor mass, 1 with C. difficile colitis, 2 with pneumonia, one with pneumobilia requiring ERCP, and 3 sepsis started after hospital admission for various reasons (one patient with GI bleed, one with rhabdomyolysis, one patient with weakness and neutropenia).

In the ISS datasets including data from 1681 patients the rates of sepsis in the 24hr infusion regimen (944 patients) was 1.9% versus 1.8% in the weekly 3hr infusion regimen (337 patients). The similar rate of sepsis in both treatment regimens further supports that the sepsis related events are unlikely related to contaminated drug product in the 24 hour infusion.

(b) (4)

[REDACTED] (b) (4)

At the 23 Nov 2010 Type C meeting, JRD explained that Yondelis is a large volume parenteral [REDACTED] (b) (4)

[REDACTED]

As requested, JRD will provide the raw data from the microbiological challenge studies, along with graphs in the NDA submission. Please note that the data will be presented in logarithmic format and the data were collected in accordance with Dr. Metcalfe's protocol. Since the study was designed to observe log increases of 0.5 log₁₀ compared to the initial count, quantification of microbial counts >1000 cfu/ml (3 log₁₀) was not performed.

Discussion during the meeting: Clarification of the November 30, 2010 discussion was acknowledged by FDA. Despite the lack of clinical correlation with sepsis and microbial growth, FDA believes that there may be inadequate data to support the infusion time from a microbiological stand point. Therefore, FDA recommended that the study be repeated with an attempt to use a lower inoculum and conducted at a laboratory that is experienced in performance of these studies. FDA also recommended that studies be conducted with a product that is reconstituted with a bacteriostatic diluent. FDA stated that said data can be submitted during review of the NDA. An in-line filter may be required for product administration depending on results submitted in the original NDA.

ADDITIONAL COMMENTS

Statistics

14. Please include the SAS programs used to create the derived datasets for the efficacy endpoints and the SAS programs used for efficacy data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs.

Janssen's October 17, 2014 electronic (email) communication: JRD acknowledged the Agency's comment with no further discussion required.

Discussion during the meeting: FDA acknowledged Janssen's response and no discussion occurred.

15. Please provide SAS programs for derived datasets and the analyses which are associated with the results presented in the proposed package insert.

Janssen's October 17, 2014 electronic (email) communication: JRD acknowledged the Agency's comment with no further discussion required.

Discussion during the meeting: FDA acknowledged Janssen's response and no discussion occurred.

16. Please provide used statistical analysis programs with adequate review guide for the audit plan analyses.

Janssen's October 17, 2014 electronic (email) communication: JRD acknowledged the Agency's comment with no further discussion required.

Discussion during the meeting: FDA acknowledged Janssen's response and no discussion occurred.

Clinical Pharmacology

Address the following clinical pharmacology related questions in the NDA submission:

17. What is the basis for selecting the dose and dosing regimen used in the registration trial?

Janssen's October 17, 2014 electronic (email) communication: JRD acknowledged the Agency's comment with no further discussion required.

Discussion during the meeting: FDA acknowledged Janssen's response and no discussion occurred.

18. What are the dose response and exposure-response relationships for efficacy and for safety?

Janssen's October 17, 2014 electronic (email) communication: JRD acknowledged the Agency's comment with no further discussion required.

Discussion during the meeting: FDA acknowledged Janssen's response and no discussion occurred.

19. How was the QT prolongation potential of trabectedin assessed? What are the conclusion and proposed labeling description?

Janssen's October 17, 2014 electronic (email) communication: JRD acknowledged the Agency's comment with no further discussion required.

Discussion during the meeting: FDA acknowledged Janssen's response and no discussion occurred.

20. What influence do intrinsic factors (such as those listed below) have on trabectedin exposure, efficacy and safety? What dose and administration modifications are recommended?
- disease
 - genetic polymorphism
 - hepatic impairment
 - renal impairment

Janssen's October 17, 2014 electronic (email) communication: JRD acknowledged the Agency's comment with no further discussion required.

Discussion during the meeting: FDA acknowledged Janssen's response and no discussion occurred.

21. What influence do the extrinsic factors (such as those listed below) have on trabectedin efficacy and safety? What dose and administration modifications are recommended?
- concomitant medications
 - CYP and/or transporter based drug-drug interactions

Janssen's October 17, 2014 electronic (email) communication: JRD acknowledged the Agency's comment with no further discussion required.

Discussion during the meeting: FDA acknowledged Janssen's response and no discussion occurred.

In addition, apply the following advice in preparing clinical pharmacology sections of the NDA submission:

22. Submit bioanalytical methods and validation reports for clinical pharmacology and biopharmaceutics studies that have not been previously submitted under NDA (b) (4)

Janssen's October 17, 2014 electronic (email) communication: JRD acknowledged the Agency's comment with no further discussion required.

Discussion during the meeting: FDA acknowledged Janssen's response and no discussion occurred.

23. Provide complete datasets for clinical pharmacology and biopharmaceutics studies that have not been previously submitted under NDA (b) (4)

Janssen's October 17, 2014 electronic (email) communication: JRD requests clarification of the FDA ClinPharm reviewers what is meant by "complete datasets".

Discussion during the meeting: FDA stated that the data sets should be designed to facilitate exploratory analysis.

Janssen's October 17, 2014 electronic (email) communication: JRD acknowledged the Agency's comment with no further discussion required.

Discussion during the meeting: FDA acknowledged Janssen's response and no discussion occurred.

24. Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

Janssen's October 17, 2014 electronic (email) communication: JRD requests clarification of the FDA ClinPharm reviewers with respect to this request, specifically, for those studies that have not been submitted under NDA (b) (4)

Discussion during the meeting: JRD will re-submit the clinical pharmacology data sets and CSRs in the original NDA.

25. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean \pm standard deviation) and median with range as appropriate in the study reports.

Janssen's October 17, 2014 electronic (email) communication: JRD acknowledged the Agency's comment with no further discussion required.

Discussion during the meeting: FDA acknowledged Janssen's response and no discussion occurred.

26. Identify individual subjects with dose reduction, interruption or discontinuation; the time to the first dose reduction, interruption or discontinuation; the reasons for dose reduction, interruption or discontinuation. Provide the relevant descriptive statistics for each of these variables in support of the proposed dose and administration.

Janssen's October 17, 2014 electronic (email) communication: Since the primary objectives of clinical pharmacology studies are to evaluate PK, PD, and drug-drug interactions based on single dose administration, there are few subjects who required dose reduction, interruption or discontinuation in the clinical pharmacology studies. Please clarify for JRD the information that is requested from the clinical pharmacology studies.

Discussion during the meeting: FDA clarified that item additional comment 26 refers to clinical studies.

27. Explore dose-response and exposure-response (measures of effectiveness, biomarkers and toxicity) relationships for trabectedin in the proposed patient population and include the results of this exploratory analysis in the NDA submission. Refer to Guidance for Industry found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf> and <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf> for more information.

Janssen's October 17, 2014 electronic (email) communication: JRD acknowledged the Agency's comment with no further discussion required.

Discussion during the meeting: FDA acknowledged Janssen's response and no discussion occurred.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- Janssen expects to submit the NDA in November 2014.

Complete Application/Late Component Agreements

- Janssen and FDA reached agreement regarding the contents of a complete application during the meeting and Janssen confirmed that there will be no minor components submitted after the submission of the marketing application. Refer to the agreements reached during the October 22, 2014 meeting, as described in FDA's minutes for this meeting and immediately below.
- Janssen will re-submit the nonclinical studies to the NDA.
- Janssen agreed to provide the data review plan (charter), identify independent-review identified radiographic progressions, methodology, and statistical analysis plan.
- FDA referenced the electronic (email) communication dated October 8, 2014, in which Janssen stated that a separate CMC Pre-NDA meeting will not be requested. FDA also referenced Janssen's email communication dated October 9, 2014, confirming Janssen's plans to address/incorporate responses to the CMC deficiencies noted in FDA's September 9, 2009, Complete Response (CR) letter in the proposed NDA (see attachment).

Clinical and Manufacturing sites

- Janssen stated that all manufacturing sites were previously inspected by FDA and are GMP ready.

Preliminary Discussion of REMS/Risk Management

- JRD does not intend to submit a REMs proposal. FDA agreed that, based on the preliminary safety information provided in the pre-meeting package, a REMs would not be required to file the NDA. Final determination regarding the need for a REMs to ensure safe and effective use will be made during review of the application.

Information regarding clinical trials

- Janssen stated that 75 US sites were operating under IND 50286.
- Janssen stated that 75 patients were currently enrolled in the Japanese study and the data obtained from the study was managed and monitored by Taiho Oncology. Janssen does not plan to rely on the data from the Japanese study to support labeling claims.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product [REDACTED] ^{(b) (4)} has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](#) (<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>).

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

5 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Attachment I

OSI Pre-NDA/BLA Request

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Part I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Part III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

Part I. Request for general study-related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

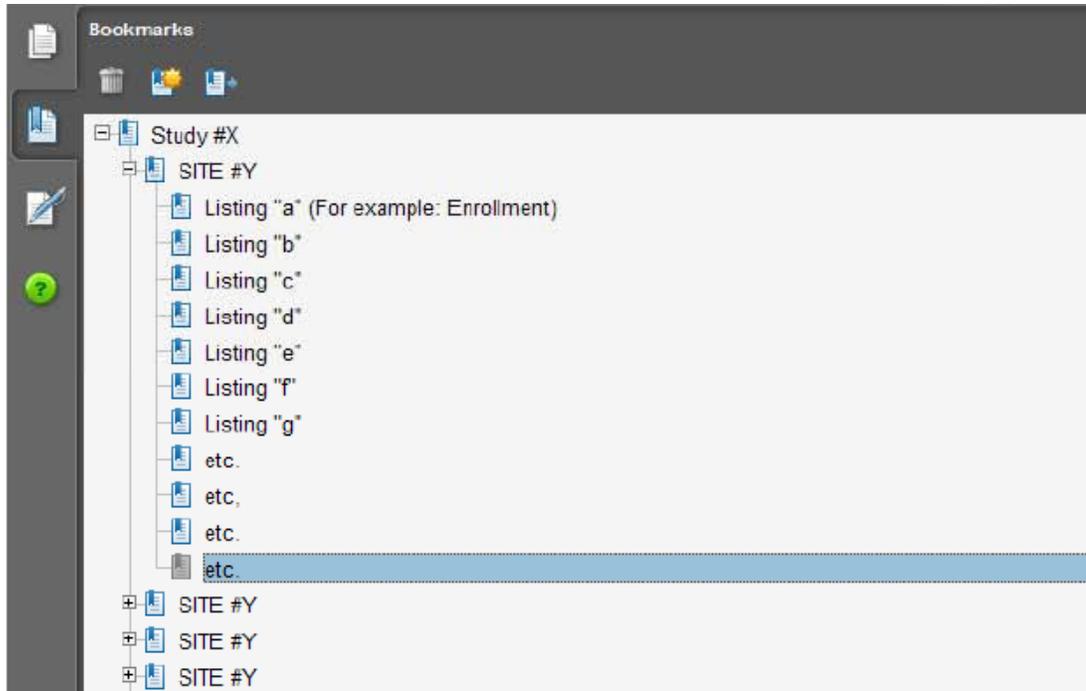
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the BA for each of the completed pivotal clinical trials:

- a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
 5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

Part II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



Part III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 2

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

OSI Pre-NDA Request Item ²	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

² Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

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

/s/

GINA M DAVIS
11/16/2014



IND 50286

MEETING MINUTES

Janssen Research and Development, LLC
Attention: Barbara Kolb
Senior Director, Global Regulatory Affairs
920 Route 202, PO Box 300
Raritan, NJ 08869

Dear Ms. Kolb:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (trabectedin) intravenous infusion.

We also refer to the teleconference between representatives of your firm and the FDA on July 7, 2014. The purpose of the teleconference was to discuss the audit results of the investigator-assessed progression-free survival (PFS) endpoint for Study ET743-SAR-3007 as assessed by the independent radiologic review

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

FINAL MEETING MINUTES

Meeting Type: C
Meeting Category: Other
Meeting Date and Time: July 7, 2014 12:30 PM – 1:00 PM
Application Number: 50286
Product Name: Yondelis (trabectedin)
Indication: [REDACTED] (b) (4)
Sponsor/Applicant Name: Janssen Research & Development, LLC

FDA ATTENDEES

Division of Oncology Products 2 (DOP 2)

Patricia Keegan, M.D., Director, DOP 2
Marc Theoret, M.D., Team Lead, DOP 2
Jennie Chang, Pharm.D., Medical Reviewer, DOP 2
Gina Davis, M.T., Senior Regulatory Health Project Manager, DOP 2

Division of Biostatistics V (DB V)

Kun He, PhD, Statistical Team Lead, DB V
Huanyu Chen, Ph.D., Statistical Reviewer, DB V

SPONSOR ATTENDEES

Janssen Research & Development, LLC (Janssen)

Craig Tendler, M.D., Vice President, Late Development and Medical Affairs
Barbara Kolb, MBA, Senior Director, North America Regulatory Lead
George Chi, Ph.D., Senior Director, Statistical Science

[REDACTED] (b) (4)

1.0 BACKGROUND

Janssen submitted a meeting request on April 30, 2014, to DOP 2 [REDACTED] (b) (4)

Study ET743-SAR-3007, “A Randomized Controlled Study of Yondelis (trabectedin) or Dacarbazine for the Treatment of Advanced Liposarcoma or Leiomyosarcoma” is an ongoing randomized, open-label, multicenter, active-controlled, trial in patients with unresectable, locally advanced or metastatic liposarcoma or leiomyosarcoma who were previously treated with either:

- an anthracycline and ifosfamide containing regimen
- an anthracycline containing regimen and one additional cytotoxic chemotherapy regimen.

The primary endpoint of the study is overall survival (OS). Progression-free survival (PFS), time-to-progression (TTP), objective response rate (ORR), and clinical benefit rate (CBR) are secondary endpoints. Randomization is stratified by number of lines of prior chemotherapy (one vs. two or more), performance status (ECOG PS 0 vs. 1), and L-type sarcoma subtype (liposarcoma vs. leiomyosarcoma).

Eligible patients are randomly assigned in a 2:1 ratio to two treatment arms:

- Trabectedin: 1.5 mg/m² as 24-h IV infusion q3wk
- Dacarbazine: 1 g/m² as a 20-120 minute IV infusion q3wk

Patients randomized to the dacarbazine treatment group whose disease progresses are not permitted to receive trabectedin as subsequent therapy. Patients who discontinue treatment are followed for documentation of subsequent anticancer therapy and survival status. Collection of survival status continues until observation of approximately 376 deaths.

Assuming that the median OS is 10 months in the dacarbazine arm and 13.5 months in the experimental arm, 376 events from 570 patients are needed to detect a hazard ratio of 0.74 with 80% power at an overall 2-sided alpha level of 0.05. An interim analysis of OS will be performed when approximately 188 (50%) deaths have been observed. The final OS analysis will occur following the clinical cutoff of 376 death events. The O'Brien Fleming boundary method is utilized with respective alpha allocation of 0.003; the alpha allocation for the final analysis is 0.047. The unstratified log-rank test will be used to evaluate OS.

PFS and ORR are secondary endpoints, and PFS is defined as the time between randomization and disease progression (either radiographic progression or clinical progression) or death regardless of the cause of death, whichever occurs first. The final PFS analysis was planned to be conducted at the time of the interim OS analysis. Assuming that the median PFS is 2.5 months in the dacarbazine arm and 3.75 months in the trabectedin arm, a total of 331 PFS events from 500 patients are projected to detect a hazard ratio of 0.667 with at least 90% power at an overall 2-sided alpha level of 0.05. The analysis methods used to evaluate PFS are similar to those used to evaluate OS. Radiographic assessment of disease is performed by the investigator according to RECIST version 1.1 guidelines, every 6 weeks for the first 36 weeks on study and every 9 weeks.

The secondary endpoints PFS, TTP, ORR, and duration of response (DOR), will be based on investigator assessment, as no central independent review of radiographic imaging was pre-specified. Hochberg test procedure is proposed to adjust for multiplicity in testing the secondary endpoints of PFS, TTP, ORR, and clinical benefit rate (CBR).

Based on a suggestion by Dr. Richard Pazdur to share the mature PFS and RR results from the ET743-SAR-3007 study with FDA as a basis for possible accelerated approval, Janssen proposed a mechanism by which the IDMC could recommend that clinically compelling PFS and RR results, available at the time of the protocol-specified interim analysis for OS, be discussed with FDA. In a written response dated June 7, 2013, FDA recommended that if Janssen sought approval based on an analysis of PFS and ORR in an open-label trial, then an independent analysis of tumor-based assessments to determine tumor response should be conducted by an independent radiologic review committee (IRC) blinded to treatment assignment. FDA also suggested that Janssen may propose a detailed auditing plan that includes a strategy to minimize potential investigator assessment bias.

FDA reviewed the proposed audit plan and notified Janssen on February 18, 2014, that the plan was acceptable and stated that whether the proposal may introduce potential bias will be determined upon review of the NDA submission. FDA further requested that Janssen provide analyses of centers with < 9 patients (unaudited subset) versus ≥ 9 patients (audited subset) to show that the patients in the two groups are comparable. The audit plan was limited to radiographic PFS (rPFS).

On March 17, 2014, Janssen submitted an addendum to the original statistical analysis plan dated October 22, 2013, to utilize an independent radiologic assessment of response by an independent radiologist review blinded to treatment assignment. Symptomatic deterioration, in the absence of radiographic evidence of progression, will not be considered a disease progression event. Comparisons between radiographic progression-free survival (rPFS) based on investigator's radiologic assessments and rPFS based on independent radiologic review will be made using the audit methodology by Dodd et al.¹

Results

Per the independent radiology review, at the pre-specified OS interim analysis (cut-off date September 16, 2013), 518 (as stated on section 11.1.3.2) or 520 (as provided by Janssen on Slide 6 in the briefing document dated May 28, 2014) patients had been randomized with 189 death events and 329 PFS events including 16 PFS events based on symptomatic progressive disease.

¹ Dodd LE, Korn EL, Freidlin B, Gray R, Bhattacharya S. An audit strategy for progression-free survival. *Biometrics* 2011;67;1092–9.

The unstratified log-rank test p-value for OS comparison was 0.37. The median OS was 12.4 (95% CI: 11.2, 14.6) months for the trabectedin arm and 12.9 (95% CI: 7.8, 16.4) months for the dacarbazine arm. The unstratified HR was 0.87 with 95% CI (0.64, 1.18).

The log-rank test p-value for the final PFS comparison was <0.0001. The median PFS was 4.2 months for the trabectedin arm and 1.5 months for the dacarbazine arm. The unstratified HR was 0.55 with 95% CI (0.44, 0.70). Per response to FDA information request dated June 24, 2014,

the ORR is 10% in the trabectedin arm and 7% in the dacarbazine arm, and median duration of response was 6.5 months in the trabectedin arm (95% CI: 3.6, 7.6) and 4.2 months in the dacarbazine arm (95% CI: 2.1, NE).

As of April 15, 2014, 577 patients have been randomized with 530 discontinued treatment and 280 death events. Janssen provided the independent review charter and audit plan to the FDA for review.

2.0 OBJECTIVE

To discuss the audit results of the investigator-assessed progression-free survival (PFS) endpoint for Study ET743-SAR-3007 as assessed by independent radiologic review.

3.0 SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSES

1. Does the Agency agree that the results of the independent audit of the investigator-assessed PFS, conducted in accordance to the agreed upon plan (FDA communication 18 February 2014), validates the treatment effect of trabectedin as compared with dacarbazine at the time of the protocol-specified IA?

FDA response: Yes, the results of the independent audit of investigator-assessed PFS appear consistent with the results of the primary analysis of PFS; however, a determination that an independent audit sufficiently evaluates introduction of bias in an investigator-assessed PFS analysis would be made during review of an NDA submission.

Janssen's July 2, 2014, response: Janssen acknowledges FDA's response.

Discussion during the teleconference: No discussion occurred.

2. Does the Agency agree that the PFS and ORR results, at the time of the protocol-specified OS interim analysis of Study ET743-SAR-3007 can form the basis of an accelerated approval in this population of L-type sarcoma patients whose disease has progressed on available therapy?

FDA response: The results from Study ET743-SAR-3007 may be adequate to support a regulatory filing; however, whether a 2.7-month median improvement in PFS in the trabectedin arm over the dacarbazine arm will support a finding of effectiveness for trabectedin and demonstrate a positive benefit: risk assessment will be a review issue after the NDA submission.

Janssen's July 2, 2014, response: The Company acknowledges FDA's response. We would like to further emphasize that the 2.7 month median improvement in PFS in the trabectedin arm is against an active control arm and not placebo. All secondary endpoints are favorable with median duration of response of 6.5 months in the trabectedin treated patients. Consequently, these results are comparable to results discussed at ODAC on March 20, 2012 where committee members agreed with the value of a 3 month improvement in PFS in a similar patient population leading to a full approval for pazopanib based on a comparison to placebo treated patients in the absence of a statistically significant improvement in OS.

Discussion during the teleconference: FDA agreed that the effects of PFS are similar in in magnitude to a recent approval for treatment of STS and agreed that this result may support accelerated approval. Janssen acknowledged this response and no further discussion occurred.

3. Does the Agency agree that the totality of the data to be included at the final analysis, including clinical meaningful improvement in PFS and ORR along with demonstration of a survival trend favoring the trabectedin treatment group, could support full approval for this indication?

FDA response: The acceptability of PFS to serve as direct evidence of clinical benefit or evidence that is reasonably likely to predict clinical benefit depends on whether FDA concludes that the improvement in PFS is clinically meaningful, statistically persuasive, free from bias, and supports an acceptable risk-benefit profile. The summary provided in the meeting briefing document suggests that there is no detrimental effect on OS in patients treated with trabectedin in Study ET743-SAR-3007; however, conclusions concerning a beneficial effect of trabectedin on overall survival, if any, requires results of the pre-specified final analysis of OS.

FDA expects the totality of the data in an NDA submission will include clinical study reports for all studies conducted in patients with soft tissue sarcoma and for studies in other disease sub-types used to support the safety of trabectedin.

Janssen's July 2, 2014, response: ET743-SAR-3007 is an active controlled trial in a patient population where an overall survival been has not been demonstrated in previous randomized controlled studies. Given the results on PFS and the interim result on Overall Survival as of September 2013, it is likely that the final Overall Survival analysis will

show a positive trend (against an active comparator dacarbazine) that may not reach statistical significance. We respectfully request clarification on whether and how in the absence of a statistically significant improvement in overall survival, the totality of the data can support full approval for trabectedin. The Company proposes to include data from ET743-STS-201 which formed the basis of approval in the EU, and long-term survival data from the Expanded Access Study ET743-SAR-3002 to support a favorable benefit-risk profile of trabectedin for the treatment of relapsed/refractory L-type soft tissue sarcoma. [REDACTED] (b) (4)

[REDACTED]. The Company appreciates the Agency's input on other data sources and/or additional confirmatory studies that could potentially support the clinical benefit of trabectedin in relapsed/refractory L-type soft tissue sarcoma in the absence of a statistically significant overall survival benefit at the final analysis of the pivotal ET743-SAR-3007 study.

Discussion during the teleconference: FDA asked for clarification regarding the date/time frame of the proposed NDA submission. Janssen stated that a submission would be expected in November 2014 based upon the final analysis of PFS and updated data sweep of OS. Janssen expects to reach the final number of OS events in December 2014.

FDA agreed that the data package, as described above, could support accelerated or regular approval. FDA does not recommend additional analyses of single arm studies for OS such as the proposal to provide this information for the expanded access program.

In terms of regular approval, Janssen should provide justification based on results across the sarcoma program that this effect on PFS constitutes direct clinical benefit. Janssen will submit a pre-NDA meeting package as soon as possible. FDA agrees that if an NDA submission supports only accelerated approval, FDA will contact Janssen to discuss approaches to conversion during the NDA review cycle.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of the criteria apply at this time to your application, you are exempt from these requirements/ because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

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/s/

PATRICIA KEEGAN
07/21/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: June 23, 2014
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: IND 50286; Janssen Research and Development; Request for information

Dear Ms. Kolb,

Please refer to your investigational new drug application (IND) for the investigational product Yondelis.

Please provide the duration of response with the 95% CI and response rates for ORR, CR, and PR for study ET743-SAR-3007.

Please provide a response to the aforementioned request by 2:00 PM Tuesday, June 24, 2014. Your submission is still under review and additional comments and requests for information may be forthcoming.

If you have any additional questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
06/23/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 18, 2014
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: IND 50286; Barbara Kolb, Senior Director, Global Regulatory Affairs; Request for additional information

Dear Ms. Kolb,

Please refer to your investigational new drug application (IND) for the investigational product Yondelis.

Please also refer to your January 9, 2014, submission which provides the Division of Oncology Products 2 (DOP 2) with interim results for overall survival (OS), progression-free survival (PFS) and response rates from Study ET743-SAR-3007, "A Randomized Controlled Study of YONDELIS (Trabectedin) or Dacarbazine for the Treatment of Advanced Liposarcoma or Leiomyosarcoma."

We have reviewed your submission and have the following comment and request for information:

The proposed audit plan is acceptable; however, whether the proposal will introduce any potential bias will be determined upon review of the NDA submission. Additionally, please provide analyses of centers with < 9 patients versus ≥ 9 patients to show that the patients in the two groups are comparable. Note that symptomatic progression alone will not be considered a progression event, and whether a 2.7-month improvement in median PFS (1.5 months vs. 4.2 months) provides compelling evidence supporting an accelerated approval will be a review issue.

If you have any additional questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
02/18/2014



IND 50286

**MEETING REQUEST-
WRITTEN RESPONSES**

Janssen Research and Development, LLC
Attention: Kelly Johnson Reid
Associate Director, Global Regulatory Affairs
920 US Highway, Suite 202
Raritan, New Jersey 08869

Dear Ms. Johnson Reid:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Yondelis.

We also refer to your submission dated April 9, 2013, containing a Type C meeting request. The purpose of the requested meeting was to discuss the progression-free survival (PFS) and response rate (RR) data from Study ET743-SAR-3007 as a basis for possible accelerated approval.

Further reference is made to our Meeting Granted letter dated April 24, 2013, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your May 8, 2013, background package.

If you have any questions, call me at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Gina M. Davis, M.T.
Senior Regulatory Health Project Manger
Division Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation Research

Enclosure:
Written Responses

**WRITTEN RESPONSES
MEMORANDUM OF MEETING MINUTES**

Meeting Type: C – Written Responses Only
Meeting Category: IND
Application Number: 50286
Product Name: Yondelis
Indication: (b) (4)
Sponsor/Applicant Name: Janssen Research and Development, LLC

1.0 BACKGROUND

On April 9, 2013, Janssen Research and Development, LLC (Janssen) submitted a Type C meeting request with the Division of Oncology Products 2 (DOP 2) to discuss the possibility of accelerated approval for the investigational product Yondelis (b) (4)

Study ET743-SAR-3007, “A Randomized Controlled Study of YONDELIS (trabectedin) or Dacarbazine for the Treatment of Advanced Liposarcoma or Leiomyosarcoma” is an ongoing randomized, open-label, multi-center, parallel-group, active-controlled, phase 3 trial in 570 patients with unresectable, locally advanced or metastatic lipo-or leiomyosarcoma who were previously treated (in any order) with at least: a) an anthracycline and ifosfamide containing regimen or b) an anthracycline containing regimen and 1 additional cytotoxic chemotherapy regimen. The primary endpoint of the study is overall survival (OS). Progression free survival (PFS) and objective response rate (ORR) are secondary endpoints. Randomization is stratified by number of lines of prior chemotherapy (1 vs. 2 or more), performance status (ECOG PS 0 vs. 1), and sarcoma subtype (liposarcoma vs. leiomyosarcoma). Eligible patients are randomly assigned in a 2:1 ratio to two treatment arms:

- trabectedin: 1.5 mg/m² as 24-h IV infusion q3wk
- dacarbazine: 1 g/m² as a 20-120 minute IV infusion q3wk

Patients randomized to the dacarbazine treatment group whose disease has progressed are not permitted to receive trabectedin as subsequent therapy. Once patients discontinue treatment on the study they are followed for the use of subsequent anticancer therapy and survival status, every 60 days for the first 2 years after the last dose of study drug, and then every 90 days thereafter. Collection of survival status will continue until approximately 376 deaths have been observed, at which time clinical cutoff will occur.

The primary endpoint is overall survival (OS). Assuming that the median OS is 10 months in the dacarbazine arm and 13.5 months in the experimental arm, a total of 376 events are needed to detect a hazard ratio of 0.74 with 80% power at an overall 2-sided alpha level of 0.05. An interim

analysis of OS will be performed when approximately 188 (50%) deaths have been observed (anticipated September 2013). The final analysis of OS will occur following the clinical cutoff of 376 death events (anticipated timing 4th quarter 2014). The OBF boundary method is utilized with respective alpha allocation of 0.003; the alpha for the final analysis is 0.047.

Progression free survival and overall response rate (ORR) are the secondary endpoints. PFS is defined as the time between randomization and disease progression (either radiographic progression or clinical progression) or death regardless of the cause of death, whichever occurs first. The analysis methods used to evaluate PFS are similar to those used to evaluate OS. Radiographic assessment of disease is being performed by the investigator, according to RECIST Version 1.1 guidelines, every 6 weeks for the first 36 weeks on study and every 9 weeks thereafter, until either the documentation of disease progression, the subject begins subsequent anticancer therapy, the study ends, or the subject dies. Information regarding target lesions, non-target lesions, and new lesions is being collected at each assessment, and reviewed by Janssen R&D medical monitors, who are blinded to treatment arm, to verify investigator determination of disease response and/or progression. ORR is calculated as the number of objective responders (defined as having a "CR" or "PR" as best overall response) divided by the number of patients in the all randomized patients analysis set (for the primary analysis of ORR) or by the number of patients in the all evaluable subject analysis set (for the sensitivity analysis of ORR). ORR will be compared between the 2 treatment groups using the Fisher's exact test.

The secondary endpoints PFS, time-to-progression (TTP), ORR, and duration of response (DR), will be based on investigator assessment, as no central independent review of radiographic imaging is being performed. Hochberg test procedure is proposed to adjust for multiplicity in testing the secondary endpoints of PFS, time to progression (TTP), ORR, and clinical benefit rate (CBR).

As of 19 April 2013, 367 patients have been randomized, 257 patients have discontinued treatment and 101 death events have occurred. By the time of conducting the interim analysis of OS (when approximately 188 deaths have been observed), Janssen anticipates that there will be approximately 331 PFS events, and that approximately 500 subjects of the 570 subjects planned will have been enrolled in the study.

Yondelis was granted marketing authorization (MA) under "exceptional circumstances" by the EMA in 2007 for the treatment of patients with soft tissue sarcomas who have progressed after both anthracycline and ifosfamide treatment or for whom these treatments are unsuitable. Authorization under "exceptional circumstances" was based primarily on results in patients with liposarcoma or leiomyosarcoma enrolled in protocol ET743-ST5-201 entitled, "A Randomized Phase 2, Multicenter, Open-Label Study of Yondelis™, ET-743 (Ecteinascidine) Administered by Two Different schedules (Weekly for 3 or 4 weeks vs. q3 Weeks) in Subjects with Locally Advanced or Metastatic Liposarcoma or Leiomyosarcoma Following Treatment With an Anthracycline and Ifosfamide." The FDA considered this an exploratory study given limitations in design and conduct.

In 2009 another MA was issued in Europe for the combination of trabectedin with pegylated liposomal doxorubicin for the treatment of patients with platinum-sensitive relapsed ovarian

cancer.

(b) (4)

Yondelis is also available in a number of other countries for the treatment of advanced soft tissue sarcoma and relapsed ovarian cancer in combination with pegylated liposomal doxorubicin.

2.0 OBJECTIVE

- To discuss the recommendation by the Office of Hematology and Oncology Products that Janssen Research and Development, LLC request a meeting with DOP 2 to share the PFS and ORR results of the Phase 3 Study ET743-SAR-3007 as a basis for possible accelerated approval.

GENERAL COMMENT

FDA notes that the requested meeting is premature as the PFS and ORR results of the Phase 3 Study ET743-SAR-3007 are not available. Therefore, FDA expects that Janssen will request a pre-sNDA meeting at a time when summary results of key efficacy and safety endpoints are available and when formal agreement on the content and format of the sNDA can be reached.

3.0 SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSES

1. Janssen R&D appreciates the suggestion by Dr. Richard Pazdur to share the PFS and RR results from the Phase 3 Study ET743-SAR-3007. Janssen R&D is proposing a mechanism to share the PFS and RR results at the time of the interim analysis for OS. Janssen R&D would like to understand the FDA's considerations for obtaining an accelerated approval based on PFS and RR data and understand if these data along with the OS data (showing no decrement in OS) at the final analysis could lead to a full approval for trabectedin (b) (4). Janssen R&D would also like to consider the possibility of alternative options for full approval.

Does the Division agree that the investigator-assessed PFS and RR results at the time of the protocol-specified OS interim analysis of Study ET743-SAR-3007, if sufficiently compelling, could form the basis of an accelerated approval?

FDA response: If Janssen seeks approval based on the final analysis of PFS and ORR in an open-label trial, FDA strongly recommends that the analysis of tumor-based endpoints utilize disease status as determined by an independent radiologic review committee masked to treatment assignment. Alternatively, Janssen may propose a detailed auditing plan that includes a strategy to detect potential assessment bias and minimize selection bias. This auditing plan should include the percentage of patients to be audited, the method used to identify the subset of images to be audited, the method for comparing the PFS/ORR results obtained by local review with the PFS/ORR results of the audit, and the

criteria for determining whether all images need to be audited. All images should be archived and easily accessible. If bias cannot be excluded based upon the audit, then FDA will consider an independent evaluation of all radiographic images to be necessary for assessments of PFS and ORR.

Please provide the estimate power, medians and hazard ratio for PFS if the final PFS will be conducted at the time of conducting the OS interim analysis. In addition, please revise the statistical analysis plan (SAP) to provide a statistical procedure for the multiplicity in testing the secondary endpoints of PFS and ORR.

2. At the time of OS interim analysis, the Company anticipates that there will be approximately 331 PFS events and approximately 500 subjects of the 570 subjects planned will have been enrolled in the study. There are no other planned analyses of efficacy endpoints until the final analysis.

[REDACTED]
Does the Division agree that this would be appropriate?

FDA response: No. [REDACTED]

[REDACTED] his question may be reconsidered when the summary results for the final analysis of PFS, ORR, and response duration are available.

3. Given the unmet medical need in this patient population, if the PFS and RR at the time of OS interim analysis are considered by the FDA for a potential accelerated approval (following the Division's review) and clinical equipoise cannot be maintained, the Company proposes that the protocol be amended to offer subjects randomized to the comparator arm the option to receive trabectedin, while continuing the study for the collection of safety and survival data. If the study results for PFS and RR, at the time of the OS interim analysis, are submitted for accelerated approval, Janssen R&D would continue to follow all subjects for OS until the pre-planned final analysis.

Given that crossover may impact the potential to demonstrate an OS advantage, would providing the OS data from the final analysis, demonstrating no decrement in OS, be considered sufficient for full approval?

FDA response: No. FDA believes that clinical equipoise can be maintained in a setting where the effect on the ultimate clinical outcome (improvement in OS) has not been demonstrated. Therefore, if FDA determines that the preliminary results of Study ET743-SAR-3007 would support only accelerated approval the protocol should not be amended but completed as planned.

While evidence that there is no detrimental effect on survival for patients treated with trabectedin would support the risk assessment at the time of accelerated approval, an improvement in OS would need to be demonstrated in order to support regular approval.

4. At the time of the NDA filing on the basis of PFS, if the protocol is amended to offer an option to the subjects who are randomized to the comparator arm to be crossed-over to the trabectedin arm and continue the study for OS analysis, the Company proposes to submit these data, demonstrating no decrement to OS, to support converting the accelerated approval to a full approval.

If the combined results of PFS and RR are compelling and an OS trend is observed, at the time of the protocol-specified interim analysis, could these results support a full approval?

FDA response: The question is premature and should be re-visited at the time of the pre-NDA meeting. The pre-meeting package for the pre-NDA meeting should contain the top-line results of the interim analysis of OS, the final analysis of PFS and the final analysis of ORR.

5. Due to the rarity and complexity of this disease, there have been few Phase 3 studies in STS, none of which have demonstrated an OS advantage including the recent approval of pazopanib. Once equipoise is not maintained based on superiority of the efficacy data and the subjects are allowed to crossover, interpretation of OS can be confounded due to the effective subsequent therapy for subjects in both treatment arms. Given this context, we would seek the FDA's consideration on attaining a full approval, if the combined results of PFS and RR are compelling and an OS trend is observed.

Does the Division agree with Janssen R&D's proposed process to share the PFS and RR data from the interim analysis with the FDA?

FDA response: See FDA response to question #4.

6. Does the Division agree with the proposed amendment to the IDMC charter?

FDA response: FDA notes that the trial is an open-label study. However, the proposed amendment to the IDMC Charter for dissemination of the top-line results "At the time of the interim analysis, the IDMC can share unblinded data (ie. OS, PFA, and RR data) with the Sponsor Committee for the purpose of sharing the data with the FDA" is acceptable.

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/s/

GINA M DAVIS
06/07/2013

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Purpose: To discuss the clinical development plan [REDACTED] (b) (4)

Meeting Date and Time: November 23, 2010
Meeting Location: FDA White Oak 22/Room 1415

Application Number: IND 050286
Product Name: Yondelis (trabectedin)
Indication: [REDACTED] (b) (4)

Sponsor/Applicant Name: Johnson & Johnson
FDA Division: Division of Drug Oncology Products (DDOP)
Meeting Request Date: August 2, 2010
Meeting BGP Date: October 21, 2010
FDA Prelim Response Date: November 18, 2010

Meeting Chair: Ke Liu, M.D., Ph.D.
Meeting Recorder: Alice Kacuba, RN, MSN, RAC

FDA ATTENDEES

Robert L. Justice, M.D., M.S., Director, DDOP
Amna Ibrahim, M.D., Deputy Director, DDOP
Ke Liu, M.D., Ph.D., Medical Team Leader, DDOP
Amir Shahlaee, M.D., Medical Reviewer, DDOP
Shenqhui Tang, Ph.D., Statistical Team Leader, OTS/Office of Biometrics/DBV
Casey Xu, Ph.D., Statistical Reviewer, OTS/Office of Biometrics/DBV
Jim McVey, Ph.D., Microbiology Reviewer, Office of Pharmaceutical Sciences, NDMS
Theresa Ferrara, B.S., Regulatory Project Manager, DDOP
Alice Kacuba, RN, MSN, RAC, Chief, Project Management Staff, DDOP

SPONSOR ATTENDEES

Johnson & Johnson

Rick Jansson, Ph.D., Senior Director, J&JPRD, Compound Development Team Leader
Sen Zhuang, M.D., Senior Director, J&JPRD, Clinical Leader
Trilok Parekh, Ph.D., Director, J&JPRD, Project Scientist
Ana Aymes, Pharm.D., Director, J&JPRD, Project Scientist

[REDACTED] (b) (4)
Bruce Chabner, Clinical Director, Board Member, MGH Cancer Center, Pharma Mar, S.A.
Craig Tendler, M.D., Vice President, J&JPRD
Youn Park, Ph.D., Director, J&JPRD, Statistical Leader
Robert White, Director, Global Technical Support

John Seaman, Pharm.D., Senior Director, J&JPRD, Global Regulatory Leader
Kelly Johnson Reid, M.S., Associate Director, J&JPRD, Regulatory Affairs
Terri Williams, Ph.D., Manager, J&JPRD, Regulatory Affairs
Pam Martin, Manager, J&JPRD, CMC Regulatory Affairs
Dawn Kracht, Director, J&JPRD, CMC Regulatory
Virginia Cuervo, Vice President, Pharma Mar, Regulatory Affairs

Background: Trabectedin is a novel tetrahydroisoquinoline compound derived from the Caribbean tunicate *Ecteinascidia turbinata*. The sponsor's primary objective for this meeting is to gain the FDA's feedback on the proposed clinical development plan of trabectedin (b) (4)

This meeting will specifically address the design of the proposed Phase 3 study ET743-SAR-3007. ET743-SAR-3007, which is a randomized, open-label, active-controlled, parallel-group, multicenter study comparing the safety and efficacy of trabectedin with dacarbazine in adults with unresectable, locally advanced or metastatic L-sarcoma who were previously treated with anthracyclines and ifosfamide. In addition the sponsor would like to discuss restricting enrollment of patients with L-sarcoma to the currently active expanded access protocol, ET743-SAR-3002, in order to optimize recruitment of eligible patients to the ET743-SAR-3007. The sponsor would also like to identify any additional information necessary to support a marketing application for this indication.

Question 1

Study Design- ET743-SAR-3007. This is a randomized, open-label, active-controlled, parallel-group, multicenter study comparing the safety and efficacy of YONDELIS with dacarbazine (DTIC) in adults with unresectable, locally advanced or metastatic L-sarcoma, who were previously treated with anthracyclines and ifosfamide. The purpose of the study is to determine whether YONDELIS treatment increases overall survival in comparison to patients treated with DTIC. Approximately 570 subjects who satisfy all inclusion and exclusion criteria will be randomly assigned in a 2:1 ratio to either YONDELIS (n=380) or DTIC (n=190) treatment groups. At the time of randomization, subjects will be stratified by the number of lines of prior chemotherapy (1 versus 2 or more), Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), and L-sarcoma subtype (liposarcoma versus leiomyosarcoma). Sample Size Justification: It was assumed that the hazards for the 2 treatment groups follow a proportional hazards model for OS. The test to detect a difference between a median OS of 10 months in the DTIC group and a median OS of 13.5 months in the YONDELIS group (HR=0.74) at the 2-tailed significance level of 0.05 with a power of 80% would require 376 events. Assuming an enrollment rate of 25 subjects per month over 23 months, a total sample size of approximately 570 subjects is planned for the study. More details can be found in Protocol ET743-SAR-3007. The OS endpoint will incorporate group sequential design by including 1 interim analysis and 1 final analysis using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method. This method ensures that the type I error rate is not inflated. The interim analysis is planned at 50% of the required number of events. The cumulative alpha spent will be 0.003 and 0.050 for the 2 analyses, respectively. This study is anticipated to reach the primary endpoint (OS) in approximately 32 months. Additional details can be found in the Protocol ET743-SAR-3007 statistical analysis plan (SAP).

Does the Division agree with the proposed study design?

FDA response: Your proposed superiority design with OS as the primary endpoint is acceptable.

- 1. Please clarify whether this proposed population will include both refractory (progressing on current therapy) and relapsed patients.**
- 2. Please clarify if patients who progress on the control will be allowed to cross over to the active treatment arm.**

Meeting discussion: The sponsor clarified that patients with refractory disease on previous regimens are eligible for the study. Patients will not be allowed to cross over to Yondelis arm.

Question 2

Comparator- Choice of Dacarbazine: Dacarbazine 1000mg/m² iv every 3 weeks was chosen as the control for the study because DTIC is considered the third most active drug behind doxorubicin and ifosfamide in the treatment of STS ([Gottlieb 1976](#), [Buesa 1991](#)) and it is also recommended treatment option by experts and guidelines for STS after failure of anthracyclines and ifosfamide ([NCCN 2009](#), [Pazdur 2009](#)). The commonly used DTIC dosing schedules range from 750-1200 mg/m² every 3 week.

- a) Does the Division agree with the choice of DTIC as the comparator?

FDA response: Please clarify why you are not using the regimen of gemcitabine/docetaxel as the control. Will US investigators agree to use DTIC as a control in the population? Please clarify clinical trial geographical locations.

Meeting discussion: The sponsor provided the rationale for use of DTIC as a control regimen. It is expected that the majority of patients in the US will have received previous therapy with gemcitabine +/- docetaxel as 1st or 2nd line therapy. Patients will be stratified based on previous lines of therapy. FDA agrees that use of DTIC is an acceptable comparator. The sponsor clarified that they expect more than 50% of patients to be enrolled from the US.

- b) Is the proposed dose and schedule of the control group acceptable?

FDA response: Yes. Also see response to Question 2a above.

Question 3

Review of Histologic Diagnosis: The concordance of L-type sarcoma histologic diagnosis is high between the investigator site and central review determination. A retrospective central histologic review was conducted for Study ET743-ST-201. Among the patients with available samples (>85% of all enrolled patients), over 90% of the patients had confirmed L-type sarcoma ([Clinical Study Report ET-743-201 ROW 2007](#)).

To ensure that only subjects with L-type sarcoma are enrolled in the ET743-SAR-3007 registration study, a pathologic report indicating a diagnosis of leiomyosarcoma or liposarcoma will be required to be submitted to and reviewed by the Sponsor for confirmation prior to randomization. The study will also prospectively collect pathology samples (tumor slides) from all randomized subjects. These samples can be used to review histologic diagnosis retrospectively if deemed necessary. Does the Division agree that this process is acceptable?

FDA response: This is acceptable. You must demonstrate an improvement on OS in ITT population.

Question 4

Acceptability for Regulatory Approval: Overall survival was selected as the primary endpoint in this study for assessment of treatment effect. Does the Division agree that if the study meets the primary objective of demonstrating superiority of YONDELIS over DTIC in terms of OS as specified in the protocol, the data will be sufficient for regulatory submission to be considered for approval?

FDA response: This will be a review issue.

Question 5

Study ET743-SAR-3002 - Mechanism for Expanded Access: Study ET743-SAR-3002, titled “A Multicenter, Open-Label Single Arm Study of YONDELIS (trabectedin) for Subjects with Locally Advanced or Metastatic Soft Tissue Sarcoma Who Have Relapsed or are Refractory to Standard of Care Treatment” was originally submitted to the IND on 01 August 2005, Serial No. 385. In November 2009, the FDA was notified that J&JPRD planned to close the Study ET743-SAR-3002 to help mitigate the impact on the clinical development of YONDELIS. It was identified that should the investigator feel a patient was benefiting from treatment, J&JPRD suggested that the investigator request a single patient IND through the FDA. After subsequent discussions and correspondence with the Division (17 December 2009; 18 December 2009; 11 January 2010; 28 January 2010; 2 February 2010), J&JPRD decided to re-open the ET743-SAR-3002 study. The objective of the ET743-SAR-3002, EAP, is to provide patient’s with temporary access to safe and appropriate YONDELIS treatment for STS until the drug is commercially available. The continuation of the current EAP with the start of a Phase 3 registration study (ET743-SAR-3007) would incur significant operational and technical risks to the registration study. For example, the difference in survival between the 2 groups may be significantly decreased due to the availability YONDELIS to DTIC-treated patients under the current EAP. Consistent with the FDA EAP guidelines, the final rule is intended to improve access to investigational drugs for patients with serious or immediately lifethreatening diseases or conditions who lack other therapeutic options and who may benefit from such therapies while not impeding the clinical development of the investigational drug that is being made available for treatment use. ([Federal Register / Vol. 74, No. 155 / Thursday, August 13, 2009 / Rules and Regulations](#)). Therefore, the Sponsor proposes to limit ET743-SAR-3002 to only patients with non L-sarcoma. Does the Division agree with our proposal to amend the EAP Study ET743-SAR-3002 to include only non-L-sarcoma subjects?

FDA response: Yes. However, please consider continuing the EAP for patients ineligible for the proposed clinical trial.

Question 6

The current infusion times for the STS indication will be 24 hours. (b) (4)

[Redacted]

Does the Division agree (b) (4)
?

FDA response: No. (b) (4)

[Redacted]

Meeting discussion: The sponsor provided the following two slides attached below and discussed the clinical and CMC rationale for the current approach. At this point the sponsor will proceed with the randomized study and information regarding infection/sepsis will be gathered prospectively. This information will be reviewed during the trial and at the time of submission of NDA. The FDA stated that the study can proceed; however, the sponsor should consider these points concerning infections.

Additional Comments:

1. The proposed study, ET743-SAR-3007, only includes patients (b) (4) Please consider revising the eligibility criteria such that patients > 15 years of age are eligible.
2. We recommend that you collect sparse pharmacokinetic samples from all patients that are treated with trabectedin in your Phase 3 trial to explore exposure-response relationship for efficacy and safety.

4.0 ACTION ITEMS

None.

5.0 ATTACHMENTS AND HANDOUTS

Two handouts used by Johnson & Johnson at the meeting.

Meeting Chair

{See appended electronic signature page}

Ke Liu, M.D., Ph.D.

Meeting Recorder

{See appended electronic signature page}

Alice Kacuba, RN, MSN, RAC

Efficacy Data 24 hr vs 3 hr Infusion Schedules

	ET-B-022-00 [®]	ET743-STS-201 [*]	
	q3wk 3-h n=68	qw 3-h n=134	q3wk 24-h n=136
Overall RR (%)	1.5	1.5	5.1
Median PFS, months	1.6	2.3	3.3 ^{**}
Progression-free rate at 6 months (%)	11.5	27.5	35.5
Median OS, months	10.1	11.8	13.9

[®]: Investigator assessed, ^{*}: Independent Review, ^{**}: p=0.0418; HR: 0.755,

1

Safety Data – Sepsis & Related Terms

- STS-201 randomized study 3 hr (n=130) vs. 24 hr (n=130)
 - 3 reports of sepsis in 24 hr (c1 d17; c2 d17; c5 d14)
 - 1 report of sepsis in 3 hr (c6 d8)
- Additional Phase 2 clinical data (n=297):
 - 2 reports of sepsis (<1%)
- SAR-3002 EAP STS program-
 - 1803 patients all treated on 24 hour infusion schedule
 - 52 reports of sepsis or related terms (2.9%)
- Post-marketing surveillance experience
 - 26,120 cycles in post-marketing patients
 - 12 reports of sepsis in STS

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/s/

KE LIU
11/30/2010

LATE-CYCLE COMMUNICATION
DOCUMENTS

Internal Late Cycle Meeting (LCM) Meeting Summary
9/14/2015

NDA: 207953- Type 1 New Molecular Entity
eCTD submission: SDN 001

Product: trabectedin, powder for reconstitution, 1 mg, intravenous
Proposed Proprietary Name: YONDELIS
Submission Date: November 24, 2014
Received Date: November 24, 2014
Applicant: Janssen Products, LP (Janssen)

Proposed Indication:

(b) (4)

Attendees:

Richard Pazdur, Patricia Keegan, Monica Hughes, Anuja Patel, Marc Theoret, Amy Barone, Dow-Chung Chi, Kun He, Huanyu Chen, Hong Zhao, Whitney Helms, Dubravka Kufirin, Tamara Johnson, Olen Stephens, Robert Wittorf, Lauren Iacono-Connor, Latonia Ford, Nazia Fatima, Otto Townshend, Naomi Redd, Idara Udoh

Review Status:

- All reviews completed and in DARRTS except for Clinical Pharmacology and Clinical

Discussion:

The team discussed items that will be included in the LCM Briefing Background. The Briefing Background template was prepared by RPM and placed on SharePoint for team review and edits following this meeting. Our Briefing Package (including our Final Late Cycle Meeting Agenda) for this Late Cycle meeting is due to applicant–**September 21**

1. Discipline Review Letters-

Discussion: No Discipline Review Letters have been issued

2. Substantive Review Issues (by discipline)

Discussion: There were no substantive issues identified by the review team.

3. Discussion of Minor Review Issues

- Clinical
- Pharm/Tox- *No issues; Review in DARRTS*
- Clinical Pharmacology- *No issues; Review in DARRTS*
- Chemistry, Manufacturing and Control (CMC)- *No issues; Review in DARRTS*

Discussion: Clinical will add two items to the LCM meeting background.

4. Advisory Committee Meeting

- An Advisory Committee meeting is not planned however, 1 Patient Rep with an expertise in advanced soft tissue sarcoma (STS) will be consulted with regard to aspects of the trabectedin application.

Discussion: SGE Background to be sent this week and tcon to be scheduled in 2 weeks (pending SGE availability)

5. REMS or other Risk Management Issues

Discussion: no REMS and no issues from DRISK

6. Postmarketing Requirements/Postmarketing Commitments

- Clinical
- Pharm/Tox
 - No PMRs/No PMCs- *No PMRc*
- Clinical Pharmacology
 - No PMRs/No PMCs
- Chemistry, Manufacturing and Control (CMC)
 - No PMRs/No PMCs

Discussion: One clinical PMR was identified for cardiomyopathy. The team agreed that since PMR/PMC language will need to be vetted through the DDS and SRT, all PMR/PMCs will need to be captured in the PMR template found on SharePoint via link below no later than September 18th

Post Meeting follow-up: A clinical pharmacology PMR for hepatic impairment that was discussed during the pNDA meeting was communicated to Janssen on September 25, 2015.

7. Major labeling issues

- SCL planned to be sent to Janssen September 14, 2015 and to Press and OMPP and OPDP at same time

Discussion: Inform Janssen that they should come prepared to discuss FDA labeling that is to be sent September 14, 2015 during the late cycle meeting.

8. OSI Summary of Inspections - Lauren Iacono-Connor (TL: Susan Thompson)

Discussion: No issues. OSI review is complete and in DARRTS

9. Manufacturing Facility Inspections Summary – Olen Stevens/Robert Wittorf

Discussion: No issues from inspections standpoint.

10. Review Plans to be communicated to Applicant during LCM – *Reviews are ongoing*

11. Upcoming Meetings

Discussion: The team was informed that the Late Cycle Meeting format was a teleconference and that the internal Wrap Up meeting was scheduled for October 5, 2015.

12. Revised Timeline with 3 Month Extension (Priority Review)- updated 9/11/15

Milestone	New PDUFA Goal Date as a result of Major Amendment (generated from Panorama)
Application Received	Monday, November 24, 2014
Acknowledgment Letter	Issued December 7, 2014
Planning/Filing Meeting (Day 45)	Planning/Kickoff Meeting held Thursday, December 11, 2014 Filing meeting held Thursday, January 8, 2015
Review Designation letter (Day 60)	Issued January 24, 2015
Deficiencies Identified Letter (74 Day Letter)	Issued February 5, 2015
Hold Mid-Cycle Communication to Sponsor	Teleconference Held Thursday, April 23, 2015
Send proposed labeling/PMR/PMC/REMS to applicant (with 1 week response)	Wednesday, July 29, 2015 SCL with Sections 5 and 6 Planned Issue Date: September 14, 2015 <i>No PMR/PMCs identified by disciplines as of 9/11/15 (SCL will also be sent to OPDP and Pt./ Labeling with comments requested in 2 week since priority NDA)</i>
Late Cycle Meeting (LCM) with Applicant	TCON confirmed for September 28, 2015
Begin Labelling Discussions with Applicant	Wednesday, August 5, 2015 Ongoing

Wrap Up Meeting	Confirmed for October 5, 2015	
<p>Review Target Due Dates:</p> <p><i>Primary Review Due</i></p> <p><i>Secondary Review Due</i></p> <p><i>CDTL Review Due (4 weeks prior to action)</i></p> <p><i>Division Director Review Due (1.5-3 weeks prior to action)</i></p> <p><i>Office Director Review Due/Sign-Off (0-1.5 weeks prior to action)</i></p>	<p>extended to May 15, 2015 <i>(Actual: Monday, July 27, 2015)</i></p> <p>** Issue Disciplinary Review letters 3 days after Primary reviews: Thursday, July 30, 2015</p> <p style="text-align: center;">Thursday, July 30, 2015</p> <p style="text-align: center;">Tuesday, September 29, 2015</p> <p style="text-align: center;">Wednesday, October 14, 2015</p> <p style="text-align: center;">Friday, October 23, 2015</p> <p><i>(Actual PDUFA: Saturday, October 24, 2015)</i></p>	<p><i>Adjusted Due Dates for Clinical Primary Reviews:</i></p> <p><i>Clinical: Primary review due July 27, 2015</i> <i>In DARRTS no later than September 30, 2015 or sooner</i></p> <p><i>In DARRTS no later than September 30, 2015 or sooner</i></p> <p><i>In DARRTS no later than September 30, 2015 or sooner</i></p> <p style="text-align: center;">Wednesday, October 14, 2015</p> <p style="text-align: center;">Friday, October 23, 2015</p>
Compile and circulate Action Letter and Action Package (3 weeks prior to action)	Monday, September 28, 2015	<p>*Prepare to circulate earlier once reviews are in DARRTS <i>Binder will circulate week of September 14th</i></p>
FINAL Action Letter Due	<p>3 Month Extended PDUFA Goal Date: Friday, October 23, 2015 <i>(Actual: Saturday, October 24, 2015)</i></p>	

APPEARS THIS WAY ON ORIGINAL



Discussion: The review team agreed to the timeline above. Any updates to the timeline will be communicated by the RPM via email.

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/s/

ANUJA PATEL
10/18/2015



NDA 207953

LATE-CYCLE MEETING MINUTES

Janssen Products, L.P.
c/o Janssen Research & Development, LLC
Attention: Barbara Kolb, Senior Director, Global Regulatory Affairs
920 U.S. Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Kolb:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Yondelis (trabectedin), injection for intravenous use, 1 mg powder.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on September 28, 2015.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Anuja Patel, Senior Regulatory Project Manager at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Marc Theoret, M.D.
Cross Discipline Team Leader (CDTL)
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: September 28, 2015; 12:00 P.M. to 1:00 PM, EST
Meeting Location: Teleconference

Application Number: NDA 207953
Product Name: trabectedin
Proposed Indication:



Sponsor/Applicant Name: Janssen Products, L.P.
Meeting Chair: Marc Theoret
Meeting Recorder: Anuja Patel

FDA ATTENDEES

Richard Pazdur, M.D. Director, OHOP
Patricia Keegan, M.D., Director DOP2
Monica Hughes, M.S., Chief, Project Management Staff, DOP2
Anuja Patel, M.P.H., Senior Regulatory Health Project Manager
Marc Theoret, M.D., Clinical Team Leader, CDTL
Amy Barone, M.D., Medical Officer, Efficacy Review
Dow-Chung Chi, M.D., Medical Officer, Safety Review
Kun He, Ph.D., Statistics, Team Leader (TL)
Hong Zhao, Ph.D., Clinical Pharmacology (TL)
Whitney Helms, Ph.D., Non-Clinical (TL)
Dubravka Kufirin, Non-Clinical Reviewer
Olen Stephens, Ph.D., ONDQA Application Team Lead (ATL)
Latonia Ford, RN, BSN, MBA, Safety Regulatory PM, OSE
Nazia Fatima, OPDP Reviewer
Sharon Mills, Patient Labeling Reviewer
Miriam Dinatale, D.O., LCDR, USPHS, Maternal Health reviewer

EASTERN RESEARCH GROUP ATTENDEES

Christopher Sesi, Independent Assessor

APPLICANT ATTENDEES

Craig Tendler, M.D., Vice President, Late Development and Global Market Affairs
Trilok Parekh, Ph.D., Compound Development Team Leader
Roland Knoblauch, M.D., Ph.D., Clinical Development Leader
Sharon McCarthy, Clinical Project Scientist
Loreta Marquez, M.D., Global Medical Safety Leader
Sandra Rattray, Ph.D., Vice President, Global Regulatory Affairs, Oncology
Hemal Morjaria, Global Regulatory Leader, Oncology
Barbara Kolb, North America Regulatory Head, Oncology
Ronald Szumigala, M.S., North America Regulatory Leader
Dawn Kracht, Director, Global CMC Regulatory Affairs
Surya Mohanty, Ph.D., Clinical Biostatistics Head
Youn Choi Park, Ph.D., Statistical Leader
Chi Keung, Ph.D., Clinical Pharmacology Leader
Ana Irigaray, PharmD., Regulatory Affairs Director – PharmaMar
Sonia Vela, Global Alliance Manager – PharmaMar

BACKGROUND

- Janssen Products, LP, submitted NDA 207953 on November 24, 2014, for Yondelis (trabectedin), for injection, for intravenous infusion, 1 mg lyophilized powder in single-dose vial for reconstitution.
- On May 1, 2015, FDA issued a Review Extension-Major Amendment letter with an extended PDUFA goal date of October 24, 2015.
- Proposed indication(s):  (b) (4)
- FDA issued a Background Package in preparation for this meeting on September 24, 2015.

DISCUSSION

Introductory Comments

Welcome, Introductions, Ground rules, Objectives of the meeting

Discussion: FDA informed Janssen that the purpose of the late cycle meeting was to exchange information and to inform Janssen of the status of the review. FDA provided ground rules for the discussion as provided in the Late Cycle Meeting Background Package that issued September 24, 2015. Janssen acknowledged the ground rules and no additional discussion occurred.

Discussion of Minor Review Issues

Each issue will be introduced by FDA and followed by a discussion.

a. Clinical

- Confirm that there are no additional data on LVEF assessments, ECG, and vital signs that have not already been submitted.

Discussion: Janssen confirmed that there is no additional data on LVEF assessments, ECG, and vital signs that have not already been submitted. Janssen also confirmed that these data are captured in the datasets at baseline. Otherwise, abnormalities based on assessments of LVEF, ECG, and vital signs would have been reported as adverse events.

- Confirm that there is no additional data entry backlog at any of the sites that has been or will be completed and that will have affect the submitted datasets in the 120-Day Safety update.

Discussion: Janssen confirmed that there is no additional data entry backlog at any of the sites that has been or will be completed and that will have affect the submitted datasets in the 120-Day Safety update.

Discussion of Upcoming Advisory Committee Meeting

Discussion: FDA stated that an Advisory Committee meeting is not planned; however, a special government employee (SGE)s with an expertise in sarcoma was consulted with regard to aspects of the trabectedin application.

REMS or Other Risk Management Actions

Discussion: FDA stated that no issues related to risk management have been identified to date and no REMS is planned.

Discussion of Postmarketing Requirements/Postmarketing Commitments

- a. Proposed Clinical Postmarketing Requirement (PMR)
- FDA acknowledges receipt of Janssen's amendment dated and received September 21, 2015, containing Janssen's response to the following PMR communication that issued via email on September 16, 2015:

Submit integrated safety analyses and supporting data from an adequate number of clinical trial(s) to characterize the risk of cardiomyopathy and its sequelae in patients receiving trabectedin, to identify risk factors for development of these sequelae, and to support labeling instructions for dose modification and monitoring. The design of the trial should include a patient population with previous exposure to anthracyclines and have sufficient cardiac monitoring to achieve these objectives.

PMR/PMC Schedule
Milestones:

Final Protocol Submission Date:	_____
Study/Clinical Trial Completion Date:	_____
Final Report Submission Date:	_____
Interim Report Submission Date:	_____

Discussion:

Janssen proposed a prospective observational study in patients who are treated according to the USPI. The study would evaluate relevant medical history as well as cardiac monitoring at baseline and during treatment with trabectedin. FDA expressed concern about the ability to collect data of sufficient quality to achieve the goals of the PMR. (b) (4)



b. Proposed Clinical Pharmacology PMR

Complete the ongoing clinical pharmacokinetic trial to determine an appropriate dose of Yondelis in patients with moderate to severe hepatic impairment in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

PMR/PMC Schedule Milestones:

Final Protocol Submission Date:	_____
Study/Clinical Trial Completion Date:	_____
Final Report Submission Date:	_____
Other:	_____

Discussion: Janssen acknowledged FDA’s PMR request to provide the report from the clinical pharmacokinetic (PK) trial of YONDELIS in patients with moderate to severe hepatic impairment. Janssen stated that ET743-OVC-1004 “An Open-Label, Multicenter, Pharmacokinetic Study of Trabectedin in Subjects with Advanced Malignancies and Hepatic Dysfunction” was designed to characterize the pharmacokinetics (PK) of trabectedin in subjects with advanced malignancies and hepatic dysfunction. The secondary objectives of this study were to assess survival and the safety of trabectedin when administered in subjects with hepatic dysfunction. Janssen referred to the October 17, 2014, pre-NDA meeting discussion and subsequently, the February 2, 2015, Information Request Response (Sequence No. 0011). As discussed with FDA, the enrollment to ET743-OVC-1004 was terminated on January 28, 2015. Janssen agreed to this PMR and proposed the milestone date of January 28, 2016, for the final study report submission. FDA agreed to this proposed milestone date for the final study report submission.

Discussion of Major Labeling Issues

- FDA acknowledges receipt of Janssen’s amendment dated and received September 23, 2015, containing Janssen’s revised labeling in response to additional FDA modifications to the package insert sent via e-mail on September 17, 2015. FDA proposes discussing Janssen’s September 23, 2015, labeling amendment during the late cycle meeting. Janssen’s response document and revised red-lined, tracked changes version of labeling submitted September 23, 2015, will be referenced during the late cycle meeting and is attached.
- An additional teleconference has been scheduled (tentatively) for October 2, 2015, from 8:30 A.M. to 9:30 A.M, EST., to discuss sections of labeling not covered during the late cycle meeting. On September 23, 2015, Janssen confirmed their availability for the October 2, 2015 teleconference.

- FDA acknowledges receipt of the amendment dated and received on September 18, 2015, containing Janssen's final draft carton and container label. FDA has no further comments on the carton and container labeling at this time.

Discussion: Janssen and FDA discussed the following CMC and clinical pharmacology sections of the Package Insert and reached agreement on the following sections:

- 2.4 Preparation for Administration
- 8.6 Hepatic Impairment
- 12.3 Pharmacokinetics

FDA stated that clinical sections of the PI were still pending clinical review of Janssen's September 23, 2015 amendment and would be discussed during the October 2, 2015 teleconference. In addition, the review team informed Janssen that FDA modified labeling would be sent to Janssen prior to the October 2, 2015, teleconference to assist in facilitating the discussion.

Discussion of Review Plans

Discussion: Janssen inquired whether there were any changes to the planned review timeline. FDA referred Janssen to Major Amendment letter that issued May 1, 2015, informing Janssen that the extended user fee goal date is October 24, 2015. FDA stated that a Press Release and (b) (4) are planned and the Office of Hematology and Oncology Products would communicate the draft (b) (4) to provide Janssen an opportunity to review prior to action.

Discussion of Other Items

Discussion: No other items were discussed.

Wrap-up

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and, therefore, this meeting did not address the final regulatory decision for the application.

Action Items

- Janssen will submit proposed milestone dates for the clinical pharmacology postmarketing requirement.
- Janssen will submit a proposal for a study intended to fulfill the clinical postmarketing requirement as well as the milestone dates for this postmarketing requirement.

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/s/

ANUJA PATEL
10/09/2015

MARC R THEORET
10/11/2015



NDA 207953

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Janssen Products, L.P.
c/o Janssen Research & Development, LLC
Attention: Barbara Kolb, Senior Director, Global Regulatory Affairs
920 U.S. Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Kolb:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Yondelis (trabectedin), injection for intravenous use, 1 mg powder.

We also refer to the Late-Cycle Meeting (LCM) scheduled for September 28, 2015 (teleconference). Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Ms. Anuja Patel, Senior Regulatory Project Manager, at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products

ENCLOSURE:

- Late-Cycle Meeting Background Package
- Janssen's September 21, 2015 Amendment containing response to FDA September 16, 2015 PMR Communication
- Janssen's September 24, 2015 Amendment containing revised labeling and response document in response to FDA additional modifications to package insert issued September 17, 2015

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: September 28, 2015; 12:00 P.M. to 1:00 PM, EST
Meeting Location: Teleconference

Application Number: NDA 207953
Product Name: trabectedin

Proposed Indication:



Sponsor/Applicant Name: Janssen Products, L.P.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

Discipline Review Letters

No Discipline Review letters have been issued to date and none are expected at this time.

Substantive Review Issues

There are no substantive review issues at this time.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned; however. A special government employee (SGE)s with an expertise in sarcoma was consulted with regard to aspects of the trabectedin application.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LATE CYCLE MEETING (LCM) AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Minor Review Issues – 5 minutes

Each issue will be introduced by FDA and followed by a discussion.

a. Clinical

- Confirm that there are no additional data on LVEF assessments, ECG, and vital signs that have not already been submitted.
- Confirm that there is no additional data entry backlog at any of the sites that has been or will be completed and that will have affect the submitted datasets in the 120-Day Safety update.

3. Postmarketing Requirements (PMR)/Postmarketing Commitments (PMC) – 10 minutes

a. Proposed Clinical PMR

- FDA acknowledges receipt of Janssen's amendment dated and received September 21, 2015 containing Janssen's response to the following PMR communication that issued via email on September 16, 2015:

Submit integrated safety analyses and supporting data from an adequate number of clinical trial(s) to characterize the risk of cardiomyopathy and its sequelae in patients receiving trabectedin; to identify risk factors for development of these sequelae; and to support labeling instructions for dose modification and monitoring. The design of the trial should include a patient population with previous exposure to anthracyclines and have sufficient cardiac monitoring to achieve these objectives.

PMR/PMC Schedule

Milestones:

Final Protocol Submission Date:	_____
Study/Clinical Trial Completion Date:	_____
Final Report Submission Date:	_____
Interim Report Submission Date:	_____

- Janssen’s September 21, 2015, response to the September 16, 2015 Memorandum has been attached to facilitate discussion during the late cycle meeting.

4. Major labeling issues – 30 minutes

- FDA acknowledges receipt of Janssen’s amendment dated and received September 23, 2015, containing Janssen’s revised labeling in response to additional FDA modifications to the package insert sent via e-mail on September 17, 2015. FDA proposes discussing Janssen’s September 23, 2015, labeling amendment during the late cycle meeting. Janssen’s response document and revised red lined labeling submitted September 23, 2015, will be referenced during the late cycle meeting and is attached.
- An additional teleconference has been scheduled (tentatively) for October 2, 2015, from 8:30 A.M. to 9:30 A.M, EST., to discuss sections not covered during the late cycle meeting. On September 23, 2015, Janssen confirmed their availability for the October 2, 2015 teleconference.
- FDA acknowledges receipt of the amendment dated and received on September 18, 2015, containing Janssen’s final draft carton and container label. FDA has no further comments on the carton and container labeling at this time.

5. Review Plans – 5 minutes

- Labeling Discussions Ongoing
- Press Release (b) (4) Planned

6. Wrap-up and Action Items – 5 minutes

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/s/

PATRICIA KEEGAN
09/24/2015