DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022406

WRITTEN REQUEST

Janssen Research & Development, LLC
Attention: Huy Q. Truong, M.S.
Associate Director, Global Regulatory Affairs
920 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869-0602

Dear Mr. Truong:

Reference is made to your May 29, 2015 Proposed Pediatric Study Request (PPSR) for rivaroxaban.

BACKGROUND:

These studies investigate the potential use of rivaroxaban in the treatment and prophylaxis of pediatric thromboembolism (TE).

We note that you have conducted and submitted the results of a Phase 1 trial (Study 12892) to evaluate pharmacokinetics/pharmacodynamics (PK/PD), safety, and tolerability of rivaroxaban single-dose administration in pediatric patients >6 months to <18 years of age using age and body weight-adjusted rivaroxaban doses equivalent to 10 mg or 20 mg exposure in adults. The requested trials described herein take into account our review findings for Study 12892.

Approved treatment and prophylaxis of pediatric thromboembolism (TE) is an important yet unmet public health need. TE occurs in children of all age groups, including neonates. An increase in the rate of TE in children by 3- to 10-fold has been observed over the last 15 years, most likely due to better survival of acutely ill patients and increased use of central venous access devices (CVAD). In contrast to adults, idiopathic TE in children is rare. Notable risk factors for TE in children include malignancy, CVAD use, congenital heart disease, infection, surgery, and inflammatory disease. Certain medications also increase thrombosis risk such as corticosteroids and L-asparaginase. A venous thromboembolism (VTE) incidence of approximately 20% is observed in children with acute lymphoblastic leukemia (ALL), CVAD, and L-asparaginase treatment. The incidence of TE in children after undergoing the Fontan procedure for palliation of certain congenital heart abnormalities is approximately 20-30%, with TE incidence split evenly across the arterial and venous circulation. TE after a Fontan carries a 25% mortality rate, and the highest risk is in the first 2 years after the surgery.

The American College of Chest Physicians has published extensive management guidelines for children with thromboembolism. As examples, children with secondary VTE (i.e., VTE that

occurred in association with a risk factor) in whom the risk factor has resolved should receive anticoagulant therapy for 6 weeks to 3 months, depending on the risk factor. In children who have ongoing risk factors, anticoagulant therapy may be continued beyond 3 months. For children with idiopathic VTE, the recommendation is anticoagulant therapy for 6 to 12 months. Warfarin and/or aspirin are recommended as TE prophylaxis in children after a Fontan procedure.

While these recommendations are based on available literature and are routinely followed by pediatric hematologists, currently there are no anticoagulants approved for use in children for treatment or prophylaxis of TEs in the United States (US) or European Union (EU). Instead, anticoagulants (namely, vitamin K antagonists [VKAs] and heparins) are currently used off-label in children. Furthermore, there is a negligible amount of published data on the safety and efficacy of novel oral anticoagulation agents, including rivaroxaban, in children for whom anticoagulation is recommended.

As studies of anticoagulation in children that are fully powered for safety and efficacy have feasibility challenges, and some aspects of TE pathophysiology are comparable between adults and children, the Food and Drug Administration (FDA) supports partial extrapolation of safety and efficacy data from adult patients treated with rivaroxaban. However, as the coagulation system in children matures with age, and the causes of TE differ between adults and children, partial extrapolation must be supported by an adequate PK and PD bridge to determine the appropriate dose, as well as sufficient safety and efficacy data to screen for large discrepancies in these endpoints between adults and children that could be caused by differences in underlying coagulation system maturity or TE pathophysiology. As children of all ages, including neonates, experience TE, studies of anticoagulants used as treatment for pediatric TE should be conducted in children from birth through late adolescence. In contrast, a study of anticoagulants used as TE prophylaxis after a Fontan procedure should only be studied in the age group appropriate for that procedure, namely, age 2-6 years.

To obtain needed pediatric information on rivaroxaban, the 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 study(ies)*:

  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:
  A single-arm, open-label study evaluating the safety, efficacy and PK/PD profile (sparse sampling) of rivaroxaban in children 6 years to <18 years of age with VTE. The study will enroll children who have been treated for at least 2 months (or, in the case of catheter-related thrombosis, for at least 6 weeks) with low-molecular weight heparin

(LMWH), fondaparinux, and/or a vitamin K antagonist (VKA) for documented symptomatic or asymptomatic VTE.

Study 2:
A single-arm, open-label study evaluating the safety, efficacy and PK/PD profile (sparse sampling) of rivaroxaban in children 6 months to <6 years of age with VTE. The study will enroll children who have been treated for at least 2 months (or, in the case of catheter-related thrombosis, for at least 6 weeks) with low-molecular weight heparin (LMWH), fondaparinux, and/or a vitamin K antagonist (VKA) for documented symptomatic or asymptomatic VTE.

Study 3:
A randomized (2:1), open-label, active-controlled study evaluating the safety, efficacy and PK/PD profile of rivaroxaban in children 6 months to <18 years of age with VTE. The study will enroll children with confirmed VTE who require anticoagulant therapy for at least 90 days.

Study 4:
A single-arm, open-label study evaluating the safety, efficacy, and PK/PD profile of rivaroxaban in children from birth to <6 months of age with VTE. The study will enroll children with documented symptomatic or asymptomatic catheter-related venous or arterial thrombosis who have been treated with anticoagulant therapy for at least 2 weeks.

Study 5:
A randomized (1:1), open-label, active-controlled study evaluating the safety, efficacy and PK/PD profile of rivaroxaban in children from birth to < 6 months of age with VTE. The study will enroll children with documented symptomatic or asymptomatic VTE who require anticoagulant therapy for at least 6 weeks.

Study 6:
A randomized, open-label, active-controlled study evaluating the safety, efficacy and PK/PD profile in children 2 years to 8 years of age who have single-ventricle physiology and who have completed the Fontan procedure within 4 months. The study will have two parts: Part A will be non-randomized and will characterize the PK/PD profile in this patient population. Part B will be randomized and will characterize the safety and efficacy of rivaroxaban in comparison to aspirin in this patient population. Part A must be completed before proceeding with Part B.

- *Objective of each study:*

Studies 1 and 4:
The primary objective is to characterize the PK/PD profile of a multiple dose treatment with oral rivaroxaban. Additional objectives include:
to assess the incidence of major bleeding and clinically relevant non-major bleeding

to assess the incidence of symptomatic recurrent thromboembolism
to assess asymptomatic deterioration of the thrombotic burden on repeat imaging

Studies 3 and 5:
The primary objective is to assess the incidence of symptomatic recurrent VTE.
Additional objectives include:
to assess the incidence of symptomatic recurrent VTE and asymptomatic deterioration of the thrombotic burden on repeat imaging
to assess the incidence of overt major and clinically relevant non major bleeding
to characterize the PK/PD profile of rivaroxaban

Study 6:
Part A: The primary objective is to characterize the single- and multiple-dose PK and PK/PD profiles after oral rivaroxaban therapy administered to pediatric patients 2 to 8 years of age with single ventricle physiology who have completed the Fontan surgery within 4 months prior to enrollment. A secondary objective is to assess the safety and tolerability of rivaroxaban treatment.

Part B: The primary objective is to evaluate the safety and efficacy of rivaroxaban (exposure matched to rivaroxaban 10 mg once daily in adults) compared to ASA, given once daily (approximately 5 mg/kg) for thromboprophylaxis in pediatric patients 2 to 8 years of age with single ventricle physiology who have completed the Fontan surgery within 4 months prior to enrollment. A secondary objective is to further characterize the PK and PK/PD profiles of rivaroxaban.

- *Patients to be Studied:*

Study 1:
Children who have been treated for at least 2 months (or, in the case of catheter-related thrombosis, for at least 6 weeks) with low-molecular weight heparin (LMWH), fondaparinux, and/or a vitamin K antagonist (VKA) for documented symptomatic or asymptomatic VTE will be studied in the following age groups:
Adolescents: ≥ 12 to < 18 years
Children: ≥ 6 to < 12 years

Study 1 will enroll at least 10 subjects in each age group.

Study 2:
Children who have been treated for at least 2 months (or, in the case of catheter-related thrombosis, for at least 6 weeks) with low-molecular weight heparin (LMWH), fondaparinux, and/or a vitamin K antagonist (VKA) for documented symptomatic or asymptomatic VTE will be studied in the following age groups.
Young children: ≥ 2 to < 6 years
Infants: ≥ 6 months to < 2 years

Study 2 will enroll at least 10 subjects in each age group.

Study 3:
Children with confirmed VTE who receive initial treatment with therapeutic dosages of unfractionated heparin, LMWH or fondaparinux who require anticoagulant therapy for at least 90 days will be studied in the following age groups:

Adolescents: ≥ 12 to < 18 years
Children: ≥ 6 to < 12 years
Young children: ≥ 2 to < 6 years
Infants: ≥ 6 months to < 2 years

Study 3 will enroll at least 150 subjects to receive rivaroxaban or standard of care anticoagulant in a ratio of 2:1. At least 30 subjects will be enrolled in the ≥ 12 to <18 year age group, at least 30 subjects will be enrolled in the ≥ 6 to <12 year age group, at least 20 subjects will be enrolled in the ≥ 2 to < 6 year age group, and at least 20 subjects will be enrolled in the ≥ 6 months to < 2 years age group.

Study 4:
Children from birth (gestational age of ≥ 37 weeks) to < 6 months with documented symptomatic or asymptomatic catheter-related venous or arterial thrombosis who have been treated with anticoagulant therapy for at least 2 weeks.

Study 4 will enroll at least 8 subjects, and a sufficient number of subjects to identify an appropriate dose for study 5. The FDA must agree with this dose before proceeding to Study 5.

Study 5:
Children from birth (gestational age of ≥ 37 weeks) to < 6 months with documented symptomatic or asymptomatic VTE who receive initial treatment with therapeutic dosages of unfractionated heparin or LMWH and require anticoagulant therapy for at least 6 weeks.

Study 5 will enroll at least 20 subjects to receive rivaroxaban or standard of care anticoagulant in a ratio of 1:1.

Study 6:
Children ages 2 years to 8 years with single ventricle physiology who have completed the Fontan surgery within 4 months prior to enrollment.

Study 6 will enroll a minimum of 100 subjects, with at least 90 subjects enrolled in the randomized (2:1) portion of the study (Part B) to receive rivaroxaban or aspirin in a 2:1 ratio.

All Studies: The cumulative safety database in pediatric subjects from birth to age < 18 years will consist of at least:

50 pediatric subjects who have been exposed to rivaroxaban for ≥ 300
150 pediatric subjects who have been exposed to rivaroxaban for ≥ 90 days
175 pediatric subjects who have been exposed to rivaroxaban for ≥ 28 days

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:*

  ☐ *Pharmacokinetic Endpoints:*
  The pharmacokinetic endpoints for *studies 1-6:* Mean and individual PK parameters in subjects who receive rivaroxaban.

  ☐ *Pharmacokinetic/Pharmacodynamic Endpoints:*
  The pharmacokinetic and pharmacodynamic endpoints for *Studies 1-6 msut include* Prothrombin time, activated partial thromboplastin time, and anti-factor Xa activity in subjects who receive rivaroxaban.

  ☐ *Efficacy Endpoints:*
  Studies 1,2, 4 and 5: Symptomatic recurrence of venous thrombosis or asymptomatic deterioration as documented by the appropriate imaging test.

  Study 3: The primary efficacy outcome will be the composite of all symptomatic recurrent VTE as confirmed by repeat imaging and evaluated by an adjudication committee. The secondary efficacy outcome will be the composite of all symptomatic recurrent VTE and asymptomatic deterioration on repeat imaging as assessed by an adjudication committee.

  Study 6: The primary efficacy outcome will be any thrombotic event (venous or arterial), defined as either the appearance of a new thrombotic burden within the cardiovascular system on either routine surveillance or clinically indicated imaging or the occurrence of a clinical event known to be strongly associated with thrombus (e.g., cardioembolic stroke, pulmonary embolism).

  ☐ *Safety Endpoints:*

  Studies 1-5: The primary safety endpoint is a composite of major bleeding and clinically relevant non-major bleeding. Other safety endpoints include all deaths and other vascular events (myocardial infarction, cerebrovascular accident, and non-CNS systemic embolism).

Major bleeding is defined as overt bleeding and:

Associated with a fall in hemoglobin of 2 g/dL or more, or
Leading to a transfusion of the equivalent of ≥ 20 mL/kg of packed red blood cells, or
Occurring in a critical site (e.g., intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal), or
Contributing to death.

Clinically relevant non-major bleeding is defined as overt bleeding not meeting the criteria for major bleeding, but associated with:

Medical intervention, or
Unscheduled contact (visit or telephone call) with a physician, or (temporary) cessation of study treatment, or
Discomfort for the child such as pain, or
Impairment of activities of daily life (e.g., loss of school days or hospitalization)

Study 6: The primary safety endpoint is major bleeding events, as described above and as adjudicated by an independent adjudication committee using International Society on Thrombosis and Haemostasis recommendations. Secondary safety endpoints are clinically-relevant non-major bleeding events (as described above) and trivial bleeding (defined as any other overt bleeding that is neither major nor clinically-relevant non-major).

- *Known Drug Safety concerns and monitoring:* As anticipated for an anticoagulant, bleeding is a drug-specific safety concern. These studies will be conducted under the monitoring of a single independent Data Monitoring Committee (DMC), whose activities are described in a DMC charter. The DMC will use their clinical and statistical judgment to recommend that the study proceed or be terminated early.

- *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:* 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 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.

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

Studies 1, 2 and 4:
The same size is based on a feasibility assessment and does not include a formal sample size calculation based on the study objectives. Appropriate summary statistics will be presented for safety and efficacy endpoints. The PK of rivaroxaban in each age group will be characterized using a population PK model of plasma concentration versus time data. PD data will be characterized with summary statistics and analyzed for any relationship to PK parameters.

Studies 3 and 5:
The sample size is based on a feasibility assessment and does not include a formal sample size calculation based on the study objectives. Demographics and baseline characteristics will be described with summary statistics. PK/PD modeling using population approaches will be used to describe the PK of rivaroxaban, including potential influence of relevant co-variables and relation of anticoagulant parameters of rivaroxaban with plasma

concentrations. The results of the primary safety and efficacy analyses will be described using incidence proportions and cumulative incidences by treatment group.

Study 6:

The sample size is based on the number of subjects required to assess safety in the setting of extended rivaroxaban exposure. The study is not powered to test a formal hypothesis for safety or efficacy. Descriptive statistics will be used to summarize all study variables by treatment group. Cumulative incidences and incidence rates over time based on time to the first bleeding event will be described by treatment group using the Kaplan-Meier method. The primary efficacy analysis will be summarized using descriptive statistics.

- *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 rivaroxaban 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 Safety Update Reports for Marketed Drugs and the Guidance addendum. 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 the

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.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 june 30, 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.

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 Suria Yesmin, Regulatory Project Manager, at 301-348-1725.

Sincerely,

{See appended electronic signature page}

Gregory Reaman, MD
Associate Director, 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
06/08/2017