NDA 202022

WRITTEN REQUEST

Janssen Products, LP
Attention: Karen Gerry
Associate Director, Global Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560

Dear Ms. Gerry:

Reference is made to your March 27, 2008, Proposed Pediatric Study Request for rilpivirine (TMC278, RPV).

The studies in this Written Request investigate the potential use of rilpivirine in combination with other antiretroviral drugs (ARVs) in treating HIV-1 infected pediatric patients 2 years to 18 years of age who are treatment-naïve or treatment-experienced but virologically suppressed.

BACKGROUND:

Global HIV statistics by UNAIDS state that approximately 37 million people were living with HIV in 2015, including 1.8 million children less than 15 years of age.

Effective treatment of HIV infection requires combination therapy with multiple active antiretrovirals. Rilpivirine is a non-nucleotide reverse transcriptase (NNRTI) and may provide an alternative NNRTI- based regimen for pediatric patients. Rilpivirine can be administered in combination with other ARVs or as part of a fixed dose combination product with TDF plus FTC or TAF plus FTC.

The Division of Antivirals (DAV) has determined the course of HIV infection and disease in pediatric patients is sufficiently similar to HIV infection and disease in adults to allow extrapolation of efficacy from the adult clinical trials to pediatric patients. As rilpivirine is an antiretroviral drug product (i.e., directly acts on the virus to prevent replication), pediatric patients with HIV infection are expected to respond similarly to adults treated with rilpivirine if they achieve similar drug exposures.

Therefore, efficacy in pediatric patients between the ages of 2 years to less than 18 years old will be in part supported and extrapolated by the adult trials that evaluated the efficacy of rilpivirine, and by pharmacokinetic/pharmacodynamic and safety data from pediatric patients.

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Rilpivirine, due to its low barrier to resistance and higher risk of virologic failure, as demonstrated during the adult Phase 3 clinical trials, is not approved for use in HIV-infected patients with HIV RNA >100,000 copies/mL. Many newly identified HIV-infected (via vertical transmission) pediatric patients have HIV RNA significantly higher than 100,000 copies/mL. Due to the challenges of identifying sufficient number of pediatric patients with baseline HIV RNA <100,000 copies/mL, rilpivirine is not a good candidate for investigation as an initial treatment in such population. An alternative design for investigating rilpivirine in pediatric patients is to identify patients who are suppressed (HIV RNA <50 copies/mL) on their current ARV regimen and have no history or virologic failure or resistance to rilpivirine. Evidence of virologic suppression should be demonstrated for at least 6 months. These subjects could switch their regimen to rilpivirine-containing regimen to allow for the investigation of the safety, PK and efficacy (antiviral activity) of rilpivirine.

Therefore, the Division will not require study of rilpivirine in pediatric patients younger than 2 years of age, including neonates, because it is difficult to find sufficient number of treatment- naive with HIV RNA <100,000 copies/mL, or treatment-experienced, virologically suppressed patients who have been on stable ARV regimen for at least 6 months without history of virologic failure or presence of resistance to rilpivirine.

Representation of Ethnic and Racial Minorities: The 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.

To obtain needed pediatric information on rilpivirine, 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 studies described below.

- *Nonclinical studies*:

  Based on review of the available nonclinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this Written Request.
- *Clinical studies:*

  Study 1*: Conduct a study in HIV-1 infected, treatment naïve patients 2 to 18 years of age with baseline HIV RNA <100,000 copies/mL to assess the pharmacokinetics, safety and tolerability, and antiviral activity of rilpivirine. Study participants must be monitored for a minimum of 24 weeks to assess safety and durability of antiviral response.*

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Or, you may choose to conduct Study 2

Study 2*: Conduct a study in HIV-1 infected patients 2 years to <18 years old who are virologically suppressed (HIV-1 RNA <50 copies/mL) and on a stable antiretroviral regimen at the time of enrollment, to assess the pharmacokinetics, safety and tolerability, and antiviral activity of rilpivirine. Study participants must be monitored for a minimum of 48 weeks to assess durability of antiviral response.*

The dose selection for all studies must be based on discussions and agreement between the sponsor and the Agency following review of the pediatric PK data.

- *Objective of each study: The objective of these studies will be to determine the pharmacokinetic and appropriate dose(s), safety and antiviral activity of rilpivirine across the age (or weight) range in HIV-1-infected treatment-naïve patients with baseline HIV RNA <100,000 copies/mL or HIV-infected virologically suppressed pediatric patients who are switching to rilpivirine.*

- *Number of Patients to be Studied: Rilpivirine must be studied in an adequate number of pediatric subjects to characterize adverse events across the weight (and age) range. A minimum of 80 subjects at the recommended dose or higher is required. The trial safety assessment should be at least 24-weeks in duration.*

- *Representation of Ethnic and Racial Minorities: The 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.*

- *Study endpoints:*

  Studies 1 and 2

  - ☐ Pharmacokinetic/Pharmacodynamic endpoints: Parameters including Cmax, Cmin, Tmax, t1/2, AUC, apparent systemic clearance and apparent volume of distribution necessary for establishing steady state.

  - ☐ Safety and tolerability: HIV-1-infected pediatric subjects must be followed for safety for a minimum of 24 weeks at the recommended dose or higher. In addition, submit plans for collecting long-term safety data for HIV-1-infected pediatric subjects who have received rilpivirine.

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- ☐ Efficacy endpoint(s): Assessment of changes in plasma HIV RNA levels, including the proportion of patients who are undetectable, and assessment of CD4 cell counts must be evaluated at Weeks 24 for treatment-naïve patients and at Week 24 for patients who are switching to rilpivirine from their current regimen.

- ☐ Resistance: Collect and submit information regarding the resistance profile (genotypic and/or phenotypic) of clinical isolates at baseline and during treatment from pediatric subjects receiving rilpivirine, particularly from those who experience loss of virologic response. Conduct HIV-1 proviral DNA resistance testing on the virologically suppressed subject's baseline sample, if needed.

- *Known Drug Safety /Monitoring:*

  - ☐ Age appropriate safety outcomes must also include: Adverse events, and tolerability. Based on available toxicity information about your product, provide specific safety parameters that your pediatric program will monitor. Safety monitoring and data collection must include, but not be limited to:
    - o Skin-related reactions
    - o Neuropsychiatric adverse events
    - o Endocrine-related adverse events
    - o Hepatic toxicity
    - o QTc prolongation and related cardiac adverse events

  A Data Monitoring Committee (DMC) may be included. See Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees https://www.fda.gov/media/75398/download

- *Statistical information, including power of study(ies) and statistical assessments:*

  Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in HIV-1- infected pediatric subjects is required. Studies must include an adequate number of subjects to characterize pharmacokinetics for dose selection. All studies must be prospectively powered to target a 95% CI within 70% and 140% of the point estimate for the geometric mean estimates of clearance for rilpivirine across the age (or weight) groups. Final selection of sample size for each age or weight group must take into account all potential sources of variability, including inter- subject and intra- subject variability. As study data are evaluated, the sample size must be increased as necessary for characterization of pharmacokinetics across the intended age range.

The following information pertains to all clinical studies in the Written Request.

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- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*
  - *dosage form*
  - *route of administration: Oral*
  - *regimen: To be determined by development program*

The selected dose(s) for study(ies) must be agreed upon with the Division prior to initiating the necessary pediatric study(ies).

Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if

(1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
(2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
(3) you have not marketed the formulation within one year after the Agency publishes such notice,

the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available

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ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *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 rilpivirine 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 choose 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. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the guidance for industry *E2C Clinical Safety Data Management: Periodic*

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Safety Update Reports for Marketed Drugs and the guidance addendum.[1] You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on FDA.gov[2] and referenced in the guidance for industry *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before March 31, 2023. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

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

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

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

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[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm
[2] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf

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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.

In accordance with section 505A(k)(1) of the FD&C 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.[3]

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 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 on the Clinical Trials website.[4]

If you have any questions, call Andrew Gentles, PharmD, BCPS AQ-ID, Senior Regulatory Project Manager, at (240) 402-5708 or the mainline at (301) 796-1500.

[3] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm
[4] www.ClinicalTrials.gov

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Sincerely,

{See appended electronic signature page}

John Farley, MD, MPH
Office Director
Office of Infectious Diseases
Center for Drug Evaluation and Research

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/s/

JOHN J FARLEY
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