A Phase 3, Double-blind, Randomized, Multicenter, Parallel Group, Placebo-controlled Sequential Dose Titration Study to Evaluate Efficacy, Safety and Pharmacokinetics of Mirabegron in Pediatric Subjects from 5 to < 18 Years of Age with Overactive Bladder

Double-blind Phase 3 Study with Mirabegron and Placebo in Pediatric Subjects from 5 to < 18 Years of Age with Overactive Bladder (Dolphin Study)

ISN/Protocol 178-CL-204

Version 2.0 Incorporating Substantial Amendment 1 [see Section 13]

11 Feb 2021

EudraCT 2016-001767-37

Pediatric Investigational Plan EMEA-000597-PIP02-10-M07

Sponsor:

Astellas Pharma Global Development Inc.

1 Astellas Way
Northbrook, IL 60062, US

Protocol History:
Version 1.0 [29 Oct 2019]
Version 1.1 Incorporating Nonsubstantial Amendment 1 [13Nov2019]

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SIGNATURES

1. SPONSOR'S SIGNATURES

Required signatures (e.g., protocol authors and contributors, etc.) are located in [Section 15 Sponsor's Signatures].

2. COORDINATING INVESTIGATOR'S SIGNATURE

The coordinating investigator's signature is located in [Section 13 Coordinating Investigator's Signature].

3. INVESTIGATOR'S SIGNATURE

A Phase 3, Double-blind, Randomized, Multicenter, Parallel Group, Placebo-controlled Sequential Dose Titration Study to Evaluate Efficacy, Safety and Pharmacokinetics of Mirabegron in Pediatric Subjects from 5 to < 18 Years of Age with Overactive Bladder

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Version 2.0 Incorporating Substantial Amendment 1

11 Feb 2021

I have read all pages of this protocol for which Astellas is the sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local regulations. I will also ensure that subinvestigator(s) and other relevant members of my personnel have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: ----------

Date (DD Mmm YYYY)

Printed Name: ---------- _____

Address: ----------

CONTACT DETAILS OF SPONSOR'S KEY PERSONNEL

24-hour Contact for Serious Adverse Events See [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events]	**Please fax or email the serious adverse events/special situations worksheet to:** Astellas Pharma Global Development Inc. US Pharmacovigilance North America fax number: +1-888-396-3750 North America alternate fax number: +1-847-317-1241 International fax number: +44-800-471-5263 Email: safety-us@astellas.com
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Clinical Research Contact(s)	PPD Astellas Pharma Global Development Inc. 1 Astellas Way Northbrook, IL, 60062 PPD Astellas Pharma Global Development Inc. 1 Astellas Way Northbrook, IL, 60062 PPD

1 PROTOCOL SUMMARY

1.1 Synopsis

Date and Version of Protocol Synopsis:	11 Feb 2021, Version 2.0
Sponsor: Astellas Pharma Global Development Inc. (APGD)	**Protocol Number:** 178-CL-204
Compound Name: YM178 (mirabegron)	**Phase of Development:** Phase 3
Title of Study: A Phase 3, Double-blind, Randomized, Multicenter, Parallel Group, Placebo-controlled Sequential Dose Titration Study to Evaluate Efficacy, Safety and Pharmacokinetics of Mirabegron in Pediatric Subjects from 5 to < 18 Years of Age with Overactive Bladder	
Planned Study Period: From approximately 1Q2020 to 2Q2023	

Study Objective(s) and Endpoint(s):

The primary, secondary and exploratory objectives and endpoints for this study are listed in the table below.

Study Objectives and Endpoints

Primary and secondary objectives and endpoints apply to children only; exploratory objectives and endpoints also apply to adolescents.

Objectives	Endpoints
Primary	
● To evaluate the efficacy of mirabegron in children (5 to < 12 years of age) with OAB	● Change from baseline at the end of the 12-week treatment period: ○ Mean number of micturitions per 24 hours
Secondary	
● To evaluate the efficacy of mirabegron in children (5 to < 12 years of age) with OAB	● Change from baseline at the end of the 12-week treatment period: ○ Mean volume voided per 24 hours ○ Maximum volume voided ○ Mean number of daytime incontinence episodes per 24 hours ○ Mean number of nighttime incontinence episodes per 24 hours ○ Mean number of daytime micturitions per 24 hours ● Number of dry (incontinence-free) days per 7 days at the end of the 12-week treatment period
● To evaluate the safety and tolerability of mirabegron in pediatric subjects with OAB	● Nature, frequency and severity of AEs ● Clinical laboratory tests (hematology, biochemistry and urinalysis) ● Vital signs (blood pressure and pulse) ● Routine 12-lead ECG ● PVR volume ● Acceptability and palatability questionnaire

Table continued on next page

Objectives	Endpoints
Secondary *continued*	
● To evaluate the pharmacokinetics after multiple dose administration of mirabegron in pediatric subjects with OAB	● Steady-state C_{max}, AUC_{tau}, C_{trough}, T_{max}, CL/F, and Vz/F. Additional parameters may be calculated based on the population pharmacokinetic model used
Exploratory	
● To evaluate the efficacy of mirabegron in pediatric subjects (5 to < 18 years) with OAB	● Percentage of subjects with a reduction in daytime incontinence episodes (< 50% reduction [nonresponder], 50% [partial responder] and 100% [responder]) ● Improvement from baseline in worst incontinence grading ● Change from baseline at the end of the 12-week treatment period adjusted for fluid intake: ○ Mean number of micturitions per 24 hours ● Change from baseline at the end of the 12-week treatment period (adolescents only): ○ Mean number of micturitions per 24 hours ○ Mean number of daytime micturitions per 24 hours ○ Mean volume voided per 24 hours ○ Mean number of incontinence episodes per 24 hours ● Number of dry (incontinence-free) days per 7 days at the end of the 12-week treatment period (adolescents only) ● Mean number of daytime grade 3 or 4 (PPIUS) urgency episodes per 24 hours (adolescents only)

AE: adverse event; ECG: electrocardiogram; OAB: overactive bladder; PPIUS: patient perception of intensity of urgency scale; PVR: post void residual.

Estimand

The estimand of most clinical importance for this study is defined by the following 4 attributes:

- Target population: all children who took at least 1 dose of the study drug, and in whom a nonmissing measurement for micturition frequency at baseline and after administration of the study drug is available
- Outcome measurement: micturition frequency/day (24 hours)
- Intercurrent events:
  1. Discontinuation from treatment (if week 12/EoT not obtained)
  2. AE urinary tract infection (UTI) (if occurred in week 12/EoT)
  3. Other muscarinic antagonists or botulinum toxin (if taken during the last 2 weeks prior to week 12/EoT assessment); in all cases, a hypothetical strategy will be applied
- Population-based summary: Change from baseline to week 12/EoT in micturition frequency/day (= primary endpoint, primary estimator), compared to placebo

For this placebo-controlled study, this “de jure” estimand chosen is considered the appropriate choice. As some effect is expected early in the study and with continued treatment could be expected to be maintained, it’s considered appropriate to impute for subjects with missing values at visit 7/week 12/EoT by their last recorded post baseline visit value prior to it. This strategy also assumes that the responses after the intercurrent event would be same as for patients continuing on their respective treatment.

Planned Total Number of Study Sites and Location(s):

Approximately 65 study sites

Europe, Latin America, Africa, Middle East, Asia-Pacific and North America

Study Population:

Male and female pediatric subjects 5 to < 18 years of age with overactive bladder (OAB; as defined according to the International Children's Continence Society [ICCS]) who have had received 4 weeks of urotherapy prior to randomization

Number of Subjects to be Enrolled/Randomized:

Approximately 368 children enrolled to achieve 184 children (5 to < 12 years of age) randomized and approximately 64 adolescents enrolled to achieve at least 32 adolescents (12 to < 18 years of age) randomized (at least 92 children and 16 adolescents must be randomized to mirabegron)

Study Design Overview:

This is a double-blind, randomized, multicenter, parallel group, placebo-controlled sequential dose titration study to evaluate efficacy, safety and pharmacokinetics of mirabegron in pediatric subjects with OAB. Subjects will have to receive 4 weeks of urotherapy prior to randomization.

The study consists of 3 periods with a total duration of 18 weeks.

- Screening period/urotherapy (4 weeks):

  This period starts with visit 1/week -4 (screening) and ends with visit 3/week 0 (baseline). After informed consent/assent has been obtained and immediately after eligibility has been confirmed at visit 1/week -4 (screening), subjects using prohibited medication will complete 1 week of washout (if applicable), while beginning 4 weeks of urotherapy.

  After a successful screening visit (visit 1/week -4 [screening]), all subjects will complete a 2-day bladder e-diary (weekend) to get acquainted with the bladder e-diary and the assessments. Completion of this bladder e-diary should start in the weekend prior to visit 2. All subjects will also complete a 7-day bladder e-diary the week prior to the baseline visit. The 7-day diary will consist of a 5-day weekday bladder e-diary and 2-day weekend e-diary.

- Double-blind, placebo-controlled period (12 weeks):

  This period starts with the day after visit 3/week 0 (baseline) and ends with visit 7/week 12 (end of treatment [EoT]).

  At visit 3/week 0 (baseline) inclusion and exclusion criteria will be evaluated. Subjects continuing urotherapy who still meet the OAB entry criteria at baseline will be randomized. Subjects whose symptoms are not satisfactorily controlled with urotherapy and still fulfill the inclusion/exclusion criteria will enter the study. These subjects will be randomized to receive mirabegron in pediatric equivalent dose 25 mg (PED25) or placebo using a 1:1 ratio. Subjects with a body weight of ≥ 35 kg are to receive the tablet unless unable to swallow tablets and would be provided the oral suspension as an alternative. Subjects with a body weight < 35 kg or those who cannot be dosed with the tablet will receive an oral suspension. Daily investigational product (IP) administration will start on day 1 (i.e., the day after this visit) and continue at this dose until visit 5/week 4 (i.e., for 4 weeks). Urotherapy will continue throughout the study treatment period until visit 7/week 12 (EoT).

  At visit 5/week 4, dose up-titration to mirabegron in pediatric equivalent dose 50 mg (PED50) will be performed unless the investigator determines that the subject is adequately treated for OAB at the PED25 dose or if there are safety concerns identified and considered associated with the use of PED25. Dose down-titration from PED50 to PED25 can be done at any time thereafter for safety reasons.

  Subjects will start with the subsequent 7-day bladder e-diaries approximately 7 days prior to the indicated visit (or TC).

  Pharmacokinetic blood samples will be collected at visit 5/week 4 and visit 7/week 12 (EoT) as indicated in the Schedule of Assessments.

- Follow-up period (2 weeks):
  This period starts the day after visit 7/week 12 (EoT) and ends with visit 8/week 14 (end of study [EoS]). The follow-up period is applicable to all subjects who have been randomized and received IP.
  At visit 7/week 12 (EoT), IP administration will be stopped and a safety observation period of 2 weeks will start.

An independent Data and Safety Monitoring Board (DSMB) will be established. A separate charter will describe the responsibilities of the DSMB.

The IP will not be provided after study completion without written approval from the sponsor.

Inclusion/Exclusion Criteria:

Inclusion Criteria

Subject is eligible for the study if all of the following apply:

Inclusion at Visit 1/Week -4 (Screening)

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written informed consent/assent and privacy language as per national regulations (e.g., General Data Protection Regulations for European Union study sites) must be obtained from the subject and/or from the subject's parent(s)/legal guardian(s) prior to any study-related procedures (including withdrawal of prohibited medication, if applicable); assent by the subject is obtained as required by local law.
2. Subject has OAB defined according to the ICCS criteria.
3. Subject is a male or female between 5 to < 18 years of age, at screening.
4. Subject weighs at least 13 kg at screening.
5. Subject is able to take the IP in accordance with the protocol.
6. Subject agrees to drink an adequate fluid volume during urine collection weekends, as instructed by the investigator.
7. Subject and subject's parent(s)/legal guardian(s) agree that the subject will not participate in another interventional study while participating in the present study.
8. Subject and subject's parent(s)/legal guardian(s) are willing and able to comply with the study requirements and with the concomitant medication restrictions.
9. Female subject is not pregnant (see [Appendix 12.3 Contraception Requirements]) and at least 1 of the following conditions apply:
   a. Not a female of childbearing potential (see [Appendix 12.3 Contraception Requirements]).
   b. Female of childbearing potential who agrees to follow the contraceptive guidance (see [Appendix 12.3 Contraception Requirements]) from the time of informed consent/assent through at least 30 days after final IP administration.
10. Female subject must agree not to breastfeed starting at screening and throughout the study period and for 30 days after final IP administration.
11. Female subject must not donate ova starting at first dose of IP and throughout the study period and for 30 days after final IP administration.
12. Male subject with female partner(s) of childbearing potential (including breastfeeding partner[s]) must agree to use contraception (see [Appendix 12.3 Contraception Requirements]) throughout the treatment period and for 30 days after final IP administration.
13. Male subject must agree not to donate sperm during the treatment period and for 30 days after final IP administration.
14. Male subject with pregnant partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy throughout the study period and for 30 days after final IP administration.

Additional Inclusion at Visit 3/Week 0 (Baseline)

15. Subject must have a micturition frequency of at least 8 times (on average) per day, in the 7 days prior to visit 3/week 0 (baseline), as recorded in the bladder e-diary.

16. Subject must have at least 1 daytime incontinence episode (on average) per day, during the 7-day period before visit 3/baseline, as recorded in the bladder e-diary.
17. Subject whose symptoms are not satisfactorily controlled with urotherapy and still fulfills the inclusion/exclusion criteria will enter the study.

Exclusion Criteria

Subject will be excluded from participation in this study if any of the following apply:

Exclusion at Visit 1/Week -4 (Screening)

1. Subject has extraordinary daytime only urinary frequency according to the ICCS definition.
   - This applies to a toilet-trained child who has the frequent need to void that is associated with small micturition volumes solely during the day.
   - The daytime voiding frequency is at least once per hour with an average voided volume of < 50% of expected bladder capacity (EBC) (typically 10% to 15%).
   - Incontinence is rare and nocturia is absent.
2. Subject has an uroflow indicative of pathology other than OAB.
3. Subject has monosymptomatic enuresis.
4. Subject has dysfunctional voiding.
5. Subject has bladder outlet obstruction, except if successfully treated.
6. Subject has anatomical anomalies (surgically treated or untreated) that affect lower urinary tract function.
7. Subject with hematuria on dipstick test. In the case of hematuria on dipstick test in a female during menstruation, the test can be repeated before randomization (after the end of menstruation).
8. Subject with diabetes insipidus.
9. Subject has kidney or bladder stones.
10. Subject has suffered from chronic UTI or has had more than 3 UTIs in the 2 months prior to visit 1/week -4 (screening).
11. *Criterion has been removed*.
12. Subject has stage 2 hypertension or subject has stage 1 hypertension that is not well controlled, as defined by the 2017 American Academy of Pediatrics Clinical Practice Guidelines.
13. Subject has QTcF > 440 msec on screening ECG, a risk of QT prolongation (e.g., hypokalemia, long QT syndrome [LQTS] or family history of LQTS or exercise-induced syncope) or is currently taking medication known to prolong the QT interval.
14. Subject's aspartate aminotransferase (AST) or alanine aminotransferase (ALT) is ≥ 2 × upper limit of normal (ULN) or total bilirubin (TBL) is ≥ 1.5 × ULN according to age and sex (subjects with Gilbert's syndrome are excepted from the bilirubin threshold).
15. Subject has mild or moderate renal impairment (estimated glomerular filtration rate according to the modified Schwartz of < 60 mL/min per 1.73 m^2).
16. Subject has a symptomatic (symptoms can include pain, fever, hematuria, new onset foul-smelling urine) UTI. Note: if the UTI is treated successfully (clinical recovery: confirmed by dipstick test and repeated dipstick test after 14 days [both should be negative]), the subject can be rescreened.
17. Subject has a history or presence of any malignancy.
18. Subject uses any drugs that are sensitive cytochrome P450 2D6 (CYP2D6) substrates with a narrow therapeutic index, sensitive P-glycoprotein (P-gp) substrates, or moderate or strong cytochrome CYP3A4/5 or P-gp inhibitors or inducers after the start of washout.
19. Subject is using or has used prohibited prior and/or concomitant medication(s) [Appendix 12.6 List of Excluded Concomitant Medications] that cannot be discontinued.
20. Subject has known or suspected hypersensitivity to mirabegron or any components of the formulations used.
21. Subject has participated in another clinical study (and/or subject has received any investigational

therapy within 30 days (or 5 half-lives of the drug, or the limit set by national law, whichever is longer) prior to visit 1/week -4 (screening).

22. Subject received urinary catheterization within 2 weeks prior to screening.
23. Subject has constipation as defined by the Rome IV criteria that cannot be successfully treated prior to study entry.
24. Female subject who has been pregnant within 6 months prior to screening or breastfeeding within 3 months prior to screening.
25. Subject has any condition, which in the opinion of the investigator, makes the subject unsuitable for study participation.

Additional Exclusion at Visit 3/Week 0 (Baseline)

26. Subject has extraordinary daytime only urinary frequency according to the ICCS definition based on the bladder e-diary.
27. Subject has monosymptomatic enuresis confirmed by the bladder e-diary.
28. Subject has a maximum voided volume (morning volume excluded) > EBC for age ([age +1] × 30) in mL, based on the bladder e-diary.
29. Subject has polyuria defined as voided urine volumes of > 40 mL/kg baseline body weight during 24 hours or > 2.8 L urine for a child weighing ≥ 70 kg (ICCS definition) [Austin et al, 2014], based on bladder e-diary.
30. Subject has PVR volume > 20 mL (lowest PVR volume result) as measured by ultrasonography.
31. Subject suffers from a symptomatic (symptoms can include pain, fever, hematuria, new onset foul-smelling urine) UTI. Note: if a symptomatic UTI is present, all visit 3/week 0 (baseline) assessments must be postponed until the UTI is successfully treated (clinical recovery: confirmed by dipstick test and repeated dipstick test after 14 days [both should be negative]), and the urotherapy should continue. The postponed visit 3/week (baseline) should be within 14 days of the intended visit 3/week 0 (baseline).
32. Subject with hematuria on dipstick test. In the case of hematuria on dipstick test in a female during menstruation, the test can be repeated before randomization (after the end of menstruation).
33. Subject has a pulse > 99th percentile for age.
34. Subject has stage 2 hypertension or subject has stage 1 hypertension that is not well controlled, as defined by the 2017 American Academy of Pediatrics Clinical Practice Guidelines.
35. Any reason, in the opinion of the investigator, that makes the subject unsuitable for study participation.

Investigational Product(s):

Name/Use:

Mirabegron tablets in 25 mg and 50 mg (test product) and matching placebo

Mirabegron oral suspension containing 8 mg/mL (test product) and matching placebo

Dose(s):

Once daily dosing according to the table below.

Body Weight-based Doses for Tablets or Suspension

	Body Weight Range† (kg)	Oral Suspension Volume‡ (mL)	Tablet Dose (mg)
PED25	13 to < 22	3	-
	22 to < 35	4	-
	≥ 35	6	25
PED50	13 to < 22	6	-
	22 to < 35	8	-
	≥ 35	11	50

PED25: pediatric equivalent dose 25 mg; PED50: pediatric equivalent dose 50 mg

† Subjects with a body weight ≥ 35 kg will receive the tablet. Subjects with a body weight < 35 kg or those who cannot be dosed with the tablet will receive an oral suspension.

‡ Oral suspension containing 8 mg/mL.

The starting dose will be PED25 starting administration the day after visit 3/week 0 (baseline). At visit 5/week 4, dose up-titration to PED50 will be performed unless the investigator determines that the subject is adequately treated for OAB at the PED25 dose or if there are safety concerns identified and considered associated with the use of PED25. Dose down-titration from PED50 to PED25 can be done at any time thereafter for safety reasons.

Mode(s) of Administration:

IP will be administered orally, once daily in the morning around the same time of day and around time of food intake (i.e., within 1 hour before or after breakfast).

Tablets will be administered with a sip of water (tablet should be taken as a whole and should not be chewed, divided or crushed). Oral suspension will be administered via an oral syringe with a sip of water afterwards.

Dose Modifications:

Dose down-titration from PED50 to PED25 can be done at any time for safety reasons.

Other Study Treatment(s):

During the screening period, all subjects will receive 4 weeks of urotherapy. At visit 3/week 0 (baseline), inclusion and exclusion criteria will be evaluated. Subjects continuing urotherapy who still meet the OAB entry criteria at baseline will be randomized. Urotherapy will continue throughout the study treatment period until visit 7/week 12 (EoT).

Concomitant Treatment (Medication and Nonmedication Therapy) Restrictions or Requirements:

Subjects are not allowed to use ongoing treatment with any of the following prohibited medications after the start of the washout:

- Any medication, other than the IP, used for the treatment of OAB (including tricyclic antidepressants, 1st generation H1 antagonists and alpha blockers)
- Any drugs that are sensitive CYP2D6 substrates with a narrow therapeutic index or sensitive P-glycoprotein substrates
- Any medications known to prolong the QT interval
- Any medication that is a moderate or strong cytochrome CYP3A4/5 or P-gp inhibitor or inducers including natural and herbal remedies
- Intradetrusor botulinum toxin injections; except if given > 9 months prior screening and symptoms reappeared comparable to those before botulinum toxin injections

- Nonmedication therapies like urotherapy, chiropractic, physical therapy will also be collected on the nonmedication therapy case report form.
    - The site will need to make special notes for those subjects who do not follow urotherapy for 7 or more consecutive days in electronic case report forms.

These treatments are prohibited from being started after the start of the washout period. All other concomitant treatment use will be reported.

The use of previous and concomitant treatment within 30 days prior to signing the informed consent and throughout the study will be documented on the appropriate electronic case report form.

Duration of Treatment:

Once daily dosing for 12 weeks

Treatment Discontinuation Criteria:

Discontinuation of Individual Subject(s) From Study Treatment(s):

A subject must discontinue study treatment for any of the following reasons:

- Subject requests to stop treatment.
- Any clinical adverse events, laboratory abnormality or intercurrent illness, in the opinion of the investigator, indicates continued treatment is not in the best interest of the subject
- If signs or symptoms of hypersensitivity to mirabegron are observed (e.g., anaphylactic reaction, erythema multiforme or exfoliative dermatitis).
- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than 2 weeks.
- ALT or AST > 3 × ULN and TBL > 2 × ULN or international normalized ratio (INR) > 1.5 (if INR testing is applicable/evaluated).
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).
- Female subject becomes pregnant.
- Prolongation of QT > QTcF > 440 msec and/or QT interval prolongation > 30 msec versus baseline.
- Subject with (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mmHg.

If a subject discontinues treatment prematurely, the subject will be encouraged to complete all scheduled visits to record all available information.

Discontinuation of the Study:

The independent data monitoring committee will review safety data periodically and provide a recommendation to the sponsor if the study should continue or be stopped due to safety concerns. The sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the sponsor terminates the study for safety reasons, the sponsor will immediately notify the investigator and subsequently provide written instructions for study termination. The study may also be stopped as a result of the outcome of the interim analysis.

Statistical Methods:

Sample Size Justification:

Efficacy of mirabegron in children will be based on both primary and secondary endpoints. Given the clinical hurdle to demonstrate efficacy in a population challenging to recruit, an alpha-level of 10% would appear reasonable and justified. In a study with propiverine in children, a difference in mean number of micturition episodes/24 hours of 0.8 between propiverine and placebo was observed, with a SD between 2.2 and 2.3. Assuming at least similar efficacy of mirabegron, with a treatment effect of 0.9 micturitions per day between mirabegron and placebo and a common SD of 2.3, a sample size of 82 evaluable subjects (children) per treatment group is assumed per treatment group would provide a

power of 80%. Under the assumption that after randomization about 10% of the subjects will not be evaluable for the analysis of the primary endpoint (i.e., not fulfilling the criteria for inclusion in full analysis set), at least 184 children (5 to < 12 years of age) must be randomized in order to have at least 164 evaluable children for the analysis of the primary efficacy endpoint. For adolescents, no formal sample size will be calculated, at least 32 adolescents (12 to < 18 years of age) must be randomized, yielding at least 16 adolescents on mirabegron. Further assuming a 50% screen failure rate, approximately 368 children have to be enrolled to achieve 184 children (5 to < 12 years of age) randomized and approximately 64 adolescents will be enrolled to achieve at least 32 adolescents (12 to < 18 years of age) randomized (at least 92 children and 16 adolescents must be randomized to mirabegron). Recruitment will continue until the minimum number to be randomized in both children and adolescents have been achieved.

Efficacy:

The primary analysis of the primary efficacy end-point in children (5 to < 12 years of age), change from baseline to visit 7/week 12 (EoT) in mean number of micturitions per 24 hours, will be analyzed using an analysis of covariance (ANCOVA). The ANCOVA model will include treatment group, sex and geographical region as fixed effects and the mean number of micturitions per 24 hours at visit 3/week 0 (baseline) as covariate.

The secondary analysis will be a repeated measures ANCOVA. This model will include treatment group, visit (week 4, 8, 12), sex, geographical region and the interaction between treatment group and visit as fixed effects and mean number of micturitions per 24 hours at baseline as covariate. Mirabegron will be compared to placebo using a linear contrast within the repeated measures ANCOVA model, with 2-sided significance level of alpha = 0.1 and 90% CI.

In addition to the parametric ANCOVA, a nonparametric ANCOVA will also be performed: (stratified) rank ANCOVA.

Safety:

Safety endpoints will be summarized using descriptive statistics. Safety parameters such as vital signs will be summarized with respect to age- and sex-specific percentiles. Clinical laboratory tests (hematology, biochemistry and urinalysis [urinalysis dipstick]) and electrocardiogram results will also be summarized.

Pharmacokinetics:

Pharmacokinetic parameters will be summarized using descriptive statistics.

Pharmacodynamics | Immunogenicity:

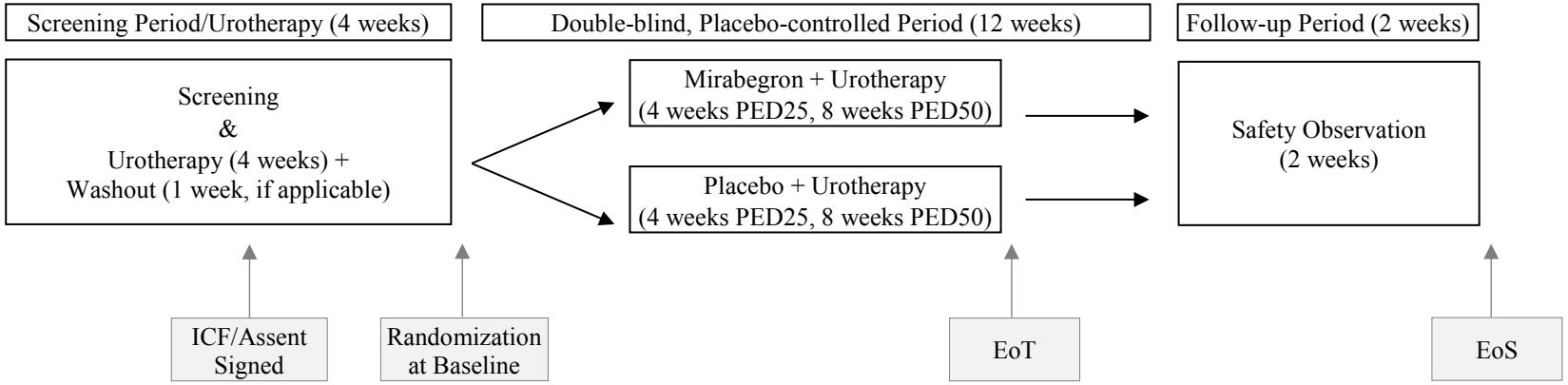
Not applicable.

Interim Analyses:

A blinded interim analysis will be performed after 50% of children planned to be randomized have had their week 12/EoT assessment. The interim analysis will determine if the chance of a positive study with respect to the primary endpoint at the EoS is high enough to justify continuation of the study; otherwise, the study will be stopped for futility.

1.2 Study Schema

Figure 1 Study Schema



EoS: end of study; EoT: end of treatment; ICF: informed consent form; PED25: pediatric equivalent dose 25 mg; PED50: pediatric equivalent dose 50 mg

1.3 Schedule of Assessments

Table 1 Schedule of Assessments

Schedule of Assessments	Screening Period/Urotherapy (4 weeks)		Double-blind Placebo-controlled Period (12 weeks)					Follow-up Period (2 weeks)
	Visit 1	Visit 2/TC[a]	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	Week -4 Screening	Week -2	Week 0 Baseline	Week 2 TC[a]	Week 4	Week 8 TC[a]	Week 12 (EoT)[b]	Week 14 (EoS)[b,c]
	Day -28 (-3 days)	Day -14 (± 5 days)	Day -1	Day 14 (± 3 days)	Day 28 (± 3 days)	Day 56 (± 3 days)	Day 84 (± 3 days)	Day 98 (+ 3 days)
Obtaining Informed Consent/Assent	X							
Inclusion and Exclusion Criteria	X		X					
Washout	X[d]							
Urotherapy	X	X	X	X	X	X	X	
Demographics and Medical History	X							
Previous and Concomitant Medication	X		X	X	X	X	X	X
Physical Examination	X				X		X	
Height and Body Weight	X		X				X	
Uroflow	X							
Dose Titration[e]					X			
Dispense IP[f]			X		X			
Drug Accountability			X		X		X	
Vital Signs[g]	X		X		X		X	X
SBPM[h]		X	X	X	X	X	X	
Routine 12-lead ECG[g]	X		X		X		X	
Clinical Laboratory Tests (Hematology and Biochemistry)	X		X[i]		X		X	X[i]
Clinical Laboratory Tests (Urinalysis)	X		X[i]		X		X	X[i]
Pregnancy Test[j]	X		X		X		X	X
PVR Volume[k]			X		X		X	X
AEs	X	X	X	X	X	X	X	X
Bladder e-diary[a,l]		X	X	X	X	X	X	

Table continued on next page

Schedule of Assessments	Screening Period/Urotherapy (4 weeks)		Double-blind Placebo-controlled Period (12 weeks)					Follow-up Period (2 weeks)
	Visit 1	**Visit 2/TC[a]**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
	Week -4 Screening	**Week -2**	**Week 0 Baseline**	**Week 2 TC[a]**	**Week 4**	**Week 8 TC[a]**	**Week 12 (EoT)[b]**	**Week 14 (EoS)[b,c]**
	Day -28 (-3 days)	Day -14 (± 5 days)	Day -1	Day 14 (± 3 days)	Day 28 (± 3 days)	Day 56 (± 3 days)	Day 84 (± 3 days)	Day 98 (+ 3 days)
Acceptability and Palatability Questionnaire[m]							X	
Pharmacokinetics[n]					X		X	

AE: adverse event; ECG: electrocardiogram; e-diary: electronic diary; EoS: end of study; EoT: end of treatment; IP: investigational product; PED25: pediatric equivalent dose 25 mg; PED50: pediatric equivalent dose 50 mg; PVR: post void residual; SBPM: self blood pressure monitoring; TC: telephone call

a. For the visits where a TC is indicated, there is no need for the subject to visit the clinic provided that the bladder e-diary data are reviewed by the investigator prior to the TC and discussed and confirmed with the subject or parent(s)/legal guardian(s) during the TC. Urotherapy is also to be discussed and confirmed with the subject or parent(s)/legal guardian(s) during each TC.

b. Subjects who withdraw early from the study after having received IP should complete both the EoT and EoS visits.

c. The EoS visit (visit 8/week 14 [EoS]) should take place at least 14 days after the EoT visit (visit 7/week 12 [EoT]).

d. Subjects using prohibited medication will complete 1 week of washout (if applicable), while beginning 4 weeks of urotherapy.

e. Dose up-titration to PED50 to occur at visit 5/week 4 unless investigator determines OAB is adequately controlled. Dose down-titration from PED50 to PED25 can be done at any time for safety reasons.

f. Daily IP administration will start on day 1 (i.e., the day after visit 3/week 0 [baseline]).

g. Blood pressure, pulse, body temperature and ECGs will all be measured in single measurements. Subject to be in the sitting position (when possible, otherwise supine, but always in the same position for each procedure). Subject should have been calm and without distress for at least 5 minutes. Preferably, the right arm should be used to measure vital signs. Body temperature will be measured with an ear thermometer. Clinic measurements will be used to assess eligibility.

h. SBPM will be measured once in the morning and evening during the 2-day weekend bladder e-diary collection period. SBPM measurements should start in the weekend prior to week -2 and be taken in the weekend prior to the indicated visit (or TC). SBPM will be measured on 2 consecutive days at 1 and 2 weeks after start of dosing with PED25 (day 1) and after up-titration to PED50, if not already covered by the scheduled SBPM. Measurements will be taken in the sitting position (when possible, otherwise supine, but always in the same position). Preferably, the right arm should be used. Subject should have been calm and without distress for at least 5 minutes. Morning measurement should be taken before IP intake and evening measurement should be taken prior to bedtime.

i. Additional hematology, biochemistry and urinalysis (urinalysis dipstick) tests will be performed at visit 3/week 0 (baseline) and visit 8/week 14 (EoS) only if an AE related to hematology, biochemistry or urinalysis parameters occurred since the previous visit or at the discretion of the investigator.

j. Urine pregnancy test will be performed for females of childbearing potential at all on-site visits.

Footnotes continued on next page

k. PVR volume will be assessed by ultrasonography at visit 3/week 0 (baseline), visit 5/week 4, visit 7/week 12 (EoT) and visit 8/week 14 (EoS). For each subject, the same method should be used throughout the study. The bladder should only be emptied when it was initially filled with preferably > 50% of the bladder capacity for age. Every attempt should be made to measure PVR volume within a minute of voiding. A PVR volume of ≤ 20 mL is sufficient and the assessment does not have to be repeated. If the PVR volume is > 20 mL, the PVR volume assessment should be repeated (filled with preferably > 50% of the bladder capacity for age). If the subject is unable to complete a second measurement, it is up to the investigator to judge whether it can be skipped (and write the reason in the case report form). At visit 3/week 0 (baseline), the lowest PVR volume result measured should be used to evaluate the exclusion criterion. In case the lowest PVR volume measured is > 20 mL at visit 3/week 0 (baseline), the subject should be excluded from the study.

l. At the end of a successful screening visit (visit 1/week -4 [screening]), all subjects will be provided with a device to collect diary information. At the weekend prior to the week -2 visit, the subject will complete the 2-day bladder e-diary to get acquainted with the data collection. The 2-day diary will be reviewed at the week -2 visit. If completion is successful, all subjects will start with the 7-day bladder e-diary completion approximately 7 days prior to the indicated visit (or TC). The bladder e-diary is used for a 7-day period to record micturition frequency and incontinence episodes; it also contains a 2-day weekend period to record additional volume measurements and vital signs.

m. The acceptability and palatability questionnaire will be completed on one weekend day proceeding at visit 7/week 12 (EoT).

n. There will be 2 pharmacokinetic sampling days at visit 5/week 4 and visit 7/week 12 (EoT). Both pharmacokinetic sampling days will consist of collecting 1 predose (trough) sample. On pharmacokinetic sampling days, dosing should occur in the clinic and breakfast should be eaten at the clinic within 1 hour before dosing.

1.3.1 Sample Collection Schedule

There will be 2 pharmacokinetic sampling days at visit 5/week 4 and visit 7/week 12 (EoT). Both pharmacokinetic sampling days will consist of collecting 1 predose (trough) sample. On pharmacokinetic sampling days, dosing should occur in the clinic and breakfast should be eaten at the clinic within 1 hour before dosing.

Table 2 Sample Collection Schedule

Visit	Time Point	Collection Window	Whole Blood Pharmacokinetics
Visit 5/week 4	Predose (trough)	Approximately 24 hours after previous dose	X
Visit 7/week 12 (EoT)	Predose (trough)	Approximately 24 hours after previous dose	X

EoT: end of treatment

2 INTRODUCTION

2.1 Background

The present study is designed to evaluate efficacy, safety and pharmacokinetics of mirabegron in pediatric subjects with overactive bladder (OAB).

The study is part of the sponsor's clinical program for development of mirabegron for the treatment OAB in pediatric patients. Current drug therapy for OAB consists of oral antimuscarinics such as oxybutynin. Although the vast majority (approximately 90%) of patients can be treated successfully with this, development of alternative therapy is desirable because of insufficient efficacy and/or the side effects of available therapies.

Mirabegron is a first-in-class, selective human beta 3-adrenergic receptor (AR) agonist, represents a class of drugs for treatment of OAB with a direct mechanism of action. Mirabegron activation of beta 3-AR in the human bladder results in a relaxation of the detrusor smooth muscle during the fill-void cycle without interfering with the voiding contraction. Mirabegron is currently available as 25 mg and 50 mg tablets. An oral suspension is also being investigated for the treatment of OAB and neurogenic detrusor overactivity (NDO) in the pediatric population.

The population for this pediatric clinical efficacy study (Study 178-CL-204) with mirabegron is pediatric patients with OAB.

2.1.1 Treatment of Overactive Bladder in Pediatric Population

Classical treatment of OAB in pediatric patients consists of urotherapy followed by antimuscarinic therapy if the urotherapy is not sufficient. Other therapies for OAB are also described.

Urotherapy

Standard urotherapy includes information on and demystification of the voiding function and dysfunction, instruction on voiding habits (such as regular voiding, voiding posture), life style advice regarding fluid intake, prevention of constipation, recording of symptoms and voiding habits in bladder diaries and support via regular follow-up by a caregiver.

Specific interventions include various forms of pelvic floor training (relaxation, contraction), behavioral modification, electrical stimulation, catherization and biofeedback (use of objective measures, e.g., uroflow or surface electromyography (EMG) to show children how far they relax their pelvic floor during voiding). Urotherapy can also include elements of cognitive behavioral therapy [Nevéus et al, 2006].

Other Therapies for OAB

Alternative drug therapy for OAB includes antimuscarinic therapy such as oxybutynin.

Neuromodulation is also used in patients who do not respond adequately to drug therapy.

2.1.2 Nonclinical and Clinical Data

Detailed information from nonclinical and clinical studies conducted with mirabegron can be found in the Investigator's Brochure. Nonclinical and clinical data are also summarized in the current locally-available product information for mirabegron.

2.1.2.1 Nonclinical Data

The standard nonclinical pharmacology studies as conducted for the use of mirabegron in adult patients with OAB are also relevant for its use in adolescent pediatric patients with OAB or NDO. Primary nonclinical pharmacology data for mirabegron qualitatively but not quantitatively translates to human clinical use in OAB. Other pharmacological effects such as the glucogenolytic effects of mirabegron in rodents did not translate to an effect in humans. These differences relate to species differences in molecular biology of the beta 3-AR, differences in receptor distribution, and differences in coupling to downstream effector mechanisms. From these factors only receptor expression or receptor-effector coupling efficiency are likely to vary by age. No detailed information is available on potential differences in expression for beta 3-AR in humans or animals during maturation. The sparse data available [Derweesh et al, 2000] suggest that any changes in beta-adrenergic responsiveness in rat urinary bladder could be expected at older age rather than at infancy or adolescence.

2.1.2.2 Clinical Data

The main clinical aspects of mirabegron prolonged-release tablets in adults are described in the current locally-available product information for mirabegron.

To support the doses and formulations (tablets and oral suspension) selected for this study, the pediatric development program for mirabegron includes 4 phase 1 studies [Table 3].

Table 3 Overview of Current Supporting Mirabegron Studies in the Pediatric Clinical Development Program for Neurogenic Detrusor Overactivity and Overactive Bladder

Study Number	Study Title	Study Progress
178-CL-201	A phase 1, single dose, 4-period crossover study to assess the bioavailability of mirabegron oral suspension relative to the mirabegron prolonged-release tablet and to assess the effect of food on the pharmacokinetics of mirabegron oral suspension in healthy young male and female subjects	Completed
178-CL-202	A multicentre, open-label, single ascending dose phase 1 study to evaluate the pharmacokinetics, safety and tolerability of mirabegron OCAS tablets in pediatric subjects from 5 to less than 18 years of age with NDO or OAB	Completed
178-CL-203	A multicentre, open-label, single dose, phase 1 study to evaluate the pharmacokinetics, safety and tolerability of mirabegron oral suspension in pediatric subjects from 3 to less than 12 years of age with NDO or OAB	Completed
178-CL-208	A phase 1, 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 and to assess the effect of food on the pharmacokinetics of the oral suspension of 8 mg/mL mirabegron in healthy male and female adult subjects	Completed
178-CL-206A	An open-label, baseline-controlled, multicenter, phase 3 dose-titration study followed by a fixed dose observation period to evaluate efficacy, safety and pharmacokinetics of mirabegron in children and adolescents from 3 to less than 18 years of age with NDO on CIC	Completed

CIC: Clean Intermittent Catheterization; NDO: neurogenic detrusor overactivity; OAB: overactive bladder; OCAS: oral-controlled absorption system.

The data from Studies 178-CL-201 and 178-CL-202 were used to support the use of tablets in pediatric subjects with a body weight of ≥ 35 kg in this study. For those pediatric subjects that cannot be dosed with tablets because their body weight is < 35 kg or because they cannot swallow the tablets, an oral suspension with a strength of 2 mg/mL was developed. The results of Studies 178-CL-201 and 178-CL-202 were used to support the use of the 2 mg/mL in Study 178-CL-203. With the results of the Study 178-CL-203, it became apparent that with a strength of 2 mg/mL the volume of the doses the patients have to take every day would be too high (up to 44 mL). To overcome this issue, an oral suspension of 8 mg/mL was developed. To support the use of this 8 mg/mL mirabegron oral suspension in pediatric subjects, Study 178-CL-208 was conducted. The study follows a single dose, 3 period, crossover design in healthy adult subjects. Subjects received the following three treatments in random order: 1) 11 mL of 8 mg/mL oral suspension of mirabegron under fasted conditions, 2) 11 mL of 8 mg/mL oral suspension of mirabegron under fed conditions and 3) 44 mL of 2 mg/mL oral suspension of mirabegron under fasted conditions.

The primary objective of Study 178-CL-208 was to assess the relative bioavailability of the 8 mg/mL oral suspension compared to the 2 mg/mL oral suspension under fasted conditions.

The results of Study 178-CL-208 show that the bioavailability of both strengths is comparable [Table 4].

Table 4 Study 178-CL-208 Results: Relative Bioavailability of the Mirabegron 8 mg/mL Oral Suspension Formulation versus 2 mg/mL Oral Suspension Formulation (Pharmacokinetics Analysis Set)

Parameter (units)	Geometric LS Mean for 8 mg/mL Suspension Fasted (n = 24)	Geometric LS Mean for 2 mg/mL Oral Suspension Fasted (n = 23)	Geometric LS Mean Ratio (%)†	90% CI of Ratio (%)†
AUC_{inf} (ng•h/mL)	253	251	100.6	(90.9, 111.3)
AUC_{last} (ng•h/mL)	234	232	100.9	(90.6, 112.4)
C_{max} (ng/mL)	12.1	11.3	106.7	(84.2, 135.2)

LS: least squares

The analysis was performed on logarithm-transformed pharmacokinetic parameters using a linear mixed model with treatment and investigational period as fixed effects and accounting for the longitudinal nature of the data by subject using a repeated statement. The covariance matrix is structured by period.

† The geometric LS mean ratios (and associated 90% CIs) were obtained by back-transforming (antilogging) the LS means of the treatment differences.

This study demonstrated that 88 mg mirabegron administered as the 8 mg/mL oral suspension formulation was bioequivalent to 88 mg mirabegron administered as the 2 mg/mL oral suspension formulation. An effect of food in line with the literature data for 50 mg mirabegron prolonged-release tablets was observed for the 8 mg/mL mirabegron oral suspension formulation.

Study 178-CL-206A was a phase 3, 52-week, open-label, baseline-controlled, dose-titration multicenter study evaluating the efficacy and safety of mirabegron tablets and oral suspension (8 mg/mL) in 86 pediatric patients with NDO using clean intermittent catheterization (CIC), including 55 children aged 3 to < 12 years and 31 adolescents aged 12 to < 18 years. Patients received mirabegron tablets or oral suspension once daily for up to 52 weeks, starting at pediatric equivalent dose 25 mg (PED25) and up-titrated to pediatric equivalent dose 50 mg (PED50).

This study showed a statistically significant improvement that was present at week 4 and sustained throughout the efficacy treatment period. Secondary and sensitivity analyses of the primary endpoint confirmed the primary analysis. Mirabegron appeared to be safe and well tolerated by pediatric patients with NDO under the condition of Study 178-CL-206A.

The detailed results of Studies 178-CL-201, 178-CL-202, 178-CL-203, 178-CL-208 and 178-CL-206A are reported in the Investigator's Brochure.

The doses described in [Section 2.1.2.2 Clinical Data] suggest tablets for subjects with a body weight of ≥ 35 kg unless unable to swallow tablets and would be provided the oral suspension as an alternative, and the 8 mg/mL oral suspension for subjects with a body weight < 35 kg.

Safety and Tolerability

In Study 178-CL-203 the safety and tolerability of the oral suspension when dosed in children was evaluated and it was concluded that it was safe and well tolerated.

From the 9 subjects who completed the study (6 with NDO and 3 with OAB) 1 treatment emergent adverse event (TEAE) was reported: pyrexia on day 1 in an NDO subject. The intensity was mild and was judged by the investigator not to be related to study drug. No clinically significant electrocardiogram (ECG) abnormalities have been seen throughout the study, there were no QT interval using Fridericia's correction formula (QTcF) values > 450 msec and no QT interval prolongation > 30 msec versus baseline was observed (mean of triplicates).

A 24-hour continuous 12-lead ECG recording was recorded in all subjects on a reference day and on the dosing day. The main objective of the continuous 12-lead ECG recording was to evaluate the effect of mirabegron on heart rate in a time-matched manner, taking into account the circadian rhythm. A median increase in 24-hour heart rate of 5.1 bpm was observed. This was not considered as clinically relevant due to the multiple blood draws, the low number of subjects and the absence of a placebo treatment group.

Some changes in laboratory values were observed, but they were not considered as clinically relevant.

For Study 178-CL-208 single doses of 88 mg mirabegron oral suspension to adults were safe and well tolerated. Eleven of 24 subjects reported 22 adverse events (AEs). All except for 2 events (1 headache moderate and 1 dysmenorrhea moderate) were mild. Twenty AEs were considered not related; 2 were considered possibly related (dizziness, mild and orthostatic dizziness mild).

For study 178-CL-206A mirabegron tablets and oral suspension (8 mg/mL) once daily for up to 52 weeks, starting at PED25 and up-titrated to PED50 was generally well tolerated by pediatric patients in the completed clinical study. One of 86 (1.2%) patients (an adolescent) reported bradycardia. Using Fleming et al [2011], 3 of 50 (6.0%) children and 2 of 28 (7.1%) adolescents had potentially clinically relevant pulse rate readings during the study. Only 1 of 78 (1.3%) patients (a child) met the criteria for a TEAE of hypertension which was considered not related to the study drug by the investigator.

There were no clinically significant vital signs, clinical laboratory value or 12-lead ECG findings. Based on the mean visual analogue scale score for palatability, the suspension was acceptable in pediatric population and did not require further taste adjustment. The oral suspension when dosed in children was considered to be safe and well tolerated.

2.1.3 Summary of Key Safety Information for Investigational Product(s)

Mirabegron has not been approved or marketed for use in pediatric subjects.

Detailed reference safety information (RSI) can be found in the Investigator's Brochure for mirabegron.

Mirabegron has been approved in more than 81 countries worldwide. In adults, the safety of mirabegron treatment has been well characterized in 5863 subjects (95% with OAB) in the phase 2/3 registration studies treated with mirabegron at doses ranging from 25 to 200 mg once daily. Identified risks include increased heart rate and tachycardia, hypersensitivity reactions, increased blood pressure and urinary retention. Potential risks include QT prolongation, urinary tract infection (UTI), fetal disorders after exposure during pregnancy and events induced by concomitant treatment with cytochrome P450 2D6 (CYP2D6) substrates with a narrow therapeutic index. The risks of QT prolongation, increased heart rate or increased blood pressure are greater with increasing exposure at supratherapeutic doses and can be mitigated with optimal dose selection. The maximum therapeutic dose of mirabegron based on the overall benefit-risk is 50 mg once daily in adults.

2.2 Study Rationale

OAB is recognized by the International Children's Continence Society (ICCS) [Austin et al, 2014], this study is intended to assess the effects of mirabegron in pediatric patients with OAB to understand its potential role in therapy. This study (Study 178-CL-204) is part of the sponsor's clinical program to develop mirabegron for OAB in pediatric subjects. In the EU, the development of mirabegron for the indication of OAB is outlined in the pediatric investigational plan (PIP) for mirabegron and has been approved by the Pediatric Committee. This study is part of PIP commitment.

2.3 Risk-Benefit Assessment

This study will be conducted as a double-blind, randomized, multicenter, parallel group, placebo-controlled sequential dose titration study in pediatric subjects from 5 to < 18 years of age with OAB.

The study design and dose rationale are presented in [Section 4 Study Design and Dose Rationale].

Mirabegron tablets have been approved for the indication of OAB in adult subjects. Mirabegron oral suspension has been shown to be safe and well tolerated in 2 phase 1 studies in healthy adult subjects (Studies 178-CL-201 and 178-CL-208). In the pediatric phase 1 studies executed thus far, mirabegron tablets and mirabegron oral suspension had an acceptable safety profile and were well tolerated. Given the available data on mirabegron in the adult population and in the pediatric population to date, the risk-benefit attributes are well defined and can be managed through ongoing safety assessments throughout study conduct as defined in the Schedule of Assessments [Table 1].

The important identified and potential risks in adults are recognized as potential drug safety risks for this study (Study 178-CL-204). These risks will be monitored on a regular basis and can be mitigated as follows:

- The initial dose of mirabegron will be based on the subject's body weight and is predicted to achieve plasma concentrations equivalent to the steady-state exposures

expected with 25 mg mirabegron administered once daily in adults (PED25). This low dose is chosen considering possible beta-adrenergic side effects of mirabegron.

- At visit 5/week 4 (i.e., after 4 weeks on PED25), dose up-titration to PED50 will be performed unless the investigator determines that the subject is adequately treated for OAB at the PED25 dose or if there are safety concerns identified and considered associated with the use of PED25. Dose down-titration from PED50 to PED25 can be done at any time thereafter for safety reasons. By striving to get an efficacious dose of mirabegron early after start of dosing, the risk for bladder and kidney damage is mitigated.
- Potential fetal disorders after exposure during pregnancy is mitigated by the inclusion criteria
- Hypersensitivity reactions (immediate or nonimmediate and cutaneous or noncutaneous) will be monitored by AE monitoring and will require discontinuation of study treatment
- Potential UTI will be monitored by urinalysis at each visit in the clinic
- Increased blood pressure will be monitored by at-home and clinic measurements and can be mitigated by dose titration
- Increased heart rate and tachycardia will be monitored by at-home and clinic measurements and can be mitigated by dose titration
- Potential QT prolongation will be monitored by ECG at each visit at the clinic and can be mitigated by dose titration
- Potential events by concomitant treatment with CYP2D6 substrates with narrow therapeutic index is mitigated by excluding these medications

For activation of thermogenesis in brown fat, weight loss will be monitored by regular body weight measurements and the potential activation of thermogenesis will be monitored by body temperature measurements.

For both the tablet and the oral suspension formulation, all excipients are pharmaceutical grade materials and are considered safe for the intended pediatric population. Their concentrations remain below the acceptable daily intake as set by the joint Food and Agriculture Organization (FAO) of the UN and the WHO (joint FAO/WHO Expert Committee on Food Additives, 2015).

The protocol is designed to monitor safety and mitigate risk to the pediatric subject by optimizing the number of vital signs, ECG and post void residual (PVR) volume assessments, minimizing the number of blood draws (safety and pharmacokinetic sampling) and focusing the number of study visits.

The use of population pharmacokinetics for the analysis of the pharmacokinetic profile of mirabegron allows reduction of the number of blood draws for pharmacokinetic analysis to 2. Butterfly needles can be used and are allowed to stay in place to reduce the number of punctures.

The blood draws for clinical laboratory tests have been minimized to lessen subject burden while ensuring subject safety. Additional hematology and biochemistry tests will be performed at visit 3/week 0 (baseline) and visit 8/week 14 (end of study [EoS]) only if an AE

related to hematology, biochemistry or urinalysis parameters occurred since the previous visit or at the discretion of the investigator.

The assessments to be performed are routine assessments and generally do not pose any particular risk to the subjects. Every effort will be made to reduce the anxiety felt by subjects, e.g., during a blood test, topical anesthetic will be offered at venipuncture to minimize distress of the subject.

Subjects may experience AEs associated with the assessments performed during the study, such as local irritations due to ECG recording, and bleeding, hematoma as a result of blood collection, or the experience of transient stinging or burning during emptying or of the passing of a little blood as a result of the urodynamic investigation. There is also a small risk of developing a bladder infection in relation to the urodynamic procedure.

An independent Data and Safety Monitoring Board (DSMB) will be established [Section 10.4 Study Organization]. A separate charter will describe the responsibilities of the DSMB.

3 STUDY OBJECTIVE(S) AND ENDPOINT(S)

The primary, secondary and exploratory objectives and endpoints for this study are listed in [Table 5]. Primary and secondary objectives and endpoints apply to children only; exploratory objectives and endpoints also apply to adolescents.

Table 5 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of mirabegron in children (5 to < 12 years of age) with OAB	• Change from baseline at the end of the 12-week treatment period: ○ Mean number of micturitions per 24 hours
Secondary	
• To evaluate the efficacy of mirabegron in children (5 to < 12 years of age) with OAB	• Change from baseline at the end of the 12-week treatment period: ○ Mean volume voided per 24 hours ○ Maximum volume voided ○ Mean number of daytime incontinence episodes per 24 hours ○ Mean number of nighttime incontinence episodes per 24 hours ○ Mean number of daytime micturitions per 24 hours • Number of dry (incontinence-free) days per 7 days at the end of the 12-week treatment period
Table continued on next page	

Objectives	Endpoints
● To evaluate the safety and tolerability of mirabegron in pediatric subjects with OAB	● Nature, frequency and severity of AEs ● Clinical laboratory tests (hematology, biochemistry and urinalysis) ● Vital signs (blood pressure and pulse) ● Routine 12-lead ECG ● PVR volume ● Acceptability and palatability questionnaire
● To evaluate the pharmacokinetics after multiple dose administration of mirabegron in pediatric subjects with OAB	● Steady-state C_{max}, AUC_{tau}, C_{trough}, T_{max}, CL/F and Vz/F. Additional parameters may be calculated based on the population pharmacokinetic model used
Exploratory	
● To evaluate the efficacy of mirabegron in pediatric subjects (5 to < 18 years) with OAB	● Percentage of subjects with a reduction in daytime incontinence episodes (< 50% reduction [nonresponder], 50% [partial responder] and 100% [responder]) ● Improvement from baseline in worst incontinence grading ● Change from baseline at the end of the 12-week treatment period adjusted for fluid intake: ○ Mean number of micturitions per 24 hours ● Change from baseline at the end of the 12-week treatment period (adolescents only): ○ Mean number of micturitions per 24 hours ○ Mean number of daytime micturitions per 24 hours ○ Mean volume voided per 24 hours ○ Mean number of incontinence episodes per 24 hours ● Number of dry (incontinence-free) days per 7 days at the end of the 12-week treatment period (adolescents only) ● Mean number of daytime grade 3 or 4 (PPIUS) urgency episodes per 24 hours (adolescents only)

AE: adverse event; ECG: electrocardiogram; OAB: overactive bladder; PPIUS: patient perception of intensity of urgency scale; PVR: post void residual.

3.1 Estimand

The estimand of most clinical importance for this study is defined by the following 4 attributes:

- Target population: all children who took at least 1 dose of the study drug, and in whom a nonmissing measurement for micturition frequency at baseline and after administration of the study drug is available
- Outcome measurement: micturition frequency/day (24 hours)
- Intercurrent events:
  1. Discontinuation from treatment (if week 12/EoT not obtained)
  2. AE UTI (if occurred in week 12/EoT)

3. Other muscarinic antagonists or botulinum toxin see [Appendix 12.6 List of Excluded Concomitant Medications]) (if taken during the last 2 weeks prior to week 12/EoT assessment); in all cases, a hypothetical strategy will be applied

- Population-based summary: Change from baseline to week 12/EoT in micturition frequency/day (= primary endpoint, primary estimator), compared to placebo

For this placebo-controlled study, this "de jure" estimand chosen is considered the appropriate choice. As some effect is expected early in the study and with continued treatment could be expected to be maintained, it's considered appropriate to impute for subjects with missing values at visit 7/week 12/EoT by their last recorded post baseline visit value prior to it. This strategy also assumes that the responses after the intercurrent event would be same as for patients continuing on their respective treatment.

4 STUDY DESIGN AND DOSE RATIONALE

4.1 Study Design

This is a double-blind, randomized, multicenter, parallel group, placebo-controlled sequential dose titration study to evaluate efficacy, safety and pharmacokinetics of mirabegron in pediatric subjects with OAB. Male and female pediatric subjects 5 to < 18 years of age with OAB; as defined according to the ICCS [Austin et al, 2014] who have had received 4 weeks of urotherapy prior to randomization.

Planned total number of study sites includes approximately 65 study sites across Europe, Latin America, Africa, Middle East, Asia-Pacific and North America.

The study consists of 3 periods with a total duration of 18 weeks.

- Screening period/urotherapy (4 weeks):

  This period starts with visit 1/week -4 (screening) and ends with visit 3/week 0 (baseline). After informed consent/assent has been obtained and immediately after eligibility has been confirmed at visit 1/week -4 (screening), subjects using prohibited medication will complete 1 week of washout (if applicable), while beginning 4 weeks of urotherapy.

  After a successful screening visit (visit 1/week -4 [screening]), all subjects will need to complete a 2-day bladder e-diary (weekend) to get acquainted with the bladder e-diary and the assessments. Completion of this bladder e-diary should start in the weekend prior to visit 2. All subjects will also complete a 7-day bladder e-diary the week prior to the baseline visit. The 7-day diary will consist of a 5-day weekday bladder e-diary and 2-day weekend e-diary.

- Double-blind, placebo-controlled period (12 weeks):

  This period starts with the day after visit 3/week 0 (baseline) and ends with visit 7/week 12 (EoT).

  At visit 3/week 0 (baseline), inclusion and exclusion criteria will be evaluated. Subjects continuing urotherapy who still meet the OAB entry criteria at baseline will be

randomized. Subjects whose symptoms are not satisfactorily controlled with urotherapy and still fulfill the inclusion/exclusion criteria will enter the study. These subjects will be randomized to receive mirabegron in PED25 or placebo using a 1:1 ratio. Subjects with a body weight of ≥ 35 kg are to receive the tablet unless unable to swallow tablets and would be provided the oral suspension as an alternative. Subjects with a body weight < 35 kg or those who cannot be dosed with the tablet will receive an oral suspension. Daily investigational product (IP) administration will start on day 1 (i.e., the day after this visit) and continue at this dose until visit 5/week 4 (i.e., for 4 weeks). Urotherapy will continue throughout the study treatment period until visit 7/week 12 (EoT).

At visit 5/week 4, dose up-titration to mirabegron in PED50 will be performed unless the investigator determines that the subject is adequately treated for OAB at the PED25 dose or if there are safety concerns identified and considered associated with the use of PED25. Dose down-titration from PED50 to PED25 can be done at any time thereafter for safety reasons.

Subjects will start with the subsequent 7-day bladder e-diaries approximately 7 days prior to the indicated visit (or TC).

Pharmacokinetic blood samples will be collected at visit 5/week 4 and visit 7/week 12 (EoT) as indicated in the Schedule of Assessments [Table 1].

- Follow-up period (2 weeks):

  This period starts the day after visit 7/week 12 (EoT) and ends with visit 8/week 14 (EoS). The follow-up period is applicable to all subjects who have been randomized and received IP.

  At visit 7/week 12 (EoT), IP administration will be stopped and a safety observation period of 2 weeks will start.

  An independent DSMB will be established. A separate charter will describe the responsibilities of the DSMB.

  A blinded interim analysis will be performed after 50% of children planned to be randomized have had their week 12/EoT assessment. The interim analysis will determine if the chance of a positive study with respect to the primary endpoint at the EoS is high enough to justify continuation of the study; otherwise, the study will be stopped for futility.

The IP will not be provided after study completion without written approval from the sponsor.

4.2 Dose Rationale

The target exposures of 69 and 188 ng•h/mL for PED25 and PED50 were derived from the adult phase 3 program and are the mean steady-state area under plasma concentration-time curve over dosing interval (AUC_{tau}) values following 25 and 50 mg prolonged-release tablets once daily in adults.

A population pharmacokinetic model was used to predict the pediatric equivalent dose for subjects in Study 178-CL-204. In brief, this population pharmacokinetic model was developed on adult phase 3 data, and allometric (weight-based) scaling was added to all clearance and volume terms to allow for scaling of the pharmacokinetics to pediatric subjects. The model was validated on pediatric data in Study 178-CL-202 (single ascending-dose study) and was shown to appropriately predict the pharmacokinetics of mirabegron in pediatric subjects.

Simulations were then performed to determine a body weight at which subjects would have steady-state exposures comparable to those in adults when dosed with 25 or 50 mg daily; this weight was determined to be ≥ 35 kg. Based on prior experience obtained in an ongoing Astellas study in another program in patients with NDO (Study 905-CL-047) the average age at which children reach a body weight of 35 kg is approximately 11 years. The dosing recommendation based on this modeling is in line with the literature [Momper et al, 2013] in which a meta-analysis of compounds submitted to the US FDA with a similar indication in adults and adolescents showed that in almost all cases, the adolescents required the same dose as the adults.

Therefore, subjects with a body weight of ≥ 35 kg can be dosed with mirabegron tablets unless unable to swallow tablets and would be provided the oral suspension as an alternative. Subjects with a body weight < 35 kg cannot be dosed with the 25 and 50 mg tablets because that would exceed the target exposures. Subjects with a body weight < 35 kg will therefore be dosed with mirabegron oral suspension.

Mirabegron oral suspension (8 mg/mL) has been developed for use in the pediatric population. The population pharmacokinetic model referred to above includes a formulation factor to account for the different (lower) relative bioavailability of the oral suspension compared to the tablet. This factor has been used in simulations to predict the suspension doses and weight categories that would have a reasonable variance around the target exposures.

For dosing with oral suspension, the weight range to be covered is from 13 kg (the approximate body weight of a 5-year-old child, according to the National Health and Nutrition Examination Survey database [McDowell et al, 2008]) to 35 kg (above which pediatric subjects could be dosed with the tablet formulation). Subjects with a body weight < 13 kg will not be included in the study. Suspension dosing for body weights ≥ 35 kg was also determined for cases in which a pediatric subject in that weight category who cannot be dosed with the tablets. The simulation resulted in the 3 body weight categories that can be found in the dosing schedule (see [Table 7]).

4.3 End of Study Definition

The study start is defined as the date the first subject and/or the subject's parent(s)/legal guardian(s) sign(s) informed consent/assent. End of the study is defined as the last visit or scheduled procedure shown in the Schedule of Assessments [Table 1] for the last subject in the study.

5 STUDY POPULATION

All screening assessments must be completed and reviewed to confirm the potential subject meets all eligibility criteria. Prospective approval of protocol deviations to eligibility criteria (also known as protocol waivers or exemptions) is not permitted.

5.1 Inclusion Criteria

Subject is eligible for the study if all of the following apply:

Inclusion at Visit 1/Week -4 (Screening)

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written informed consent/assent and privacy language as per national regulations (e.g., General Data Protection Regulations for European Union study sites) must be obtained from the subject and/or from the subject's parent(s)/legal guardian(s) prior to any study-related procedures (including withdrawal of prohibited medication, if applicable); assent by the subject is obtained as required by local law.
2. Subject has OAB defined according to the ICCS criteria.
3. Subject is a male or female between 5 to < 18 years of age, at screening.
4. Subject weighs at least 13 kg at screening.
5. Subject is able to take the IP in accordance with the protocol.
6. Subject agrees to drink an adequate fluid volume during urine collection weekends, as instructed by the investigator.
7. Subject and subject's parent(s)/legal guardian(s) agree that the subject will not participate in another interventional study while participating in the present study.
8. Subject and subject's parent(s)/legal guardian(s) are willing and able to comply with the study requirements and with the concomitant medication restrictions.
9. Female subject is not pregnant (see [Appendix 12.3 Contraception Requirements]) and at least 1 of the following conditions apply:
    a. Not a female of childbearing potential (see [Appendix 12.3 Contraception Requirements]).
    b. Female of childbearing potential who agrees to follow the contraceptive guidance (see [Appendix 12.3 Contraception Requirements]) from the time of informed consent/assent through at least 30 days after final IP administration.
10. Female subject must agree not to breastfeed starting at screening and throughout the study period and for 30 days after final IP administration.
11. Female subject must not donate ova starting at first dose of IP and throughout the study period and for 30 days after final IP administration.
12. Male subject with female partner(s) of childbearing potential (including breastfeeding partner[s]) must agree to use contraception (see [Appendix 12.3 Contraception Requirements]) throughout the treatment period and for 30 days after final IP administration.
13. Male subject must agree not to donate sperm during the treatment period and for 30 days after final IP administration.

14. Male subject with pregnant partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy throughout the study period and for 30 days after final IP administration.

Additional Inclusion at Visit 3/Week 0 (Baseline)

15. Subject must have a micturition frequency of at least 8 times (on average) per day, in the 7 days prior to visit 3/week 0 (baseline), as recorded in the bladder e-diary.
16. Subject must have at least 1 daytime incontinence episode (on average) per day, during the 7-day period before visit 3/baseline, as recorded in the bladder e-diary.
17. Subject whose symptoms are not satisfactorily controlled with urotherapy and still fulfills the inclusion/exclusion criteria will enter the study.

5.2 Exclusion Criteria

Subject will be excluded from participation in this study if any of the following apply:

Exclusion at Visit 1/Week -4 (Screening)

1. Subject has extraordinary daytime only urinary frequency according to the ICCS definition.
   - This applies to a toilet-trained child who has the frequent need to void that is associated with small micturition volumes solely during the day.
   - The daytime voiding frequency is at least once per hour with an average voided volume of < 50% of expected bladder capacity (EBC) (typically 10% to 15%).
   - Incontinence is rare and nocturia is absent.
2. Subject has an uroflow indicative of pathology other than OAB.
3. Subject has monosymptomatic enuresis.
4. Subject has dysfunctional voiding.
5. Subject has bladder outlet obstruction, except if successfully treated.
6. Subject has anatomical anomalies (surgically treated or untreated) that affect lower urinary tract function.
7. Subject with hematuria on dipstick test. In the case of hematuria on dipstick test in a female during menstruation, the test can be repeated before randomization (after the end of menstruation).
8. Subject with diabetes insipidus.
9. Subject has kidney or bladder stones.
10. Subject has suffered from chronic UTI or has had more than 3 UTIs in the 2 months prior to visit 1/week -4 (screening).
11. *Criterion has been removed*.
12. Subject has stage 2 hypertension or subject has stage 1 hypertension that is not well controlled, as defined by the 2017 American Academy of Pediatrics Clinical Practice Guidelines.
13. Subject has QTcF > 440 msec on screening ECG, a risk of QT prolongation (e.g., hypokalemia, long QT syndrome [LQTS] or family history of LQTS or exercise-induced syncope) or is currently taking medication known to prolong the QT interval.

14. Subject's aspartate aminotransferase (AST) or alanine aminotransferase (ALT) is ≥ 2 × upper limit of normal (ULN) or total bilirubin (TBL) is ≥ 1.5 × ULN according to age and sex (subjects with Gilbert's syndrome are excepted from the bilirubin threshold).
15. Subject has mild or moderate renal impairment (estimated glomerular filtration rate according to the modified Schwartz of < 60 mL/min per 1.73 m^2).
16. Subject has a symptomatic (symptoms can include pain, fever, hematuria, new onset foul-smelling urine) UTI. Note: if the UTI is treated successfully (clinical recovery: confirmed by dipstick test and repeated dipstick test after 14 days [both should be negative]), the subject can be rescreened.
17. Subject has a history or presence of any malignancy.
18. Subject uses any drugs that are sensitive cytochrome P450 2D6 (CYP2D6) substrates with a narrow therapeutic index, sensitive P-glycoprotein (P-gp) substrates, or moderate or strong cytochrome CYP3A4/5 or P-gp inhibitors or inducers after the start of washout.
19. Subject is using or has used prohibited prior and/or concomitant medication(s) [Appendix 12.6 List of Excluded Concomitant Medications] that cannot be discontinued.
20. Subject has known or suspected hypersensitivity to mirabegron or any components of the formulations used.
21. Subject has participated in another clinical study (and/or subject has received any investigational therapy within 30 days (or 5 half-lives of the drug, or the limit set by national law, whichever is longer) prior to visit 1/week -4 (screening).
22. Subject received urinary catheterization within 2 weeks prior to screening.
23. Subject has constipation as defined by the Rome IV criteria that cannot be successfully treated prior to study entry.
24. Female subject who has been pregnant within 6 months prior to screening or breastfeeding within 3 months prior to screening.
25. Subject has any condition, which in the opinion of the investigator, makes the subject unsuitable for study participation.

<u>Additional Exclusion at Visit 3/Week 0 (Baseline)</u>

26. Subject has extraordinary daytime only urinary frequency according to the ICCS definition based on the bladder e-diary.
27. Subject has monosymptomatic enuresis confirmed by the bladder e-diary.
28. Subject has a maximum voided volume (morning volume excluded) > EBC for age ([age +1] × 30) in mL, based on the bladder e-diary.
29. Subject has polyuria defined as voided urine volumes of > 40 mL/kg baseline body weight during 24 hours or > 2.8 L urine for a child weighing ≥ 70 kg (ICCS definition) [Austin et al, 2014], based on bladder e-diary.
30. Subject has PVR volume > 20 mL (lowest PVR volume result) as measured by ultrasonography.
31. Subject suffers from a symptomatic (symptoms can include pain, fever, hematuria, new onset foul-smelling urine) UTI. Note: if a symptomatic UTI is present, all visit 3/week 0 (baseline) assessments must be postponed until the UTI is successfully treated (clinical recovery: confirmed by dipstick test and repeated dipstick test after

14 days [both should be negative]), and the urotherapy should continue. The postponed visit 3/week 0 (baseline) should be within 14 days of the intended visit 3/week 0 (baseline).

32. Subject with hematuria on dipstick test. In the case of hematuria on dipstick test in a female during menstruation, the test can be repeated before randomization (after the end of menstruation).
33. Subject has a pulse > 99th percentile for age.
34. Subject has stage 2 hypertension or subject has stage 1 hypertension that is not well controlled, as defined by the 2017 American Academy of Pediatrics Clinical Practice Guidelines.
35. Any reason, in the opinion of the investigator, that makes the subject unsuitable for study participation.

5.3 Restrictions During the Study

Restrictions for foods and drinks are not applicable. On visit days where a pharmacokinetic sample is planned in the clinic, dosing should occur in the clinic and breakfast should be eaten at the clinic within 1 hour before dosing.

5.4 Screen Failures

A screen failure is defined as a potential subject who signed the informed consent form (ICF)/assent and/or whose parent(s)/legal guardian(s) signed the ICF/assent, but did not meet 1 or more criteria required for participation in the study and was not enrolled.

For screen failures, the demographic data, date of signing the ICF/assent, inclusion and exclusion criteria, AEs up to the time of screen failure and reason for screen failure will be collected in the electronic data source. Rescreening is only allowed once for an individual subject.

5.4.1 Rescreen

5.4.1.1 Rescreen for Urinary Tract Infection or Constipation

In addition, if a subject has UTI/constipation at visit 3/week 0 (baseline), all visit 3/week 0 (baseline) assessments must be postponed until the UTI/constipation is successfully treated (clinical recovery), and the urotherapy should continue. Then the subject's postponed visit 3/week 0 (baseline) assessments should be completed within 14 days of the intended visit 3/week 0 (baseline) or the subject will be documented as a screen failure and can be re-screened. If the postponed visit 3/week 0 (baseline) is rescheduled within 14 days of the intended visit 3/week 0 (baseline) visit, then the subject's 7-day e-diary will be restarted with respect to the postponed visit 3/week 0 (baseline) visit.

5.4.1.2 Rescreen for Other Eligibility Criteria

Results of screening assessments that do not meet the parameters required by eligibility criteria (e.g., clinical laboratory tests, vital signs, physical examination, ECG, etc.) may be repeated once within the 4-week screening period without the need to register the subject as a screen failure. If any exclusion criteria are met or more than 4 weeks elapse from the date of signing the ICF/assent, the subject must be documented as a screen failure. In order to

rescreen a subject previously registered as a screen failure, a new ICF/assent must be signed and the subject will be entered into screening with a new subject identification number. The old subject number will also be entered to link the subject's data.

6 INVESTIGATIONAL PRODUCT(S) AND OTHER STUDY TREATMENT(S)

6.1 Investigational Product(s) Administered and Other Study Treatment(s)

6.1.1 Investigational Product(s)

Mirabegron prolonged-release (or extended-release) tablets were approved in Japan in 2011, and to date have been approved in more than 81 countries worldwide; trade names include Betanis® [BETANIS® prescribing information, Jun 2012], Betmiga® [BETMIGA® prescribing information, Apr 2018] and Myrbetric® [MYRBETRIC® prescribing information, Jun 2012]. The approved indication is the treatment of OAB with symptoms of urge urinary incontinence, urgency and urinary frequency in adults.

Mirabegron oral suspension has been developed as an appropriate formulation for weight-based dosing in smaller children.

Table 6 Investigational Product(s)

Name	Mirabegron	Matching Placebo	Mirabegron	Matching Placebo
Use	Test product	Placebo	Test product	Placebo
Dosage Formulation	Tablet	Tablet	Oral suspension	Oral suspension
Physical Description	Brown (25 mg) or yellow (50 mg) film-coated tablet	Brown (25 mg) or yellow (50 mg) film-coated tablet	Yellowish white granules reconstituted with water to prepare oral suspension	Yellowish white granules reconstituted with water to prepare oral suspension
Unit Dose Strength	25 and 50 mg	To match mirabegron	8 mg/mL	To match mirabegron
Packaging and Labeling	-35 tablets of Mirabegron 25 mg in a wallet -35 tablets of Mirabegron 50 mg and 7 tablets of Mirabegron 25 mg in a wallet	35 tablets of Mirabegron 25 mg placebo in a wallet -35 tablets of Mirabegron 50 mg placebo and 7 tablets of Mirabegron 25 mg placebo in a wallet	1 bottle of Mirabegron 830 mg granules for oral suspension	1 bottle of placebo Mirabegron 830 mg granules for oral suspension
Route of Administration	Oral	Oral	Oral	Oral
Administration Instruction	IP will be administered orally, once daily in the morning around the same time of day and around time of food intake (i.e., within 1 hour before or after breakfast). Tablets will be administered with a sip of water (tablet should be taken as a whole and should not be chewed, divided or crushed).		IP will be administered orally, once daily in the morning around the same time of day and around time of food intake (i.e., within 1 hour before or after breakfast). Oral suspension will be administered via an oral syringe with a sip of water afterwards. Detailed information on the preparation of the mirabegron oral suspension will be provided to the subject and subject's parent(s)/legal guardian(s) in local language.	
IMP or Non-IMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by sponsor	Provided centrally by sponsor	Provided centrally by sponsor	Provided centrally by sponsor

IMP: investigational medicinal product; IP: investigational product

For detailed information on mirabegron prolonged-release tablets, please refer to the current locally-available product information for mirabegron. For detailed information on mirabegron granules for oral suspension, please refer to the Investigator's Brochure and Investigational Medicinal Product Dossier.

IP will be administered according to [Table 7].

Table 7 Body Weight-based Doses for Tablets or Suspension

	Body Weight Range† (kg)	Oral Suspension Volume‡ (mL)	Tablet Dose (mg)
PED25	13 to < 22	3	-
	22 to < 35	4	-
	≥ 35	6	25
PED50	13 to < 22	6	-
	22 to < 35	8	-
	≥ 35	11	50

PED25: pediatric equivalent dose 25 mg; PED50: pediatric equivalent dose 50 mg

† Subjects with a body weight ≥ 35 kg will receive the tablet. Subjects with a body weight< 35 kg or those who cannot be dosed with the tablet will receive an oral suspension.

‡ Oral suspension containing 8 mg/mL.

The starting dose will be PED25 starting administration the day after visit 3/week 0 (baseline). At visit 5/week 4, dose up-titration to PED50 will be performed unless the investigator determines that the subject is adequately treated for OAB at the PED25 dose or if there are safety concerns identified and considered associated with the use of PED25. Dose down-titration from PED50 to PED25 can be done at any time thereafter for safety reasons.

6.1.2 Other Study Treatment(s)

During the screening period, all subjects will receive 4 weeks of urotherapy. At visit 3/week 0 (baseline) inclusion and exclusion criteria will be evaluated. Subjects continuing urotherapy who still meet the OAB entry criteria at baseline will be randomized. Urotherapy will continue throughout the study treatment period until visit 7/week 12 (EoT).

Urotherapy is to be discussed and confirmed with the subject or parent(s)/legal guardian(s) during each visit (or TC) to ensure compliance.

Standard urotherapy includes information on and demystification of the voiding function and dysfunction, instruction on voiding habits (such as regular voiding, voiding posture), life style advice regarding fluid intake, prevention of constipation, recording of symptoms and voiding habits in bladder diaries and support via regular follow-up by a caregiver.

Specific interventions include various forms of pelvic floor training (relaxation, contraction), behavioral modification, electrical stimulation, catherization and biofeedback (use of objective measures, e.g., uroflow or EMG to show children how far they relax their pelvic floor during voiding). Urotherapy can also include elements of cognitive behavioral therapy [Nevéus et al, 2006].

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Packaging and Labeling

All IP used in this study will be prepared, packaged and labeled under the responsibility of qualified personnel at Astellas Pharma Europe B.V. (APEB) or sponsor's designee in accordance with APEB or sponsor's designee standard operating procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines, and applicable local laws/regulations.

Each IP package will bear a label conforming to regulatory guidelines, GMP and local laws and regulations that identifies the contents as an investigational drug.

A qualified person of APEB or sponsor's designee will perform the final release of the medication according to the requirements of the EU Directive 2003/94/EC annex 13.

6.2.2 Handling, Storage and Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IP received and any discrepancies are reported and resolved before use of the IP.
2. Only subjects enrolled in the study may receive IP and only authorized study site personnel (listed under delegation log) may supply or administer IP. Only IP with appropriate expiry/retest dating may be dispensed.
3. All IP must be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions and access must be limited to the investigator and authorized study site personnel.
4. The investigator, institution or the head of the medical institution (where applicable) is responsible for accountability, reconciliation and record maintenance (i.e., receipt, reconciliation and final disposition records).

The site must return IP to the Sponsor or designee at the EoS or upon expiration. If due to institutional policy or local law, used IP cannot be returned to the Sponsor or designee the IP may be destroyed according to local law.

6.3 Randomization and Blinding

6.3.1 Blinding Method

This is a double-blind study. Subjects will be randomized to receive mirabegron or placebo in a blinded manner such that neither the investigator, sponsor's study management team, clinical personnel, nor the subject will know which IP is being administered. The randomization number will be assigned based on information obtained from the interactive response technology (IRT) system.

6.3.2 Confirmation of the Indistinguishability of the Investigational Product

The appearance of both the dosage form and packaging of mirabegron are identical to those of their matching placebo.

6.3.3 Retention of the Assignment Schedule and Procedures for Treatment Code Breaking

The randomization list and treatment assignment blind will be maintained by the IRT system.

6.3.4 Breaking the Treatment Code for Emergency

The treatment code for each randomized subject will be obtained from the IRT system in the event of a medical emergency requiring knowledge of the treatment assigned to the subject. The IRT system will be programmed with blind-breaking instructions that can only be requested by the investigator or sub investigator(s) designated to have access to perform blind-breaking. In case of a medical emergency, the investigator has the sole responsibility for determining if unblinding of the subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a subject's treatment assignment unless this could delay emergency treatment for the subject.

Prior to the initial IP shipment, the investigator must have confirmed ability to access code-break through the IRT system and must have a designated backup (e.g., redundant processes) to support emergency unblinding requirements.

Prior to randomization, subjects should be provided with information that includes the study site emergency contact number and back-up contact number in case of a medical emergency. Any unblinding by the investigational personnel must be reported immediately to the sponsor and include an explanation of why the IP was unblinded. If unblinding is associated with a serious adverse event (SAE), the investigator is to follow the instructions in [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events].

Care will be taken to limit knowledge of the treatment assignment, in case this can affect the blinding of other subjects or future study assessment for the subject.

6.3.5 Breaking the Treatment Code by the Sponsor

The sponsor may break the treatment code for subjects who experience a suspected unexpected serious adverse reaction (SUSAR) in order to determine if the individual case or a group of cases requires expedited regulatory reporting. Individual emergency codes will be provided to the limited personnel who are responsible to break the codes for all SUSAR cases for reporting purposes.

6.3.6 Assignment and Allocation

6.3.6.1 Subject Number

Subjects will be assigned a subject number at study entry (i.e., signing the ICF/assent). The subject numbers will be sequential and rising. The subject number will comprise of 10 digits; 5 digits for the site number (provided by the sponsor) and 5 digits for the consecutive subject number.

Subjects will be randomized to receive IP according to the randomization schedule obtained via the IRT system. The study site personnel will dispense the treatment according to the IRT system's assignment. Specific procedures for randomization through the IRT system are contained in the study procedures manual.

6.3.6.2 Randomization Number

Subjects will be randomized in a 1:1 ratio to receive treatment according to the randomization schedule obtained via the IRT system. The study site personnel will dispense the treatment according to the IRT system's assignment. Specific procedures for randomization through the IRT system are contained in the study procedures manual.

6.3.6.3 Subject Replacement

An enrolled subject who withdraws or discontinues before dosing or before randomization will be considered a screen failure. Randomized subjects who withdraw or discontinue will not be replaced.

6.4 Investigational Product(s) and Other Study Treatment(s) Compliance

6.4.1 Investigational Product(s)

Subject compliance with IP and other study treatment(s) will be assessed at each visit. Compliance will be assessed by counting or weighing returned IP at each clinic visit. Deviations from the prescribed dose regimen will be recorded in the electronic data source.

If compliance less than 80%, the investigator or designee is to counsel the subject and/or the subject's parent(s)/legal guardian(s) and ensure steps are taken to improve compliance.

6.4.2 Other Study Treatment(s)

Subjects will have to receive 4 weeks of urotherapy prior to randomization and will continue urotherapy throughout the study. Urotherapy is to be discussed and confirmed with the subject or parent(s)/legal guardian(s) during each TC to ensure subject compliance.

Specific interventions include various forms of pelvic floor training (relaxation, contraction), behavioral modification, electrical stimulation, catherization and biofeedback (use of objective measures, e.g., uroflow or surface EMG to show children how far they relax their pelvic floor during voiding). Urotherapy can also include elements of cognitive behavioral therapy [Nevéus et al, 2006].

6.5 Previous and Concomitant Treatment (Medication and Nonmedication Therapy)

Subjects are not allowed to use ongoing treatment with any of the following prohibited medications after the start of the washout:

- Any medication, other than the IP, used for the treatment of OAB (including tricyclic antidepressants, 1st generation H1 antagonists and alpha blockers)

- Any drugs that are sensitive CYP2D6 substrates with a narrow therapeutic index or sensitive P-gp substrates
- Any medications known to prolong the QT interval
- Any medication that is a moderate or strong cytochrome CYP3A4/5 or P-gp inhibitor or inducers including natural and herbal remedies
- Intradetrusor botulinum toxin injections; except if given > 9 months prior screening and symptoms reappeared comparable to those before botulinum toxin injections
- Nonmedication therapies like urotherapy, chiropractic, physical therapy will also be collected on the nonmedication therapy case report form (CRF).
    - The site will need to make special notes for those subjects who do not follow urotherapy for 7 or more consecutive days in electronic case report forms (eCRFs).

Please refer to [Appendix 12.6 List of Excluded Concomitant Medications] for drug classes or specific medications that are prohibited during participation in the study. These treatments are prohibited from being started after the start of the washout period. All other concomitant treatment use will be reported.

The use of previous and concomitant treatment within 30 days prior to signing the informed consent and throughout the study will be documented on the appropriate eCRF.

6.6 Dose Modification

At visit 5/week 4 (i.e., after 4 weeks on PED25), dose up-titration to PED50 will be performed unless the investigator determines that the subject is adequately treated for OAB at the PED25 dose or if there are safety concerns identified and considered associated with the use of PED25.

At any time, down-titration from PED50 to PED25 can be performed if there is an AE possibly related to the drug that is considered bothersome by the subject or that leads to medical intervention (e.g., initiation of medication therapy to treat the AE). Of note, PED25 is the lowest dose to be used in this study.

Criteria for discontinuation of individual subject(s) from study treatment are listed in [Section 8.1 Discontinuation of Individual Subject(s) from Study Treatment(s)].

6.7 Criteria for Continuation of Treatment(s)

Mirabegron (PED25/PED50) will not be made available after conclusion of the study to subjects who are still receiving and benefitting from study treatment in countries where the product does not have marketing approval and is not commercially available.

7 STUDY PROCEDURES AND ASSESSMENTS

Refer to the Alternate Schedule of Assessments [Table 12] in [Appendix 12.13 Clinical Study Continuity] for acceptable alternate methods to assess safety and efficacy parameters in the event the study is interrupted due to a crisis (e.g., natural disaster, pandemic).

7.1 Efficacy Assessments

7.1.1 Bladder Electronic Diary

The bladder diary is part of the subject's e-diary. After a successful visit 1/screening, all subjects start with the completion of a 2-day weekend e-diary to get acquainted with the e-diary and the assessments. Completion of this diary should start in the weekend prior to visit 2.

The e-diary data is reviewed by the investigator or designee prior to the start of visit 2 and discussed and confirmed with the subject or the subject's parent(s)/caregiver(s) during the (telephone) visit 2. If the investigator is under the impression that the subject and/or the subject's parent(s)/caregiver(s) can perform all the required assessments and are able to complete all required forms with credible data, completion is considered successful.

If successful completion of the 2-day weekend e-diary is confirmed at visit 2, subjects will start with collection of the 7-day bladder e-diary approximately 7 days prior to visit 3/week 0 (baseline). The 7-day bladder e-diary consists of a 5-day weekday bladder e-diary, which is used to collect micturition frequency and incontinence episodes; the remaining consists of the 2-day weekend diary.

After successful randomization, subsequent bladder e-diaries will be completed by the subject or subject's parent(s)/caregiver(s) in the week prior to visit 4/week 2, visit 5/week 4, visit 6/week 8 and visit 7/week 12. Completion of 7-day bladder diaries should start approximately 7 days prior to the indicated visit (or telephone contact).

7.2 Safety Assessments

7.2.1 Adverse Events

See [Section 7.3 Adverse Events and Other Safety Aspects] for information regarding AE collection and data handling.

7.2.2 Laboratory Assessments

Blood samples for hematology and biochemistry and urine samples for urinalysis will be collected as indicated in the Schedule of Assessments [Table 1]. All clinical laboratory assessments will be performed at a central laboratory except for urinalysis dipsticks which will be conducted locally to support study eligibility or AEs. A urine pregnancy test in female subjects of childbearing potential will be performed at all on-site visits. A topical anesthetic cream or plaster must be offered at the point of venipuncture to minimize distress of the subject. For sampling the arm opposite to the arm used for blood pressure measurements should be used (i.e., preferably the left arm). Blood sampling should occur after vital signs and ECG measurements.

Sample collection, handling and storage will be described in a laboratory manual. All clinical laboratory test results, including ULNs used in exclusion and discontinuation criteria, will be compared to age appropriate norms.

Scheduled blood sampling will only be performed at screening (visit 1), week 4 (visit 5) and EoT (visit 7) to keep the burden to subjects at a minimum. Additional hematology, biochemistry and urinalysis (urinalysis dipstick) tests will be performed at visit 3/week 0 (baseline) and visit 8/week 14 (EoS) only if an AE related to hematology, biochemistry or urinalysis parameters occurred since the previous visit or at the discretion of the investigator. If any of the clinical laboratory tests results are outside the normal range at any scheduled time point during the study, the investigator may decide to repeat the test(s) on new samples. The clinical relevance of the abnormal results will be documented. Clinically relevant changes will be recorded as AEs (see [Section 7.3 Adverse Events and Other Safety Aspects]).

Refer to the Alternate Schedule of Assessments [Table 12] for acceptable alternate methods to assess safety and efficacy parameters in the event the study is interrupted due to a crisis (e.g., natural disaster, pandemic).

7.2.3 Vital Signs and Electrocardiograms

7.2.3.1 Clinic-measurement of Vital Signs and Electrocardiograms

Blood pressure (systolic blood pressure [SBP] and diastolic blood pressure [DBP]), pulse, and routine 12-lead ECG measurements will be taken as indicated in the Schedule of Assessments [Table 1].

The preferred method of measurement is via the auscultatory technique. If this method is not available at the study site, measurements will be per standard clinic practices. Single measurements of blood pressure, pulse, body temperature and ECGs will be measured in the sitting position (when possible, otherwise supine, but always in the same position). Subject should have been calm and without distress for at least 5 minutes. Preferably, the right arm should be used to measure vital signs. Body temperature will be measured with an ear thermometer as per standard of care. Clinic measurements will be used to assess eligibility.

For ECGs, dates and times may be generated by the machine's internal clock and are considered source data. The results are to be interpreted by qualified personnel in real time for the management of the subjects' clinical condition. The principal investigator/designee will initial and date and provide his/her clinical interpretation on each report. Any abnormalities must be evaluated in clinical context (based on subject's medical history and concomitant medication) and the investigator should determine if it is clinically significant. The results (normal, abnormal not clinically significant, abnormal clinically significant) are to be recorded in the eCRFs.

The original print-out and an electronic copy of all scheduled and unscheduled ECG tracings should be maintained on site as source data.

Clinic measurements will be used to assess eligibility. Clinically relevant adverse changes in vital signs and ECGs will be recorded as an AE (see [Appendix 12.4.1 Definition of Adverse Events]).

7.2.3.2 Self-measurement of Vital Signs

Self-blood pressure monitoring (SBPM; SBP and DBP) will be measured as indicated in the Schedule of Assessments [Table 1] and whenever deemed necessary by the investigator.

SBPM will be measured once in the morning and evening during the 2-day weekend bladder e-diary collection period. Measurements will be taken in the sitting position (when possible, otherwise supine, but always in the same position). Preferably, the right arm should be used. Subject should have been calm and without distress for at least 5 minutes. Morning measurement should be taken before IP intake and evening measurement should be taken prior to bedtime.

Devices for measuring blood pressure will be provided to subjects for home measurements. Detailed on-site training to use the SBPM device and a booklet with operating instructions in local language will be provided to the subject and the subject's parent(s)/legal guardian(s). Results will be directly entered by the subject or subject's parent(s)/legal guardian(s) in the e-diary (see [Section 10.1 Data Collection]).

7.2.4 Physical Examination

Physical examination will be performed as indicated in the Schedule of Assessments [Table 1] and whenever there is a medical indication.

The physical examination will be performed as described in the study site's SOPs for physical examination. In this study, the physical examination will be done to evaluate general physical condition and encompasses standard, full physical examinations to assess general appearance, skin, eyes, ears, nose, throat, neck, cardiovascular, chest and lungs, abdomen, musculoskeletal, neurologic status, mental status and lymphatic systems.

New or worsening clinically significant physical examination findings after signing of ICF will be recorded as AEs if they meet the criteria in [Section 7.3 Adverse Events and Other Safety Aspects].

7.2.5 Post Void Residual Volume Assessments

PVR volume will be assessed by ultrasonography at visit 3/week 0 (baseline), visit 5/week 4, visit 7/week 12 (EoT) and visit 8/week 14 (EoS). For each subject, the same method should be used throughout the study. The bladder should only be emptied when it was initially filled with preferably > 50% of the bladder capacity for age. Every attempt should be made to measure PVR volume within a minute of voiding. A PVR volume of ≤ 20 mL is sufficient and the assessment does not have to be repeated. If the PVR volume is > 20 mL, the PVR volume assessment should be repeated (filled with preferably > 50% of the bladder capacity for age). If the subject is unable to complete a second measurement, it is up to the investigator to judge whether it can be skipped (and write the reason in the CRF). At visit 3/week 0 (baseline), the lowest PVR volume result measured should be used to evaluate the exclusion criterion. In case the lowest PVR volume measured is > 20 mL at visit 3/week 0 (baseline), the subject should be excluded from the study.

7.2.6 Acceptability and Palatability Questionnaire

The acceptability and palatability questionnaire will be completed as indicated in the Schedule of Assessments [Table 1]. For each IP formulation, a separate questionnaire is available [Appendix 12.8 Acceptability and Palatability Questionnaire for Tablets and Appendix 12.9 Acceptability and Palatability Questionnaire for Oral Suspension].

7.2.7 Order of Assessments

The following order should be followed when more than 1 assessment is required at a time point with blood sampling for pharmacokinetics/metabolic profiling being collected nearest to the scheduled time point:

1. ECG
2. Vital signs
3. Blood collection

7.3 Adverse Events and Other Safety Aspects

The definitions of an AE or SAE can be found in [Appendix 12.4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up or Reporting].

The investigator and medically qualified designee(s) are responsible for detecting, documenting and recording events that meet the definition of an AE or SAE.

7.3.1 Time Period for Collecting Adverse Event and Serious Adverse Event Information

In order to identify any events that may be associated with study procedures and could lead to a change in the conduct of the study, Astellas collects AEs even if the subject has not received IP. AE collection begins after the signing of the ICF/assent and will be collected until 30 days after the final IP administration or when the subject is determined to be a screen failure.

7.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The methods of recording, evaluating and assessing seriousness, causality and severity of AEs and SAEs are described in [Appendix 12.4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up or Reporting]. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

An AE with a change in severity is recorded as a new AE.

7.3.3 Follow-up of Adverse Events

All AEs occurring during or after the subject has discontinued the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized by the investigator.

If after the protocol-defined AE collection period (see [Section 7.3.1 Time Period for Collecting Adverse Event and Serious Adverse Event Information]), an AE progresses to an

SAE, or the investigator learns of any (S)AE (serious adverse event or adverse event) including death, where he/she considers there is reasonable possibility it is related to the IP or study participation, the investigator must promptly notify the sponsor.

7.3.4 Reporting of Serious Adverse Events

Prompt notification by the investigator to the sponsor of an SAE is essential, so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study intervention under clinical investigation are met.

In the case of an SAE, the investigator must contact the sponsor by fax or email immediately (within 24 hours of awareness).

Procedures for reporting SAEs to the sponsor are described in [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events].

7.3.5 Disease-related Events and/or Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

Under this protocol, the following event(s) will not be considered as an SAE:

- Disease progression: events including defined study endpoints that are clearly consistent with the expected pattern of progression of the underlying disease are not to be recorded as AEs. These data will be captured as efficacy assessment data as outlined in [Section 7.1 Efficacy Assessments]. If there is any uncertainty as to whether an event is due to anticipated disease progression and/or if there is evidence suggesting a causal relationship between the IP and the event, it should be reported as an SAE. All deaths up to 30 days after the final IP administration must be reported as an SAE, even if attributed to disease progression.
- Preplanned and elective hospital/clinical procedures/interventions or procedures for diagnostic, therapeutic, or surgical procedures for a pre-existing condition that did not worsen during the course of the study. These procedures are collected per the electronic data source's completion guidelines.

7.3.6 Adverse Events of Special Interest

Adverse Events of Special Interest include:

- Increased blood pressure
- Cardiac electrophysiology (including QTc prolongation) and cardiac arrhythmia (including increased heart rate, tachycardia, atrial fibrillation and palpitations)
- Hypersensitivity reactions
- Urinary retention
- Hepatotoxicity
- Seizure/syncope

AEs (serious or nonserious) of special interest are to be collected via the SAE worksheet and reported within 24 hours as described in [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events].

7.3.7 Special Situations

Certain special situations observed in association with the IP, such as incorrect administration (e.g., wrong dose of IP or background therapy) are collected in the electronic data source, as protocol deviation per [Section 10.3 Major Protocol Deviations] or may require special reporting, as described below. These special situations are not considered AEs, but do require to be communicated to Astellas as per the timelines defined below.

If a special situation is associated with, or results in, an AE, the AE is to be assessed separately from the special situation and captured as an AE in the electronic data source. If the AE meets the definition of an SAE, the SAE is to be reported as described in [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events] and the details of the associated special situation are to be included in the clinical description on the SAE worksheet.

The special situations are:

- Pregnancy
- Medication error/overdose
- Misuse/abuse
- Occupational exposure
- Suspected drug-drug interaction

Instructions and procedures for reporting special situations are provided in [Appendix 12.4.6 Reporting Procedures for Special Situations].

7.3.8 Supply of New Information Affecting the Conduct of the Study

When new information becomes available that is necessary for conducting the study properly, the sponsor will inform all investigators involved in the study as well as the appropriate regulatory authorities. Investigators should inform the IRB/IEC of such information when needed.

The investigator will also inform the subjects, who will be required to sign an updated ICF/assent in order to continue in the study.

7.3.9 Urgent Safety Measures

An urgent safety measure (USM) is an intervention that is not defined by the protocol and can be put in place with immediate effect without needing to gain prior approval by the sponsor, relevant competent authorities and IRB/IEC, where applicable, in order to protect subjects from any immediate hazard to their health and/or safety. Either the investigator or the sponsor can initiate a USM. The cause of a USM can be safety-, product- or procedure-related.

7.3.10 Reporting Urgent Safety Measures

In the event of a potential USM, the investigator must contact the study physician (within 24 hours of awareness). Full details of the potential USM are to be recorded in the subject's

medical records. The sponsor may request additional information related to the event to support their evaluation.

If the event is confirmed to be a USM, the sponsor will take appropriate action to ensure the safety and welfare of the subjects. These actions may include but are not limited to a change in study procedures or study treatment, halting further enrollment in the study, or stopping the study in its entirety. The sponsor or sponsor's designee will notify the relevant competent authorities and concerned ethics committee within the timelines required per current local regulations, and will inform the investigators, as required. When required, investigators must notify their IRB/IEC within timelines set by regional regulations.

7.4 Pharmacokinetics

Blood samples for the analysis of mirabegron in plasma will be collected as indicated in the Schedule of Assessments [Table 1] for the evaluation of pharmacokinetics.

The actual date and time of each blood sample collection will be documented. Sample collection, handling and storage will be described in the laboratory manual. Bioanalysis of mirabegron will be performed using a validated method.

A topical anesthetic cream or plaster must be offered at the point of venipuncture to minimize distress of the subject. For sampling the arm opposite to the arm used for blood pressure measurements should be used (i.e., preferably the left arm). Blood sampling should occur after vital signs and ECG measurements.

The pharmacokinetic parameters that will be calculated as part of the secondary pharmacokinetic endpoint are steady-state C_{max}, AUC_{tau}, C_{trough}, T_{max}, CL/F and V_z/F. Additional parameters may be calculated based on the population pharmacokinetic model used.

7.5 Pharmacodynamics | Immunogenicity

Not applicable.

7.6 Electronic Clinical Outcome Assessment

For this study, it has been decided that there are justifiable scientific reasons (i.e., recall bias) to limit subject reported changes to changes reported by the subject to the site within 1 business day of its entry, as changes outside of this window could potentially impact the data integrity of the study. The data that will be under this rule are all subject/guardian/ parent-entered primary and secondary endpoints data. However, the site/investigator can remove/inactivate any data that they determine to be in error at any time with source documentation to support the change including subject confirmation. Data will never be deleted from the electronic database by the electronic clinical outcome assessment (eCOA) service provider, but will be removed logically as per investigator's request and approval. All data changes are audit trailed showing the original entries alongside all changes including who requested the change, why it was requested, who made the change and when it was

made. Audit trails are reviewed by the sponsor/clinical research organization (CRO) to ensure adherence to the protocol and appropriate source exists at site to substantiate the change.

Subject bladder diaries, questionnaires and other data will be completed by the subject or the subject's parent(s)/legal guardian(s)/caregiver(s) on an electronic device (e-diary). The information on the electronic device will be automatically uploaded to a central website. The investigator or site designee should review the diaries and questionnaire data on the website to ensure completion and protocol compliance before each planned visit of the subject (on site visit or TC) and discuss the results or retrain the subject and/or subject's parent(s)/legal guardian(s)/caregiver(s), if applicable. In case clinically relevant adverse changes are noticed during review of the e-diary, these will be recorded as an AE [Appendix 12.4.1 Definition of Adverse Events].

The bladder e-diary, questionnaire results and other data collected in the e-diary will be transferred electronically to the sponsor or designee at predefined intervals during the study. The vendor will provide the sponsor or designee with a complete and clean copy of the study data. The ownership of this data is with the investigator and subsequently any changes requested to these subject-reported or nonsubject reported data will be made using the vendor's established process (e.g., a data clarification form to the vendor). The requested change must be supported by documented evidence at study site.

For this study the following information will be collected and entered by the subject or subject's parent(s)/legal guardian(s) in the e-diary (see [Sections 7.2.6 Acceptability and Palatability Questionnaire and 7.2.3.2 Self-measurement of Vital Signs] for detailed information per visit):

- Bladder e-diary:
  - Each day on weekend prior to week -2: volume measurements
  - Each day for 7 days before visit 3/week 0: micturition frequency
  - Each day for 7 days before visit 3/week 0: incontinence episodes
  - On the 2-day weekend period: volume measurements
- SBPM (blood pressure and pulse):
  - Each day of the 2-day weekend period: twice per day
  - On 2 consecutive weekend days at around 1 and 2 weeks after start of dosing with PED25 (day 1) and after up-titration to PED50, if not already covered by the scheduled SBPM
- Acceptability and Palatability Questionnaire:
  - On 1 weekend day preceding visit 7/week 12 (EoT)

The investigator must guide the subject and subject's parent(s)/legal guardian(s) to ensure that on the evening before and during the 2-day weekend period collection of volume, the subject's fluid intake should be regulated (as per investigator guidance) to an appropriate level considering, e.g., age, sex and subject's condition into account. The intake must remain as consistent as possible on these volume collecting days throughout the entire study.

7.7 Other Assessments

Acceptability and palatability questionnaire will be completed on 1 weekend day preceding Visit 7/Week 12 (EoT). For each formulation a separate questionnaire is available, please see Appendices 12.8 Acceptability and Palatability Questionnaire for Tablets and 12.9 Acceptability and Palatability Questionnaire for Oral Suspension.

Questionnaires are to be completed by the subject or the subject's parent(s)/caregiver(s) in the local language and provided via the e-diary. Results will be directly entered in the e-diary by the subject or subject's parent(s)/caregiver(s).

7.8 Total Amount of Blood

The total amount of blood for each subject will vary depending on the course of their disease, duration on treatment and central laboratory requirements. At any time during the study, if any laboratory abnormalities are found for a subject, additional blood may be drawn for safety monitoring.

The maximum blood volume to be collected within 24 hours is approximately 9.5 mL per subject on pharmacokinetic sampling days at visit 5/week 4 and visit 7/week 12 (EoT).

The total blood volume to be collected will be as follows

Table 8 Total Blood Volume per Subject over the Entire Study Period

Sample Type	Number of Samples	Sample Volume (mL)	Total Volume (mL)
Pharmacokinetics	2	5.0	10.0
Clinical Laboratory Tests† Biochemistry/hematology	3	4.5‡	13.5
Total			23.5

† Additional hematology and biochemistry tests of approximately 4.5 mL total will be performed at visit 3/week 0 (baseline) and visit 8/week 14 (EoS) only if an adverse event related to hematology or biochemistry parameters occurred since the previous visit or at the discretion of the investigator. The total amount of blood drawn from subjects who require additional hematology and biochemistry tests due to AEs could be up to 32.5 mL.

‡ Volume does not take any unscheduled visits or repeat tests into account (e.g., follow up of adverse events).

8 DISCONTINUATION

8.1 Discontinuation of Individual Subject(s) From Study Treatment(s)

A discontinuation from treatment is defined as a subject who is randomized and for whom study treatment is permanently discontinued for any reason.

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to discontinue the participant from study treatment or to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

The reason for discontinuation from study treatment must be documented in the subject's medical records.

A subject must discontinue study treatment for any of the following reasons:

- Subject requests to stop treatment.
- Any clinical AEs, laboratory abnormality or intercurrent illness, in the opinion of the investigator, indicates continued treatment is not in the best interest of the subject.
- If signs or symptoms of hypersensitivity to mirabegron are observed (e.g., anaphylactic reaction, erythema multiforme or exfoliative dermatitis).
- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than 2 weeks.
- ALT or AST > 3 × ULN and TBL > 2 × ULN or international normalized ratio (INR) > 1.5 (if INR testing is applicable/evaluated).
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).
- Female subject becomes pregnant.
- Prolongation of QT > QTcF > 440 msec and/or QT interval prolongation > 30 msec versus baseline.
- Subject with (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mmHg.

If a subject discontinues treatment prematurely, the subject will be encouraged to complete all scheduled visits to record all available information.

8.2 Discontinuation of Individual Subject(s) From Study

All subjects who discontinue study treatment will remain in the study and must continue to be followed for protocol-specific follow-up procedures as outlined in the Schedule of Assessments [Table 1]. The subject will also be encouraged to attend all planned visits until the planned End of Study visit to provide data even if not on treatment anymore. The only exception to this is when the subject specifically withdraws consent/assent for any further contact with him/her or persons previously authorized by the subject to provide this information.

8.2.1 Lost to Follow-up

Every reasonable effort is to be made to contact any subject lost to follow-up during the course of the study to complete study-related assessments, record outstanding data and retrieve IP.

8.3 Discontinuation of the Study Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the sponsor.

8.4 Discontinuation of the Study

The DSMB will review safety data periodically and provide a recommendation to the sponsor if the study should continue or be stopped due to safety concerns. The sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided

that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the sponsor terminates the study for safety reasons, the sponsor will immediately notify the investigator and subsequently provide written instructions for study termination. The study may also be stopped as a result of the outcome of the interim analysis [Section 9.10 Interim Analysis and Early Discontinuation of the Study].

9 STATISTICAL METHODOLOGY

A statistical analysis plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures to be produced. The SAP will be finalized before database hardlock. Changes from the planned analyses planned in the final SAP that impact the statistical analyses will be justified in the clinical study report (CSR).

In general, all data will be summarized with descriptive statistics frequency and percentage for categorical data. Data will be summarized by age group, treatment group and visit unless otherwise stated.

9.1 Sample Size

Efficacy of mirabegron in children will be based on both primary and secondary endpoints. Given the clinical hurdle to demonstrate efficacy in a population challenging to recruit, an alpha-level of 10% would appear reasonable and justified. In a study with propiverine in children, Marschall-Kehrel (2009) showed a difference in mean number of micturition episodes/24 hours of 0.8 between propiverine and placebo, with a SD between 2.2 and 2.3. Assuming at least similar efficacy of mirabegron, with a treatment effect of 0.9 micturitions per day between mirabegron and placebo and a common SD of 2.3, a sample size of 82 evaluable subjects (children) per treatment group is assumed per treatment group would provide a power of 80%.

These assumptions, together with levels for Type-1 error and power were agreed upon with Pediatric Committee in the current Pediatric Investigation Plan.

Under the assumption that after randomization about 10% of the subjects will not be evaluable for the analysis of the primary endpoint (i.e., not fulfilling the criteria for inclusion in full analysis set [FAS]), at least 184 children (5 to < 12 years of age) must be randomized in order to have at least 164 evaluable children for the analysis of the primary efficacy endpoint.

For adolescents, no formal sample size will be calculated; at least 32 adolescents (12 to < 18 years of age) must be randomized, yielding at least 16 adolescents on mirabegron. Further assuming a 50% screen failure rate, approximately 368 children have to be enrolled to achieve 184 children (5 to < 12 years of age) randomized and approximately 64 adolescents will be enrolled to achieve at least 32 adolescents (12 to < 18 years of age) randomized (at least 92 children and 16 adolescents must be randomized to mirabegron).

Recruitment will continue until the minimum number to be randomized in both children and adolescents have been achieved.

9.2 Analysis Sets

Detailed criteria for analysis sets will be laid out in classification specifications and the allocation of subjects to analysis sets will be determined prior to database hardlock.

9.2.1 Full Analysis Set

The FAS will consist of all subjects who are randomized and receive at least 1 dose of IP and have at least 1 post baseline measurement for mean number of micturitions per 24 hours. The FAS will be analyzed by treatment arm as randomized (i.e., treatment arm based on randomization assignment). This will be the primary analysis set for efficacy analyses. Selected demographic and baseline characteristics will also be summarized for the FAS.

9.2.2 Per Protocol Set

The per protocol set (PPS) will consist of all subjects who are randomized and receive at least 1 dose of IP and have at least 1 post baseline measurement for mean number of micturitions per 24 hours, and who do not meet criteria for PPS exclusion. These criteria are to capture relevant nonadherence to the protocol and will be defined in the SAP. Further criteria may be defined in the SAP. The PPS will be a secondary analysis set for efficacy analyses.

Selected demographic and baseline characteristics may also be summarized for the PPS.

9.2.3 Safety Analysis Set

The safety analysis set (SAF) will consist of all subjects who took at least 1 dose of IP. The safety set will be analyzed by treatment arm as treated (i.e., based on the treatment the subject actually received rather than the treatment to which the subject was randomized). The SAF will be used for all summaries of demographic and baseline characteristics and all safety- and tolerability-related variables.

9.2.4 Pharmacokinetics Analysis Set

The pharmacokinetics analysis set (PKAS) will consist of all subjects who took at least 1 dose of IP for whom sufficient plasma concentration data are available to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day before sampling. Additional subjects may be excluded from the PKAS at the discretion of the pharmacokineticist. Any formal definitions for exclusion of subjects or time points from the PKAS will be documented in the classification specifications and be determined at the classification meeting.

9.2.5 Pharmacodynamic Analysis Set

Not applicable.

9.3 Demographics and Baseline Characteristics

The summaries to be provided for demographics and baseline characteristics will be described here.

9.3.1 Demographics

The demographic summary will include age, sex, race, ethnicity, body weight, height, body mass index (BMI) (at screening) and EBC. Baseline characteristics will include, among others, medical history, OAB diagnosis and history. Selected demographic and baseline characteristics will be summarized at least for the SAF and FAS.

Demographic data will be listed.

9.3.2 Subject Disposition

The number and percentage of subjects who completed and discontinued treatment and reasons for treatment discontinuation will be presented for all randomized subjects and for subjects in the SAF by age group, treatment group and overall. Similar tables for screening disposition, investigational period disposition and follow-up disposition will also be presented for all enrolled subjects by age group and overall. All disposition details and dates of first and last evaluations for each subject will be listed.

9.3.3 Previous and Concomitant Treatment (Medication and Nonmedication Therapy)

Previous and concomitant medications will be coded with WHO-Drug Dictionary (WHO-DD), and will be summarized by therapeutic subgroup (Anatomical Therapeutic Chemical [ATC] Classification System 2nd level), chemical subgroup (ATC 4th level) and preferred WHO name for the SAF. Subjects taking the same medication multiple times will be counted once per ATC level. A medication which can be classified into several chemical and/or therapeutic subgroups will be presented in all chemical and therapeutic subgroups.

A listing of previous and concomitant medications with ATC codes by WHO preferred name will be provided for all screened subjects.

9.3.4 Medical History

Medical history will be coded in MedDRA and will be summarized by SOC and preferred term (PT) for the SAF. Subjects will only be counted once per MedDRA level.

Medical history for each subject will be listed.

9.3.5 Investigational Product Exposure

Descriptive statistics for cumulative amount of the IP the subject was exposed to and average daily dose.

Duration of exposure will be summarized in the following by descriptive statistics.

Exposure time will be categorized according to the following categories for the treatment period:

- < 14 days
- At least 14 days, < 28 days
- At least 28 days, < 56 days
- At least 56 days

- Unknown

All IP exposure data will be listed.

9.4 Analysis of Efficacy

Efficacy analysis will be conducted on the FAS and PPS, and interpretation of results from statistical tests in children (5 to < 12 years of age) will be based on the FAS.
The PPS will be used to assess the robustness of the results from the statistical tests based on the FAS. Efficacy analysis in adolescents will only be exploratory.

9.4.1 Analysis of Primary Endpoint

9.4.1.1 Primary Analysis

The primary estimator for the primary estimand as defined in [Section 3.1 Estimand] will be calculated according to the evaluation of the primary efficacy endpoint. The primary efficacy endpoint change from baseline to week 12/EoT in mean micturitions per 24 hours (in children [5 to < 12 years of age]), will be analyzed using an analysis of covariance (ANCOVA). The ANCOVA model will include treatment group, sex and geographical region as fixed effects and the mean number of micturitions per 24 hours at baseline as covariate. This analysis will be performed and once with imputation of missing week 12 data using the last observation carried forward (LOCF) method.

The hypothesis for comparisons is given as follows:

H0: The adjusted mean change from baseline at week 12 in mean number of micturitions per 24 hours for mirabegron and placebo are the same.

H1: The adjusted mean change from baseline at week 12 in mean number of micturitions per 24 hours for mirabegron and placebo are not the same.

Statistical testing will be done at a 2-sided 0.1 significance level. A 90% CI for the treatment difference (mirabegron – placebo) will be provided. The primary analysis will use the FAS. The plausibility of the underlying assumption of missing at random for the primary estimator will be evaluated, and; therefore, the estimation of the treatment effect. Sensitivity analyses under alternative assumptions for missing data mechanisms such as missing not at random to show robustness of the estimates will be further specified in the SAP.

9.4.1.2 Secondary Analysis

The same analysis of the primary endpoint as described in [Section 9.4.1.1 Primary Analysis] will be conducted using the PPS, and without imputation using FAS.

The change from visit 3/week 0 (baseline) to visit 7/week 12 (EoT) in mean number of micturitions per 24 hours in children (5 to < 12 years of age) will be analyzed. The primary analysis for the primary endpoint will be using a repeated measures ANCOVA model with treatment group, visits (week 4, 8 and 12), sex, geographical region and the interaction between treatment group and visit as fixed effects and mean number of micturitions per 24 hours at baseline as covariate. Mirabegron will be compared to placebo using a linear

contrast within the repeated measures ANCOVA model, with 2-sided significance level of alpha = 0.1 and 90% CI. This analysis will be conducted using the FAS.

In addition to the parametric ANCOVA, a nonparametric ANCOVA will also be performed: (stratified) rank ANCOVA. This analysis will be conducted using the FAS.

9.4.1.3 Subgroup Analysis

For the primary efficacy endpoint, descriptive statistics (n, mean, 95% confidence interval around the mean, SD, minimum, median, maximum) will be calculated for mean change from baseline at each visit by sex, race, ethnicity, geographical region, formulation (tablets vs. oral suspension), prior OAB treatment and symptomatic UTI.

9.4.2 Analysis of Secondary Endpoints

The same analysis (ANCOVA) as for the primary endpoint will be applied to change from baseline at the end of the 12-week treatment period in children (5 to < 12 years of age) for:

- Mean volume voided per 24 hours
- Maximum volume voided
- Mean number of daytime incontinence episodes per 24 hours
- Mean number of nighttime incontinence episodes per 24 hours
- Mean number of daytime micturitions per 24 hours

Change from baseline in the number of dry (incontinence free) days per 7 days at the end of the 12-week treatment period will be analyzed with a negative binomial regression model including treatment group, sex, geographical region as factors and the log baseline rate of number of dry days (e.g., the log of the number of dry days divided by number of diary days at baseline) as covariate.

9.4.3 Analysis of Exploratory Endpoints

All efficacy endpoints for adolescents will be analyzed descriptively.

Data of the following explorative endpoints will be summarized, separately, for pediatric subjects:

- Percentage of subjects with a reduction in daytime incontinence episodes (< 50% reduction [nonresponder], 50% [partial responder] and 100% [responder])
- Improvement from baseline in worst incontinence grading
- Change from baseline at the end of the 12-week treatment period adjusted for fluid intake:
  - Mean number of micturitions per 24 hours
- Change from baseline at the end of the 12-week treatment period (adolescents only):
  - Mean number of micturitions per 24 hours
  - Mean number of daytime micturitions per 24 hours
  - Mean volume voided per 24 hours
  - Mean number of incontinence episodes per 24 hours

- Number of dry (incontinence-free) days per 7 days at the end of the 12-week treatment period (adolescents only)

Mean number of daytime grade 3 or 4 (Patient Perception of Intensity of Urgency Scale [PPIUS]) urgency episodes per 24 hours (adolescents only) will be summarized.

Correlations between the primary endpoint and mean volume voided, as well as incontinence episodes, will be explored.
Scatter plots will be presented to access the correlation between the primary end point, and mean volume voided and number of incontinence episodes at week 12.

9.5 Analysis of Safety

Safety analysis will be conducted on the SAF and conducted separately for children, adolescents and overall. Safety endpoints will be summarized using descriptive statistics.

9.5.1 Adverse Events

AEs will be coded using MedDRA. A TEAE is defined as an AE observed after starting administration of the IP and 30 days after the final administration of IP. An IP-related TEAE is defined as any TEAE with a causal relationship assessed as "yes" by the investigator.

The number and percentage of TEAEs, drug-related TEAEs, serious TEAEs, drug-related serious TEAEs, TEAEs leading to leading to withdrawal of treatment and drug-related TEAEs leading to leading to withdrawal of treatment will be summarized by SOC, preferred term, age group and treatment group. The number and percentage of TEAEs by severity will also be summarized. The worst severity will be summarized if the same AE is recorded more than once for a subject.

AE data will be listed.

9.5.2 Laboratory Assessments

For quantitative clinical laboratory measurements (hematology, biochemistry and urinalysis), descriptive statistics will be used to summarize results and change from baseline by treatment group and within treatment group and across age group.

Shifts relative to normal ranges from baseline to each visit during the treatment period in clinical laboratory tests will be tabulated.

Laboratory data will be listed.

The laboratory parameters that will be assessed during the conduct of the study are listed in [Appendix 12.7 Laboratory Assessments].

In cases where laboratory evaluations are conducted locally, the values obtained will be adjusted to values obtained by the central laboratory. Details will be described in the SAP.

9.5.3 Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline by treatment group and within treatment group and across age group. For clinic

measurements Z-scores and percentiles for SBP and DBP will be calculated and summarized based on a comparison with age and height norms supplied by the Center for Disease Control and Prevention. Details to calculate Z-scores and percentiles will be provided in the SAP.

Z-scores and percentiles for pulse rate will be calculated and summarized based on a comparison with age norms based on Fleming [Fleming et al, 2011]. Details to calculate Z-scores and percentiles will be provided in the SAP.

Vital signs data will be listed.

9.5.4 Physical Examination

Abnormal findings/conditions identified during the physical examinations will be listed as part of the medical history for the screening visit, or as AEs at later visits.

9.5.5 Electrocardiogram

The routine 12-lead ECG results will be summarized separately for children (5 to < 12 years of age) and adolescents (12 to < 18 years of age) by treatment group and visit. ECGs will be recorded prior to blood draw.

9.5.6 Post Void Residual Volume

The PVR volume data and change from baseline data will be summarized by treatment group and within treatment group and across age.

9.5.7 Acceptability and Palatability Questionnaire

Results from the acceptability and palatability questionnaire for tablets [Appendix 12.8 Acceptability and Palatability Questionnaire for Tablets] and for oral suspension [Appendix 12.9 Acceptability and Palatability Questionnaire for Oral Suspension] will be summarized at week 12/EoT by age group and treatment group.

9.6 Analysis of Pharmacokinetics

Pharmacokinetic analysis will be conducted on the PKAS and conducted separately for children, adolescents and overall. Descriptive statistics (n, mean, SD, minimum, median, maximum, coefficient of variation (CV), geometric mean and geometric CV) will be used to summarize plasma concentrations of mirabegron by visit and time point. Further details will be specified in the SAP.

9.6.1 Estimation of Pharmacokinetic Parameters

The plasma concentrations will be analyzed with nonlinear mixed effects modeling (population pharmacokinetics) using Non-Linear Mixed Effects Modeling (NONMEM) software (version 7.3 or higher, ICON Development Solutions, Ellicott City, MD, US) to estimate the pharmacokinetic parameters. Results will be reported separately.

9.7 Analysis of Pharmacodynamics | Immunogenicity

Not applicable.

9.8 Other Analyses

Not applicable.

9.9 Major Protocol Deviations

Major protocol deviations as defined in [Section 10.3 Major Protocol Deviations] will be summarized for all randomized subjects by study site, treatment group and overall separately for children (5 to < 12 years of age) and adolescents (12 to < 18 years of age).

Major protocol deviation data will be listed by study site and subject.

The major protocol deviation criteria will be uniquely identified in the summary table and listing.

9.10 Interim Analysis (and Early Discontinuation of the Study)

A blinded interim analysis will be performed after 50% of children planned to be randomized have had their week 12/EoT assessment. The interim analysis will determine if the chance of a positive study with respect to the primary endpoint at the EoS is high enough to justify continuation of the study; otherwise, the study will be stopped for futility.

Given the data at the interim analysis, the independent data analysis center (IDAC) will calculate the predictive probability of a positive study. A positive study is defined as the final 1-sided p-value ≤ 0.05 when comparing Mirabegron vs. placebo in the primary efficacy analysis (in children [5 to < 12 years of age]). If the predictive probability is ≤ 5% at this interim evaluation, the study will be recommended to stop for futility. Otherwise, the study will continue.

Detailed information on the decision rule of futility and simulations illustrating the operating characteristics of futility criterion will be presented in the SAP.

9.11 Additional Conventions

Missing data for efficacy endpoints will be imputed as EoT values, details will be described in the SAP. Handling of incomplete dates will also be described in the SAP.

Geographical regions that do not enroll sufficient subjects to allow estimation of the geographical effect will be pooled for analyses by geographical region. The pooling decisions will be made and documented prior to study hardlock.

10 OPERATIONAL CONSIDERATIONS

10.1 Data Collection

The investigator or site designee will enter data collected using an electronic data capture system. In the interest of collecting data in the most efficient manner, the investigator or designee should record data (including clinical laboratory values, if applicable) in the electronic case report form within 5 days after the subject's visit.

The monitor should verify the data in the electronic case report forms with the source and confirm that there are no inconsistencies among them.

Clinical laboratory tests are performed at central laboratory. Central laboratory data will be transferred electronically to the sponsor or designee at predefined intervals during the study. The central laboratory will provide the sponsor or designee with a complete and clean copy of the data.

Subject bladder e-diaries and questionnaires as described in [Section 7.6 Electronic Clinical Outcome Assessment] will be completed by the subject on an electronic device and the collected electronic data source will be hosted at the vendor.

The investigator or designee will review the diaries and questionnaire data throughout the study to ensure completion and protocol compliance.

10.2 Demographics and Baseline Characteristics

10.2.1 Demographics

Demographics and baseline characteristics will be collected as indicated in the Schedule of Assessments [Table 1]. This will include age, sex, race, ethnicity, body weight and height.

10.2.2 Medical History

A complete medical history will be collected as indicated in the Schedule of Assessments [Table 1].

10.2.3 Diagnosis of the Target Disease, Severity and Duration of Disease

A detailed OAB history for each subject will be collected at visit 1/screening. This history includes the underlying condition, comorbidities associated with OAB and treatment history for OAB.

10.3 Major Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. All deviations from the protocol are to be recorded. A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety and well-being of subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to subjects.

A major protocol deviation is 1 that may potentially impact the completeness, accuracy or reliability of data contributing to the primary endpoint or affect the rights, safety or well-being of a subject. Major protocol deviations will have additional reporting requirements.

When a major deviation from the protocol is identified for an individual subject, the investigator or designee must ensure the sponsor is notified. The sponsor will follow up with

the investigator, as applicable, to assess the deviation and the possible impact to the safety and/or efficacy of the subject to determine subject continuation in the study.

The major protocol deviation criteria that will be summarized at the EoS are as follows:

PD1 - Entered into the study even though the subject did not satisfy entry criteria

PD2 - Developed withdrawal criteria during the study and was not withdrawn

PD3 - Received wrong treatment or incorrect dose

PD4 - Received excluded concomitant treatment

The investigator will also assure that deviations meeting IRB/IEC and appropriate regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and appropriate regulatory authorities will be provided to the sponsor and maintained within the Trial Master File.

10.4 Study Organization

10.4.1 Data and Safety Monitoring Board

A DSMB will be implemented to act in an advisory capacity to the sponsor to monitor participant safety and data quality.

Subject safety overviews will be prepared by the IDAC and will be reviewed on a regular basis by the DSMB, who will advise the sponsor on appropriate steps to protect study participants, which may include the early termination of the study.

A separate charter will describe the responsibilities, remit and timing of DSMB meetings.

10.4.2 Independent Data Analysis Center

An IDAC for this study will serve the 2 purposes: (1) to generate periodic safety overviews for the DSMB and (2) to calculate the futility analysis. The statistical member of the DSMB may also serve as the IDAC statistician, as described in the DSMB charter. A SAP describing the details of the periodic safety review of outputs will be developed with input from the DSMB members.

10.4.3 Other Study Organization

Not applicable.

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12 APPENDICES

12.1 Ethical, Regulatory and Study Oversight Considerations

12.1.1 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

12.1.2 Institutional Review Board/Independent Ethics Committee/Competent Authorities

GCP requires that the protocol, any protocol amendments, Investigator's Brochure, ICF/assent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IRB/IEC. The IRB/IEC will review the ethical, scientific and medical appropriateness of the study before it is conducted. IRB/IEC approval of the protocol, ICF/assent and subject information and/or advertising, as relevant, will be obtained prior to initiation of any study-specific procedures.

Any substantial amendments to the protocol will require competent authority and IRB/IEC approval before implementation, except for changes necessary to eliminate an immediate hazard to subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the study site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, EU Regulation No. 536/2014 for studies (if applicable), and all other applicable local regulations

12.1.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments: substantial amendments and/or nonsubstantial amendments. Depending on the nature of the amendment, either IRB/IEC or competent authority approval or notification may be required. The changes will become effective only after the approval of the sponsor, investigator, IRB/IEC and appropriate regulatory authorities.

Amendments to this protocol must be signed by the sponsor and investigator. Written verification of IRB/IEC approval will be obtained before any amendment is implemented. Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by local regulations.

If there are changes to the ICF/assent, written verification of IRB/IEC approval must be forwarded to the sponsor. An approved copy of the new ICF/assent must also be forwarded to the sponsor.

12.1.4 Financial Disclosure

Investigators and subinvestigator(s) will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

12.1.5 Informed Consent/Assent of Subjects

12.1.5.1 Subject Information and Consent/Assent

For this pediatric study in subjects aged 5 to < 18 years of age, in addition to information sheets and consent forms/assent for subjects (according to applicable local regulations), parent/legal guardian information sheets and consent forms/assent will also be prepared.

The investigator or his/her representative will explain the nature of the study to the subject and his/her parent(s)/legal guardian(s) and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the ICF/assent will be reviewed, signed and dated by the subject or his/her parent(s)/legal guardian(s), the person who administered the ICF/assent and any other signatories according to local requirements. A copy of the signed ICF/assent will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that the ICF/assent was signed prior to any study-related procedures and that the subject received a signed copy of the ICF/assent.

The following general rules apply but these may vary by local regulations for pediatric studies:

- The investigator/subinvestigator(s) is responsible for explaining the nature and purpose of the study as well as other study-related matters to subjects and their parent(s)/legal guardian(s), using the written information, and for obtaining the child's assent and the parent(s)'/guardian(s)' full understanding and written consent/assent to participate in the study of their own free will.
- In cases where there might be an explicit wish of a minor or an incapacitated adult, who is capable of forming an opinion and assessing this information, to refuse to participate or to be withdrawn from the clinical study at any time, this will have to be considered by the investigator, even if consent/assent is given by the parent(s)/legal guardian(s). Every effort should be made to understand and respect differences of opinion between the subject and their parent(s)/legal guardian(s). Strong and definitive objections from the child should be respected.
- The investigator or other responsible personnel who provided explanations (including collaborators who gave supportive information, if applicable) and the subject and

parent(s)/legal guardian(s) should sign and date the written information, or write down his/her name, and date the form.

- Informed consent/assent must be obtained prior to any study-related procedures (including discontinuation of prohibited medication, if applicable). Consent/assent should be obtained from the subject and his/her parent(s)/legal guardian(s), before start of pre-investigational period. Consent/assent will be obtained per local regulations.
- The investigator or other responsible personnel must give a copy of the signed consent/assent form to the subject and parent(s)/legal guardian(s) and store the original appropriately in accordance with the rules at the study site concerned.
- The investigator or other responsible personnel should note the following when obtaining consent/assent from subjects and parent(s)/legal guardian(s):
    - No subject may be subjected to undue influence, such as compulsory enrollment into a study.
    - The language and expressions used in the written information should be as plain and understandable as possible. Subjects and their parent(s)/legal guardian(s) should be given the opportunity to ask questions and receive satisfactory answers to the inquiry and should have adequate time to decide whether or not to participate in the study. Written information should not contain any language or contents that causes the subject to waive or appears to waive any legal rights, or that releases/mitigates or appears to release/mitigate the study site, the investigator/subinvestigator(s), collaborators, or the sponsor from liability for negligence.

The signed ICFs/assents will be retained by the investigator and made available (for review only) to the study monitor, auditor and appropriate regulatory authorities and other applicable individuals upon request.

12.1.5.2 Supply of New and Important Information Influencing the Subject's Consent/Assent and Revision of the Written Information

1. The investigator or his/her representative will immediately inform the subject verbally whenever new information becomes available that may be relevant to the subject's consent/assent or may influence the subject's willingness to continue participating in the study (e.g., report of serious adverse drug reaction). The communication must be documented in the subject's medical records and whether the subject is willing to remain in the study or not must be confirmed and documented.
2. The investigator must update the subject's ICF/assent and submit it for approval to the IRB/IEC. The investigator or his/her representative must obtain written informed consent/assent from the subject on all updated ICFs/assents throughout their participation in the study. The investigator or his/her designee must reconsent subjects with the updated ICF/assent even if relevant information was provided verbally. The investigator or his/her representative who obtained the written informed consent/assent and the subject should sign and date the ICF/assent. A copy of the signed ICF/assent will be given to the subject and the original will be placed in the subject's medical record. An entry must be made in the subject's records documenting the reconsent process.

12.1.6 Source Documents

1. Source data must be available at the study site to document the existence of the subjects and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.
2. The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
3. The investigator is responsible for ensuring the source data are attributable, legible, contemporaneous, original, accurate and complete whether the data are handwritten on paper or entered electronically. If source data are created (first entered), modified, maintained, achieved, retrieved or transmitted electronically via computerized systems (and/or other kind of electronic devices) as part of regulated study activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records, protocol-related assessments, AE tracking, electronic clinical outcome assessment eCOA and/or drug accountability.
4. Paper records from electronic systems used in place of electronic format must be certified copies. A certified copy must be an exact copy and must have all the same attributes and information as the original. Certified copies must include signature and date of the individual completing the certification. Certified copies must be a complete and chronological set of study records (including notes, attachments, and audit trail information, if applicable). All printed records must be kept in the subject file and be available for archiving.
5. Study monitors will perform ongoing source data review to confirm that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP and all applicable regulatory requirements.

12.1.7 Record Retention

The investigator will archive all study data (e.g., subject identification code list, source data electronic data source and investigator's file) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation. The sponsor will notify the study site/investigator if the European Medicines Agency (EMA) is approved or if the IND/investigational medicinal product dossier is discontinued. The investigator agrees to obtain the sponsor's agreement prior to disposal, moving or transferring of any study-related records. The sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subject's medical records and/or study progress notes.

The documents of the efficacy and safety evaluation committee (minutes and SOPs and others) and the judgment committee outside the study sites (minutes and SOPs and others) shall be retained by the sponsor.

12.1.8 Subject Confidentiality and Privacy

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited unless the subject provides written consent/assent or approval. Additional medical information may be given only after approval of the subject to the investigator or to other appropriate medical personnel responsible for the subject's well-being.

The sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the study without justifiable reasons.

Even though any individuals involved in the study, including the study monitors and auditors, may get to know matters related to a subject's privacy due to direct access to source documents, or from other sources, they may not disclose the content to third parties.

The sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number will identify subject data retrieved by the sponsor. However, the sponsor requires the investigator to permit the sponsor, sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The sponsor agrees to comply and process personal data in accordance with all applicable privacy laws and regulations, including, without limitation, the Personal Information Protection Law in Japan and privacy laws in the US. If the services will involve the collection or processing of personal data (as defined by applicable data protection legislation) within the European Economic Area (EEA), then the sponsor shall serve as the controller of such data, as defined by the EU Data Protection Directive (DPD), and investigator and/or third party shall act only under the instructions of the sponsor in regard to personal data. If the sponsor is not based in the EEA, the sponsor must appoint a third party to act as its local data protection representative or arrange for a co-controller established in the EU for data protection purposes in order to comply with the DPD.

12.1.9 Arrangement for Use of Information and Publication of the Study

Information concerning the test product, patent applications, processes, unpublished scientific data, the Investigator's Brochure and other pertinent information is confidential and remains the property of the sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the sponsor will use the information obtained during the study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this study, the investigator understands that he/she has an obligation to provide the sponsor with all data obtained during the study.

Publication of the study results is discussed in the study agreement.

12.1.10 Insurance of Subjects and Others

The sponsor has covered this study by means of an insurance of the study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the investigator's file.

12.1.11 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final CSR that forms part of a marketing authorization application, be signed by the representative for the coordinating investigator(s) or the principal investigator(s). The representative for the coordinating investigator(s) or the principal investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for the coordinating investigator(s) or the principal investigator(s) will be selected from the participating investigators by the sponsor prior to database hardlock.

12.2 Procedure for Study Quality Control

12.2.1 Study Monitoring

The sponsor is responsible for monitoring the study to ensure that the rights, safety and well-being of subjects are protected, the study is properly conducted in adherence to the current protocol and GCP. The sponsor is responsible for assigning the study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

12.2.2 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the sponsor, as well as inspections from the IRB/IEC and appropriate regulatory authorities. In these instances, they must provide all study-related records including source documents when they are requested by the sponsor monitors and auditors, the CRO, the IRB/IEC or appropriate regulatory authorities. The confidentiality of the subject's identity shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

12.2.3 Data Management

Data management will be coordinated by the Data Science department or designee of the sponsor in accordance with the SOPs for data management. All study-specific processes and definitions will be documented by data management. Electronic data source completion will be described in the electronic data source instructions. Coding of medical terms and medications will be performed using MedDRA and the WHO Drug Dictionary, respectively. Data management is accountable for eCOA.

12.2.4 Quality Assurance

The sponsor is implementing and maintaining quality assurance (QA) and quality control (QC) systems with written SOPs to ensure that studies are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP and applicable regulatory requirement(s). Where applicable, the QA and QC systems and written SOPs of the CRO will be applied.

The sponsor or sponsor's designee may arrange to audit the study at any or all study sites and facilities. The audit may include on-site review of regulatory documents, CRFs and source documents. Direct access to these documents will be required by the auditors.

To support quality around subject safety and reliability of study results, quality tolerance limits (QTLs) are defined and monitored. QTLs represent the acceptable variation of study data, taking into consideration the current state of medical and statistical knowledge about the variables to be analyzed as well as the statistical design of the study. It is a level, point, or value associated with a parameter that should trigger an evaluation if a deviation is detected to determine if there is a possible systematic issue (i.e., a trend has occurred). The QTLs defined for this study are provided below.

Table 9 Quality Tolerance Limit

QTL #: Name and Parameter	Definition	Parameter Justification
Subject ePRO diary completion: Proportion (%) of randomized subjects who provide the number of micturitions in 7 days of ePRO diary data at week 4, week 8 and week 12.	Proportion (%) of randomized subject with missing number of micturitions in 7 days of diary data at week 4, week 8 and week 12.	If subject diaries are not completed accurately or are discrepant with source data, there is a risk of inaccurate data which may impact primary endpoint.
Subject ePRO diary completion: Proportion (%) of randomized subjects who provide urine volume voided data over 2 days of ePRO diary data at week 4, week 8 and week 12.	Proportion (%) of randomized subjects with missing urine volume voided data over 2 days of diary data at week 4, week 8 and week 12.	If subject diaries are not completed accurately or are discrepant with source data, there is a risk of inaccurate data which may impact secondary endpoints.
Subject ePRO diary completion: Proportion (%) of randomized subjects who provide number of dry days and number of wet days for 7 days of ePRO diary data at week 4, week 8 and week 12.	Proportion (%) of randomized subjects with missing number of dry days and number of wet days for 7 days of diary data at week 4, week 8 and week 12.	If subject diaries are not completed accurately or are discrepant with source data, there is a risk of inaccurate data which may impact secondary endpoints.
Subject ePRO diary completion: Proportion (%) of randomized subjects with missing acceptability and palatability questionnaire at week 12.	Proportion (%) of randomized subjects with missing acceptability and palatability questionnaire at week 12.	A high number of missing acceptability and palatability questionnaire will have a negative impact on the interpretation of the secondary endpoints.
Pharmacokinetic sample results: Proportion (%) missing week 4 and week 12 pharmacokinetic sample results.	Proportion (%) of overall planned sampling time points with a missing result due to any reason, such as missed collection, lost or mishandled.	A high number of missing pharmacokinetic sample results can have a negative impact on interpretation of secondary endpoints.

ePRO: electronic patient-reported outcome; QTL: quality tolerance limit

QTL Management Activities:

For control of risks associated with QTLs, refer to the Study Monitoring Plan.

12.3 Contraception Requirements

Contraception for Pediatric Male Subjects of Reproductive Potential

Male children/adolescents in the following categories are not considered of reproductive potential:

1. Tanner stage 1 development
2. Documented surgically sterile

Documentation from the site personnel's review of the male subject's medical records, medical exam and medical history interview is necessary.

Contraception guidance for male children/adolescents of reproductive potential:

- Male children/adolescents of reproductive potential (Tanner Stage 2 and above) receiving non-genotoxic agents should use a condom during treatment and for 3 weeks + 5 × half-life of drug after last dose.
- Male children/adolescents of reproductive potential receiving genotoxic agents should use a condom during treatment and for 90 days + 5 × half-life of drug after last dose.
- Male participants should inform their female partners that they are participating in a clinical trial and effective methods of contraception should be used.
- Female partners of male subjects who have not undergone bilateral orchiectomy should consider use of highly effective methods of contraception until the end of relevant systemic exposure, as defined above.

Contraception for Pediatric Female Subjects of Childbearing Potential

Female children/adolescents in the following categories are not considered of childbearing potential:

1. Pre-menarchal
2. Documented surgically sterile (hysterectomy, bilateral salpingectomy, bilateral oophorectomy)

Documentation from the site personnel's review of the female subject's medical records, medical exam and medical history interview is necessary.

Contraception guidance for female children/adolescents of childbearing potential:

- Female children/adolescents of childbearing potential receiving non-genotoxic agents should use highly effective contraception during treatment and for 30 days after last dose.
- Female children/adolescents of childbearing potential receiving genotoxic agents should use contraception during treatment and for 180 days + 5 × half-life of drug after last dose.
- Pregnancy testing for female children/adolescents of childbearing potential
  - At all on-site visits and 30 days after end of relevant systemic exposure

One of the highly effective methods of contraception listed below is required at the time of informed consent and until the end of relevant systemic exposure as defined above.

Highly Effective Birth Control Methods-failure rate < 1%/year

1. Combined estrogen and progestogen containing hormonal contraception
   a. Oral
   b. Intravaginal
   c. Transdermal-Patch
   d. Injectable-Cyclofem, Mesigyna
   e. Intrauterine device
   f. Intrauterine hormone-releasing system
2. Progestogen-only hormonal contraception
   a. Oral
   b. Injectable-DMPA-IM or -SC
   c. Implantable-Norplant
3. Bilateral tubal occlusion
4. Vasectomized male partner
5. True abstinence*

*True abstinence: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. It is not necessary to use any other method of contraception when complete abstinence is elected.

Birth control methods considered unacceptable:

1. Periodic abstinence (calendar, symptothermal, post-ovulation methods)
2. Withdrawal (coitus interruptus)
3. Spermicides only
4. Lactational amenorrhea

12.4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

12.4.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a subject administered an IP, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of IP whether or not considered related to the IP.

12.4.1.1 Abnormal Laboratory Findings

Any abnormal laboratory test result (e.g., hematology, biochemistry or urinalysis dipstick) or other safety assessment (e.g., vital signs, physical examination, ECGs or radiographic scans), including those that worsen from baseline should be considered to be reported as an (S)AE.

Any abnormal laboratory finding or other abnormal safety assessment, which is associated with the underlying disease or with concomitant medication, will not be considered an AE unless judged by the investigator to be more severe than expected for the subject's condition or not associated with the known side effects of the concomitant medication. Additionally, minor laboratory deviations or fluctuations outside of normal ranges of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen and/or that are not reproducible with re-testing will not to be considered an AE.

Repeating an abnormal laboratory test or other safety assessment, in the absence of any of the above criteria, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

12.4.1.2 Potential Cases of Drug-induced Liver Injury

Refer to [Appendix 12.5 Liver Safety Monitoring and Assessment] for detailed instructions on drug induced liver injury. Abnormal values in AST and/or ALT concurrent or with abnormal elevations in TBL that meet the criteria outlined in [Appendix 12.5 Liver Safety Monitoring and Assessment], in the absence of other causes of liver injury, are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and are always to be considered important medical events and reported per [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events].

12.4.2 Definition of Serious Adverse Events

An AE is considered "serious" if, in the view of either the investigator or sponsor, the event:

- Results in death
- Is life-threatening (An AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death; it does not include an AE that, had it occurred in a more severe form, might have caused death)

- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization (except for planned procedures as allowed per study) or leads to prolongation of hospitalization (except if prolongation of planned hospitalization is not caused by an AE)
- Other medically important events (defined in paragraph below)

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, usually are considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

12.4.3 Criteria for Causal Relationship to Investigational Product

A medically qualified investigator is obligated to assess the relationship between IP and each occurrence of each (S)AE. This investigator will use medical judgment as well as the reference safety information [Section 2.1.3 Summary of Key Safety Information for Investigational Product(s)] to determine the relationship. The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

The investigator is requested to provide an explanation for the causality assessment for each (S)AE and must document in the medical notes that he/she has reviewed the (S)AE and has provided an assessment of causality.

Following a review of the relevant data, the causal relationship between the IP and each (S)AE will be assessed by answering “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the IP?”

When making an assessment of causality, the following factors are to be considered when deciding if there is evidence and/or arguments to suggest there is a “reasonable possibility” that an (S)AE may have been caused by the IP (rather than a relationship cannot be ruled out) or if there is evidence to reasonably deny a causal relationship:

- Has the subject been administered IP?
- Plausibility (i.e., could the event have been caused by the suspect drug? Consider biologic and/or pharmacologic mechanism, half-life, literature evidence, drug class, preclinical and study data, etc.)
- Dechallenge/dose reduction/rechallenge:
    - Dechallenge: did the (S)AE resolve or improve after only stopping the dose of the suspect drug without any treatment?
    - Dose reduction: did the (S)AE resolve or improve after reducing the dose of the suspect drug?

  - Rechallenge: did the (S)AE reoccur if the suspected drug was reintroduced after having been stopped?
- Laboratory or other test results: a specific lab investigation supports the assessment of the relationship between the (S)AE and the IP (e.g., based on values pre-, during and post-treatment)
- Available alternative explanations independent of IP exposure; such as other concomitant drugs, past medical history, concurrent or underlying disease, risk factors including medical and family history, season, location, etc., and strength of the alternative explanation
- Finally, judging which are more likely based on all the above contents, factors of reasonable possibility or confounding factors, comprehensive judgment of plausible temporal relationship between exposure to the IP and (S)AE onset and/or resolution will be provided. Did the (S)AE occur in a reasonable temporal relationship to the administration of the IP?

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always assesses causality for every event before the initial transmission of the SAE data to the sponsor. With limited or insufficient information about the event to make an informed medical judgment and in absence of any indication or evidence to establish a causal relationship, a causality assessment of "no" is to be considered. In such instance, the investigator is expected to obtain additional information regarding the event as soon as possible and to re-evaluate the causality upon receipt of additional information. The medically qualified investigator may revise his/her assessment of causality in light of new information regarding the SAE and shall send an SAE follow-up report and update the electronic data source with the new information and updated causality assessment.

12.4.4 Criteria for Defining the Severity of an Adverse Event

The investigator will use the following definitions to rate the severity of each AE:

- Mild: No disruption of normal daily activities
- Moderate: Affects normal daily activities
- Severe: Inability to perform daily activities

12.4.5 Reporting Procedures for Serious Adverse Events

The investigator must complete and submit an SAE worksheet containing all information that is required by local and/or regional regulations to the sponsor by fax or email immediately (within 24 hours of awareness).

The SAE worksheet must be signed by a medically qualified investigator (as identified on delegation of authority log). Signature confirms accuracy and completeness of the SAE data as well as the investigator causality assessment including the explanation for the causality assessment.

If the SAE is associated with emergency unblinding by the investigator as outlined in [Section 6.3.4 Breaking the Treatment Code for Emergency], this is to be recorded on the

SAE worksheet. On the SAE worksheet, the investigator is to include when unblinding took place in association with the SAE.

For contact details, see [Contact Details of sponsor's Key Personnel]. Fax or email the SAE/special situations worksheet to:

Astellas Pharma Global Development Inc.
US Pharmacovigilance
North America fax number: +1-888-396-3750
North America alternate fax number: +1-847-317-1241
International fax number: +44 800 471 5263
Email: safety-us@astellas.com

If there are any questions, or if clarification is needed regarding the SAE, please contact the sponsor's medical monitor/study physician or their designee [Contact Details of Sponsor's Key Personnel].

Follow-up information for the event should be sent promptly (as soon as available but no longer than within 7 days of the initial notification).

Full details of the SAE should be recorded on the medical records, SAE/special situation worksheet and on the electronic data source.

The following minimum information is required:

- International study number/study number
- Subject number, sex and age
- Date of report
- Description of the SAE (event and seriousness criteria)
- Causal relationship to the IP (including reason)
- Blinded regimen

The sponsor or sponsor's designee will medically evaluate the SAE and determine if the report meets the requirements for expedited reporting based on seriousness, causality, and expectedness of the events (e.g., SUSAR reporting) according to current local/regional regulatory requirements. The sponsor or sponsor's designee will submit expedited safety reports to competent authorities and concerned ethics committee per current local regulations and will inform the investigators of such regulatory reports as required. Investigators must submit safety reports as required by their IRB/IEC within timelines set by regional regulations (e.g., EMA, FDA) where required. Documentation of the submission to and receipt by the IRB/ IEC of expedited safety reports should be retained by the study site. In the US, FDA expedited IND reporting guidelines will be followed.

The sponsor will notify all investigators responsible for ongoing clinical studies with the test product of all SUSARs, which require submission per local requirements IRB/IEC.

The investigators should provide written documentation of IRB/IEC notification for each report to the sponsor.

The investigator may contact the sponsor's medical monitor/study physician for any other problem related to the rights, safety or well-being of the subject.

12.4.6 Reporting Procedures for Special Situations

12.4.6.1 Pregnancy

If a female subject becomes pregnant during the study dosing period or within 30 days from the discontinuation of dosing, the investigator is to report the information to the sponsor according to the timelines in **[**Appendix 12.4.5 Reporting Procedures for Serious Adverse Events] using the SAE worksheet as a special situation and in the electronic data source.

The investigator will attempt to collect pregnancy information on any female partner of a male subject who becomes pregnant during the study dosing period or within 30 days from the discontinuation of dosing and report the information to the sponsor according to the timelines in [Appendix 12.4.5 Reporting Procedures for Serious Adverse Event**s**] using the SAE worksheet as a special situation.

The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data, etc., should be included in this information.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or termination (including elective termination) of a pregnancy is to be reported for a female subject as an AE in the electronic data source or SAE per [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events]. For (S)AEs experienced by a female partner of a male subject, (S)AEs are to be reported via the SAE worksheet.

Additional information regarding the outcome of a pregnancy when also categorized as an SAE is mentioned below:

- "Spontaneous abortion" includes miscarriage, abortion and missed abortion
- Death of a newborn or infant within 1 month after birth is to be reported as an SAE regardless of its relationship with the IP
- If an infant die more than 1 month after the birth, it is to be reported if a relationship between the death and intrauterine exposure to the IP is judged as "possible" by the investigator
- Congenital anomaly (including anomaly in miscarried fetus)

Unless a congenital anomaly is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination or other means as appropriate. (S)AEs experienced by the newborn/infant should be reported via the pregnancy reporting form. Generally, follow up will be no longer than 6 to 8 weeks following the estimated delivery date.

12.4.6.2 Lack of Efficacy

Not applicable.

12.4.6.3 Medication Error, Overdose and "Off-label Use"

If a medication error (defined as an unintended failure in the treatment process that leads to, or has the potential to lead to, harm to the subject), overdose or "off-label use" (i.e., use outside of what is stated in the protocol) is suspected, refer to [Section 10.3 Major Protocol Deviations]. Any associated (S)AEs are to be reported in the electronic data source. If the AE meets the definition of an SAE, the SAE is also to be reported as described in [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events] together with the details of the medication error, overdose and/or "off-label use."

In the event of suspected overdose, refer to the approved package insert, summary of product characteristics, or local product information supplied by the manufacturer for each IP.

12.4.6.4 Misuse/Abuse

Definition of misuse: Situations where the IP is/are intentionally and inappropriately used not in accordance with the intended use as defined in the protocol.

Definition of abuse: Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.

If misuse or abuse of the IP is suspected, the investigator must forward the special situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the electronic data source. If the AE meets the definition of an SAE, the SAE is also to be reported as described in [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events] together with details of the misuse or abuse of the IP.

12.4.6.5 Occupational Exposure

If occupational exposure (e.g., inadvertent exposure to the IP of study site personnel while preparing it for administration to the subject) to the IP occurs, the investigator must forward the special situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs occurring to the individual associated with or resulting from the special situation are to be reported on the special situations worksheet.

12.4.6.6 (Suspicion of) Transmission of Infectious Agent

Not applicable.

12.4.6.7 Suspected Drug-drug Interaction

If a drug-drug interaction associated with the IP is suspected, the investigator must forward the special situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the electronic data source. If the AE meets the definition of an SAE, the SAE is also to be reported as described in [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events] together with details of the suspected drug-drug interaction.

12.5 Liver Safety Monitoring and Assessment

The purpose of this appendix is to provide guidance for the monitoring of drug-induced liver injury during the course of the study. It should be noted that this section does not specify the EoS analyses of liver enzymes. The EoS liver enzymes analyses will be described in the SAP. Any subject enrolled in a study with active drug therapy and reveals an increase of serum aminotransferases (AT) to > 3 × ULN or bilirubin > 2 × ULN should undergo detailed testing for liver enzymes (including at least alkaline phosphatase [ALP], ALT, AST and TBL). Testing should be repeated within 72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central laboratory regarding moderate and severe liver abnormality to inform the investigator and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN is as shown below.

Table 10 Moderate and Severe Liver Abnormalities

	ALT or AST		TBL
Moderate	> 3 × ULN	or	> 2 × ULN
Severe	> 3 × ULN	and†	> 2 × ULN

ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBL: total bilirubin; ULN: upper limit of normal

† Samples taken simultaneously or within maximum 24 hours.

In addition, the subject should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks
- ALT or AST > 3 × ULN and† and TBL > 2 × ULN or international normalized ratio (INR) > 1.5 (if INR testing is applicable/evaluated)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)

† Samples taken simultaneously or within a maximum of 24 hours.

The investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and clinical laboratory tests. The study site personnel are to complete the liver abnormality case report form (LA-CRF). Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal liver function tests should be repeated 2 to 3 times weekly, and then weekly or less if abnormalities stabilize or the IP has been discontinued and the subject is asymptomatic.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology, may be considered an important medical event and may be reported as a SAE. The sponsor should be contacted and informed of all subjects for whom severe hepatic liver function abnormalities possibly attributable to IP are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new-onset diseases are to be recorded as "AEs" within the electronic data source. Illnesses and conditions such as hypotensive events and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis is seen in obese hyperlipoproteinemic and/or diabetic subjects and may be associated with fluctuating AT levels. The investigator should ensure that the medical history form captures any illness that predates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including nonprescription medication, complementary and alternative medications), alcohol use, recreational drug use and special diets. Medications are to be entered in the electronic data source. Information on alcohol, other substance use and diet should be entered on the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents.
- Based on the subject's history, other testing may be appropriate including:
    - Acute viral hepatitis (A, B, C, D, E or other infectious agents)
    - Ultrasound or other imaging to assess biliary tract disease
    - Other clinical laboratory tests, including INR and direct bilirubin
- Consider gastroenterology or hepatology consultations.
- Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Treatment Discontinuation

In the absence of an explanation for increased liver function tests, such as viral hepatitis, preexisting or acute liver disease, or exposure to other agents associated with liver injury, the subject may be discontinued from study treatment. The investigator may determine that it is not in the subject's best interest to continue study treatment. Discontinuation of study treatment should be considered if:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks
- ALT or AST > 3 × ULN and† TBL > 2 × ULN or INR > 1.5) (if INR testing is applicable/evaluated)

- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)

† Samples taken simultaneously or within a maximum of 24 hours.

In addition, if close monitoring for a subject with moderate or severe hepatic laboratory tests is not possible, study treatment should be discontinued.

Hy's Law definition: Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10% to 50% mortality (or transplant).

The 2 "requirements" for Hy's Law are:

1. Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in AT elevations > 3 × ULN ("2 × ULN elevations are too common in treated and untreated subjects to be discriminating").
2. Cases of increased TBL (at least 2 × ULN) with concurrent AT elevations at least 3 × ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated ALP) or Gilbert's syndrome [Temple, 2006].

FDA Guidance for Industry titled, "Drug-induced Liver Injury: Premarketing Clinical Evaluation" issued by the FDA on July 2009:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo.
2. Among subjects showing such AT elevations, often with ATs much greater than 3 × ULN, 1 or more also show elevation of serum TBL to > 2 × ULN, without initial findings of cholestasis (elevated serum ALP).
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

References

Temple R. Hy's Law: Predicting Serious Hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006; 15:241-3.

12.6 List of Excluded Concomitant Medications

Any medication used for the management of OAB (including tricyclic antidepressants, 1st generation H1-antagonists and alpha-blockers) and any drugs that are sensitive CYP2D6 substrates with a narrow therapeutic index and sensitive P-gp substrates.

Use of these medications is not permitted during the study phase. This list is not exhaustive. In case of doubt, the investigator should contact the local study monitor.

Anticholinergics/antimuscarinics	**Tricyclic/heterocyclic antidepressants**	**1st generation H1-antagonists†**
Darifenacin	Alimemazine /Trimipramine	Tripelennamine
Dicyclomine/Dicycloverine	Amitriptyline	Dimenhydrinate
Fesoterodine	Amoxapine	Clemastine
Flavoxate	Clomipramine	Bromazine
Isopropamide	Desipramine	Orphenadrine
Oxybutynin	Dosulepin/Dothiepin	Doxylamine
Oxyphencyclimine	Doxepine	Carbinoxamine
Propantheline	Imipramine	Diphenhydramine
Propiverine	Lofepramine	Cyclizine
Tolterodine	Maprotiline	Chlorcyclizine
Trospium	Mianserin	Hydroxyzine
Solifenacin	Mirtazapine	Meclizine
	Nortriptyline	
	Protriptyline	
Alpha-blockers	**CYP2D6 with narrow therapeutic index**	**Sensitive P-gp substrates**
Tamsulosin	Thioridazine	Digoxin
Alfuzosin	Flecainide	Dabigatran
Doxazosin	Propafenone	
Terazosin	Imipramine	
Silodosin	Desipramine	
Moderate CYP3A4 inhibitors	**Strong CYP3A4 inhibitors**	**Moderate CYP3A4 inducers**
Fluconazole	Itraconazole	Cenobamate
Ciprofloxacin	Ketoconazole	Tipranavir
Erythromycin	Ritonavir	Ritonavir
Clotrimazole	Clarthromycin	Thioridazine
Fluvoxamine	Voriconazole	Rifabutin
Verapamil	Posaconazole	Nafcillin
Dronedarone	Troleandomycin	Lopinavir
Cimetidine	Telithromycin	Modafinil
Grapefruit Juice		Phenobarbital

Table continued on next page

Strong CYP3A4 inducers	P-gp inhibitors‡	P-gp Inducers‡
Rifampin	Amiodarone	Rifampin
Rifapentine	Carvedilol	Carbamazepine
Phenytoin	Clarithromycin	Dexamethasone
Carbamazepine	Dronedarone	Phenobarbital
St. John's wort	Itraconazole	Phenytoin
	Lopinavir, Ritonavir	Rifampicin
	Quinidine	St. John's wort
	Verapamil	Trazodone
QT prolongating medications	**Other**	
Amiodarone	Mirabegron (except for study drug)	
Sotalol	Botulinum toxin	
Quinidine	Opioids	
Levofloxacin, Ciprofloxacin		
Clarithromycin, Erythromycin		
Ketoconazole, Itraconazole		
Amitriptyline, Fluoxetine		
Haloperidol, Droperidol		
Cisapride		
Sumatriptan, Zolmitriptan		

P-gp: P-glycoprotein

† Incidental use for motion sickness is accepted.

‡ Moderate or strong not specified.

12.7 Laboratory Assessments

Laboratory tests will be performed according to the schedule of assessments and sent to a central laboratory for analysis.

Table 11 Clinical Laboratory Tests

Panel/Assessments	Parameters to be Analyzed
Hematology	Hematocrit Hemoglobin Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Platelets Red blood cell count White blood cell count White blood cell count differential
Biochemistry	Albumin Alanine aminotransferase Alkaline phosphatase Aspartate aminotransferase Bicarbonate Blood urea nitrogen Calcium Chloride Corrected serum calcium Creatinine Creatinine kinase Glucose Lactate dehydrogenase Magnesium Phosphate Potassium Serum hCG for female subjects Sodium Total bilirubin (total and direct) Total protein
Urinalysis	Leukocyte esterase Nitrites pH Protein Red blood cells

hCG: human chorionic gonadotropin

12.8 Acceptability and Palatability Questionnaire for Tablets

Questions

1. How was the TASTE of the study drug?

0	1	2	3	4
				
Really bad	Bad	Not bad, not good	Good	Really good
☐	☐	☐	☐	☐

2. How was it to SWALLOW the study drug?

0	1	2	3	4
				
Really difficult	Difficult	Not difficult, not easy	Easy	Really easy
☐	☐	☐	☐	☐

12.9 Acceptability and Palatability Questionnaire for Oral Suspension

Questions

1. How was the TASTE of the study drug?

0	1	2	3	4
				
Really bad	Bad	Not bad, not good	Good	Really good
☐	☐	☐	☐	☐

2. How was the SMELL of the study drug?

0	1	2	3	4
				
Really bad	Bad	Not bad, not good	Good	Really Good
☐	☐	☐	☐	☐

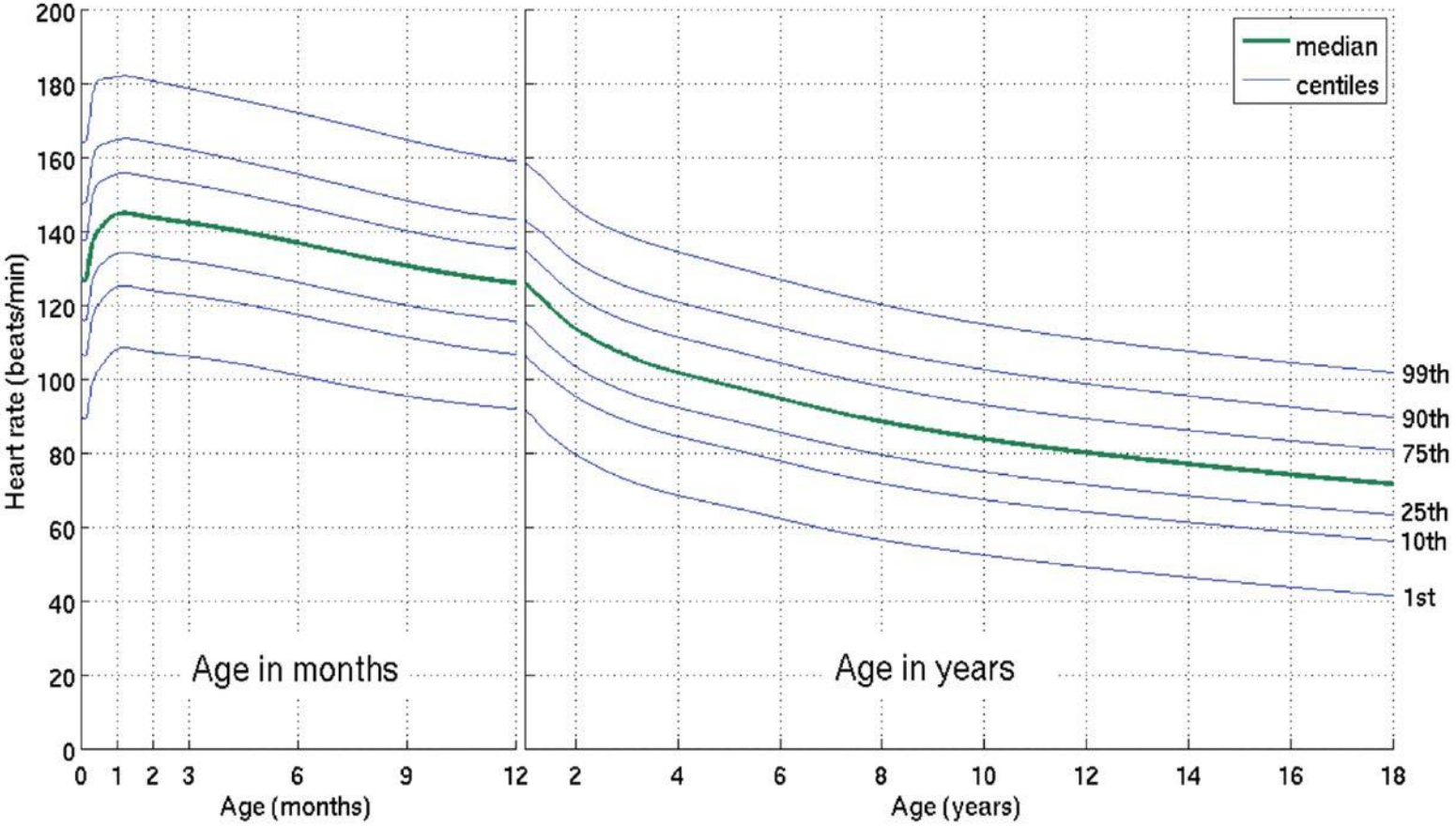
3. How was it to TAKE the study drug?

0	1	2	3	4
				
Really difficult	Difficult	Not difficult, not easy	Easy	Really easy
☐	☐	☐	☐	☐

4. How was it to <u>PREPARE</u> the study drug?

0	1	2	3	4
				
Really difficult	Difficult	Not difficult, not easy	Easy	Really easy
☐	☐	☐	☐	☐

12.10 Centiles of Heart Rate for Normal Children from Birth to 18 Years of Age



12.11 Centers for Disease Control and Prevention Data Table of Stature for Age Chart for Males

Males, Stature, Ages 2-20 Years

Age (in months)	3rd Percentile Stature (in centimeters)	5th Percentile Stature (in centimeters)	10th Percentile Stature (in centimeters)	25th Percentile Stature (in centimeters)	50th Percentile Stature (in centimeters)	75th Percentile Stature (in centimeters)	90th Percentile Stature (in centimeters)	95th Percentile Stature (in centimeters)	97th Percentile Stature (in centimeters)
24	79.91084	80.72977	81.99171	84.10289	86.4522	88.80525	90.92619	92.19688	93.02265
24.5	80.26037	81.08868	82.36401	84.49471	86.86161	89.22805	91.35753	92.63177	93.45923
25.5	81.00529	81.83445	83.11387	85.25888	87.65247	90.05675	92.22966	93.53407	94.38278
26.5	81.73416	82.56406	83.84716	86.00517	88.42326	90.8626	93.07608	94.40885	95.27762
27.5	82.44846	83.27899	84.56534	86.73507	89.17549	91.64711	93.89827	95.25754	96.14512
28.5	83.14945	83.98045	85.26962	87.44977	89.91041	92.41159	94.69757	96.08149	96.98663
29.5	83.83819	84.66948	85.96098	88.15028	90.62908	93.15719	95.47522	96.88198	97.80345
30.5	84.51558	85.34694	86.64027	88.83745	91.33242	93.88496	96.23239	97.66027	98.59691
31.5	85.18238	86.01357	87.3082	89.51202	92.02127	94.59585	96.97022	98.41758	99.36828
32.5	85.83925	86.66999	87.9654	90.17464	92.69638	95.2908	97.68978	99.15514	100.1189
33.5	86.48678	87.3168	88.61244	90.82592	93.35847	95.97068	98.39218	99.87416	100.8501
34.5	87.12552	87.95452	89.24986	91.46645	94.00823	96.63637	99.07848	100.5759	101.5631
35.5	87.75597	88.58366	89.87816	92.0968	94.64637	97.28875	99.74979	101.2615	102.2593
36.5	88.37864	89.20473	90.49789	92.71756	95.27359	97.9287	100.4072	101.9324	102.9402
37.5	88.93297	89.77301	91.08608	93.3344	95.91475	98.58525	101.069	102.593	103.5983
38.5	89.47916	90.33306	91.66589	93.94268	96.54734	99.23358	101.7234	103.247	104.2503
39.5	90.01766	90.88532	92.23779	94.54291	97.17191	99.87426	102.3709	103.8948	104.8967
40.5	90.54891	91.43025	92.80225	95.13557	97.78898	100.5078	103.012	104.537	105.538
41.5	91.07337	91.96832	93.35972	95.72115	98.39903	101.1348	103.6473	105.1739	106.1747
42.5	91.59152	92.49999	93.91068	96.30009	99.00254	101.7556	104.2771	105.8061	106.8071
43.5	92.10382	93.0257	94.45556	96.87286	99.59998	102.3708	104.9021	106.434	107.4357
44.5	92.61073	93.54592	94.99482	97.43989	100.1918	102.9807	105.5225	107.0579	108.0609
45.5	93.11271	94.06109	95.52888	98.00159	100.7783	103.5858	106.1387	107.6784	108.683
46.5	93.61022	94.57166	96.05817	98.55838	101.36	104.1865	106.7513	108.2956	109.3024
47.5	94.10371	95.07806	96.5831	99.11064	101.9373	104.7831	107.3604	108.9101	109.9193
48.5	94.59361	95.5807	97.10407	99.65875	102.5105	105.3759	107.9665	109.522	110.5342
49.5	95.08035	96.08	97.62147	100.2031	103.0799	105.9654	108.5698	110.1317	111.1473
50.5	95.56435	96.57635	98.13566	100.7439	103.6459	106.5518	109.1706	110.7394	111.7588
51.5	96.046	97.07013	98.64701	101.2817	104.2087	107.1354	109.7693	111.3454	112.369
52.5	96.52568	97.5617	99.15585	101.8166	104.7687	107.7165	110.366	111.95	112.9781
53.5	97.00376	98.05141	99.6625	102.3491	105.3262	108.2953	110.9609	112.5533	113.5863
54.5	97.48058	98.53958	100.1673	102.8792	105.8813	108.872	111.5543	113.1555	114.1937
55.5	97.95648	99.02654	100.6705	103.4074	106.4343	109.4469	112.1464	113.7568	114.8006

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Males, Stature, Ages 2-20 Years

Age (in months)	3rd Percentile Stature (in centimeters)	5th Percentile Stature (in centimeters)	10th Percentile Stature (in centimeters)	25th Percentile Stature (in centimeters)	50th Percentile Stature (in centimeters)	75th Percentile Stature (in centimeters)	90th Percentile Stature (in centimeters)	95th Percentile Stature (in centimeters)	97th Percentile Stature (in centimeters)
56.5	98.43175	99.51256	101.1723	103.9339	106.9855	110.0201	112.7374	114.3574	115.4072
57.5	98.90667	99.99791	101.6731	104.4588	107.535	110.5919	113.3273	114.9575	116.0134
58.5	99.38151	100.4828	102.173	104.9825	108.083	111.1623	113.9164	115.557	116.6194
59.5	99.8565	100.9676	102.6723	105.505	108.6296	111.7316	114.5047	116.1561	117.2254
60.5	100.3318	101.4523	103.1712	106.0265	109.1751	112.2998	115.0924	116.755	117.8314
61.5	100.8077	101.9372	103.6697	106.5472	109.7196	112.8671	115.6795	117.3536	118.4374
62.5	101.2843	102.4225	104.1682	107.0673	110.2631	113.4335	116.2661	117.9521	119.0435
63.5	101.7618	102.9082	104.6666	107.5868	110.8058	113.9992	116.8522	118.5505	119.6498
64.5	102.2401	103.3945	105.1651	108.1058	111.3477	114.5641	117.438	119.1487	120.2562
65.5	102.7195	103.8814	105.6638	108.6244	111.889	115.1284	118.0234	119.7469	120.8627
66.5	103.2	104.369	106.1627	109.1427	112.4296	115.6921	118.6084	120.345	121.4694
67.5	103.6815	104.8574	106.6619	109.6607	112.9696	116.2551	119.1931	120.943	122.0761
68.5	104.1642	105.3466	107.1614	110.1785	113.509	116.8176	119.7774	121.5408	122.6829
69.5	104.6479	105.8364	107.6611	110.696	114.0479	117.3794	120.3613	122.1384	123.2897
70.5	105.1326	106.327	108.1612	111.2132	114.5861	117.9407	120.9447	122.7359	123.8965
71.5	105.6183	106.8182	108.6614	111.7302	115.1238	118.5012	121.5277	123.333	124.5031
72.5	106.1048	107.3099	109.1619	112.2469	115.6609	119.0611	122.1101	123.9297	125.1095
73.5	106.5921	107.8021	109.6624	112.7631	116.1973	119.6203	122.6918	124.526	125.7156
74.5	107.0799	108.2946	110.1629	113.2789	116.7329	120.1786	123.2729	125.1217	126.3212
75.5	107.5682	108.7873	110.6633	113.7942	117.2678	120.7361	123.8532	125.7168	126.9263
76.5	108.0566	109.2801	111.1634	114.3089	117.8018	121.2926	124.4327	126.3111	127.5307
77.5	108.5451	109.7727	111.6631	114.8229	118.3348	121.848	125.0111	126.9045	128.1344
78.5	109.0335	110.2649	112.1623	115.336	118.8668	122.4024	125.5884	127.4969	128.7371
79.5	109.5214	110.7566	112.6608	115.8481	119.3977	122.9555	126.1646	128.0882	129.3387
80.5	110.0086	111.2476	113.1583	116.3592	119.9272	123.5073	126.7394	128.6782	129.9391
81.5	110.495	111.7375	113.6548	116.869	120.4554	124.0576	127.3128	129.2668	130.5381
82.5	110.9801	112.2263	114.1499	117.3774	120.9821	124.6064	127.8846	129.8538	131.1356
83.5	111.4638	112.7135	114.6436	117.8842	121.5072	125.1535	128.4547	130.4392	131.7314
84.5	111.9459	113.1991	115.1356	118.3893	122.0305	125.6987	129.023	131.0226	132.3253
85.5	112.4259	113.6827	115.6257	118.8926	122.552	126.2421	129.5893	131.6041	132.9172
86.5	112.9036	114.1642	116.1136	119.3938	123.0714	126.7834	130.1535	132.1834	133.507
87.5	113.3789	114.6431	116.5992	119.8927	123.5886	127.3225	130.7154	132.7605	134.0943
88.5	113.8513	115.1194	117.0822	120.3893	124.1035	127.8594	131.275	133.335	134.6792

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Age (in months)	3rd Percentile Stature (in centimeters)	5th Percentile Stature (in centimeters)	10th Percentile Stature (in centimeters)	25th Percentile Stature (in centimeters)	50th Percentile Stature (in centimeters)	75th Percentile Stature (in centimeters)	90th Percentile Stature (in centimeters)	95th Percentile Stature (in centimeters)	97th Percentile Stature (in centimeters)
89.5	114.3206	115.5927	117.5625	120.8833	124.616	128.3937	131.8321	133.907	135.2615
90.5	114.7867	116.0629	118.0398	121.3746	125.1259	128.9256	132.3865	134.4763	135.8409
91.5	115.2491	116.5297	118.5139	121.863	125.6331	129.4547	132.9381	135.0426	136.4173
92.5	115.7077	116.9928	118.9847	122.3483	126.1374	129.981	133.4868	135.606	136.9906
93.5	116.1623	117.4521	119.4519	122.8305	126.6388	130.5044	134.0325	136.1662	137.5607
94.5	116.6127	117.9074	119.9153	123.3092	127.137	131.0247	134.5751	136.7231	138.1274
95.5	117.0587	118.3585	120.3749	123.7845	127.632	131.5419	135.1144	137.2767	138.6906
96.5	117.5	118.8053	120.8305	124.2562	128.1237	132.0559	135.6504	137.8267	139.2502
97.5	117.9366	119.2475	121.2819	124.7242	128.6119	132.5664	136.1829	138.3731	139.806
98.5	118.3683	119.6851	121.729	125.1882	129.0966	133.0736	136.7118	138.9159	140.358
99.5	118.7949	120.1179	122.1716	125.6484	129.5777	133.5771	137.2371	139.4548	140.9062
100.5	119.2165	120.5459	122.6099	126.1045	130.055	134.0771	137.7587	139.9899	141.4503
101.5	119.633	120.969	123.0435	126.5565	130.5286	134.5734	138.2765	140.5211	141.9904
102.5	120.0442	121.3872	123.4726	127.0044	130.9983	135.066	138.7905	141.0484	142.5263
103.5	120.4502	121.8004	123.897	127.4481	131.4641	135.5548	139.3006	141.5716	143.0582
104.5	120.851	122.2086	124.3168	127.8876	131.926	136.0397	139.8069	142.0908	143.586
105.5	121.2467	122.6119	124.7319	128.3228	132.384	136.5209	140.3093	142.6061	144.1096
106.5	121.6372	123.0103	125.1425	128.7539	132.8381	136.9982	140.8077	143.1173	144.6291
107.5	122.0228	123.4039	125.5485	129.1807	133.2882	137.4717	141.3023	143.6245	145.1445
108.5	122.4034	123.7928	125.9501	129.6035	133.7345	137.9414	141.793	144.1278	145.656
109.5	122.7793	124.1771	126.3473	130.0222	134.1769	138.4073	142.28	144.6272	146.1634
110.5	123.1506	124.5569	126.7402	130.4369	134.6155	138.8696	142.7632	145.1228	146.6671
111.5	123.5175	124.9325	127.1291	130.8477	135.0504	139.3282	143.2428	145.6148	147.167
112.5	123.8803	125.304	127.514	131.2548	135.4818	139.7833	143.7188	146.1032	147.6633
113.5	124.2391	125.6717	127.8953	131.6584	135.9097	140.235	144.1915	146.5882	148.1562
114.5	124.5943	126.0358	128.273	132.0585	136.3343	140.6835	144.661	147.0699	148.6459
115.5	124.9462	126.3966	128.6474	132.4555	136.7557	141.1289	145.1273	147.5486	149.1325
116.5	125.295	126.7544	129.0189	132.8495	137.1742	141.5713	145.5909	148.0245	149.6163
117.5	125.6413	127.1096	129.3876	133.2407	137.5899	142.0111	146.0518	148.4979	150.0977
118.5	125.9852	127.4624	129.754	133.6295	138.0032	142.4484	146.5103	148.9689	150.5767
119.5	126.3272	127.8132	130.1183	134.0161	138.4143	142.8835	146.9668	149.438	151.0539
120.5	126.6678	128.1625	130.4809	134.4008	138.8234	143.3168	147.4214	149.9053	151.5294
121.5	127.0073	128.5106	130.8422	134.7841	139.231	143.7484	147.8747	150.3714	152.0038

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Males, Stature, Ages 2-20 Years

Age (in months)	3rd Percentile Stature (in centimeters)	5th Percentile Stature (in centimeters)	10th Percentile Stature (in centimeters)	25th Percentile Stature (in centimeters)	50th Percentile Stature (in centimeters)	75th Percentile Stature (in centimeters)	90th Percentile Stature (in centimeters)	95th Percentile Stature (in centimeters)	97th Percentile Stature (in centimeters)
122.5	127.3462	128.8579	131.2026	135.1663	139.6373	144.1789	148.3268	150.8365	152.4773
123.5	127.6851	129.2051	131.5625	135.5477	140.0427	144.6085	148.7782	151.301	152.9504
124.5	128.0243	129.5524	131.9224	135.9288	140.4477	145.0377	149.2294	151.7655	153.4235
125.5	128.3643	129.9004	132.2828	136.3101	140.8527	145.4669	149.6808	152.2303	153.8972
126.5	128.7058	130.2496	132.6441	136.692	141.2582	145.8965	150.1329	152.696	154.3718
127.5	129.0491	130.6005	133.0068	137.075	141.6646	146.3272	150.5861	153.1631	154.848
128.5	129.3949	130.9536	133.3714	137.4597	142.0725	146.7593	151.041	153.6321	155.3263
129.5	129.7436	131.3094	133.7386	137.8466	142.4824	147.1936	151.4982	154.1035	155.8072
130.5	130.0958	131.6686	134.1089	138.2362	142.8949	147.6305	151.9583	154.578	156.2913
131.5	130.452	132.0316	134.4828	138.6292	143.3107	148.0707	152.4218	155.0562	156.7792
132.5	130.8127	132.399	134.8608	139.0262	143.7304	148.5147	152.8894	155.5386	157.2715
133.5	131.1785	132.7714	135.2437	139.4278	144.1545	148.9633	153.3617	156.0258	157.7688
134.5	131.5498	133.1491	135.6318	139.8346	144.5838	149.4172	153.8394	156.5186	158.2717
135.5	131.9272	133.5329	136.026	140.2472	145.019	149.8769	154.323	157.0174	158.7806
136.5	132.311	133.9232	136.4266	140.6664	145.4607	150.3433	154.8133	157.5229	159.2964
137.5	132.7018	134.3205	136.8343	141.0928	145.9097	150.8169	155.3109	158.0356	159.8193
138.5	133.1	134.7252	137.2496	141.5269	146.3665	151.2984	155.8164	158.5562	160.35
139.5	133.5059	135.1378	137.673	141.9694	146.832	151.7885	156.3303	159.0851	160.889
140.5	133.9199	135.5588	138.105	142.4209	147.3066	152.2878	156.8532	159.6228	161.4365
141.5	134.3423	135.9885	138.5461	142.882	147.7911	152.7969	157.3857	160.1697	161.993
142.5	134.7733	136.4271	138.9968	143.3532	148.2859	153.3164	157.928	160.7262	162.5588
143.5	135.2132	136.8751	139.4573	143.835	148.7917	153.8466	158.4807	161.2924	163.1339
144.5	135.6621	137.3326	139.928	144.3277	149.3088	154.3881	159.0439	161.8686	163.7185
145.5	136.1202	137.7998	140.4091	144.8317	149.8376	154.941	159.6179	162.4549	164.3126
146.5	136.5875	138.2769	140.9009	145.3473	150.3784	155.5056	160.2026	163.0511	164.916
147.5	137.064	138.7638	141.4034	145.8746	150.9313	156.0819	160.7981	163.6571	165.5285
148.5	137.5496	139.2605	141.9167	146.4137	151.4964	156.6699	161.4041	164.2726	166.1497
149.5	138.0442	139.767	142.4407	146.9645	152.0735	157.2694	162.0203	164.8972	166.7791
150.5	138.5477	140.2831	142.9752	147.5269	152.6624	157.88	162.6462	165.5302	167.416
151.5	139.0597	140.8085	143.52	148.1005	153.2627	158.5012	163.2811	166.1711	168.0596
152.5	139.5799	141.3429	144.0746	148.6849	153.8738	159.1324	163.9243	166.8187	168.7091
153.5	140.108	141.8859	144.6388	149.2795	154.4951	159.7725	164.5748	167.4723	169.3634
154.5	140.6435	142.4369	145.2117	149.8836	155.1255	160.4207	165.2314	168.1305	170.0213

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Males, Stature, Ages 2-20 Years

Age (in months)	3rd Percentile Stature (in centimeters)	5th Percentile Stature (in centimeters)	10th Percentile Stature (in centimeters)	25th Percentile Stature (in centimeters)	50th Percentile Stature (in centimeters)	75th Percentile Stature (in centimeters)	90th Percentile Stature (in centimeters)	95th Percentile Stature (in centimeters)	97th Percentile Stature (in centimeters)
155.5	141.1858	142.9955	145.7928	150.4962	155.7642	161.0758	165.893	168.7923	170.6817
156.5	141.7345	143.5608	146.3813	151.1165	156.4099	161.7364	166.5581	169.4561	171.343
157.5	142.2889	144.1322	146.9763	151.7433	157.0612	162.401	167.2253	170.1205	172.004
158.5	142.8482	144.7089	147.5767	152.3754	157.7168	163.0682	167.8929	170.784	172.663
159.5	143.4118	145.29	148.1815	153.0113	158.3751	163.7363	168.5594	171.445	173.3186
160.5	143.9788	145.8746	148.7896	153.6498	159.0344	164.4035	169.2231	172.1018	173.9691
161.5	144.5483	146.4615	149.3998	154.2892	159.6931	165.0681	169.8822	172.7528	174.6131
162.5	145.1196	147.0498	150.0107	154.928	160.3493	165.7283	170.535	173.3965	175.249
163.5	145.6915	147.6385	150.621	155.5647	161.0015	166.3823	171.1798	174.0312	175.8753
164.5	146.2633	148.2262	151.2295	156.1977	161.6478	167.0284	171.8151	174.6554	176.4906
165.5	146.8339	148.812	151.8348	156.8253	162.2865	167.665	172.4393	175.2677	177.0935
166.5	147.4023	149.3947	152.4355	157.4462	162.9161	168.2905	173.0509	175.8668	177.6829
167.5	147.9674	149.9731	153.0304	158.0587	163.535	168.9033	173.6486	176.4515	178.2575
168.5	148.5284	150.5461	153.6181	158.6615	164.1418	169.5022	174.2313	177.0206	178.8165
169.5	149.0842	151.1127	154.1975	159.2532	164.7352	170.0859	174.7978	177.5733	179.3589
170.5	149.6338	151.6717	154.7674	159.8327	165.314	170.6535	175.3473	178.1088	179.884
171.5	150.1763	152.2221	155.3268	160.3988	165.8771	171.2039	175.879	178.6264	180.3913
172.5	150.7107	152.763	155.8746	160.9506	166.4236	171.7364	176.3923	179.1256	180.8804
173.5	151.2363	153.2935	156.4099	161.4872	166.9528	172.2504	176.8868	179.6061	181.3509
174.5	151.7521	153.8127	156.9319	162.0078	167.4641	172.7455	177.3622	180.0676	181.8027
175.5	152.2575	154.32	157.4399	162.5118	167.9571	173.2213	177.8183	180.5102	182.2358
176.5	152.7517	154.8147	157.9334	162.9988	168.4313	173.6778	178.2551	180.9338	182.6503
177.5	153.2342	155.2961	158.4118	163.4685	168.8867	174.1148	178.6727	181.3385	183.0463
178.5	153.7043	155.7638	158.8747	163.9205	169.3231	174.5324	179.0712	181.7247	183.4242
179.5	154.1615	156.2174	159.3218	164.3547	169.7405	174.9309	179.451	182.0927	183.7842
180.5	154.6056	156.6566	159.7529	164.7713	170.1393	175.3105	179.8124	182.4429	184.127
181.5	155.036	157.0811	160.168	165.1701	170.5195	175.6716	180.1559	182.7757	184.4528
182.5	155.4526	157.4907	160.5669	165.5514	170.8815	176.0146	180.482	183.0918	184.7624
183.5	155.8552	157.8853	160.9498	165.9154	171.2257	176.34	180.7912	183.3916	185.0562
184.5	156.2436	158.265	161.3167	166.2625	171.5525	176.6483	181.0841	183.6757	185.3349
185.5	156.6178	158.6298	161.6679	166.5929	171.8626	176.9402	181.3614	183.9449	185.599
186.5	156.9777	158.9798	162.0035	166.9072	172.1563	177.2163	181.6236	184.1997	185.8493
187.5	157.3235	159.315	162.3239	167.2057	172.4343	177.4771	181.8715	184.4408	186.0863

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Age (in months)	3rd Percentile Stature (in centimeters)	5th Percentile Stature (in centimeters)	10th Percentile Stature (in centimeters)	25th Percentile Stature (in centimeters)	50th Percentile Stature (in centimeters)	75th Percentile Stature (in centimeters)	90th Percentile Stature (in centimeters)	95th Percentile Stature (in centimeters)	97th Percentile Stature (in centimeters)
188.5	157.6551	159.6359	162.6294	167.489	172.6972	177.7234	182.1056	184.6687	186.3107
189.5	157.9729	159.9425	162.9204	167.7576	172.9456	177.9558	182.3267	184.8843	186.5231
190.5	158.277	160.2352	163.1973	168.012	173.1801	178.175	182.5353	185.0879	186.724
191.5	158.5676	160.5143	163.4605	168.2528	173.4014	178.3815	182.7322	185.2804	186.9142
192.5	158.845	160.7802	163.7104	168.4805	173.6101	178.5762	182.9179	185.4623	187.0941
193.5	159.1095	161.0332	163.9476	168.6958	173.8067	178.7595	183.0931	185.6341	187.2643
194.5	159.3614	161.2738	164.1725	168.8991	173.992	178.9321	183.2583	185.7965	187.4254
195.5	159.6011	161.5023	164.3856	169.0911	174.1665	179.0946	183.414	185.9498	187.5779
196.5	159.829	161.7191	164.5873	169.2722	174.3308	179.2476	183.5609	186.0948	187.7222
197.5	160.0455	161.9247	164.7782	169.4431	174.4854	179.3915	183.6995	186.2318	187.8588
198.5	160.2508	162.1196	164.9587	169.6041	174.631	179.5271	183.8302	186.3613	187.9881
199.5	160.4456	162.3041	165.1292	169.756	174.768	179.6547	183.9535	186.4837	188.1106
200.5	160.63	162.4786	165.2903	169.8991	174.8969	179.7748	184.0699	186.5995	188.2267
201.5	160.8046	162.6437	165.4424	170.0339	175.0182	179.888	184.1797	186.7091	188.3368
202.5	160.9697	162.7997	165.586	170.1608	175.1323	179.9946	184.2835	186.8128	188.4411
203.5	161.1258	162.947	165.7214	170.2804	175.2398	180.095	184.3815	186.911	188.54
204.5	161.2733	163.086	165.8491	170.3931	175.341	180.1896	184.4741	187.004	188.6338
205.5	161.4125	163.2172	165.9694	170.4991	175.4362	180.2789	184.5617	187.0922	188.7229
206.5	161.5438	163.3409	166.0828	170.599	175.5259	180.3631	184.6446	187.1757	188.8075
207.5	161.6676	163.4575	166.1897	170.693	175.6104	180.4426	184.723	187.255	188.8878
208.5	161.7843	163.5673	166.2903	170.7816	175.6901	180.5176	184.7972	187.3302	188.9642
209.5	161.8942	163.6708	166.3851	170.865	175.7652	180.5885	184.8676	187.4016	189.0368
210.5	161.9977	163.7682	166.4743	170.9436	175.836	180.6555	184.9343	187.4694	189.1058
211.5	162.0951	163.8598	166.5583	171.0176	175.9028	180.7189	184.9975	187.5338	189.1715
212.5	162.1866	163.9461	166.6373	171.0873	175.9658	180.7789	185.0576	187.5951	189.234
213.5	162.2727	164.0272	166.7116	171.1529	176.0254	180.8357	185.1146	187.6534	189.2936
214.5	162.3537	164.1034	166.7816	171.2148	176.0816	180.8895	185.1687	187.7088	189.3503
215.5	162.4297	164.1751	166.8474	171.2732	176.1348	180.9405	185.2202	187.7617	189.4044
216.5	162.5011	164.2424	166.9094	171.3282	176.185	180.9889	185.2692	187.812	189.456
217.5	162.5681	164.3057	166.9676	171.3801	176.2326	181.0348	185.3159	187.86	189.5052
218.5	162.631	164.3651	167.0224	171.429	176.2776	181.0784	185.3603	187.9057	189.5522
219.5	162.69	164.4209	167.074	171.4752	176.3202	181.1199	185.4026	187.9494	189.5971
220.5	162.7453	164.4733	167.1224	171.5188	176.3606	181.1593	185.443	187.9911	189.6399

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Males, Stature, Ages 2-20 Years

Age (in months)	3rd Percentile Stature (in centimeters)	5th Percentile Stature (in centimeters)	10th Percentile Stature (in centimeters)	25th Percentile Stature (in centimeters)	50th Percentile Stature (in centimeters)	75th Percentile Stature (in centimeters)	90th Percentile Stature (in centimeters)	95th Percentile Stature (in centimeters)	97th Percentile Stature (in centimeters)
221.5	162.7972	164.5224	167.168	171.5599	176.3989	181.1968	185.4815	188.0309	189.6809
222.5	162.8458	164.5686	167.2109	171.5988	176.4352	181.2325	185.5182	188.069	189.7201
223.5	162.8914	164.6119	167.2513	171.6355	176.4697	181.2666	185.5534	188.1054	189.7575
224.5	162.9341	164.6526	167.2892	171.6701	176.5024	181.299	185.5869	188.1402	189.7934
225.5	162.9741	164.6907	167.325	171.7029	176.5335	181.33	185.619	188.1736	189.8277
226.5	163.0115	164.7265	167.3585	171.7339	176.563	181.3595	185.6497	188.2055	189.8606
227.5	163.0465	164.76	167.3902	171.7632	176.5911	181.3877	185.6791	188.236	189.8922
228.5	163.0793	164.7915	167.4199	171.791	176.6179	181.4147	185.7073	188.2653	189.9224
229.5	163.11	164.821	167.4479	171.8172	176.6433	181.4405	185.7343	188.2934	189.9513
230.5	163.1387	164.8487	167.4742	171.8421	176.6676	181.4651	185.7601	188.3204	189.9791
231.5	163.1656	164.8746	167.499	171.8657	176.6907	181.4887	185.7849	188.3462	190.0058
232.5	163.1907	164.8989	167.5224	171.888	176.7127	181.5113	185.8087	188.3711	190.0314
233.5	163.2142	164.9217	167.5444	171.9091	176.7337	181.533	185.8316	188.3949	190.056
234.5	163.2361	164.9431	167.5651	171.9292	176.7538	181.5538	185.8535	188.4178	190.0797
235.5	163.2566	164.9631	167.5846	171.9483	176.773	181.5737	185.8746	188.4399	190.1024
236.5	163.2757	164.9819	167.6029	171.9663	176.7913	181.5928	185.8949	188.461	190.1242
237.5	163.2936	164.9995	167.6203	171.9835	176.8088	181.6111	185.9144	188.4814	190.1452
238.5	163.3103	165.016	167.6366	171.9998	176.8255	181.6287	185.9331	188.501	190.1654
239.5	163.3259	165.0315	167.6519	172.0153	176.8415	181.6456	185.9512	188.5198	190.1849
240	163.3333	165.0389	167.6593	172.0227	176.8492	181.6538	185.9599	188.529	190.1943

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12.12 Centers for Disease Control and Prevention Data Table of Stature for Age Chart for Females

Females, Stature, Ages 2-20 Years

Age (in months)	3rd Percentile Stature (in centimeters)	5th Percentile Stature (in centimeters)	10th Percentile Stature (in centimeters)	25th Percentile Stature (in centimeters)	50th Percentile Stature (in centimeters)	75th Percentile Stature (in centimeters)	90th Percentile Stature (in centimeters)	95th Percentile Stature (in centimeters)	97th Percentile Stature (in centimeters)
24	78.43754	79.25982	80.52476	82.63524	84.97556	87.31121	89.40951	90.66355	91.47729
24.5	78.82133	79.64777	80.91946	83.04213	85.39732	87.74918	89.86316	91.12707	91.94741
25.5	79.60198	80.44226	81.73541	83.8943	86.29026	88.68344	90.83505	92.12168	92.95685
26.5	80.37555	81.22666	82.53699	84.72592	87.15714	89.58751	91.77421	93.08254	93.93209
27.5	81.1357	81.9954	83.31968	85.53389	87.99602	90.46018	92.67969	94.00873	94.87215
28.5	81.87746	82.74411	84.07998	86.31589	88.80551	91.30065	93.55097	94.89974	95.77649
29.5	82.59712	83.46957	84.81532	87.07028	89.58477	92.10859	94.38793	95.75551	96.64505
30.5	83.29206	84.16953	85.52398	87.79609	90.33342	92.88403	95.19083	96.57635	97.47814
31.5	83.96065	84.84264	86.205	88.49291	91.05154	93.62741	95.9603	97.36295	98.27646
32.5	84.6021	85.4883	86.85807	89.16084	91.73964	94.33951	96.69729	98.11632	99.04107
33.5	85.2163	86.10656	87.48344	89.80045	92.39854	95.0214	97.40303	98.83778	99.77332
34.5	85.80379	86.69803	88.08186	90.4127	93.02945	95.67446	98.07904	99.52891	100.4748
35.5	86.36557	87.26379	88.6545	90.99891	93.63382	96.30029	98.72705	100.1915	101.1474
36.5	86.90307	87.80528	89.20285	91.56066	94.21336	96.90071	99.34899	100.8276	101.7931
37.5	87.43482	88.34236	89.74875	92.12298	94.79643	97.50724	99.97896	101.4726	102.4485
38.5	87.95945	88.87256	90.28811	92.67925	95.37392	98.10855	100.604	102.1129	103.0991
39.5	88.4785	89.39733	90.82228	93.2307	95.94693	98.70568	101.2251	102.7494	103.746
40.5	88.9933	89.91797	91.35246	93.7784	96.51645	99.29957	101.8432	103.383	104.3901
41.5	89.50502	90.43559	91.87972	94.32334	97.08337	99.89104	102.459	104.0144	105.032
42.5	90.01466	90.95115	92.40497	94.86634	97.64848	100.4808	103.0732	104.6444	105.6727
43.5	90.52307	91.46549	92.92901	95.40817	98.21247	101.0696	103.6866	105.2736	106.3126
44.5	91.031	91.97932	93.45252	95.94946	98.77593	101.6579	104.2996	105.9025	106.9523
45.5	91.53905	92.49325	93.97609	96.49076	99.3394	102.2462	104.9128	106.5316	107.5922
46.5	92.04774	93.00778	94.50021	97.03254	99.90331	102.835	105.5264	107.1613	108.2328
47.5	92.55748	93.52333	95.02528	97.57519	100.4681	103.4247	106.141	107.7919	108.8744
48.5	93.06862	94.04022	95.55164	98.11905	101.0339	104.0154	106.7567	108.4238	109.5172
49.5	93.58141	94.55872	96.07954	98.66436	101.6012	104.6075	107.3737	109.057	110.1614
50.5	94.09605	95.07903	96.60918	99.21132	102.17	105.2012	107.9924	109.6918	110.8073
51.5	94.61267	95.60128	97.14072	99.76009	102.7406	105.7965	108.6127	110.3283	111.4548
52.5	95.13134	96.12555	97.67423	100.3108	103.313	106.3936	109.2347	110.9665	112.1041
53.5	95.65211	96.65189	98.20976	100.8634	103.8873	106.9925	109.8585	111.6066	112.7552
54.5	96.17495	97.18029	98.74731	101.418	104.4635	107.5933	110.4841	112.2483	113.4079
55.5	96.69982	97.71069	99.28686	101.9745	105.0415	108.1958	111.1114	112.8917	114.0624

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Females, Stature, Ages 2-20 Years

Age (in months)	3rd Percentile Stature (in centimeters)	5th Percentile Stature (in centimeters)	10th Percentile Stature (in centimeters)	25th Percentile Stature (in centimeters)	50th Percentile Stature (in centimeters)	75th Percentile Stature (in centimeters)	90th Percentile Stature (in centimeters)	95th Percentile Stature (in centimeters)	97th Percentile Stature (in centimeters)
56.5	97.22663	98.24303	99.82832	102.5329	105.6213	108.8001	111.7404	113.5368	114.7184
57.5	97.75525	98.77719	100.3716	103.093	106.2029	109.406	112.3709	114.1833	115.3759
58.5	98.28555	99.31303	100.9165	103.6549	106.7861	110.0134	113.0028	114.8312	116.0347
59.5	98.81735	99.85039	101.463	104.2182	107.3707	110.6222	113.6359	115.4802	116.6945
60.5	99.35047	100.3891	102.0109	104.7829	107.9566	111.2321	114.2701	116.1301	117.3552
61.5	99.8847	100.9289	102.5599	105.3488	108.5436	111.8431	114.9052	116.7808	118.0166
62.5	100.4198	101.4696	103.1098	105.9156	109.1316	112.4548	115.5408	117.432	118.6783
63.5	100.9555	102.011	103.6604	106.4831	109.7202	113.0671	116.1768	118.0834	119.3402
64.5	101.4916	102.5529	104.2115	107.0512	110.3092	113.6797	116.813	118.7348	120.0019
65.5	102.0279	103.0948	104.7628	107.6194	110.8984	114.2923	117.449	119.3858	120.6632
66.5	102.564	103.6367	105.3141	108.1877	111.4876	114.9048	118.0845	120.0362	121.3238
67.5	103.0996	104.1782	105.865	108.7556	112.0764	115.5167	118.7193	120.6857	121.9832
68.5	103.6346	104.7191	106.4154	109.323	112.6646	116.1278	119.3531	121.334	122.6413
69.5	104.1685	105.259	106.9648	109.8895	113.2519	116.7379	119.9855	121.9807	123.2977
70.5	104.7012	105.7976	107.5131	110.4549	113.838	117.3466	120.6163	122.6256	123.9521
71.5	105.2323	106.3348	108.0599	111.0189	114.4226	117.9537	121.2452	123.2684	124.6042
72.5	105.7615	106.8701	108.605	111.5812	115.0055	118.5588	121.8718	123.9086	125.2536
73.5	106.2886	107.4033	109.148	112.1415	115.5863	119.1616	122.4959	124.5461	125.9
74.5	106.8132	107.9342	109.6888	112.6996	116.1648	119.7619	123.1171	125.1804	126.5432
75.5	107.3351	108.4624	110.227	113.255	116.7406	120.3594	123.7352	125.8114	127.1827
76.5	107.8541	108.9877	110.7623	113.8077	117.3136	120.9537	124.3499	126.4387	127.8184
77.5	108.3698	109.5099	111.2944	114.3572	117.8833	121.5447	124.9608	127.062	128.45
78.5	108.882	110.0285	111.8232	114.9034	118.4496	122.132	125.5678	127.6811	129.0771
79.5	109.3905	110.5435	112.3483	115.446	119.0123	122.7154	126.1705	128.2957	129.6996
80.5	109.8949	111.0545	112.8696	115.9847	119.571	123.2946	126.7688	128.9056	130.3171
81.5	110.3952	111.5613	113.3867	116.5193	120.1254	123.8695	127.3623	129.5105	130.9295
82.5	110.8909	112.0638	113.8995	117.0496	120.6755	124.4397	127.951	130.1103	131.5365
83.5	111.3821	112.5616	114.4077	117.5754	121.221	125.0051	128.5345	130.7047	132.138
84.5	111.8684	113.0546	114.9112	118.0964	121.7617	125.5655	129.1127	131.2936	132.7338
85.5	112.3496	113.5427	115.4097	118.6125	122.2974	126.1207	129.6855	131.8768	133.3238
86.5	112.8257	114.0256	115.9031	119.1235	122.8279	126.6706	130.2526	132.4542	133.9077
87.5	113.2963	114.5031	116.3913	119.6293	123.3531	127.215	130.814	133.0256	134.4857
88.5	113.7615	114.9752	116.874	120.1297	123.8728	127.7539	131.3696	133.5911	135.0574

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Females, Stature, Ages 2-20 Years

Age (in months)	3rd Percentile Stature (in centimeters)	5th Percentile Stature (in centimeters)	10th Percentile Stature (in centimeters)	25th Percentile Stature (in centimeters)	50th Percentile Stature (in centimeters)	75th Percentile Stature (in centimeters)	90th Percentile Stature (in centimeters)	95th Percentile Stature (in centimeters)	97th Percentile Stature (in centimeters)
89.5	114.2211	115.4418	117.3512	120.6246	124.387	128.287	131.9194	134.1505	135.623
90.5	114.6749	115.9026	117.8228	121.1138	124.8956	128.8144	132.4631	134.7038	136.1824
91.5	115.123	116.3577	118.2886	121.5974	125.3985	129.3359	133.0009	135.251	136.7356
92.5	115.5651	116.8069	118.7486	122.0753	125.8956	129.8516	133.5328	135.7922	137.2826
93.5	116.0012	117.2502	119.2028	122.5473	126.3869	130.3615	134.0587	136.3273	137.8236
94.5	116.4314	117.6875	119.6511	123.0135	126.8724	130.8656	134.5787	136.8565	138.3585
95.5	116.8555	118.1189	120.0935	123.4739	127.3522	131.364	135.093	137.3798	138.8876
96.5	117.2737	118.5443	120.53	123.9285	127.8263	131.8567	135.6015	137.8975	139.411
97.5	117.6858	118.9638	120.9607	124.3774	128.2947	132.3438	136.1046	138.4097	139.9289
98.5	118.092	119.3774	121.3855	124.8207	128.7576	132.8255	136.6024	138.9166	140.4415
99.5	118.4924	119.7852	121.8047	125.2584	129.2152	133.302	137.095	139.4184	140.9492
100.5	118.8869	120.1873	122.2182	125.6906	129.6675	133.7734	137.5828	139.9155	141.4521
101.5	119.2757	120.5838	122.6263	126.1177	130.1148	134.2401	138.066	140.4082	141.9507
102.5	119.659	120.9748	123.0291	126.5396	130.5574	134.7023	138.545	140.8968	142.4454
103.5	120.037	121.3606	123.4268	126.9568	130.9954	135.1604	139.0201	141.3817	142.9364
104.5	120.4097	121.7413	123.8196	127.3694	131.4293	135.6146	139.4918	141.8633	143.4244
105.5	120.7775	122.1171	124.2078	127.7777	131.8593	136.0654	139.9604	142.3422	143.9098
106.5	121.1405	122.4884	124.5916	128.1822	132.2859	136.5132	140.4265	142.8188	144.393
107.5	121.4991	122.8555	124.9715	128.5831	132.7094	136.9585	140.8906	143.2937	144.8747
108.5	121.8537	123.2186	125.3478	128.9808	133.1304	137.4018	141.3532	143.7674	145.3555
109.5	122.2044	123.5782	125.7208	129.3759	133.5493	137.8437	141.8149	144.2406	145.8359
110.5	122.5518	123.9347	126.0911	129.7689	133.9667	138.2847	142.2764	144.7139	146.3167
111.5	122.8963	124.2885	126.4592	130.1603	134.3832	138.7256	142.7382	145.1879	146.7984
112.5	123.2384	124.6402	126.8255	130.5506	134.7995	139.1669	143.2012	145.6634	147.2818
113.5	123.5785	124.9902	127.1907	130.9406	135.2163	139.6094	143.666	146.141	147.7676
114.5	123.9173	125.3393	127.5554	131.3309	135.6342	140.0538	144.1333	146.6215	148.2564
115.5	124.2553	125.688	127.9203	131.7223	136.054	140.501	144.6039	147.1056	148.7491
116.5	124.5933	126.0371	128.2861	132.1156	136.4766	140.9516	145.0785	147.594	149.2461
117.5	124.932	126.3872	128.6537	132.5115	136.9027	141.4065	145.5579	148.0874	149.7484
118.5	125.2721	126.7392	129.0238	132.9109	137.3333	141.8665	146.0429	148.5865	150.2564
119.5	125.6144	127.094	129.3973	133.3147	137.7691	142.3324	146.5341	149.092	150.7707
120.5	125.9599	127.4524	129.7752	133.7239	138.2112	142.8051	147.0322	149.6044	151.292
121.5	126.3095	127.8154	130.1584	134.1394	138.6602	143.2852	147.5379	150.1242	151.8205

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Females, Stature, Ages 2-20 Years

Age (in months)	3rd Percentile Stature (in centimeters)	5th Percentile Stature (in centimeters)	10th Percentile Stature (in centimeters)	25th Percentile Stature (in centimeters)	50th Percentile Stature (in centimeters)	75th Percentile Stature (in centimeters)	90th Percentile Stature (in centimeters)	95th Percentile Stature (in centimeters)	97th Percentile Stature (in centimeters)
122.5	126.6641	128.184	130.5479	134.562	139.1172	143.7735	148.0517	150.652	152.3568
123.5	127.0248	128.5591	130.9446	134.9929	139.5829	144.2707	148.5741	151.188	152.9011
124.5	127.3926	128.9419	131.3496	135.4328	140.0581	144.7773	149.1054	151.7325	153.4534
125.5	127.7687	129.3334	131.7639	135.8826	140.5435	145.2938	149.646	152.2856	154.0139
126.5	128.1541	129.7346	132.1885	136.3433	141.0397	145.8206	150.196	152.8473	154.5824
127.5	128.5499	130.1467	132.6243	136.8154	141.5472	146.3579	150.7552	153.4174	155.1586
128.5	128.9573	130.5705	133.0721	137.2997	142.0664	146.9059	151.3236	153.9955	155.742
129.5	129.3772	131.0071	133.5329	137.7967	142.5974	147.4643	151.9008	154.5812	156.3321
130.5	129.8106	131.4573	134.0072	138.3067	143.1404	148.0329	152.4861	155.1737	156.928
131.5	130.2585	131.9218	134.4955	138.83	143.695	148.6111	153.079	155.7721	157.5288
132.5	130.7217	132.4013	134.9983	139.3664	144.2609	149.1984	153.6783	156.3755	158.1335
133.5	131.2006	132.8962	135.5157	139.9157	144.8376	149.7937	154.283	156.9825	158.7407
134.5	131.6958	133.4067	136.0476	140.4775	145.424	150.3959	154.8918	157.5918	159.3491
135.5	132.2074	133.9328	136.5937	141.051	146.0192	151.0036	155.5032	158.202	159.9571
136.5	132.7354	134.4742	137.1534	141.6352	146.6217	151.6153	156.1156	158.8115	160.5633
137.5	133.2795	135.0304	137.7259	142.2288	147.23	152.2293	156.7273	159.4185	161.166
138.5	133.8388	135.6004	138.31	142.8304	147.8424	152.8438	157.3365	160.0213	161.7634
139.5	134.4125	136.1831	138.9043	143.4381	148.4569	153.4568	157.9413	160.6182	162.3541
140.5	134.9993	136.7769	139.507	144.0501	149.0714	154.0662	158.5398	161.2075	162.9363
141.5	135.5973	137.3801	140.1161	144.6641	149.6839	154.67	159.1302	161.7874	163.5084
142.5	136.2047	137.9905	140.7295	145.278	150.292	155.2663	159.7107	162.3564	164.069
143.5	136.8191	138.6058	141.3448	145.8893	150.8936	155.8529	160.2796	162.9129	164.6167
144.5	137.4381	139.2236	141.9594	146.4958	151.4866	156.428	160.8353	163.4555	165.1503
145.5	138.0588	139.841	142.5709	147.0949	152.0687	156.9899	161.3764	163.983	165.6685
146.5	138.6784	140.4554	143.1767	147.6845	152.6381	157.5369	161.9016	164.4943	166.1706
147.5	139.2941	141.064	143.7741	148.2623	153.193	158.0677	162.4097	164.9885	166.6555
148.5	139.9028	141.6641	144.3607	148.8263	153.7317	158.581	162.8999	165.4648	167.1228
149.5	140.5019	142.253	144.9342	149.3747	154.2529	159.0758	163.3715	165.9227	167.572
150.5	141.0885	142.8283	145.4925	149.9059	154.7555	159.5513	163.8239	166.3618	168.0027
151.5	141.6602	143.3877	146.0338	150.4184	155.2385	160.007	164.2568	166.7819	168.4147
152.5	142.2148	143.9294	146.5564	150.9113	155.7012	160.4425	164.6701	167.1829	168.808
153.5	142.7504	144.4516	147.059	151.3835	156.1432	160.8576	165.0637	167.5648	169.1827
154.5	143.2654	144.953	147.5405	151.8346	156.5643	161.2524	165.4378	167.9278	169.5391

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Females, Stature, Ages 2-20 Years

Age (in months)	3rd Percentile Stature (in centimeters)	5th Percentile Stature (in centimeters)	10th Percentile Stature (in centimeters)	25th Percentile Stature (in centimeters)	50th Percentile Stature (in centimeters)	75th Percentile Stature (in centimeters)	90th Percentile Stature (in centimeters)	95th Percentile Stature (in centimeters)	97th Percentile Stature (in centimeters)
155.5	143.7584	145.4325	148.0002	152.2642	156.9644	161.627	165.7928	168.2723	169.8773
156.5	144.2287	145.8894	148.4376	152.6721	157.3437	161.9818	166.1289	168.5987	170.1979
157.5	144.6756	146.3232	148.8525	153.0584	157.7025	162.3172	166.4466	168.9074	170.5013
158.5	145.0987	146.7338	149.2449	153.4234	158.0411	162.6338	166.7467	169.199	170.7881
159.5	145.4981	147.1213	149.615	153.7674	158.3603	162.9321	167.0296	169.4742	171.0587
160.5	145.874	147.4859	149.9633	154.0911	158.6606	163.2129	167.2961	169.7335	171.314
161.5	146.2269	147.8281	150.2902	154.3951	158.9427	163.477	167.5469	169.9777	171.5544
162.5	146.5573	148.1487	150.5966	154.6801	159.2075	163.725	167.7826	170.2074	171.7807
163.5	146.866	148.4483	150.8831	154.947	159.4557	163.9577	168.0042	170.4234	171.9935
164.5	147.1539	148.7279	151.1507	155.1966	159.6882	164.1761	168.2122	170.6263	172.1936
165.5	147.4219	148.9885	151.4003	155.4298	159.9058	164.3808	168.4075	170.817	172.3816
166.5	147.6712	149.2309	151.6329	155.6475	160.1094	164.5726	168.5907	170.9959	172.5582
167.5	147.9026	149.4562	151.8494	155.8507	160.2997	164.7523	168.7626	171.1639	172.7239
168.5	148.1173	149.6655	152.0508	156.0401	160.4777	164.9206	168.9239	171.3216	172.8796
169.5	148.3164	149.8598	152.2381	156.2167	160.6441	165.0783	169.0751	171.4696	173.0257
170.5	148.5009	150.04	152.4121	156.3813	160.7995	165.226	169.217	171.6085	173.1628
171.5	148.6717	150.2072	152.5738	156.5348	160.9449	165.3644	169.3501	171.7388	173.2915
172.5	148.8299	150.3621	152.7241	156.6778	161.0808	165.4941	169.4749	171.8611	173.4124
173.5	148.9764	150.5059	152.8638	156.8112	161.2079	165.6157	169.5921	171.976	173.5258
174.5	149.1121	150.6392	152.9936	156.9356	161.3268	165.7297	169.7022	172.0839	173.6324
175.5	149.2377	150.7629	153.1143	157.0517	161.4381	165.8366	169.8055	172.1853	173.7326
176.5	149.3542	150.8777	153.2266	157.16	161.5423	165.9369	169.9026	172.2806	173.8267
177.5	149.4622	150.9843	153.3312	157.2612	161.6399	166.0312	169.9939	172.3701	173.9152
178.5	149.5623	151.0833	153.4286	157.3558	161.7315	166.1197	170.0798	172.4544	173.9984
179.5	149.6553	151.1754	153.5193	157.4443	161.8174	166.2029	170.1606	172.5337	174.0768
180.5	149.7416	151.2611	153.604	157.5271	161.898	166.2812	170.2366	172.6084	174.1505
181.5	149.8219	151.341	153.683	157.6047	161.9738	166.3549	170.3083	172.6787	174.22
182.5	149.8967	151.4154	153.7569	157.6775	162.045	166.4244	170.3759	172.7451	174.2855
183.5	149.9663	151.4848	153.826	157.7458	162.112	166.4898	170.4396	172.8076	174.3472
184.5	150.0312	151.5497	153.8907	157.8099	162.1752	166.5516	170.4997	172.8667	174.4055
185.5	150.0918	151.6103	153.9513	157.8702	162.2347	166.6099	170.5566	172.9225	174.4606
186.5	150.1484	151.6671	154.0082	157.927	162.2908	166.6649	170.6103	172.9752	174.5125
187.5	150.2014	151.7203	154.0616	157.9804	162.3439	166.717	170.6611	173.025	174.5617

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Females, Stature, Ages 2-20 Years

Age (in months)	3rd Percentile Stature (in centimeters)	5th Percentile Stature (in centimeters)	10th Percentile Stature (in centimeters)	25th Percentile Stature (in centimeters)	50th Percentile Stature (in centimeters)	75th Percentile Stature (in centimeters)	90th Percentile Stature (in centimeters)	95th Percentile Stature (in centimeters)	97th Percentile Stature (in centimeters)
188.5	150.251	151.7702	154.1119	158.0308	162.394	166.7663	170.7091	173.0722	174.6082
189.5	150.2975	151.8171	154.1592	158.0784	162.4414	166.8129	170.7546	173.1168	174.6522
190.5	150.3412	151.8612	154.2037	158.1234	162.4862	166.8571	170.7978	173.1591	174.6938
191.5	150.3823	151.9027	154.2457	158.1659	162.5287	166.899	170.8387	173.1992	174.7333
192.5	150.4209	151.9418	154.2854	158.2061	162.569	166.9388	170.8775	173.2373	174.7708
193.5	150.4573	151.9787	154.3229	158.2442	162.6072	166.9766	170.9144	173.2734	174.8063
194.5	150.4917	152.0135	154.3584	158.2803	162.6435	167.0125	170.9494	173.3077	174.84
195.5	150.5241	152.0465	154.3919	158.3146	162.6781	167.0466	170.9827	173.3402	174.8721
196.5	150.5547	152.0776	154.4238	158.3472	162.7109	167.0791	171.0144	173.3712	174.9025
197.5	150.5837	152.1072	154.454	158.3782	162.7421	167.11	171.0446	173.4007	174.9314
198.5	150.6111	152.1352	154.4827	158.4077	162.7719	167.1395	171.0733	173.4288	174.959
199.5	150.6372	152.1617	154.51	158.4357	162.8002	167.1676	171.1007	173.4555	174.9852
200.5	150.6619	152.187	154.5359	158.4625	162.8273	167.1944	171.1268	173.481	175.0102
201.5	150.6854	152.211	154.5607	158.4879	162.8531	167.22	171.1517	173.5053	175.034
202.5	150.7077	152.2339	154.5842	158.5123	162.8778	167.2444	171.1754	173.5284	175.0567
203.5	150.7289	152.2556	154.6067	158.5355	162.9013	167.2677	171.1981	173.5505	175.0783
204.5	150.7491	152.2764	154.6281	158.5577	162.9238	167.29	171.2198	173.5716	175.099
205.5	150.7684	152.2962	154.6486	158.5789	162.9454	167.3114	171.2405	173.5918	175.1187
206.5	150.7868	152.3151	154.6681	158.5992	162.966	167.3318	171.2604	173.6111	175.1376
207.5	150.8044	152.3332	154.6868	158.6187	162.9858	167.3514	171.2793	173.6295	175.1556
208.5	150.8211	152.3504	154.7047	158.6373	163.0047	167.3701	171.2975	173.6471	175.1728
209.5	150.8372	152.3669	154.7218	158.6551	163.0228	167.3881	171.3149	173.664	175.1892
210.5	150.8525	152.3827	154.7382	158.6722	163.0402	167.4053	171.3315	173.6802	175.205
211.5	150.8672	152.3979	154.754	158.6886	163.0569	167.4218	171.3475	173.6956	175.2201
212.5	150.8812	152.4124	154.769	158.7043	163.0729	167.4376	171.3628	173.7104	175.2345
213.5	150.8947	152.4263	154.7835	158.7194	163.0882	167.4528	171.3775	173.7246	175.2483
214.5	150.9076	152.4396	154.7974	158.7339	163.103	167.4674	171.3915	173.7382	175.2616
215.5	150.92	152.4524	154.8107	158.7478	163.1172	167.4814	171.405	173.7513	175.2742
216.5	150.9319	152.4647	154.8235	158.7612	163.1308	167.4948	171.418	173.7638	175.2864
217.5	150.9433	152.4765	154.8358	158.774	163.1439	167.5078	171.4304	173.7758	175.2981
218.5	150.9542	152.4878	154.8476	158.7864	163.1565	167.5202	171.4424	173.7873	175.3093
219.5	150.9647	152.4987	154.859	158.7983	163.1686	167.5321	171.4538	173.7984	175.32
220.5	150.9749	152.5092	154.8699	158.8097	163.1802	167.5436	171.4649	173.809	175.3303

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Females, Stature, Ages 2-20 Years

Age (in months)	3rd Percentile Stature (in centimeters)	5th Percentile Stature (in centimeters)	10th Percentile Stature (in centimeters)	25th Percentile Stature (in centimeters)	50th Percentile Stature (in centimeters)	75th Percentile Stature (in centimeters)	90th Percentile Stature (in centimeters)	95th Percentile Stature (in centimeters)	97th Percentile Stature (in centimeters)
221.5	150.9846	152.5192	154.8804	158.8207	163.1914	167.5546	171.4755	173.8192	175.3402
222.5	150.9939	152.5289	154.8905	158.8313	163.2022	167.5653	171.4856	173.829	175.3497
223.5	151.0029	152.5382	154.9003	158.8415	163.2126	167.5755	171.4954	173.8384	175.3588
224.5	151.0115	152.5472	154.9096	158.8514	163.2226	167.5853	171.5049	173.8474	175.3675
225.5	151.0198	152.5558	154.9187	158.8608	163.2322	167.5948	171.5139	173.8561	175.376
226.5	151.0279	152.5641	154.9273	158.8699	163.2415	167.6039	171.5226	173.8645	175.384
227.5	151.0356	152.5721	154.9357	158.8787	163.2504	167.6127	171.531	173.8725	175.3918
228.5	151.043	152.5798	154.9438	158.8872	163.259	167.6211	171.5391	173.8802	175.3993
229.5	151.0501	152.5873	154.9516	158.8953	163.2673	167.6293	171.5468	173.8877	175.4064
230.5	151.057	152.5944	154.959	158.9032	163.2753	167.6371	171.5543	173.8948	175.4133
231.5	151.0636	152.6013	154.9663	158.9107	163.283	167.6446	171.5615	173.9017	175.42
232.5	151.07	152.6079	154.9732	158.918	163.2904	167.6519	171.5684	173.9083	175.4264
233.5	151.0762	152.6143	154.9799	158.9251	163.2976	167.6589	171.5751	173.9147	175.4325
234.5	151.0821	152.6205	154.9864	158.9319	163.3045	167.6657	171.5815	173.9208	175.4384
235.5	151.0879	152.6265	154.9926	158.9384	163.3111	167.6722	171.5877	173.9267	175.4441
236.5	151.0934	152.6322	154.9986	158.9447	163.3175	167.6785	171.5937	173.9324	175.4496
237.5	151.0987	152.6377	155.0044	158.9508	163.3237	167.6845	171.5994	173.9379	175.4548
238.5	151.1038	152.6431	155.01	158.9567	163.3297	167.6904	171.6049	173.9432	175.4599
239.5	151.1088	152.6482	155.0154	158.9624	163.3354	167.696	171.6103	173.9482	175.4648
240	151.1112	152.6507	155.0181	158.9651	163.3383	167.6987	171.6129	173.9507	175.4671

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12.13 Clinical Study Continuity

INTRODUCTION

The purpose of this appendix is to provide acceptable alternate methods to assess safety and efficacy parameters, as appropriate, in the event the clinical study is interrupted at the country, state, site or participant level during any crisis (e.g., natural disaster, pandemic).

BENEFIT-RISK RATIONALE

Maintaining the safety of clinical study participants and delivering continuity of care in the clinical study setting is paramount during any crisis. The site is expected to follow the protocol and associated Schedule of Assessments [Table 1] unless the site principal investigator discusses the need with the Astellas medical monitor to implement the alternate measures.

The approach outlined within this appendix defines which assessments are required to maintain a favorable benefit/risk to the participant, to maintain overall study integrity and to provide acceptable alternate methods to complete the study required assessments and procedures if study activities are unable to be performed as described in [Section 7 Study Procedures and Assessments] due to a crisis.

INFORMED CONSENT

Participants who need to follow any or all of the alternate measures outlined in this Appendix will be required to provide informed consent, which explicitly informs them of the nature of and rationale for these changes, and gain their agreement to continue participation in the study prior to the implementation of any of these changes. In the event the urgency of implementing the alternate measures does not allow for the participant to provide written consent prior to implementation, the principal investigator or designee will obtain oral agreement from the subject followed by written documentation as soon as is feasible. A separate addendum to the study informed consent will be provided to document the participant's consent of the changes.

PARTICIPANT PROCEDURES ASSESSMENT

Sites with participants who are currently enrolled into this clinical study may consider implementing the alternate methods outlined below if one or more of the following conditions are met due to the crisis:

- Regional or local travel has been restricted, inclusive of mandatory shelter in place measures, which makes participant travel to/from the study site nearly impossible
- Site facilities have been closed for clinical study conduct
- Site has been restricted to treating patients with conditions outside of the scope of the study
- Site personnel have temporarily relocated the conduct of the study to a location that place a burden on the participant with respect to time and travel

- Participant(s) have temporarily relocated from the current study site to an alternate study site to avoid placing a burden on the participant with respect to travel
- Participant(s) have temporarily relocated from their home location and the new distances from the site would cause undue burden with respect to time and travel
- Participant has risk factors for which traveling to the site poses an additional risk to the participant's health and safety

Adherence to the original protocol as reflected in the Schedule of Assessments [Table 1] is expected, where plausible, in the case of a crisis. The alternate measures as noted in [Table 12] below are only permissible in the event of a crisis, and after discussing the need with the Astellas medical monitor to implement the alternate measures. This is to allow for continuity of receiving IP and maintaining critical safety and efficacy assessments for patients participating in the study at a time of crisis.

If one or more of the alternate measures noted below is implemented for a participant, the site should document in the participant's source document the justification for implementing the alternate measure and the actual alternate measures that were implemented, along with the corresponding time point(s).

Table 12 Alternate Schedule of Assessments in Response to a Crisis

Critical Assessments	Alternate Approach(es)	Double-blind Placebo-controlled Period (12 weeks)					Follow-up Period (2 weeks)
		Visit 3	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
		Week 0 Baseline	**Week 2 TC[a]**	**Week 4**	**Week 8 TC[a]**	**Week 12 (EoT)[b]**	**Week 14 (EoS)[b,c]**
		Day -1	Day 14 (± 3 days)	Day 28 (± 3 days)	Day 56 (± 3 days)	Day 84 (± 3 days)	Day 98 (+ 3 days)
Previous and Concomitant Medication	Remote/Virtual/Telemedicine Visits allowed. Please refer to protocol schedule of assessments.	X	X	X	X	X	X
Physical Examination	The exam can be done at a local clinic and the results submitted to PI.			X		X	
Height and Body Weight	Can be obtained at a local clinic or at home	X				X	
Dose Titration[d]	Courier service directly to subject. Titration to occur based on PI's evaluation via phone. For tablets: subject to take spare 25 mg tablets until 50 mg wallet is delivered via courier.			X			
Dispense IP[e]	Courier service directly to subject	X		X			
Drug Accountability	Used product can be shipped back to site via courier.	X				X	
Vital Signs[f]	Can be performed at a local clinic and results submitted to PI for evaluation OR Blood pressure and pulse collected via SBPM and temperature collected at home and reported to site (respiration rate missing).	X		X		X	X
SBPM[g]	Will be sent to subject's home address	X	X	X	X	X	

Table continued on next page

Critical Assessments	Alternate Approach(es)	Double-blind Placebo-controlled Period (12 weeks)					Follow-up Period (2 weeks)
		Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
		Week 0 Baseline	Week 2 TC[a]	Week 4	Week 8 TC[a]	Week 12 (EoT)[b]	Week 14 (EoS)[b,c]
		Day -1	Day 14 (± 3 days)	Day 28 (± 3 days)	Day 56 (± 3 days)	Day 84 (± 3 days)	Day 98 (+ 3 days)
Routine 12-lead ECG[f]	ECG testing can be completed at local clinic.	X		X		X	
Clinical Laboratory Tests (Hematology and Biochemistry)[h]	Visit collection of samples at local facility acceptable if results can be made available to investigative site.	X[i]		X		X	X[i]
Clinical Laboratory Tests (Urinalysis)[h]	Visit collection of samples at local facility acceptable if results can be made available to investigative site.	X[i]		X		X	X[i]
Pregnancy Test[i]	Visit collection of samples at local facility acceptable if results can be made available to investigative site.	X		X		X	X
AEs	Remote/Virtual/Telemedicine Visits allowed. Please refer to protocol schedule of assessments.	X	X	X	X	X	X
Bladder e-diary	Will be sent to subject's home address	X	X	X	X	X	
Acceptability and Palatability Questionnaire[j]	To be performed remotely via e-diary.					X	
Pharmacokinetics[k]	Astellas Medical Monitor to assess. Not allowed at an alternate clinical due to special sample handling.			X		X	

AE: adverse event; ECG: electrocardiogram; e-diary: electronic diary; EoS: end of study; EoT: end of treatment; IP: investigational product; OAB: overactive bladder; PED25: pediatric equivalent dose 25 mg; PED50: pediatric equivalent dose 50 mg; PI: principal investigator; SBPM: self blood pressure monitoring; TC: telephone call

Footnotes continued on next page

a. For the visits where a TC is indicated, there is no need for the subject to visit the clinic provided that the bladder e-diary data are reviewed by the investigator prior to the TC and discussed and confirmed with the subject or parent(s)/legal guardian(s) during the TC. Urotherapy is also to be discussed and confirmed with the subject or parent(s)/legal guardian(s) during each TC as indicated in Table 1.
b. Subjects who withdraw early from the study after having received IP should complete both the EoT and EoS visits.
c. The EoS visit (visit 8/week 14 [EoS]) should take place at least 14 days after the EoT visit (visit 7/week 12 [EoT]).
d. Dose up-titration to PED50 to occur at visit 5/week 4 unless investigator determines OAB is adequately controlled. Dose down-titration from PED50 to PED25 can be done at any time for safety reasons.
e. Daily IP administration will start on day 1 (i.e., the day after visit 3/week 0 [baseline]).
f. Blood pressure, pulse, body temperature and ECGs will all be measured in single measurements. Subject to be in the sitting position (when possible, otherwise supine, but always in the same position for each procedure). Subject should have been calm and without distress for at least 5 minutes. Preferably, the right arm should be used to measure vital signs. Body temperature will be measured with an ear thermometer. Clinic measurements will be used to assess eligibility.
g. SBPM will be measured once in the morning and evening during the 2-day weekend bladder e-diary collection period. SBPM measurements should start in the weekend prior to week -2 and be taken in the weekend prior to the indicated visit (or TC). SBPM will be measured on 2 consecutive days at 1 and 2 weeks after start of dosing with PED25 (day 1) and after up-titration to PED50, if not already covered by the scheduled SBPM. Measurements will be taken in the sitting position (when possible, otherwise supine, but always in the same position). Preferably, the right arm should be used. Subject should have been calm and without distress for at least 5 minutes. Morning measurement should be taken before IP intake and evening measurement should be taken prior to bedtime.
h. Additional hematology, biochemistry and urinalysis (urinalysis dipstick) tests will be performed at visit 3/week 0 (baseline) and visit 8/week 14 (EoS) only if an AE related to hematology, biochemistry or urinalysis parameters occurred since the previous visit or at the discretion of the investigator.
i. Urine pregnancy test will be performed for females of childbearing potential at all on-site visits.
j. The acceptability and palatability questionnaire will be completed on one weekend day preceding at visit 7/week 12 (EoT).
k. There will be 2 pharmacokinetic sampling days at visit 5/week 4 and visit 7/week 12 (EoT). Both pharmacokinetic sampling days will consist of collecting 1 predose (trough) sample. On pharmacokinetic sampling days, dosing should occur in the clinic and breakfast should be eaten at the clinic within 1 hour before dosing.

INVESTIGATIONAL PRODUCT SUPPLY

If any of the conditions outlined above in the Participant Procedures Assessment are met, if the following mitigating strategy will be employed, as needed, to ensure continuity of IP supply to the participants:

- Increase stock of IP on site to reduce number of shipments required, if site space will allow.
- Direct-to-subject shipments of IP from the site to the subject's home.

DATA COLLECTION REQUIREMENTS

Additional data may be collected in order to indicate how participation in the study may have been affected by a crisis and to accommodate data collection resulting from alternate measures implemented to manage the conduct of the study and participant safety.

- Critical assessments for safety and efficacy based on study endpoints to be identified as missing or altered (performed virtually, at alternative locations, out of window, or other modifications) due to the crisis.

12.14 List of Abbreviations and Definition of Key Study Terms

List of Abbreviations

Abbreviation	Description
APEB	Astellas Pharma Europe B.V.
APGD	Astellas Pharma Global Development Inc.
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AR	adrenergic receptor
AST	aspartate aminotransferase
AT	aminotransferases
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration-time curve
AUC_{24}	area under the concentration-time curve from time zero to 24 hours
AUC_{tau}	area under concentration-time curve over dosing interval
AUC_{inf}	area under the concentration-time curve from the time of dosing extrapolated to time infinity
AUC_{last}	area under the concentration-time curve from the time of dosing to the last measurable concentration
BMI	body mass index
C_{max}	maximum drug concentration
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CV	coefficient of variation
CY	cytochrome
DBP	diastolic blood pressure
DPD	Data Protection Directive
DSMB	Data and Safety Monitoring Board
EBC	expected bladder capacity
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
e-diary	electronic diary
EEA	European Economic Area
EMA	European Medicines Agency
EMG	electromyography
EoS	end of study
EoT	end of treatment
FAO	Food and Agricultural Organization
FAS	full analysis set
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
hCG	human chorionic gonadotropin
ICCS	International Children's Continence Society
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Abbreviation	Description
IDAC	independent data analysis center
IEC	Independent Ethics Committee
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
ISN	international study number
LA-CRF	liver abnormality case report form
LOCF	last observation carried forward
LQTS	long QT syndrome
LS	least squares
NDO	neurogenic detrusor overactivity
NONMEM	non-linear mixed effects modeling
OAB	overactive bladder
OCAS	oral-controlled absorption system
PED	pediatric equivalent dose
P-gp	P-glycoprotein
PIP	pediatric investigational plan
PKAS	pharmacokinetic analysis set
PPIUS	Patient perception of intensity of urgency scale
PPS	per protocol set
PVR	post void residual
QA	quality assurance
QC	quality control
QTL	quality tolerance limit
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SBP	systolic blood pressure
SBPM	self-blood pressure measurement
SOP	standard operating procedure
SUSAR	serious unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TBL	total bilirubin
TC	telephone call
USM	urgent safety measure
ULN	upper limit of normal
UTI	urinary tract infection
WHO-DD	WHO-Drug Dictionary

Definition of Key Study Terms

Terms	Definition of Terms
Baseline	Assessments of subjects as they enter a study before they receive any treatment.
Endpoint	Variable that pertains to the efficacy or safety evaluations of a study. Note: Not all endpoints are themselves assessments since certain endpoints might apply to populations or emerge from analysis of results. That is, endpoints might be facts about assessments (e.g., prolongation of survival).
Enroll	To register or enter a subject into a study. Note: Once a subject has received the IP or placebo, the protocol applies to the subject.
Intervention	The drug, device, therapy or process under investigation in a study that is believed to have an effect on outcomes of interest in a study (e.g., health-related quality of life, efficacy, safety and pharmacokinetics).
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test product or comparative drug (sometimes without randomization) is given to a subject and continues until the last assessment after completing administration of the test product or comparative drug.
Post investigational period	Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events and/or survival are done in this period.
Randomization	The process of assigning subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias. NOTE: Unequal randomization is used to allocate subjects into groups at a differential rate; for example, three subjects may be assigned to a treatment group for everyone assigned to the control group.
Screening	A process of active consideration of potential subjects for randomization in a study.
Screen failure	Potential subject who signed the ICF/assent but did not meet 1 or more criteria required for participation in the study and was not randomized.
Screening period	Period of time before entering the investigational period, usually from the time when a subject signs the consent/assent form until just before the test product or comparative drug (sometimes without randomization) is given to a subject.
Study period	Period of time from the first study site initiation date to the last study site completing the study.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

13 ATTACHMENT 1: SUBSTANTIAL AMENDMENT 1

I. The purpose of this amendment is:

Substantial Changes
1. Update Schedule of Assessments
DESCRIPTION OF CHANGE:
The schedule of assessments is updated with the following changes: • Physical examination is added to visit 5 (week 4). • Height and body weight measurement is added to visit 7 (week 12). • Clinical Laboratory Tests (Hematology and Biochemistry) footnote is removed from visit 5 (week 4) • Self-blood pressure measurement (SBPM) is added visit 2 (week -2) and removed from visit 8 (week 14). • Pregnancy tests are added to visit 3 (week 0), visit 5 (week 4) and visit 7 (week 12). • Additional text is added to footnote h to explain that the SBPM should be done during the weekend preceding the study visit. • Footnote i is revised to remove visit 5 (week 4). • Footnote j is revised to clarify that urine pregnancy tests will be performed for females of childbearing potential at all on-site visits.
RATIONALE:
This is a combination of regulatory commitments to include additional pregnancy testing and laboratory testing, as well as fixing some errors for clarification. Footnote i was removed from the Clinical Laboratory Tests at visit 5 (week 4), because this visit is now required.
2. Update Subject Weight Range
DESCRIPTION OF CHANGE:
The minimum weight of subjects is changed from 11 kg to 13 kg. This is updated in the dose rationale and Inclusion Criterion #4.
RATIONALE:
This study should only include children and adolescents from 5 years to 18 years; therefore, the lower weight limit was revised.
3. Delete Exclusion Criterion #11
DESCRIPTION OF CHANGE:
A criterion (#11) that subjects must have a pulse of > 99th percentile for age at Screening is deleted.

RATIONALE:
This criterion is the same as exclusion criterion #33 because the criterion was originally checked at screening and baseline. The criterion itself still applies to subjects, but is only needed at baseline.
4. Update Exclusion Criterion #13
DESCRIPTION OF CHANGE:
Text is added to allow the option that the subject is currently taking medication known to prolong the QT interval.
RATIONALE:
This revision is made for consistency with Table 21 in the Investigator's Brochure.
5. Update Exclusion Criterion #18
DESCRIPTION OF CHANGE:
The criterion is updated to exclude subjects who use moderate or strong cytochrome CYP3A4/5 or P-gp inhibitors or inducers.
RATIONALE:
This revision is made per a Regulatory request.

Nonsubstantial Changes
1. Update Key Sponsor Personnel
DESCRIPTION OF CHANGE:
Contact details for medical monitor are updated.
RATIONALE:
Contact details of medical monitor are updated based on changes to study personnel.
2. Update Compound Name
DESCRIPTION OF CHANGE:
The compound name has been updated to YM178 (from ED178).
RATIONALE:
This revision is made to correct an error. ED178 is the project name for pediatric.

3. Update Planned Study Period
DESCRIPTION OF CHANGE:
The planned completion date is extended to 2Q2023 (from 3Q2022).
RATIONALE:
This revision is made based on current enrollment projections.
4. Update Background
DESCRIPTION OF CHANGE:
Text regarding mirabegron mechanism of action is added to the Background section.
RATIONALE:
This revision is made for consistency with the current Mirabegron Investigator's Brochure.
5. Updated Total Number and Location of Study Sites
DESCRIPTION OF CHANGE:
The number of planned study sites is increased to 65 (from 50) and North America is added as a study site location.
RATIONALE:
The planned number of study sites is increased to account for the current number of approved sites. The revision to study location is made to correct an error. During development of the statistical analysis plan, it was noted that North America was not listed in the protocol.
6. Update Study Objectives and Endpoints
DESCRIPTION OF CHANGE:
Text is added to note that primary and secondary objectives and endpoints apply to children only; exploratory objectives and endpoints also apply to adolescents. Subject age is added to the exploratory objective. Mean number of micturitions per 24 hours is added as an exploratory endpoint.
RATIONALE:
These revisions are made for clarification. To ensure mean micturitions is analyzed for adolescents. The mean number of micturitions endpoint is added ensure mean micturitions is analyzed for adolescents.
7. Clarify Exclusion Criterion #19
DESCRIPTION OF CHANGE:
The criterion is updated to add the text 'and cannot be discontinued.'

RATIONALE:
This revision is made to for clarification. If the prohibited medication can be discontinued, the subject may be enrolled in the study.
8. Clarify Reference for Investigational Products (IP)
DESCRIPTION OF CHANGE:
Section 6.1.1 is updated to clarify that detailed information on mirabegron granules for oral suspension is located in the Investigator's Brochure and Investigational Medicinal Product Dossier.
RATIONALE:
The original protocol stated where to locate additional information for tablets only, so text is added on where to find additional information for the granules.
9. Update Subject Compliance
DESCRIPTION OF CHANGE:
Weighing is added a method for assessing compliance of subject compliance with IP.
RATIONALE:
This revision is made for clarification. Tablets will be counted and granules for oral suspension will be weighed.
10. Expand Urotherapy Information in Section 6.4.2
DESCRIPTION OF CHANGE:
Additional information about urotherapy is added to Section 6.4.2.
RATIONALE:
This revision is made for clarification.
11. Update Concomitant Medications
DESCRIPTION OF CHANGE:
Medications that prolong the QT interval, and medications that are moderate or strong cytochrome CYP3A4/5 or P-gp inhibitors, are added to the list of prohibited concomitant medications. Examples of medications used for the treatment of overactive bladder are added.

RATIONALE:
In accordance with Section 6.5.3 of the Investigator's Brochure, these medications are added on the list of concomitant medications excluded from the protocol.
12. Update Description of Physical Examination
DESCRIPTION OF CHANGE:
Additional details of the physical examination are added to Section 7.2.4.
RATIONALE:
This revision is made for clarification.
13. Update Total Amount of Blood
DESCRIPTION OF CHANGE:
The number of clinical laboratory samples and total blood volume are updated.
RATIONALE:
This revision is made since visit 5 (week 4) is now mandatory. The blood volumes are updated to account for the clinical laboratory tests at this visit.
14. Define Pharmacokinetic Parameters
DESCRIPTION OF CHANGE:
The pharmacokinetic parameters that will be calculated as part of the secondary pharmacokinetic endpoint are defined.
RATIONALE:
The specific pharmacokinetic parameters to be calculated were not previously defined.
15. Clarify Electronic Clinical Outcome Assessments
DESCRIPTION OF CHANGE:
Section 7.6, Electronic Clinical Outcome Assessment, is updated to provide additional information about the integrity of the data. Additional text from the latest Global Protocol Format (GPF) is added.
RATIONALE:
These revisions are made to describe how the integrity of the data is ensured, especially the data subjects enter into electronic forms.

16. Update Subject Discontinuation Criteria
DESCRIPTION OF CHANGE:
The following criteria are added as reasons that a subject may be discontinued from study treatment: • Pregnancy • Prolongation of QT > QTcF > 440 msec and/or QT interval prolongation > 30 msec • Systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mmHg Follow-up for prolongation of QT intervals is added to Section 9.5.5.
RATIONALE:
These revisions are made due to regulatory agency feedback/request.
17. Update Rationale for Sample Size
DESCRIPTION OF CHANGE:
Text is added to state that the assumptions about sample size, in addition to the levels for Type-1 error and power, were agreed upon with Pediatric Committee in the current Pediatric Investigation Plan.
RATIONALE:
This revision is made for clarification of assumptions.
18. Clarify Local Laboratory Evaluations
DESCRIPTION OF CHANGE:
Text is added to clarify that when local laboratory evaluations are conducted, the values obtained will be adjusted to values obtained by the central laboratory. A reference is made to the statistical analysis plan.
RATIONALE:
This revision is made to indicate how the local lab values will be analyzed when the modified schedule of assessments is utilized.
19. Add Section for Independent Data Analysis Center (IDAC)
DESCRIPTION OF CHANGE:
A new section is added to Section 10, Operational Considerations, to describe the purpose of the IDAC and its members.
RATIONALE:
This revision is made to clarify the role of the IDAC and the interactions between the IDAC and the Data and Safety Monitoring Board.

20. Update Source Documents
DESCRIPTION OF CHANGE:
Appendix 12.1.6, Source Documents, is updated with compulsory text from the latest GPF.
RATIONALE:
This revision is made to align the study protocol with the current GPF and to add additional information for ensuring integrity of data.
21. Remove Source Data Verification
DESCRIPTION OF CHANGE:
Information about source data verification is removed from Section 10.1, *Data Collection* and 12.2.1, *Study Monitoring*. Information about source data review is added to Appendix 12.1.6, *Source Documents*.
RATIONALE:
This revision is made to comply with the European guidelines published by the European Commission regarding the remote source data verification during the COVID-19 pandemic.
22. Update Contraception Requirements
DESCRIPTION OF CHANGE:
Appendix 12.3 is updated with standard text from the latest GPF in regards to contraception requirements for pediatric subjects.
RATIONALE:
This revision is made to align the study protocol with the current GPF and to provide pediatric-specific contraception requirements.
23. Clarify Abnormal Laboratory Findings
DESCRIPTION OF CHANGE:
Updates are made to Appendix 12.4.1.1 to clarify abnormal laboratory findings and the process for reporting them.
RATIONALE:
This revision is made in accordance to the Agency's comment on laboratory values,
24. Update List of Excluded Concomitant Medications
DESCRIPTION OF CHANGE:
The List of Excluded Concomitant Medications in Appendix 12.6 is updated to include moderate and strong CYP3A4 inhibitors and inducers, and P-gp inhibitors and inducers

RATIONALE:
This revision is made to incorporate the moderate and strong cytochrome CYP3A4/5 and P-gp inhibitors and inducers that are added to Exclusion Criterion #18.
25. Add Appendix for Clinical Study Continuity
DESCRIPTION OF CHANGE:
A Clinical Study Continuity appendix is added to the protocol. This appendix contains procedures for continuity of care during a crisis. An alternative schedule of assessments is provided. A reference to this appendix is added to Section 7.
RATIONALE:
This appendix is added to provide acceptable alternate methods to assess safety and efficacy parameters in the event the clinical study is interrupted at the country, state, site or participant level during any crisis (e.g., natural disaster or pandemic).
26. Minor Administrative-type Changes
DESCRIPTION OF CHANGE:
Include minor administrative-type changes (e.g., typos, format, numbering and consistency throughout the protocol); change ‘woman of childbearing potential’ to ‘female of childbearing potential;=’ revise wording of Inclusion Criterion #13 from ‘must not donate’ to ‘must agree not to donate;’ remove ‘Draft’ from ‘Draft Results’ in title of Table 4; add “or designee” as a reviewer for e-diary data in Section 7.1.1; and remove ‘WOCBP’ from the List of Abbreviations.
RATIONALE:
To provide clarifications to the protocol and to ensure complete understanding of study procedures.

II. Amendment Summary of Changes:

IIA. Substantial Changes

1 Protocol Summary

1.3 Schedule of Assessments

WAS:

Schedule of Assessments	Screening Period/Urotherapy (4 weeks)		Double-blind Placebo-controlled Period (12 weeks)					Follow-up Period (2 weeks)
	Visit 1	Visit 2/TC[a]	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	Week -4 Screening	Week -2	Week 0 Baseline	Week 2 TC[a]	Week 4	Week 8 TC[a]	Week 12 (EoT)[b]	Week 14 (EoS)[b,c]
	Day -28 (-3 days)	Day -14 (± 5 days)	Day -1	Day 14 (± 3 days)	Day 28 (± 3 days)	Day 56 (± 3 days)	Day 84 (± 3 days)	Day 98 (+ 3 days)
Physical Examination	X						X	
Height and Body Weight	X		X					
Clinical Laboratory Tests (Hematology and Biochemistry)	X		X[i]		X[i]		X	X[i]
Clinical Laboratory Tests (Urinalysis)	X		X[i]		X		X	X[i]
SBPM[h]			X	X	X	X	X	X
Pregnancy Test[j]	X							X
Bladder e-diary[a,l]	X	X	X	X	X	X	X	

h. SBPM will be measured once in the morning and evening during the 2 day weekend bladder e-diary collection period. SBPM will be measured on 2 consecutive days at 1 and 2 weeks after start of dosing with PED25 (day 1) and after up-titration to PED50, if not already covered by the scheduled SBPM. Measurements will be taken in the sitting position (when possible, otherwise supine, but always in the same position). Preferably, the right arm should be used. Subject should have been calm and without distress for at least 5 minutes. Morning measurement should be taken before IP intake and evening measurement should be taken prior to bedtime.

i. Additional hematology, biochemistry and urinalysis (urinalysis dipstick) tests will be performed at visit 3/week 0 (baseline), visit 5/week 4 and visit 8/week 14 (EoS) only if an AE related to hematology, biochemistry or urinalysis parameters occurred since the previous visit or at the discretion of the investigator.

j. Serum pregnancy test at screening and EoS (visit 8/week 14).

l. After a successful screening visit (visit 1/week -4 [screening]), all subjects will start with the completion of a 2-day bladder e-diary to get acquainted with the bladder e-diary and the assessments. Completion of this bladder e-diary should start in the weekend prior to week -2. Subjects will start with the 7-day bladder e diaries, approximately 7 days prior to the indicated visit (or TC). The bladder e-diary is used for a 7-day period to record micturition frequency and incontinence episodes; it also contains a 2-day weekend period to record additional volume measurements and vital signs.

IS AMENDED TO:

Schedule of Assessments	Screening Period/Urotherapy (4 weeks)		Double-blind Placebo-controlled Period (12 weeks)					Follow-up Period (2 weeks)
	Visit 1	Visit 2/TC[a]	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	Week -4 Screening	Week -2	Week 0 Baseline	Week 2 TC[a]	Week 4	Week 8 TC[a]	Week 12 (EoT)[b]	Week 14 (EoS)[b,c]
	Day -28 (-3 days)	Day -14 (± 5 days)	Day -1	Day 14 (± 3 days)	Day 28 (± 3 days)	Day 56 (± 3 days)	Day 84 (± 3 days)	Day 98 (+ 3 days)
Physical Examination	X				**X**		X	
Height and Body Weight	X		X				**X**	
Clinical Laboratory Tests (Hematology and Biochemistry)	X		X[i]		X[i]		X	X[i]
Clinical Laboratory Tests (Urinalysis)	X		X[i]		X		X	X[i]
SBPM[h]		**X**	X	X	X	X	X	~~X~~
Pregnancy Test[j]	X		**X**		**X**		**X**	X
Bladder e-diary[a,l]	~~X~~	X	X	X	X	X	X	

h. SBPM will be measured once in the morning and evening during the 2 day weekend bladder e-diary collection period. **SBPM measurements should start in the weekend prior to week -2 and be taken in the weekend prior to the indicated visit (or TC).** SBPM will be measured on 2 consecutive days at 1 and 2 weeks after start of dosing with PED25 (day 1) and after up-titration to PED50, if not already covered by the scheduled SBPM. Measurements will be taken in the sitting position (when possible, otherwise supine, but always in the same position). Preferably, the right arm should be used. Subject should have been calm and without distress for at least 5 minutes. Morning measurement should be taken before IP intake and evening measurement should be taken prior to bedtime.

i. Additional hematology, biochemistry and urinalysis (urinalysis dipstick) tests will be performed at visit 3/week 0 (baseline)~~, visit 5/week 4~~ and visit 8/week 14 (EoS) only if an AE related to hematology, biochemistry or urinalysis parameters occurred since the previous visit or at the discretion of the investigator.

j. **Urine**~~Serum~~ pregnancy test **will be performed for females of childbearing potential** at ~~screening and EoS (visit 8/week 14)~~ **all on-site visits**.

l. **At the end of**~~After~~ a successful screening visit (visit 1/week -4 [screening]), all subjects will **be provided with a device to collect diary information. At** ~~start with the completion of a 2-day bladder e-diary to get acquainted with the bladder e-diary and the assessments. Completion of this bladder e-diary should start in~~ the weekend prior to **the** week -2 **visit, the subject will complete the 2-day bladder e-diary to get acquainted with the data collection. The 2-day diary will be reviewed at the week -2 visit. If completion is successful, all**~~.~~ ~~S~~subjects will start with the 7-day bladder e-diary~~ies~~ **completion**, approximately 7 days prior to the indicated visit (or TC). The bladder e-diary is used for a 7-day period to record micturition frequency and incontinence episodes; it also contains a 2-day weekend period to record additional volume measurements and vital signs.

1 Protocol Summary and 5 Study Population *5.1 Inclusion Criterion #4*
WAS:
Subject weighs at least 11 kg at screening.
IS AMENDED TO:
Subject weighs at least **13**~~11~~ kg at screening.

1 Protocol Summary and 5 Study Population *5.1 Exclusion Criterion #11*
WAS:
Subject has a pulse > 99th percentile for age
IS AMENDED TO:
~~Subject has a pulse > 99th percentile for age~~***Criterion has been removed***.

1 Protocol Summary and 5 Study Population *5.1 Exclusion Criterion #13*
WAS:
Subject has QTcF > 440 msec on screening ECG or a risk of QT prolongation (e.g., hypokalemia, long QT syndrome [LQTS] or family history of LQTS or exercise-induced syncope).
IS AMENDED TO:
Subject has QTcF > 440 msec on screening ECG**,** ~~or~~ a risk of QT prolongation (e.g., hypokalemia, long QT syndrome [LQTS] or family history of LQTS or exercise-induced syncope) **or is currently taking medication known to prolong the QT interval**.

1 Protocol Summary and 5 Study Population *5.1 Exclusion Criterion #18*
WAS:
Subject uses any drugs that are sensitive cytochrome P450 2D6 (CYP2D6) substrates with a narrow therapeutic index or sensitive P-glycoprotein (P-gp) substrates after the start of washout.
IS AMENDED TO:
Subject uses any drugs that are sensitive cytochrome P450 2D6 (CYP2D6) substrates with a narrow therapeutic index**,** ~~or~~ sensitive P-glycoprotein (P-gp) substrates**, or moderate or strong cytochrome CYP3A4/5 or P-gp inhibitors or inducers** after the start of washout.

IIB. Nonsubstantial Changes

Contact Details of Sponsor's Key Personnel	
WAS:	
Medical Monitor/Study Physician	PPD Medical and Development Astellas Pharma Global Development Inc. 1 Astellas Way Northbrook, IL, 60062 PPD
IS AMENDED TO:	
Medical Monitor/Study Physician	PPD **Medical Specialties Therapeutic Area, Tokyo** Astellas Pharma ~~Global Development~~ Inc. **2-5-1, Nihonbashi-Honcho, Chuo-ku**~~1 Astellas Way~~ **Tokyo 103-8411, Japan**~~Northbrook, IL, 60062~~ PPD

2 Introduction *2.1 Background*
ADDED:
Mirabegron activation of beta 3-AR in the human bladder results in a relaxation of the detrusor smooth muscle during the fill-void cycle without interfering with the voiding contraction.

2 Introduction *2.1.2.2 Clinical Data (Table 4)*
WAS:
The data from Studies 178 CL 201 and 178 CL 202 were used to support the use of tablets in pediatric subjects with a body weight of ≥ 35 kg in this study. For those pediatric subjects that cannot be dosed with tablets because their body weight is < 35 kg or because they cannot be dosed with tablets, an oral suspension with a strength of 2 mg/mL was developed. Study 178-CL-208 Draft Results: Relative Bioavailability of the Mirabegron 8 mg/mL Oral

Suspension Formulation Versus 2 mg/mL Oral Suspension Formulation (Pharmacokinetics Analysis Set) The doses described in [Section 2.1.2.2 Clinical Data] suggest tablets for subjects with a body weight of ≥ 35 kg unless unable to swallow tablets and would be provided the oral suspension as an alternative, and the 8 mg/mL oral suspension for subjects with a body weight < 35 kg or those who cannot be dosed with the tablets.
IS AMENDED TO:
The data from Studies 178 CL 201 and 178 CL 202 were used to support the use of tablets in pediatric subjects with a body weight of ≥ 35 kg in this study. For those pediatric subjects that cannot be dosed with tablets because their body weight is < 35 kg or because they cannot ~~be dosed with~~**swallow the** tablets, an oral suspension with a strength of 2 mg/mL was developed. Study 178-CL-208 ~~Draft~~ Results: Relative Bioavailability of the Mirabegron 8 mg/mL Oral Suspension Formulation Versus 2 mg/mL Oral Suspension Formulation (Pharmacokinetics Analysis Set) The doses described in [Section 2.1.2.2 Clinical Data] suggest tablets for subjects with a body weight of ≥ 35 kg unless unable to swallow tablets and would be provided the oral suspension as an alternative, and the 8 mg/mL oral suspension for subjects with a body weight < 35 kg ~~or those who cannot be dosed with the tablets~~.

2 Introduction *2.3 Risk-Benefit Assessment*
WAS:
• Potential UTI will be monitored by urinalysis at each visit in the clinic and will require discontinuation of study treatment The blood draws for clinical laboratory tests have been minimized to lessen subject burden while ensuring subject safety. Additional hematology and biochemistry tests will be performed at visit 3/week 0 (baseline), visit 5/week 4 and visit 8/week 14 (end of study [EoS]) only if an AE related to hematology, biochemistry or urinalysis parameters occurred since the previous visit or at the discretion of the investigator.
IS AMENDED TO:
• Potential UTI will be monitored by urinalysis at each visit in the clinic ~~and will require discontinuation of study treatment~~ The blood draws for clinical laboratory tests have been minimized to lessen subject burden while ensuring subject safety. Additional hematology and biochemistry tests will be performed at visit 3/week 0 (baseline)~~, visit 5/week 4~~ and visit 8/week 14 (end of study [EoS]) only if an AE related to hematology, biochemistry or urinalysis parameters occurred since the previous visit or at the discretion of the investigator.

1 Protocol Summary and 3 Study Objectives and Endpoints
1.1 Synopsis

WAS:

Secondary *continued*	
● To evaluate the pharmacokinetics after multiple dose administration of mirabegron in pediatric subjects with OAB	● Appropriate pharmacokinetic parameters will be calculated based on the population pharmacokinetic model used
Exploratory	
● To evaluate the efficacy of mirabegron in pediatric subjects with OAB	● Percentage of subjects with a reduction in daytime incontinence episodes (< 50% reduction [nonresponder], 50% [partial responder] and 100% [responder]) ● Improvement from baseline in worst incontinence grading ● Change from baseline at the end of the 12-week treatment period adjusted for fluid intake: ○ Mean number of micturitions per 24 hours ● Change from baseline at the end of the 12-week treatment period (adolescents only): ○ Mean number of daytime micturitions per 24 hours ○ Mean volume voided per 24 hours ○ Mean number of incontinence episodes per 24 hours ● Number of dry (incontinence-free) days per 7 days at the end of the 12-week treatment period (adolescents only) ● Mean number of daytime grade 3 or 4 (PPIUS) urgency episodes per 24 hours (adolescents only)

IS AMENDED TO:

Primary and secondary objectives and endpoints apply to children only; exploratory objectives and endpoints also apply to adolescents.

Secondary *continued*	
● To evaluate the pharmacokinetics after multiple dose administration of mirabegron in pediatric subjects with OAB	● **Steady-state C_{max}, AUC_{tau}, C_{trough}, T_{max}, CL/F and Vz/F. Additional parameters may be calculated based on the population pharmacokinetic model used** ~~Appropriate pharmacokinetic parameters will be calculated based on the population pharmacokinetic model used~~
Exploratory	
● To evaluate the efficacy of mirabegron in pediatric subjects (**5 to < 18 years)** with OAB	● Percentage of subjects with a reduction in daytime incontinence episodes (< 50% reduction [nonresponder], 50% [partial responder] and 100% [responder]) ● Improvement from baseline in worst incontinence grading ● Change from baseline at the end of the 12-week treatment period adjusted for fluid intake:

	○ Mean number of micturitions per 24 hours ● Change from baseline at the end of the 12-week treatment period (adolescents only): ○ **Mean number of micturitions per 24 hours** ○ Mean number of daytime micturitions per 24 hours ○ Mean volume voided per 24 hours ○ Mean number of incontinence episodes per 24 hours ● Number of dry (incontinence-free) days per 7 days at the end of the 12-week treatment period (adolescents only) ● Mean number of daytime grade 3 or 4 (PPIUS) urgency episodes per 24 hours (adolescents only)

1 Protocol Summary and 4 Study Design and Dose Rationale *4.1 Study Design*
WAS:
Planned total number of study sites include approximately 50 study sites across Europe, Latin America, Africa, Middle East, and Asia-Pacific and North America.
IS AMENDED TO:
Planned total number of study sites include**s** approximately **65**~~50~~ study sites across Europe, Latin America, Africa, Middle East**,** ~~and~~ Asia-Pacific **and North America**

4 Study Design and Dose Rationale *4.2 Dose Rationale*
WAS:
For dosing with oral suspension, the weight range to be covered is from 11 kg (the approximate body weight of a 3 year old child, according to the National Health and Nutrition Examination Survey database [McDowell et al, 2008]) to 35 kg (above which pediatric subjects could be dosed with the tablet formulation). Subjects with a body weight < 11 kg will not be included in the study.
IS AMENDED TO:
For dosing with oral suspension, the weight range to be covered is from **13**~~11~~ kg (the approximate body weight of a **5**~~3~~-year old child, according to the National Health and Nutrition Examination Survey database [McDowell et al, 2008]) to 35 kg (above which pediatric subjects could be dosed with the tablet formulation). Subjects with a body weight < **13**~~11~~ kg will not be included in the study.

1 Protocol Summary and 5 Study Population *5.1 Inclusion Criterion #9*
WAS:

Female subject is not pregnant (see [Appendix 12.3 Contraception Requirements]) and at least 1 of the following conditions apply: c. Not a woman of childbearing potential (WOCBP) (see [Appendix 12.3 Contraception Requirements]). d. WOCBP who agrees to follow the contraceptive guidance (see [Appendix 12.3 Contraception Requirements]) from the time of informed consent/assent through at least 30 days after final IP administration.
IS AMENDED TO:
Female subject is not pregnant (see [Appendix 12.3 Contraception Requirements]) and at least 1 of the following conditions apply: a. Not a ~~woman~~**female** of childbearing potential ~~(WOCBP)~~ (see [Appendix 12.3 Contraception Requirements]). b. **Female of childbearing potential**~~WOCBP~~ who agrees to follow the contraceptive guidance (see [Appendix 12.3 Contraception Requirements]) from the time of informed consent/assent through at least 30 days after final IP administration.

1 Protocol Summary and 5 Study Population *5.1 Inclusion Criterion #13*
WAS:
Male subject must not donate sperm during the treatment period and for 30 days after final IP administration.
IS AMENDED TO:
Male subject must **agree** not **to** donate sperm during the treatment period and for 30 days after final IP administration.

1 Protocol Summary and 5 Study Population *5.1 Exclusion Criterion #19*
WAS:
Subject is using or has used prohibited prior and/or concomitant medication(s) [Appendix 12.6 List of Excluded Concomitant Medications].
IS AMENDED TO:
Subject is using or has used prohibited prior and/or concomitant medication(s) [Appendix 12.6 List of Excluded Concomitant Medications] **that cannot be discontinued**.

1 Protocol Summary and 6 Investigational Product(s) and Other Study Treatment(s) *1.1 Synopsis, 6.1.1 Investigational Product(s)*
WAS:
For detailed information on mirabegron prolonged release tablets and mirabegron granules for oral suspension, please refer to the current locally-available product information for mirabegron.

Table 7 Body Weight-based Doses for Tablets or Suspension

	Body Weight Range† (kg)	Oral Suspension Volume‡ (mL)	Tablet Dose (mg)
PED25	11 to < 22	3	-
	22 to < 35	4	-
	≥ 35‡	6	25
PED50	11 to < 22	6	-
	22 to < 35	8	-
	≥ 35‡	11	50

IS AMENDED TO:

For detailed information on mirabegron prolonged release tablets ~~and mirabegron granules for oral suspension~~, please refer to the current locally-available product information for mirabegron. **For detailed information on mirabegron granules for oral suspension, please refer to the Investigator's Brochure and Investigational Medicinal Product Dossier.**

Table 7 Body Weight-based Doses for Tablets or Suspension

	Body Weight Range† (kg)	Oral Suspension Volume‡ (mL)	Tablet Dose (mg)
PED25	**13**~~11~~ to < 22	3	-
	22 to < 35	4	-
	≥ 35‡	6	25
PED50	**13**~~11~~ to < 22	6	-
	22 to < 35	8	-
	≥ 35‡	11	50

6 Investigational Product(s) and Other Study Treatment(s)
6.1.2 Other Study Treatment(s)

WAS:

Urotherapy is to be discussed and confirmed with the subject or parent(s)/legal guardian(s) during each TC to ensure compliance.

IS AMENDED TO:

Urotherapy is to be discussed and confirmed with the subject or parent(s)/legal guardian(s) during each **visit (or** TC**)** to ensure compliance.

6 Investigational Product(s) and Other Study Treatment(s)
6.4.1 Investigational Product(s)

WAS:

Subject compliance with IP and other study treatment(s) will be assessed at each visit. Compliance will be assessed by counting returned IP at each clinic visit.

IS AMENDED TO:
Subject compliance with IP and other study treatment(s) will be assessed at each visit. Compliance will be assessed by counting **or weighing** returned IP at each clinic visit.

6 Investigational Product(s) and Other Study Treatment(s) *6.4.2 Other Study Treatment(s)*
ADDED:
Specific interventions include various forms of pelvic floor training (relaxation, contraction), behavioral modification, electrical stimulation, catherization and biofeedback (use of objective measures, e.g., uroflow or surface EMG to show children how far they relax their pelvic floor during voiding). Urotherapy can also include elements of cognitive behavioral therapy [Nevéus et al, 2006].

1 Protocol Summary and 6 Investigational Product(s) and Other Study Treatment(s) *1.1 Synopsis, Treatment Discontinuation Criteria, 6.5 Previous and Concomitant Treatment (Medication and Nonmedication Therapy)*
WAS:
Subjects are not allowed to use ongoing treatment with any of the following prohibited medications after the start of the washout: ● Any medication, other than the IP, used for the treatment of OAB
IS AMENDED TO:
Subjects are not allowed to use ongoing treatment with any of the following prohibited medications after the start of the washout: ● Any medication, other than the IP, used for the treatment of OAB **(including tricyclic antidepressants, 1st generation H1 antagonists and alpha blockers)** ● **Any medications known to prolong the QT interval** ● **Any medication that is a moderate or strong cytochrome CYP3A4/5 or P-gp inhibitor or inducers including natural and herbal remedies** **These treatments are prohibited from being started after the start of the washout period. All other concomitant treatment use will be reported.** **The use of previous and concomitant treatment within 30 days prior to signing the informed consent and throughout the study will be documented on the appropriate eCRF.**

7 Study Procedures and Assessments
ADDED:
Refer to the Alternate Schedule of Assessments [Table 12] in [Appendix 12.13 Clinical Study Continuity] for acceptable alternate methods to assess safety and efficacy

parameters in the event the study is interrupted due to a crisis (e.g., natural disaster, pandemic).

7 Study Procedures and Assessments
7.1.1 Bladder Electronic-Diary

WAS:

The e-diary data is reviewed by the investigator prior to the start of visit 2 and discussed and confirmed with the subject or the subject's parent(s)/caregiver(s) during the (telephone) visit 2.

IS AMENDED TO:

The e-diary data is reviewed by the investigator **or designee** prior to the start of visit 2 and discussed and confirmed with the subject or the subject's parent(s)/caregiver(s) during the (telephone) visit 2.

7 Study Procedures and Assessments
7.2.2 Laboratory Assessments

WAS:

Pregnancy test in female subjects will be performed in serum at screening and visit 8/week 14 (EoS).
Additional hematology, biochemistry and urinalysis (urinalysis dipstick) tests will be performed at visit 3/week 0 (baseline), visit 5/week 4 and visit 8/week 14 (EoS) only if an AE related to hematology, biochemistry or urinalysis parameters occurred since the previous visit or at the discretion of the investigator.

IS AMENDED TO:

A urine ~~P~~**p**regnancy test in female subjects **of childbearing potential** will be performed ~~in serum~~ at ~~screening and visit 8/week 14 (EoS)~~ **all on-site visits**.

Scheduled blood sampling will only be performed at screening (visit 1), week 4 (visit 5) and EoT (visit 7) to keep the burden to subjects at a minimum. Additional hematology, biochemistry and urinalysis (urinalysis dipstick) tests will be performed at visit 3/week 0 (baseline)~~, visit 5/week 4~~ and visit 8/week 14 (EoS) only if an AE related to hematology, biochemistry or urinalysis parameters occurred since the previous visit or at the discretion of the investigator.

Refer to the Alternate Schedule of Assessments [Table 12] for acceptable alternate methods to assess safety and efficacy parameters in the event the study is interrupted due to a crisis (e.g., natural disaster, pandemic).

7 Study Procedures and Assessments
7.2.3.1 Clinic-measurement of Vital Signs and Electrocardiograms

WAS:

Body temperature will be measured with an ear thermometer. Clinic measurements will be used to assess eligibility.
IS AMENDED TO:
Body temperature will be measured with an ear thermometer **as per standard of care**. Clinic measurements will be used to assess eligibility.

7 Study Procedures and Assessments *7.2.4 Physical Examination*
ADDED:
In this study, the physical examination will be done to evaluate general physical condition and encompasses standard, full physical examinations to assess general appearance, skin, eyes, ears, nose, throat, neck, cardiovascular, chest and lungs, abdomen, musculoskeletal, neurologic status, mental status and lymphatic systems.

7 Study Procedures and Assessments *7.4 Pharmacokinetics*
WAS:
Blood samples for the analysis of ED178/mirabegron and ethanol in plasma will be collected as indicated in the Schedule of Assessments [Table 1] for the evaluation of pharmacokinetics.
IS AMENDED TO:
Blood samples for the analysis of ~~ED178/~~mirabegron ~~and ethanol~~ in plasma will be collected as indicated in the Schedule of Assessments [Table 1] for the evaluation of pharmacokinetics. **The pharmacokinetic parameters that will be calculated as part of the secondary pharmacokinetic endpoint are steady-state C_{max}, AUC_{tau}, C_{trough}, T_{max}, CL/F and Vz/F. Additional parameters may be calculated based on the population pharmacokinetic model used.**

7 Study Procedures and Assessments *7.6 Electronic Clinical Outcome Assessment*
WAS:
For this study, it has been decided that there are justifiable scientific reasons (i.e., recall bias) to limit subject reported changes to changes reported by the subject to the site within 1 business day of its entry, as changes outside of this window could potentially impact the data integrity of the study. The data that will be under this rule are: all subject/guardian/parent entered, primary and secondary endpoints data. However, the site/investigator can remove/inactivate any data that they determine to be in error at any time. Subject bladder diaries, questionnaires and other data completed by the subject or the

subject's parent(s)/legal guardian(s) will be entered on an electronic device (e-diary). The information on the electronic device will be automatically uploaded to a central website. The investigator or site designee should review the diaries and questionnaire data on the website for correct completion before each planned visit of the subject (on site visit or TC) and discuss the results or retrain the subject and/or subject's parent(s)/legal guardian(s) if applicable. In case clinically relevant adverse changes are noticed during review of the e diary, these will be recorded as an AE [Appendix 12.4.1 Definition of Adverse Events].

The bladder e-diary, questionnaire results and other data collected in the e-diary will be transferred electronically to sponsor or designee at predefined intervals during the study. The vendor will provide sponsor or designee with a complete and clean copy of the data.

IS AMENDED TO:

For this study, it has been decided that there are justifiable scientific reasons (i.e., recall bias) to limit subject reported changes to changes reported by the subject to the site within 1 business day of its entry, as changes outside of this window could potentially impact the data integrity of the study. The data that will be under this rule are: all subject/guardian/parent-entered~~,~~ primary and secondary endpoints data. However, the site/investigator can remove/inactivate any data that they determine to be in error at any time **with source documentation to support the change including subject confirmation. Data will never be deleted from the electronic database by the electronic clinical outcome assessment (eCOA) service provider, but will be removed logically as per investigator's request and approval. All data changes are audit trailed showing the original entries alongside all changes including who requested the change, why it was requested, who made the change and when it was made. Audit trails are reviewed by the sponsor/clinical research organization (CRO) to ensure adherence to the protocol and appropriate source exists at site to substantiate the change**.

Subject bladder diaries, questionnaires and other data **will be** completed by the subject or the subject's parent(s)/legal guardian(s)**/caregiver(s)** ~~will be entered~~ on an electronic device (e-diary). The information on the electronic device will be automatically uploaded to a central website. The investigator or site designee should review the diaries and questionnaire data on the website ~~for correct~~**to ensure** completion **and protocol compliance** before each planned visit of the subject (on site visit or TC) and discuss the results or retrain the subject and/or subject's parent(s)/legal guardian(s)**/caregiver(s),** if applicable. In case clinically relevant adverse changes are noticed during review of the e diary, these will be recorded as an AE [Appendix 12.4.1 Definition of Adverse Events].

The bladder e-diary, questionnaire results and other data collected in the e-diary will be transferred electronically to the sponsor or designee at predefined intervals during the study. The vendor will provide **the** sponsor or designee with a complete and clean copy of the **study** data. **The ownership of this data is with the investigator and subsequently any changes requested to these subject-reported or nonsubject reported data will be made using the vendor's established process (e.g., a data clarification form to the vendor). The requested change must be supported by documented evidence at study site.**

7 Study Procedures and Assessments

7.8 Total Amount of Blood (Table 8)

WAS:

Sample Type	Number of Samples	Sample Volume (mL)	Total Volume (mL)
Pharmacokinetics	2	5.0	10.0
Clinical Laboratory Tests† Biochemistry/hematology	2	4.5§‡	9.0
Total			19.0

† Additional hematology and biochemistry tests of approximately 4.5 mL total will be performed at visit 3/week 0 (baseline), visit 5/week 4 and visit 8/week 14 (EoS) only if an adverse event related to hematology or biochemistry parameters occurred since the previous visit or at the discretion of the investigator.

‡ Includes pregnancy test in female subjects who experienced menarche (if blood is drawn); no additional blood is required. Volume does not take any unscheduled visits or repeat tests into account (e.g., follow up of adverse events).

IS AMENDED TO:

Sample Type	Number of Samples	Sample Volume (mL)	Total Volume (mL)
Pharmacokinetics	2	5.0	10.0
Clinical Laboratory Tests† Biochemistry/hematology	~~3~~**2**	4.5§‡	**13.5**~~9.0~~
Total			**23.5**~~19.0~~

† Additional hematology and biochemistry tests of approximately 4.5 mL total will be performed at visit 3/week 0 (baseline)~~, visit 5/wee 4~~ and visit 8/week 14 (EoS) only if an adverse event related to hematology or biochemistry parameters occurred since the previous visit or at the discretion of the investigator.

‡ ~~Includes pregnancy test in female subjects who experienced menarche (if blood is drawn); no additional blood is required.~~ Volume does not take any unscheduled visits or repeat tests into account (e.g., follow up of adverse events).

8 Discontinuation

8.1 Discontinuation of Individual Subject(s) From Study Treatment(s)

ADDED:

A discontinuation from treatment is defined as a subject who is randomized and for whom study treatment is permanently discontinued for any reason.

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to discontinue the participant from study treatment or to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

…

The reason for discontinuation from study treatment must be documented in the subject's medical records.

- **Female subject becomes pregnant.**

- **Prolongation of QT > QTcF > 440 msec and/or QT interval prolongation > 30 msec versus baseline.**
- **Subject with (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mmHg.**

9 Statistical Methodology
9.1 Sample Size

ADDED:

These assumptions, together with levels for Type-1 error and power were agreed upon with Pediatric Committee in the current Pediatric Investigation Plan

9 Statistical Methodology
9.4.1.3 Subgroup Analysis

WAS:

For the primary efficacy endpoint, descriptive statistics (n, mean, 95% confidence interval around the mean, SD, minimum, median, maximum) will be calculated for mean change from baseline at each visit by sex, race, ethnicity, geographical region, formulation (tablets vs. oral suspension) and prior OAB treatment, with and without LOCF.

IS AMENDED TO:

For the primary efficacy endpoint, descriptive statistics (n, mean, 95% confidence interval around the mean, SD, minimum, median, maximum) will be calculated for mean change from baseline at each visit by sex, race, ethnicity, geographical region, formulation (tablets vs. oral suspension)**,** ~~and~~ prior OAB treatment~~, with and without LOCF~~ **and symptomatic UTI**.

9 Statistical Methodology
9.4.3 Analysis of Exploratory Endpoints

ADDED:

- **Mean number of micturitions per 24 hours**

9 Statistical Methodology
9.5.2 Laboratory Assessments

ADDED:

In cases where laboratory evaluations are conducted locally, the values obtained will be adjusted to values obtained by the central laboratory. Details will be described in the SAP.

9 Statistical Methodology *9.5.5 Electrocardiogram*
ADDED:
ECGs will be recorded prior to blood draw.

9 Statistical Methodology *9.6.1 Estimation of Pharmacokinetic Parameters*
WAS:
The plasma concentrations will be analyzed with nonlinear mixed effects modeling (population pharmacokinetics) using Non-Linear Mixed Effects Modeling software (version 7.3 or higher, ICON Development Solutions, Ellicott City, MD, US) to estimate the pharmacokinetic parameters. Results will be reported separately.
IS AMENDED TO:
The plasma concentrations will be analyzed with nonlinear mixed effects modeling (population pharmacokinetics) using Non-Linear Mixed Effects Modeling **(NONMEM)** software (version 7.3 or higher, ICON Development Solutions, Ellicott City, MD, US) to estimate the pharmacokinetic parameters. Results will be reported separately.

10 Operational Considerations *10.1 Data Collection*
DELETED:
~~The investigator or site designee is responsible to ensure that all data in the electronic case report forms and queries are accurate and complete and that all entries are verifiable with the source. These documents should be appropriately maintained by the study site.~~ ~~The e-diary and questionnaire data will be transferred electronically to the sponsor or designee at predefined intervals during the study. The vendor will provide the investigator with a complete and clean copy of the study site's data and will provide the sponsor or designee with a complete and clean copy of the study data. The ownership of this data is with the investigator and subsequently any changes requested to these subject reported data will be made using a data clarification form to the vendor. The requested change must be supported by documented evidence at study site.~~

10 Operational Considerations
ADDED:

10.4.2 Independent Data Analysis Center

An IDAC for this study will serve the 2 purposes: (1) to generate periodic safety overviews for the DSMB and (2) to calculate the futility analysis. The statistical member of the DSMB may also serve as the IDAC statistician, as described in the DSMB charter. A SAP describing the details of the periodic safety review or outputs will be developed with input from the DSMB members.

11 References
WAS:
Investigator's Brochure Mirabegron (ED178), Astellas.
IS AMENDED TO
Investigator's Brochure Mirabegron (**YM~~ED~~**178), Astellas.

12 Appendices *12.1.6 Source Documents*
ADDED:
3. The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. **5. Study monitors will perform ongoing source data review to confirm that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP and all applicable regulatory requirements.**

12 Appendices *12.2.1 Study Monitoring*
WAS:
The sponsor is responsible for monitoring the study to ensure that the rights, safety and well-being of subjects are protected, the study is properly conducted in adherence to the current protocol and GCP and the study data reported by the investigator/subinvestigator(s) are accurate, complete and verifiable with the source.
IS AMENDED TO
The sponsor is responsible for monitoring the study to ensure that the rights, safety and well-being of subjects are protected, the study is properly conducted in adherence to the current protocol and GCP ~~and the study data reported by the investigator/subinvestigator(s) are accurate, complete and verifiable with the source~~.

12 Appendices
12.3 Contraception Requirements

WAS:

WOCBP who are eligible for participation in the study, including those who choose complete abstinence, must have pregnancy tests as specified in the Schedule of Assessments. Pregnancy test results must confirm that the subject is not pregnant.

WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION DEFINITIONS

A female is considered fertile (i.e., WOCBP) following menarche and until becoming postmenopausal unless permanently sterile.

Females in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal with 1 of the following (i.e., permanently sterile):
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Documentation of any of these categories can come from the study site personnel's review of the female subject's medical records, medical examination or medical history interview.

CONTRACEPTION GUIDANCE FOR FEMALE SUBJECTS OF CHILDBEARING POTENTIAL

Female subjects of childbearing potential are eligible for participation in the study if they agree to use 1 of the highly effective methods of contraception listed below from the time of signing the ICF/assent and until the end of relevant systemic exposure, defined as 30 days after the final IP administration.[a]

Highly effective methods of contraception (failure rate of < 1% per year when used consistently and correctly)[b]:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable
  - Implantable
- Other combined (estrogen- and progesterone-containing) methods
  - Vaginal ring
  - Injectable
  - Implantable

- Intrauterine hormone-releasing system or intrauterine device
- Bilateral tubal occlusion
- Vasectomized partner
- A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
- Sexual abstinence
- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the test product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject. It is not necessary to use any other method of contraception when complete abstinence is elected.

[a]Local laws and regulations may require use of alternative and/or additional contraception methods.

[b]Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

CONTRACEPTION GUIDANCE FOR MALE SUBJECTS WITH PARTNER(S) OF CHILDBEARING POTENTIAL

Male subjects with female partners of childbearing potential are eligible for participation in the study if they agree to the following during treatment and until the end of relevant systemic exposure defined as 30 days after final drug administration.[a]

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator
- Use a condom
- Female partners of male subjects who have not undergone a vasectomy with the absence of sperm confirmed or a bilateral orchiectomy should consider use of effective methods of contraception

[a]Local laws and regulations may require use of alternative and/or additional contraception methods.

IS AMENDED TO:

<u>Contraception for Pediatric Male Subjects of Reproductive Potential</u>

Male children/adolescents in the following categories are not considered of reproductive potential:

1. **Tanner stage 1 development**
2. **Documented surgically sterile**

Documentation from the site personnel's review of the male subject's medical records, medical exam and medical history interview is necessary.

Contraception guidance for male children/adolescents of reproductive potential:

- **Male children/adolescents of reproductive potential (Tanner Stage 2 and above)**

receiving non-genotoxic agents should use a condom during treatment and for 3 weeks + 5 × half-life of drug after last dose.

- **Male children/adolescents of reproductive potential receiving genotoxic agents should use a condom during treatment and for 90 days + 5 × half-life of drug after last dose.**
- **Male participants should inform their female partners that they are participating in a clinical trial and effective methods of contraception should be used.**
- **Female partners of male subjects who have not undergone bilateral orchiectomy should consider use of highly effective methods of contraception until the end of relevant systemic exposure, as defined above.**

<u>Contraception for Pediatric Female Subjects of Childbearing Potential</u>

Female children/adolescents in the following categories are not considered of childbearing potential:

1. **Pre-menarchal**
2. **Documented surgically sterile (hysterectomy, bilateral salpingectomy, bilateral oophorectomy)**

Documentation from the site personnel's review of the female subject's medical records, medical exam and medical history interview is necessary.

Contraception guidance for female children/adolescents of childbearing potential:

- **Female children/adolescents of childbearing potential receiving non-genotoxic agents should use highly effective contraception during treatment and for 30 days after last dose.**
- **Female children/adolescents of childbearing potential receiving genotoxic agents should use contraception during treatment and for 180 days + 5 × half-life of drug after last dose.**
- **Pregnancy testing for female children/adolescents of childbearing potential**
  - **At all on-site visits and 30 days after end of relevant systemic exposure**

One of the highly effective methods of contraception listed below is required at the time of informed consent and until the end of relevant systemic exposure as defined above.

<u>Highly Effective Birth Control Methods-failure rate < 1%/year</u>

1. **Combined estrogen and progestogen containing hormonal contraception**
   a. **Oral**
   b. **Intravaginal**
   c. **Transdermal-Patch**
   d. **Injectable-Cyclofem, Mesigyna**
   e. **Intrauterine device**
   f. **Intrauterine hormone-releasing system**
2. **Progestogen-only hormonal contraception**
   d. **Oral**

e. Injectable-DMPA-IM or -SC
f. Implantable-Norplant
3. Bilateral tubal occlusion
4. Vasectomized male partner
5. True abstinence*

***True abstinence: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. It is not necessary to use any other method of contraception when complete abstinence is elected.**

Birth control methods considered unacceptable:

1. Periodic abstinence (calendar, symptothermal, post-ovulation methods)
2. Withdrawal (coitus interruptus)
3. Spermicides only
4. Lactational amenorrhea

~~WOCBP who are eligible for participation in the study, including those who choose complete abstinence, must have pregnancy tests as specified in the Schedule of Assessments. Pregnancy test results must confirm that the subject is not pregnant.~~

~~WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION DEFINITIONS~~

~~A female is considered fertile (i.e., WOCBP) following menarche and until becoming postmenopausal unless permanently sterile.~~

~~Females in the following categories are not considered WOCBP~~

- ~~Premenarchal~~
- ~~Premenopausal with 1 of the following (i.e., permanently sterile):~~
  - ~~Documented hysterectomy~~
  - ~~Documented bilateral salpingectomy~~
  - ~~Documented bilateral oophorectomy~~

~~Documentation of any of these categories can come from the study site personnel's review of the female subject's medical records, medical examination or medical history interview.~~

~~CONTRACEPTION GUIDANCE FOR FEMALE SUBJECTS OF CHILDBEARING POTENTIAL~~

~~Female subjects of childbearing potential are eligible for participation in the study if they agree to use 1 of the highly effective methods of contraception listed below from the time of signing the ICF/assent and until the end of relevant systemic exposure, defined as 30 days~~

after the final IP administration.[a]

Highly effective methods of contraception (failure rate of < 1% per year when used consistently and correctly)[b]:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable
  - Implantable
- Other combined (estrogen- and progesterone-containing) methods
  - Vaginal ring
  - Injectable
  - Implantable
  - Intrauterine hormone-releasing system or intrauterine device
- Bilateral tubal occlusion
- Vasectomized partner
- A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
- Sexual abstinence
- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the test product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject. It is not necessary to use any other method of contraception when complete abstinence is elected.

[a]Local laws and regulations may require use of alternative and/or additional contraception methods.

[b]Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

CONTRACEPTION GUIDANCE FOR MALE SUBJECTS WITH PARTNER(S) OF CHILDBEARING POTENTIAL

Male subjects with female partners of childbearing potential are eligible for participation in the study if they agree to the following during treatment and until the end of relevant systemic exposure defined as 30 days after final drug administration.[a]

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator
- Use a condom
- Female partners of male subjects who have not undergone a vasectomy with the absence

~~of sperm confirmed or a bilateral orchiectomy should consider use of effective methods of contraception~~

~~*Local laws and regulations may require use of alternative and/or additional contraception methods.~~

12 Appendices
12.4.1.1 Abnormal Laboratory Findings

WAS:

Any abnormal laboratory test result (e.g., hematology, biochemistry or urinalysis dipstick) or other safety assessment (e.g., vital signs, physical examination, ECGs or radiographic scans), including those that worsen from baseline, that is considered to be clinically significant in the medical and scientific judgment of the investigator and not related to underlying disease, is to be reported as an (S)AE.

Any clinically significant abnormal laboratory finding or other abnormal safety assessment, which is associated with the underlying disease, does not require reporting as an (S)AE, unless judged by the investigator to be more severe than expected for the subject's condition.

IS AMENDED TO:

Any abnormal laboratory test result (e.g., hematology, biochemistry or urinalysis dipstick) or other safety assessment (e.g., vital signs, physical examination, ECGs or radiographic scans), including those that worsen from baseline~~, that is considered to be clinically significant in the medical and scientific judgment of the investigator and not related to underlying disease, is~~ **should be considered** to be reported as an (S)AE.

Any ~~clinically significant~~ abnormal laboratory finding or other abnormal safety assessment, which is associated with the underlying disease **or with concomitant medication will not be considered an AE**~~, does not require reporting as an (S)AE,~~ unless judged by the investigator to be more severe than expected for the subject's condition **or not associated with the known side effects of the concomitant medication. Additionally, minor laboratory deviations or fluctuations outside of normal ranges of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen and/or that are not reproducible with re-testing will not to be considered an AE**.

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12.6 List of Excluded Concomitant Medications

WAS:

Anticholinergics/antimuscarinics	Tricyclic/heterocyclic antidepressants	1st generation H1-antagonists†
Darifenacin	Alimemazine / Trimipramine	Tripelennamine
Dicyclomine/Dicycloverine	Amitriptyline	Dimenhydrinate
Fesoterodine	Amoxapine	Clemastine
Flavoxate	Clomipramine	Bromazine
Isopropamide	Desipramine	Orphenadrine

Oxybutynin	Dosulepin/ Dothiepin	Doxylamine
Oxyphencyclimine	Doxepine	Carbinoxamine
Propantheline	Imipramine	Diphenhydramine
Propiverine	Lofepramine	Cyclizine
Tolterodine	Maprotiline	Chlorcyclizine
Trospium	Mianserin	Hydroxyzine
Solifenacin	Mirtazapine	Meclizine
	Nortriptyline	
	Protriptyline	
pha-blockers	P2D6 with narrow therapeutic index	Sensitive P-gp substrates
Tamsulosin	Thioridazine	Digoxin
Alfuzosin	Flecainide	Dabigatran
Doxazosin	Propafenone	
Terazosin	Imipramine	
Silodosin	Desipramine	
Strong CYP3A4 inhibitors	Other	
Itraconazole	Mirabegron (except for study drug)	
Ketoconazole	Botulinum toxin	
Ritonavir	Opioids	
Clarthromycin		

IS AMENDED TO

Anticholinergics/antimuscarinics	Tricyclic/heterocyclic antidepressants	1st generation H1-antagonists†
Darifenacin	Alimemazine /Trimipramine	Tripelennamine
Dicyclomine/Dicycloverine	Amitriptyline	Dimenhydrinate
Fesoterodine	Amoxapine	Clemastine
Flavoxate	Clomipramine	Bromazine
Isopropamide	Desipramine	Orphenadrine
Oxybutynin	Dosulepin/Dothiepin	Doxylamine
Oxyphencyclimine	Doxepine	Carbinoxamine
Propantheline	Imipramine	Diphenhydramine
Propiverine	Lofepramine	Cyclizine
Tolterodine	Maprotiline	Chlorcyclizine
Trospium	Mianserin	Hydroxyzine
Solifenacin	Mirtazapine	Meclizine
	Nortriptyline	
	Protriptyline	
Alpha-blockers	CYP2D6 with narrow therapeutic index	Sensitive P-gp substrates
Tamsulosin	Thioridazine	Digoxin
Alfuzosin	Flecainide	Dabigatran
Doxazosin	Propafenone	

Terazosin	Imipramine	
Silodosin	Desipramine	
Moderate CYP3A4 inhibitors	**Strong CYP3A4 inhibitors**	**Moderate CYP3A4 inducers**
Fluconazole	**Itraconazole**	**Cenobamate**
Ciprofloxacin	**Ketoconazole**	**Tipranavir**
Erythromycin	**Ritonavir**	**Ritonavir**
Clotrimazole	**Clarthromycin**	**Thioridazine**
Fluvoxamine	**Voriconazole**	**Rifabutin**
Verapamil	**Posaconazole**	**Nafcillin**
Dronedarone	**Troleandomycin**	**Lopinavir**
Cimetidine	**Telithromycin**	**Modafinil**
Grapefruit Juice		**Phenobarbital**
Strong CYP3A4 inducers	**P-gp inhibitors‡**	**P-gp Inducers‡**
Rifampin	**Amiodarone**	**Rifampin**
Rifapentine	**Carvedilol**	**Carbamazepine**
Phenytoin	**Clarithromycin**	**Dexamethasone**
Carbamazepine	**Dronedarone**	**Phenobarbital**
St. John's wort	**Itraconazole**	**Phenytoin**
	Lopinavir, Ritonavir	**Rifampicin**
	Quinidine	**St. John's wort**
	Verapamil	**Trazodone**
QT prolongating medications~~Strong CYP3A4 inhibitors~~	Other	
Amiodarone~~Itraconazole~~	Mirabegron (except for study drug)	
Sotalol~~Ketoconazole~~	Botulinum toxin	
Quinidine~~Ritonavir~~	Opioids	
Levofloxacin, Ciprofloxacin~~Clarthromycin~~		
Clarithromycin, Erythromycin		
Ketoconazole, Itraconazole		
Amitriptyline, Fluoxetine		
Haloperidol, Droperidol		
Cisapride		
Sumatriptan, Zolmitriptan		

‡ Moderate or strong not specified.

12 Appendices

ADDED:

12.13 Clinical Study Continuity

INTRODUCTION

The purpose of this appendix is to provide acceptable alternate methods to assess safety and efficacy parameters, as appropriate, in the event the clinical study is interrupted at the country, state, site or participant level during any crisis (e.g., natural disaster, pandemic).

BENEFIT-RISK RATIONALE

Maintaining the safety of clinical study participants and delivering continuity of care in the clinical study setting is paramount during any crisis. The site is expected to follow the protocol and associated Schedule of Assessments [Table 1] unless the site principal investigator discusses the need with the Astellas medical monitor to implement the alternate measures.

The approach outlined within this appendix defines which assessments are required to maintain a favorable benefit/risk to the participant, to maintain overall study integrity and to provide acceptable alternate methods to complete the study required assessments and procedures if study activities are unable to be performed as described in [Section 7 Study Procedures and Assessments] due to a crisis.

INFORMED CONSENT

Participants who need to follow any or all of the alternate measures outlined in this Appendix will be required to provide informed consent, which explicitly informs them of the nature of and rationale for these changes, and gain their agreement to continue participation in the study prior to the implementation of any of these changes. In the event the urgency of implementing the alternate measures does not allow for the participant to provide written consent prior to implementation, the principal investigator or designee will obtain oral agreement from the subject followed by written documentation as soon as is feasible. A separate addendum to the study informed consent will be provided to document the participant's consent of the changes.

PARTICIPANT PROCEDURES ASSESSMENT

Sites with participants who are currently enrolled into this clinical study may consider implementing the alternate methods outlined below if one or more of the following conditions are met due to the crisis:

- **Regional or local travel has been restricted, inclusive of mandatory shelter in place measures, which makes participant travel to/from the study site nearly impossible**
- **Site facilities have been closed for clinical study conduct**
- **Site has been restricted to treating patients with conditions outside of the scope of the study**
- **Site personnel have temporarily relocated the conduct of the study to a location that place a burden on the participant with respect to time and travel**
- **Participant(s) have temporarily relocated from the current study site to an alternate study site to avoid placing a burden on the participant with respect to travel**
- **Participant(s) have temporarily relocated from their home location and the new distances from the site would cause undue burden with respect to time and travel**

- **Participant has risk factors for which traveling to the site poses an additional risk to the participant's health and safety**

Adherence to the original protocol as reflected in the Schedule of Assessments [Table 1] is expected, where plausible, in the case of a crisis. The alternate measures as noted in [Table 12] below are only permissible in the event of a crisis, and after discussing the need with the Astellas medical monitor to implement the alternate measures. This is to allow for continuity of receiving IP and maintaining critical safety and efficacy assessments for patients participating in the study at a time of crisis.

If one or more of the alternate measures noted below is implemented for a participant, the site should document in the participant's source document the justification for implementing the alternate measure and the actual alternate measures that were implemented, along with the corresponding time point(s).

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ADDED:

Table 12 Alternate Schedule of Assessments in Response to a Crisis

Critical Assessments	Alternate Approach(es)	Double-blind Placebo-controlled Period (12 weeks)					Follow-up Period (2 weeks)
		Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
		Week 0 Baseline	Week 2 TC[a]	Week 4	Week 8 TC[a]	Week 12 (EoT)[b]	Week 14 (EoS)[b,c]
		Day -1	Day 14 (± 3 days)	Day 28 (± 3 days)	Day 56 (± 3 days)	Day 84 (± 3 days)	Day 98 (+ 3 days)
Previous and Concomitant Medication	Remote/Virtual/Telemedicine Visits allowed. Please refer to protocol schedule of assessments.	X	X	X	X	X	X
Physical Examination	The exam can be done at a local clinic and the results submitted to PI.			X		X	
Height and Body Weight	Can be obtained at a local clinic or at home	X				X	
Dose Titration[d]	Courier service directly to subject. Titration to occur based on PI's evaluation via phone. For tablets: subject to take spare 25 mg tablets until 50 mg wallet is delivered via courier.			X			
Dispense IP[e]	Courier service directly to subject	X		X			
Drug Accountability	Used product can be shipped back to site via courier.	X				X	
Vital Signs[f]	Can be performed at a local clinic and results submitted to PI for evaluation OR Blood pressure and pulse collected via	X		X		X	X

	SBPM and temperature collected at home and reported to site (respiration rate missing).						
SBPM[g]	**Will be sent to subject's home address**	**X**	**X**	**X**	**X**	**X**	
Routine 12-lead ECG[f]	**ECG testing can be completed at local clinic.**	**X**		**X**		**X**	
Clinical Laboratory Tests (Hematology and Biochemistry)[h]	**Visit collection of samples at local facility acceptable if results can be made available to investigative site.**	**X[i]**		**X**		**X**	**X[i]**
Clinical Laboratory Tests (Urinalysis)[h]	**Visit collection of samples at local facility acceptable if results can be made available to investigative site.**	**X[i]**		**X**		**X**	**X[i]**
Pregnancy Test[i]	**Visit collection of samples at local facility acceptable if results can be made available to investigative site.**	**X**		**X**		**X**	**X**
AEs	**Remote/Virtual/Telemedicine Visits allowed. Please refer to protocol schedule of assessments.**	**X**	**X**	**X**	**X**	**X**	**X**
Bladder e-diary	**Will be sent to subject's home address**	**X**	**X**	**X**	**X**	**X**	
Acceptability and Palatability Questionnaire[j]	**To be performed remotely via e-diary.**					**X**	
Pharmacokinetics[k]	**Astellas Medical Monitor to assess. Not allowed at an alternate clinical due to special sample handling.**			**X**		**X**	

AE: adverse event; ECG: electrocardiogram; e-diary: electronic diary; EoS: end of study; EoT: end of treatment; IP: investigational product; OAB: overactive bladder; PED25: pediatric equivalent dose 25 mg; PED50: pediatric equivalent dose 50 mg; PI: principal investigator; SBPM: self blood pressure monitoring; TC: telephone call

a. For the visits where a TC is indicated, there is no need for the subject to visit the clinic provided that the bladder e-diary data are reviewed by the investigator prior to the TC and discussed and confirmed with the subject or parent(s)/legal guardian(s) during the TC. Urotherapy is also to be discussed and confirmed with the subject or parent(s)/legal guardian(s) during each TC as indicated in Table 1.

b. Subjects who withdraw early from the study after having received IP should complete both the EoT and EoS visits.

c. The EoS visit (visit 8/week 14 [EoS]) should take place at least 14 days after the EoT visit (visit 7/week 12 [EoT]).

d. Dose up-titration to PED50 to occur at visit 5/week 4 unless investigator determines OAB is adequately controlled. Dose down-titration from PED50 to PED25 can be done at any time for safety reasons.

e. Daily IP administration will start on day 1 (i.e., the day after visit 3/week 0 [baseline]).

f. Blood pressure, pulse, body temperature and ECGs will all be measured in single measurements. Subject to be in the sitting position (when possible, otherwise supine, but always in the same position for each procedure). Subject should have been calm and without distress for at least 5 minutes. Preferably, the right arm should be used to measure vital signs. Body temperature will be measured with an ear thermometer. Clinic measurements will be used to assess eligibility.

g. SBPM will be measured once in the morning and evening during the 2-day weekend bladder e-diary collection period. SBPM measurements should start in the weekend prior to week -2 and be taken in the weekend prior to the indicated visit (or TC). SBPM will be measured on 2 consecutive days at 1 and 2 weeks after start of dosing with PED25 (day 1) and after up-titration to PED50, if not already covered by the scheduled SBPM. Measurements will be taken in the sitting position (when possible, otherwise supine, but always in the same position). Preferably, the right arm should be used. Subject should have been calm and without distress for at least 5 minutes. Morning measurement should be taken before IP intake and evening measurement should be taken prior to bedtime.

h. Additional hematology, biochemistry and urinalysis (urinalysis dipstick) tests will be performed at visit 3/week 0 (baseline) and visit 8/week 14 (EoS) only if an AE related to hematology, biochemistry or urinalysis parameters occurred since the previous visit or at the discretion of the investigator.

i. Urine pregnancy test will be performed for females of childbearing potential at all on-site visits.

j. The acceptability and palatability questionnaire will be completed on one weekend day preceding at visit 7/week 12 (EoT).

k. There will be 2 pharmacokinetic sampling days at visit 5/week 4 and visit 7/week 12 (EoT). Both pharmacokinetic sampling days will consist of collecting 1 predose (trough) sample. On pharmacokinetic sampling days, dosing should occur in the clinic and breakfast should be eaten at the clinic within 1 hour before dosing.

INVESTIGATIONAL PRODUCT SUPPLY

If any of the conditions outlined above in the Participant Procedures Assessment are met, if the following mitigating strategy will be employed, as needed, to ensure continuity of IP supply to the participants:

- **Increase stock of IP on site to reduce number of shipments required, if site space will allow.**
- **Direct-to-subject shipments of IP from the site to the subject's home.**

DATA COLLECTION REQUIREMENTS

Additional data may be collected in order to indicate how participation in the study may have been affected by a crisis and to accommodate data collection resulting from alternate measures implemented to manage the conduct of the study and participant safety.

- **Critical assessments for safety and efficacy based on study endpoints to be identified as missing or altered (performed virtually, at alternative locations, out of window, or other modifications) due to the crisis.**

12 Appendices
12.4 List of Abbreviations and Definition of Key Study Terms

WAS:

WOCBP	Woman of childbearing potential

IS AMENDED TO:

NONMEM	**non-linear mixed effects modeling**
~~WOCBP~~	~~Woman of childbearing potential~~

12 Appendices
12.4 List of Abbreviations and Definition of Key Study Terms

WAS:

Intervention	The drug, device, therapy or process under investigation in a study that is believed to have an effect on outcomes of interest in a study (e.g., health-related quality of life, efficacy, safety and pharmacoeconomics).

IS AMENDED TO:

Intervention	The drug, device, therapy or process under investigation in a study that is believed to have an effect on outcomes of interest in a study (e.g., health-related quality of life, efficacy, safety and pharmaco**kinetics**~~economics~~).

14 COORDINATING INVESTIGATOR'S SIGNATURE

A Phase 3, Double-blind, Randomized, Multicenter, Parallel Group, Placebo-controlled Sequential Dose Titration Study to Evaluate Efficacy, Safety and Pharmacokinetics of Mirabegron in Pediatric Subjects from 5 to < 18 Years of Age with Overactive Bladder

ISN/Protocol 178-CL-204

Version 2.0 Incorporating Substantial Amendment 1

11 Feb 2021

I have read all pages of this protocol for which Astellas is the sponsor. I agree that it contains all the information required to conduct this study.

Coordinating Investigator:

Signature: .....

Date (DD Mmm YYYY)

Printed Name: ....

Address: .....

.....

15 SPONSOR'S SIGNATURES

(Electronic signatures are attached at the end of the document.)

PPD	Medical and Development
PPD	Data Science