DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202611

WRITTEN REQUEST

Astellas Pharma Global Development, Inc.
Attention: Judy Kannenberg
Senior Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Ms. Kannenberg:

Reference is made to your December 2, 2015, Proposed Pediatric Study Request for MYRBETRIQ® (mirabegron), 25mg and 50 mg extended-release tablets.

BACKGROUND:

These studies investigate the potential use of mirabegron in the treatment of children with neurogenic detrusor overactivity (NDO).

Mirabegron is a beta-3 adrenergic agonist indicated for the treatment of overactive bladder (OAB) in adults with symptoms of urge urinary incontinence, urgency and urinary frequency.

NDO is defined by the International Children's Continence Society as detrusor overactivity when there is a relevant neurologic condition [Austin et al, 2014]. Detrusor overactivity is defined as:

> "…the occurrence of involuntary detrusor contractions during filling cystometry. They may be spontaneous or provoked and produce a waveform of variable duration and amplitude. Contractions may be phasic or terminal. Symptoms of urgency and/or urgency incontinence may or may not occur [Austin et al, 2014]."

NDO can develop as a result of a lesion at any level in the nervous system, including the cerebral cortex, spinal cord or peripheral nervous system. In children, the most prevalent cause of NDO is spina bifida, a group of developmental abnormalities that result from defects that occur during neural tube closure. Lesions may include myelomeningocele, meningocele and occult spinal dysraphism (spina bifida occulta). Another congenital cause is total or partial sacral agenesis, with absence of part or all sacral vertebrae [Tekgül et al, 2008]. The most common acquired cause for NDO is cerebral palsy, caused by damage to the motor control centers of the developing brain. An injury in the perinatal period (e.g., perinatal infection, anoxia) can produce a neuromuscular disability or a specific cerebral dysfunction. Other acquired causes, such as spinal cord tumors, trauma or sequelae of transverse myelitis, are less frequent.

The medical need for treatment is the highest in patients with NDO with detrusor sphincter dyssynergia (DSD). These patients require constant and fastidious bladder management to normalize urinary function as much as possible, and to preserve renal function. The primary treatment aim should be to maintain low average and peak bladder pressures. Further treatment goals are to prevent future serious complications of the disease, including recurrent urinary tract, permanent bladder wall damage, and renal failure. These complications can be avoided by clean intermittent catheterization (CIC) accompanied by medications to decrease detrusor pressure and overactive detrusor contractions.

The overall prevalence of NDO in combination with detrusor sphincter dyssynergia (DSD) is estimated as 1.8 per 10000 live births in the European Union and 2.2 per 10000 live births in the USA. In the rest of the world, incidences are generally higher.

Because anticholinergic medications (e.g., oxybutynin) are the only available oral treatment, current practice is to increase the dose of anticholinergic medication, which can still result in incomplete response in some children. Furthermore, in a fraction of children, anticholinergic medications are not well tolerated. If anticholinergic medications in combination with CIC are not effective or are not tolerated, bladder augmentation surgery may be necessary. Bladder augmentation carries substantial risks, including the risk of death due to perforation of the augmented bladder. Therefore, there is a need for an alternative oral therapy in this patient population.

The use of mirabegron in combination with CIC as an alternative therapy to control detrusor pressures in patients with NDO has not yet been established in controlled clinical trials. The available nonclinical and clinical data suggest that mirabegron may have a beneficial effect on NDO by increasing bladder compliance and decreasing detrusor pressure. Mirabegron may also prevent permanent bladder wall damage due to NDO and may also allow NDO patients to gain improved continence.

The Food and Drug Administration (FDA) is not requesting studies in children 0 to less than 3 years of age because urodynamic study investigations in this population may not consistently show reproducible results, and technical artifact may influence accurate interpretation of study results.

To obtain needed pediatric information on mirabegron, 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 studies*:

  Based on review of the available non-clinical 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 pediatric pharmacokinetic and safety study in children with NDO.

Study 2: A pediatric efficacy, safety and pharmacokinetic study in children and adolescents with NDO.

Of note:

- Study 2 will not be initiated until preliminary results from the neoplasm post-marketing requirement study are submitted and reviewed by the Agency.

- Study 2 will not be initiated until results from Study 1 and from an adult bioavailability study comparing the 2 mg/mL and 8 mg/mL suspensions[1] are submitted and reviewed by the Agency.

- *Objective of each study:*

Study 1: Pediatric pharmacokinetic study in NDO	The primary objective is to evaluate the pharmacokinetics of mirabegron oral suspension after single-dose administration in children with NDO. The secondary objectives are to evaluate the safety, tolerability and acceptability and palatability of mirabegron oral suspension after single-dose administration in children with NDO. All subjects from Study 1 will have the opportunity to participate in Study 2.
Study 2: Pediatric efficacy, safety and pharmacokinetic study in NDO	The primary objective is to evaluate the efficacy of mirabegron after multiple-dose administration in the pediatric population. The secondary objectives are to evaluate the safety and tolerability of mirabegron and to evaluate the pharmacokinetics of mirabegron after multiple-dose administration in the pediatric population. Dose selection for Study 2 will be confirmed with FDA once the results from Study 1 are available.

- *Patients to be Studied:*

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

Study 1: Pediatric pharmacokinetic study in NDO	A total of 6 evaluable patients, male and female children from 3 years to less than 12 years of age with NDO will be included.

[1] A phase 1, single center, open-label, randomized, single dose, 3 period crossover study to assess the bioavailability of an oral suspension of 8 mg/mL mirabegron relative to the oral suspension of 2 mg/mL mirabegron in healthy adult male and female subjects.

Study 2: Pediatric efficacy, safety and pharmacokinetic study in NDO	At least 44 evaluable male and female pediatric patients with NDO on CIC completing a postbaseline visit (estimated 63 enrolled) with at least 10 patients from each age group (children 3 years to less than 12 years of age; adolescents 12 years to less than 18 years of age).

- *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:*

Study 1: Pediatric pharmacokinetic study in NDO	Primary: Pharmacokinetic variables C_{max}, AUC_{inf}, t_{max} and $t_{1/2}$ Secondary: Safety variables Nature, frequency and severity of adverse events (AEs), clinical laboratory evaluations, vital signs, electrocardiogram (ECG) and postvoid residual volume Secondary: Acceptability and palatability of the suspension
Study 2: Pediatric efficacy, safety and pharmacokinetic study in NDO	Primary: Efficacy Change from baseline in maximum cystometric capacity (MCC) after 24 weeks of treatment based on filling urodynamics. Secondary: Efficacy Change from baseline at weeks 4 and 24 in: ● MCC (only at week 4) ● Bladder compliance ($\Delta V/\Delta P$) ● Number of overactive detrusor contractions (> 15 cm H_2O) until end of filling ● Detrusor pressure at end of filling ● Filling volume until first overactive detrusor contraction (> 15 cm H_2O) Change from baseline at weeks 2, 4, 8, 12, 24, 36 and 52 (End of Study) in: ● Average catheterized volume per catheterization ● Maximum catheterized volume

- Maximum catheterized daytime volume
- Average morning catheterized volume (based on first catheterization after patient woke up)
- Mean number of leakage episodes per day (day and night time)
- Number of dry (leakage-free) days per 7 days (day and night time)

Secondary: Acceptability questionnaire

Secondary: Safety

- Incidence and severity of treatment-emergent AEs
- Vital signs
- Clinical laboratory evaluations (hematology, biochemistry, urinalysis)
- ECG (including QT interval)
- Renal ultrasound assessment
- Estimated glomerular filtration rate

Secondary: Pharmacokinetics

- C_{max}, t_{max}, AUC_{24} and C_{trough} will be assessed when the patient reaches steady state.

- *Known drug safety concerns and monitoring:all known and important adverse events will be actively monitored throughout the studies.*

  The important identified risks in adults are:
  - Increased heart rate and tachycardia
  - Hypersensitivity reactions
  - Increased blood pressure
  - Urinary retention

  Other important potential risks are:
  - QT prolongation
  - UTI
  - Fetal disorders after exposure during pregnancy
  - Concomitant treatment with cytochrome P450 (CYP) 2D6 substrates with narrow therapeutic indices or individually dose-titrated.
  - Neoplasm

- *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:* Oral suspension formulation (2 mg/mL) in Study 1, oral suspension formulation (8 mg/mL) and extended-release tablets (25 and 50 mg) in Study 2

  - *Route of administration:* Oral

  - *Regimen:* Single-dose (Study 1) and multiple-dosing once daily in the morning (Study 2)

  - *Doses:*

Study 1: Pediatric pharmacokinetic study in NDO	Weight-based single-doses (mg/kg of body weight) of mirabegron oral suspension containing 2 mg/mL mirabegron.
Study 2: Pediatric efficacy, safety and pharmacokinetic study in NDO	To be determined based on results from Study 1 and other pediatric and adult mirabegron studies.

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:*

Study 1: Pediatric pharmacokinetic study in NDO	A safety analysis set and a pharmacokinetic analysis set will be defined. Individual mirabegron plasma concentrations and pharmacokinetic parameters will be summarized with descriptive statistics.
Study 2: Pediatric efficacy, safety and pharmacokinetic study in NDO	Four analysis populations will be defined: the safety analysis set, full analysis set, per protocol set, and pharmacokinetic analysis set for pharmacokinetic population analysis. The primary analysis method will be a paired t-test for the change from baseline to week 24 for patients included in the full analysis set to test the hypothesis that the change from baseline in MCC is not equal to 0 with a 2-sided alpha level of 0.05. A 95% CI will be calculated for mean change from baseline and it will be assessed whether the lower bound of the interval is greater than 0. Additionally 95% CIs per age group will be presented. With respect to the primary efficacy analysis, the protocol should describe the estimand of primary interest. If the estimand of interest is the treatment effect in all patients randomized regardless of adherence, you should include provisions to limit missing data through study design and education of investigators and patients, and pre-specify analysis methods to account for missing data for the primary and key secondary efficacy analyses. We recommend designs that encourage continued collection of efficacy data even after study treatment discontinuation. If you believe the treatment effect in all patients randomized regardless of adherence is not the most clinically important estimand, the protocol should specify which estimand is of most clinical importance and why. Statistical methods to quantify this estimand should be specified in the protocol.

Pharmacokinetic parameters will be summarized for the pharmacokinetic analysis set using descriptive statistics.

Safety endpoints will be summarized for the safety analysis set using descriptive statistics. Safety parameters such as vital signs, height and weight will also be summarized with respect to age-, height- and sex-specific percentiles.

- *Labeling that may result from the studies*: You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the studies demonstrate that mirabegron 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 studies. 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 studies.

- *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 studies 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 Study 1 and 2 must be submitted to the Agency on or before June 30, 2024. 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 studies. 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 studies, 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 studies 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 studies 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, please call Nenita Crisostomo, R.N., Regulatory Health Project Manager, at 301-796-0875.

Sincerely,

{See appended electronic signature page}

Julie G. Beitz, M.D.
Director
Office of Drug Evaluation III
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/

JULIE G BEITZ
03/18/2016