DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207953

WRITTEN REQUEST

Janssen Products, LP
Attention: Julie Brennan, MS, RAC
Manager, Regulatory Affairs
Janssen Research & Development, LLC
920 U.S. Highway 202
P.O. Box 300
Raritan, NJ 08869

Dear Ms. Brennan:

Please refer to your correspondence dated March 30, 2017, requesting changes to our March 15, 2012, Written Request, issued under IND 50286, for pediatric studies for YONDELIS (trabectedin).

We also refer to our July 31, 2017, Amended Written Request issued under NDA 207953. Although you submitted a request for an amendment to extend the timeline (beyond March 31, 2017) for submission of the Complete Study Reports for the studies included in the original Written Request on March 30, 2017, there was insufficient time for us to review and act on an amendment in a timely manner. Thus, it has been determined that the Written Request expired on March 31, 2017, because an Amended Written Request was not issued prior to the date of expiration of the Written Request.

As a result, we are issuing a new Written Request for YONDELIS (trabectedin) that incorporates the content of the expired Written Request and addresses your March 30, 2017, request for additional changes.

This document serves as the new original Written Request and replaces the March 15, 2012, Written Request.

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

Non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) comprise 4% of pediatric malignancies. Current standard of care for patients, depending upon disease stage and grade, includes surgery, radiotherapy and chemotherapy with alkylating agents and anthracyclines. Cure rates, however, remain poor for patients with metastatic or refractory disease and advances have been limited.

Additionally, although this family of tumors represents a significant portion of pediatric cancers, very few prospective clinical trials have been performed in these patients. Furthermore, this family of diseases disproportionately affects adolescents, a subgroup of pediatric patients that are underrepresented in clinical trials.

Trabectedin, currently approved in EU for the treatment of soft tissue sarcomas, is approved in the US in adults for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen. Continued study of this agent in the pediatric and adolescent patient population is needed to further define the role of this agent in the management of pediatric cancers.

- *Type of studies:*

  Phase 1 studies:

  Study 1: A study, including pharmacokinetics, that defines age appropriate dosing in pediatric patients when trabectedin is administered as a 3-hour infusion.

  Study 2: A study, including pharmacokinetics, that defines age appropriate dosing in pediatric patients when trabectedin is administered as a 24-hour infusion.

  Phase 2 studies:

  Study 3: A study of trabectedin, infused over 24 hours, in patients with recurrent osteosarcoma.

  Study 4: A study of trabectedin, infused over 3 hours, in patients with relapsed or refractory non rhabdomyosarcoma tissue sarcomab) Ewing sarcoma, c) osteosarcoma, and d) rhabdomyosarcoma.

  Study 5: A study of trabectedin, infused over 24 hours, in patients with relapsed or refractory a) rhabdomyosarcoma, b) Ewing family tumors, and c) non rhabdomyosarcomatous soft tissue sarcoma.

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

- *Indications to be studied:*

  Phase 1 studies:

  Study 1: Relapsed or refractory solid tumors.

  Study 2: Relapsed or refractory solid tumors.

Phase 2 studies:

Study 3: Relapsed or refractory osteosarcoma.

Study 4: Relapsed or refractory b) Ewing-type sarcoma, c) osteosarcoma, and d) rhabdomyosarcoma.

Study 5: Relapsed or refractory a) rhabdomyosarcoma, b) Ewing family tumors, and c) non-rhabdomyosarcomatous soft tissue sarcoma.

- *Age group in which study(ies) will be performed:*

  Phase 1 studies:

  Study 1: Patients > 1 year and < 18 years of age

  Study 2: Patients ≥ 4 and < 17 years of age

  Phase 2 studies:

  Study 3: Patients ≥ 12 years of age

  Study 4: Patients ≥ 13 years of age

  Study 5: Patients ≥ 1 year of age at the time of study entry and no more than 21 years of age when initially diagnosed with the malignancy to be treated

- *Number of patients to be studied:*

  Phase 1 studies:

  Study 1: The number of patients entered must be sufficient to achieve Phase 1objectives.

  Study 2: The number of patients entered must be sufficient to achieve Phase 1objectives.

  Phase 2 studies:

  Study 3: at least 25 patients (at least 14 patients of age ≤ 18 years)

  Study 4: at least 75 patients (at least 12 patients of age ≤ 18 years)

  Study 5: at least 50 patients

- *Study endpoints/objectives:*

  Phase 1 studies:

  Study 1: Determine the maximal tolerated dose (MTD), pharmacokinetics and safety of trabectedin when administered over 3 hours.

  Study 2: Determine the MTD, pharmacokinetics and safety of trabectedin when administered over 24 hours.

  Phase 2 studies:

  Study 3: Determine the antitumor activity (in terms of response rate) of trabectedin administered over 24 hours in previously treated osteosarcoma.

  Study 4: Determine the antitumor activity (in terms of response rate) of trabectedin administered over 3 hours in patients with relapsed or refractory b) Ewing-type sarcoma, c) osteosarcoma, and d) rhabdomyosarcoma.

  Study 5: Determine the antitumor activity (in terms of response rate) of trabectedin administered over 24 hours in patients with relapsed or refractory a) rhabdomyosarcoma, b) Ewing family tumors, and c) nonrhabdomyosarcoma soft tissue sarcoma.

  Pharmacokinetic endpoints:

  Pharmacokinetic data must be appropriately analyzed to obtain relevant pharmacokinetic parameters (for example AUC, Cmax, Clearance, and volume of distribution, etc). The effect of age and body size on the pharmacokinetics of trabectedin in pediatric patients must be evaluated. If appropriate, combine data from the Phase 1 and Phase 2 studies to develop pharmacokinetic and pharmacodynamic (PK-PD) models to explore exposure-response relationships for measures of safety and effectiveness.

- *Drug information*
  - *dosage form:* Lyophilized powder for injection (1.0 mg or 0.25 mg single-use vial)
  - *route of administration:* Intravenous infusion (I.V.)
  - *regimen: 3 hr. or 24 hr. infusion q 3 weeks*

  Phase 1 studies:

  Study 1: Escalating dose levels administered as a 3-hour infusion once every 3 weeks

  Study 2: Escalating dose levels administered as a 24-hour infusion once every 3 weeks

Phase 2 studies: (doses as determined in phase 1 studies)

Study 3: 1500 µg/m2/day as a 24-hour infusion once every 3 weeks

Study 4: 1500 µg/m2/day as a 3-hour infusion once every 3 weeks

Study 5: 1300 µg/m2/day or 1500 µg/m2/day as a 24-hour infusion once every 3 weeks

- *Drug specific safety concerns:* Cardiotoxicity, hepatotoxicity, rhabdomyolysis, respiratory failure, mucositis, myelotoxicity, infection.

- *Statistical information, including power of study(ies) and statistical assessments:* Descriptive statistics appropriate for the phase of the study.

- *Labeling that may result from the study(ies):* You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that trabectedin is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted:* You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you chose to use other categories, you should obtain agency agreement.

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

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

Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before March 31, 2018. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

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

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

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

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

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

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

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

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

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

Sincerely,

{See appended electronic signature page}

Gregory Reaman, M.D.
Associate Director for Oncology Sciences
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

GREGORY H REAMAN
11/07/2017