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 Neurogenic Detrusor Overactivity (NDO) on Clean Intermittent Catheterization (CIC)

Open-label Phase 3 Study with Mirabegron in Children From 3 to Less Than 18 Years of Age with Neurogenic Detrusor Overactivity (Crocodile Study)

ISN/Protocol 178-CL-206A

ClinicalTrials.gov Identifier: NCT02751931

Date of Protocol v2: 02 Nov 2016

Sponsor: Astellas Pharma Europe B.V. (APEB)

Sylviusweg 62

2333 BE Leiden, the Netherlands

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Version 2.0

Incorporating Substantial Amendment 1 [See Attachment 1]

02 November 2016

EudraCT 2015-002876-25

Sponsor:
Astellas Pharma Europe B.V. (APEB)
Sylviusweg 62
2333 BE Leiden, the Netherlands

Protocol History:
Version 1.0 [09 Dec 2015]

Investigator: Investigator information is on file at Astellas

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I. SIGNATURES

1. SPONSOR'S SIGNATURE

Required signatures (e.g., Protocol authors, Sponsor's reviewers and contributors, etc.) are located in Section 14, Sponsor's Signatures; e-Signatures (when applicable) are located at the end of this document.

2. INVESTIGATOR'S SIGNATURE

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 Neurogenic Detrusor Overactivity (NDO) on Clean Intermittent Catheterization (CIC)

ISN/Protocol 178-CL-206A

Version 2.0 Incorporating Substantial Amendment 1

02 November 2016

I have read all pages of this clinical study 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 ICH GCP guidelines and applicable local regulations. I will also ensure that sub-investigator(s) and other relevant members of my staff 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: .....

<Insert name and qualifications of the investigator> Date (DD Mmm YYYY)

Printed Name: .....

Address: .....

.....

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

24h-Contact for Serious Adverse Events (SAEs) **See Section 5.5.5**	[redacted]
Medical Expert:	[redacted]
Medical Monitor	[redacted]
Clinical Research Contact:	[redacted]

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviation	Description
APEB	Astellas Pharma Europe B.V.
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC_{24}	Area under the plasma concentration-time curve from time zero to 24 h
CIC	clean intermittent catheterization
CGI-C	Clinician Global Impression of Change
CL/F	apparent total clearance of the drug from plasma after oral administration
C_{max}	maximum (peak) plasma drug concentration
CRO	contract research organization
CSR	clinical study report
C_{trough}	trough plasma concentration (measured concentration at the end of a dosing interval at steady state)
CYP	cytochrome P450
DSD	detrusor sphincter dyssynergia
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
eGFR	estimated glomerular filtration rate
EOS	end of study
EOT	end of treatment
FAS	full analysis set
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMPD	Investigational Medicinal Product Dossier
INR	international normalized ratio
ISN	international study number
IUD	intrauterine device
IUS	intrauterine system
LA-CRF	liver abnormality case report form
LC-MS/MS	liquid chromatography-mass spectrometry and tandem mass spectrometry
LOCF	last observation carried forward
LFT	liver function test
LQTS	long QT syndrome
MCC	maximum cystometric capacity
NDO	neurogenic detrusor overactivity
OAB	overactive bladder
PED	pediatric equivalent dose

Abbreviation	Description
PGI-S	Patient Global Impression of Severity Scale
P-gp	P-glycoprotein
PIN-Q	Pediatric Incontinence Questionnaire
PKAS	pharmacokinetics analysis set
PND	postnatal day
popPK	population pharmacokinetics
PPS	per protocol set
QTcB	QT interval corrected by Bazett's formula
QTcF	QT interval corrected by Fridericia's formula
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SBPM	self blood pressure measurement
SMIP	self-measurement of intravesical pressure
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TBL	total bilirubin
TLF	tables, listings and figures
t_{max}	time to reach maximum (peak) plasma concentration following drug administration
ULN	upper limit of normal
UTI	urinary tract infection
V_z/F	apparent volume of distribution after nonintravenous administration

Definition of Key Study Terms

Terms	Definition of terms
Baseline	Observed values/findings which are considered to be the starting point for comparison.
Discontinuation	The act of concluding participation in a trial by an enrolled subject, prior to completion of all protocol required elements. Note: subject discontinuation does not necessarily imply exclusion of subject data from analysis that was collected prior to discontinuation.
Enroll	To register or enter into a clinical trial, i.e., signing the informed consent form (ICF). Once a subject has been enrolled, the clinical trial protocol applies to the subject.
Investigational period	Period of time where major interests of protocol objectives are observed, and where the study drug is given to a subject. This period continues until the last assessment after completing the last dose of the study drug.
Pediatric equivalent dose (PEDx)	Weight-range based doses predicted to achieve plasma concentrations equivalent to steady state exposures expected with "x" mg mirabegron administered once daily in adults.
Postinvestigational 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.
Screening	A process of active consideration of potential subjects for a trial.
Screening period	Period of time before entering the investigational period, usually from the time the subject signed informed consent until just before the first dose of the study drug is given to a subject.
Screening failure	Screened subject who did not fulfill protocol inclusion and/or exclusion criteria, or decided not to participate anymore (withdrew consent) prior to first dose of study drug.
Source data	All information in original records or certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records, certified copies).
Source documents	Original documents, data, and records including source data.
Steady state	When the amount of drug intake is equilibrium with the rate of drug elimination. Note: for mirabegron steady state is considered to be reached after 10 days of daily dosing.
Study completion	Status of subject who completed the last protocol-defined assessment.
Study period	Period of time from the first site initiation date to the last site completing the study.
Subject	An individual in the population of interest who participates in a clinical trial as recipient of the investigational product.

Terms	Definition of terms
Treatment emergent adverse event	An adverse event observed after starting administration of the study drug.
Trough sample	Pharmacokinetic sample taken just prior to the next dose of study drug.

IV. SYNOPSIS

Date and Version # of Protocol Synopsis:	02 November 2016, Version 2.0
Sponsor: Astellas Pharma Europe BV (APEB)	**Protocol Number:** 178-CL-206A
Name of Study Drug: Mirabegron	**Phase of Development:** Phase 3

Title of Study:

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 Neurogenic Detrusor Overactivity (NDO) on Clean Intermittent Catheterization (CIC)

Planned Study Period:

From 2Q2016 to 3Q2019.

Study Objectives:

Primary objective:

- To evaluate the efficacy of mirabegron after multiple-dose administration in the pediatric population.

Secondary objectives:

- To evaluate the safety and tolerability of mirabegron after multiple-dose administration in the pediatric population.
- To evaluate the pharmacokinetics of mirabegron after multiple-dose administration in the pediatric population.

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

Approximately 50 enrolling study centers in Europe, Latin America, Africa, Middle East and Asia-Pacific.

Study Population:

Male and female pediatric child and adolescent subjects aged 3 to less than 18 years of age with neurogenic detrusor overactivity (NDO) on clean intermittent catheterization (CIC).

Number of Subjects to be Enrolled/Randomized:

At least 44 evaluable subjects (estimate 63 enrolled), with at least 10 subjects from each age group (children aged 3 to less than 12 years of age; adolescents aged 12 to less than 18 years of age) are planned. A subject is considered being evaluable if the subject has a valid (as by the central reviewer's assessment) nonmissing maximum cystometric capacity (MCC) measurement at baseline and at a postbaseline visit.

Study Design Overview:

This is a phase 3, open-label, baseline-controlled, multicenter study. The study will consist of 3 periods:

- Pretreatment period: for a maximum of 28 days before baseline, including screening, washout (if applicable) and baseline
- Efficacy treatment period: beginning the day after baseline and continuing to visit 8/week 24
- Long-term safety period: beginning after visit 8/week 24 and continuing to visit 10/week 52 (end of study [EOS]), or to the end of treatment (EOT)

Pretreatment Period

After informed consent and visit 1/screening, subjects are grouped according to their current NDO therapy and/or other medication:

- Group A: Subjects who are currently not receiving any prohibited medication including any oral drug treatment to manage their NDO, or when botulinum toxin is no longer considered effective
- Group B: Subjects who currently are receiving oral drug treatment to manage their NDO or receive any other prohibited medication.

After the screening visit a 2-day weekend e-diary has to be completed by the subjects to get acquainted with the electronic diary (e-diary) and the home assessments:

- Group A: Following successful completion of the first 2-day weekend e-diary, confirmed at visit 2, the subjects will start to complete the 7-day baseline e-diary followed by visit 3/baseline.
- Group B: Following successful completion of the first 2-day weekend e-diary, confirmed at visit 2, the subjects will start their 2-week washout period. In the second week of their washout period, they will complete the 7-day baseline e-diary followed by visit 3/baseline.

If a subject is suffering from a symptomatic urinary tract infection (UTI) at visit 1/screening or is diagnosed with one between visit 1/screening and visit 3/baseline, the UTI should be treated successfully (clinical recovery) prior to baseline. If a symptomatic UTI is present at baseline, all baseline assessments should be postponed for a maximum of 7 days until the UTI is successfully treated (clinical recovery).

The 7-day baseline e-diary does not have to be repeated if at least the 2-day weekend e-diary and 1 day of the weekday e-diary were completed while the subject did not suffer from a symptomatic UTI.

Subjects will enter the efficacy treatment period if they meet the eligibility criteria and satisfactorily complete the pretreatment period (ability to complete bladder diary, catheterized volumes and questionnaires).

In case the subject or the subject's parent(s)/caregiver(s) are not able or willing to perform the SMIP, the measuring device is not available at the site, or there is a technical problem, the SMIP may be omitted.

Efficacy Treatment Period

Daily study drug administration will begin the day after the baseline visit. The initial dose of mirabegron will be based on the subject's weight, and is predicted to achieve plasma concentrations equivalent to the steady state exposures expected with 25 mg mirabegron administered once daily in adults (pediatric equivalent dose [PED25]).

At visit 4/week 2, visit 5/week 4 or visit 6/week 8, subjects must be up-titrated to the pediatric equivalent dose of 50 mg in adults (PED50) based on the given dose titration criteria.

At visit 8/week 24, the primary efficacy endpoint will be assessed, which is the change from baseline in MCC.

If a subject is suffering from a symptomatic UTI in the week prior to any (un)scheduled urodynamic investigation (e.g., visit 5/week 4, visit 8/week 24), the UTI should be treated successfully first (until clinical recovery). To allow for treatment of the UTI, these visits may be postponed with an additional maximum of 7 days on top of the already existing visit window.

The 7-day e-diary does not have to be repeated if at least the 2-day weekend e-diary and 1 day of the weekday e-diary were completed while the subject did not suffer from a symptomatic UTI.

If a subject suffers from a symptomatic UTI in the week prior to any other study visit, these visits do not need to be postponed and the 7-day e-diary does not have to be repeated.

Long-term Safety Period

For long-term safety evaluation, following visit 8/week 24, subjects will stay on their individual dose level until visit 10/week 52 (EOS or EOT).

Dose Titration

The aim is to obtain a safe low-pressure bladder, to inhibit overactive detrusor contractions and to reach continence.

Dose up-titration to PED50 must be performed at visit 4/week 2, visit 5/week 4 or visit 6/week 8, unless:

1. The investigator considers the subject to be effectively treated with PED25, based on urodynamics and the e-diary;
2. There are safety or tolerability issues with PED25.

Dose down-titration to PED25 can be performed at any time if there is a safety issue.

If an insufficient control of the NDO is observed at the highest tolerated mirabegron dose due to insufficient effect (based on, for example, ultrasound showing upper tract dilation; the appearance of a high grade reflux; high intravesical pressures; high detrusor pressures or high amplitude overactive contractions), the investigator should reconsider the subject's further participation in the study and consider an alternative treatment.

Inclusion/Exclusion Criteria:

Inclusion:

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

1. Independent Ethics Committee (IEC)/Institutional Review Board (IRB)-approved written Informed Consent and privacy language as per national regulations must be obtained from the subject and/or from the subject's parent(s) or legal guardian(s) prior to any study-related procedures (including discontinuation of prohibited medication, if applicable); assent by the subject is given as required by local law.
2. Subject is male or female from 3 to less than 18 years of age.
3. Subject has a body weight of ≥ 11 kg.
4. Subject suffers from NDO confirmed by urodynamic investigation at baseline. The diagnosis of NDO must be confirmed by the presence of at least 1 involuntary detrusor contraction > 15 cm H_2O from baseline detrusor pressure, and/or a decrease in compliance leading to an increase in baseline detrusor pressure of > 20 cm H_2O.
5. Subject has been using CIC for at least 4 weeks prior to visit 1/screening.
6. Subject has a current indication for drug therapy to manage NDO.
7. Subject is able to take the study drugs in accordance with the protocol.
8. Female subject must either:
   - Be of nonchildbearing potential:
     - Clearly premenarchal or in the judgment of the investigator is premenarchal,
     - Documented surgically sterile,
   - Or, if of childbearing potential:
     - Agree not to try to become pregnant during the study and for 28 days after the final study drug administration,
     - And have a negative pregnancy test at visit 1/screening and at visit 3/baseline,
     - And, if sexually active must agree to use a highly effective method of birth control, which includes established use of oral, injected or implanted hormonal methods of contraception, OR placement of an intrauterine device (IUD) or intrauterine system (IUS). Birth control must be practiced from visit 1/screening and continuing throughout the study period, and for 28 days after the final study drug administration.

9. Male subject and their female spouse/partner who are of childbearing potential must be using a highly effective method of birth control, which includes established use of oral, injected or implanted hormonal methods of contraception, placement of an IUD or IUS. Birth control must be practiced from visit 1/screening and continuing throughout the study period, and for 28 days after the final study drug administration.
10. Female subject must not be breastfeeding from visit 1/screening until 28 days after last study drug administration.
11. Subject and subject's parent(s)/legal guardian(s) agree that the subject will not participate in another interventional study while participating in the study.
12. 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.

Waivers to the inclusion criteria will NOT be allowed.

Exclusion:

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

1. Subject has a known genitourinary condition (other than NDO) that may cause overactive contractions or incontinence (e.g., bladder extrophy, urinary tract obstruction, urethral diverticulum or fistula) or kidney/bladder stones or another persistent local pathology that may cause urinary symptoms.
2. Subject has one of following gastrointestinal problems: partial or complete obstruction, decreased motility such as paralytic ileus, subject at risk of gastric retention.
3. Subject has a urinary indwelling catheter within 4 weeks prior to visit 1/screening
4. Subject has a surgically treated underactive urethral sphincter
5. Subject has vesico-ureteral reflux grade 3 to 5.
6. Subject has undergone bladder augmentation surgery.
7. Subject receives electrostimulation therapy, if started within 30 days before visit 1/screening or is expected to start during the study period. Subjects who are on an established regimen may remain on this for the duration of the study.
8. Subject suffers from a symptomatic urinary tract infection (UTI) at baseline (symptomatic is defined as pain, fever, hematuria, new onset foul-smelling urine). If present at visit 1/screening or diagnosed between visit 1/screening and visit 3/baseline, the UTI should be treated successfully (clinical recovery) prior to baseline. If a symptomatic UTI is present at baseline, all baseline assessments should be postponed for a maximum of 7 days until the UTI is successfully treated (clinical recovery).
9. Subject has a (mean) resting pulse rate > 99^{th} percentile [Fleming et al, 2011].
10. Subject has an established hypertension and a systolic or diastolic blood pressure greater than the 99th percentile of the normal range determined by sex, age and height, plus 5 mmHg [NIH 2005].
11. Subject has a risk of QT prolongation (e.g., hypokalemia, long QT syndrome [LQTS]; or family history of LQTS, exercise-induced syncope).
12. Subject has severe renal impairment (estimated glomerular filtration rate [eGFR] according to Larsson equation < 30 mL/min).
13. Subject's aspartate aminotransferase (AST) or alanine aminotransferase (ALT) is greater than or equal to 2 times the upper limit of normal (ULN) or total bilirubin greater than or equal to 1.5 times the ULN according to age and sex.

14. Subject has a history or presence of any malignancy prior to visit 1/screening.
15. Subject has known or suspected hypersensitivity to mirabegron, any of the excipients used in the current formulations or previous severe hypersensitivity to any drug.
16. Subject has participated in another clinical trial (and/or has taken an investigational drug) within 30 days (or 5 half-lives of the drug, or the limit set by national law, whichever is longer) prior to visit 1/screening.
17. Subject uses any of the following prohibited medications (after start of washout):
    - Any medication, other than the study drug, used for the management of NDO;
    - Any drugs that are sensitive cytochrome (CYP) 2D6 substrates with a narrow therapeutic index or sensitive P-glycoprotein (P-gp) substrates
    - Any strong cytochrome P450 (CYP) 3A4 inhibitors if the subject has a mild to moderate renal impairment (eGFR 30 – 89 mL/min).
18. Subject has been administered intravesical botulinum toxin; except if given > 4 months prior to visit 1/screening and the subject experiences symptoms comparable to those existing prior to the botulinum toxin injections.
19. Subject has any other condition, which in the opinion of the Investigator, precludes the subject's participation in the study.
20. Subject's parent/legal guardian is an employee of the Astellas Group, the Contract Research Organization (CRO) involved, or the investigator site executing the study.

Waivers to the exclusion criteria will NOT be allowed.

Investigational Products:

Mirabegron prolonged-release tablets, strengths 25 mg and 50 mg

Mirabegron oral suspension, strength 8 mg/mL

Doses:

Selection of the formulation:

Subjects with a body weight < 35 kg: mirabegron oral suspension.

Subjects with a body weight ≥ 35 kg: mirabegron tablets.

Selection of the dose:

Doses are calculated weight-based. The bodyweight at visit 3/baseline determines the weight range for the starting dose (PED25) and the up-titration dose (PED50) to be used in the table below:

Weight-based Doses for Tablets or Suspension

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

PED25: Pediatric equivalent dose 25 mg; PED50: Pediatric equivalent dose 50 mg
† Suspension strength: 8 mg/mL

Further dosing information:

- For subjects with a body weight ≥ 35 kg who do not want to or are unable to take tablets, the oral suspension can be supplied.
- At visit 8/week 24 subjects on mirabegron oral suspension may switch to tablets if the body weight turns to be ≥ 35 kg.
- Subjects receiving mirabegron tablets can switch to mirabegron oral suspension (and vice versa) for acceptability reasons after Sponsor's prior approval and on a case-by-case basis.

Mode of Administration:

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

Mirabegron tablets will be taken with a sip of water (tablet should be taken as a whole and should not be chewed, divided or crushed).

Mirabegron oral suspension will be administered via an oral syringe with a sip of water afterwards.

On visit days where a pharmacokinetic sample is planned in the clinic, completion of breakfast and study drug dosing should occur in the clinic.

Comparative Drug(s):

Not applicable

Dose(s):

Not applicable

Mode of Administration:

Not applicable

Concomitant Medication Restrictions or Requirements:

During the study, starting from visit 2 until visit 10/week 52 (EOT/EOS), subjects are not allowed to use treatment with any of the following prohibited medications:

- Any medication, other than the study drug, used for the management of NDO.
- Any drugs that are sensitive CYP2D6 substrates with a narrow therapeutic index or sensitive P-gp substrates
- Any strong CYP 3A4 inhibitors if the subject has a mild to moderate renal impairment (eGFR 30 – 89 mL/min).

Duration of Treatment:

Once a day for 52 weeks

Formal Stopping Rules:

Criteria for treatment discontinuation for individual subjects:

- If, within 7 days of the first dose of mirabegron:
  - The centrally read urodynamic trace reveals no evidence of NDO
  - The centrally read electrocardiogram (ECG) has an average QT interval corrected by Bazett's formula (QTcB) greater than 450 ms, based on the QTcB mean from the visit 1/screening and visit 3/baseline ECG triplicates
- If signs or symptoms of hypersensitivity to mirabegron are observed (e.g., anaphylactic reaction, erytheme multiforme or exfoliative dermatitis).

Discontinuation of 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%).
- In addition, if close monitoring for a subject with moderate or severe hepatic laboratory tests is not possible, the drug should be discontinued.

Endpoints for Evaluation:

Primary:

Efficacy

Change from baseline in MCC after 24 weeks of treatment (based on filling urodynamics)

Secondary:

Efficacy

Based on filling urodynamics:

Change from baseline at visit 5/week 4 and visit 8/week 24 in:

- MCC (only visit 5/week 4)
- Bladder compliance (ΔV/ΔP)
- Number of overactive detrusor contractions (> 15 cm H_20) until end of filling
- Detrusor pressure at end of filling
- Filling volume until first overactive detrusor contraction (> 15 cm H_20)

Based on e-diary:

Change from baseline at visit 4/week 2, visit 5/week 4, visit 6/week 8, visit 7/week 12, visit 8/week 24, visit 9/week 36 and visit 10/week 52 (EOT/EOS) in:

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

Based on questionnaires:

- Change from baseline at visit 8/week 24 and visit 10/week 52 (EOT/EOS) in Pediatric Incontinence Questionnaire (PIN-Q)
- Change from baseline at visit 8/week 24 and visit 10/week 52 (EOT/EOS) in Patient Global Impression of Severity Scale (PGI-S)
- Acceptability questionnaire at visit 5/week 4, visit 8/week 24 and visit 10/week 52 (EOT/EOS)
- Clinician Global Impression of Change (CGI-C) at visit 8/week 24 and visit 10/week 52 (EOT/EOS)

Safety

- Incidence and severity of treatment-emergent adverse events (TEAEs)
- Change from baseline in vital signs (clinic measurements): systolic blood pressure, diastolic blood pressure, pulse rate and temperature at visit 5/week 4, visit 7/week 12, visit 8/week 24 and visit 10/week 52 (EOT/EOS)
- Change from baseline in vital signs (self blood pressure measurement [SBPM]): systolic blood pressure, diastolic blood pressure, pulse rate at visit 4/week 2, visit 5/week 4, visit 6/week 8, visit 7/week 12, visit 8/week 24, visit 9/week 36 and visit 10/week 52 (EOT/EOS) and on 2 consecutive days at around 1 and 2 weeks after start of dosing with PED25 (day 1) and after up-titration to PED50 (visit 4/week 2, visit 5/week 4 or visit 6/week 8), if not already covered by the scheduled visit 4/week 2 and/or visit 5/week 4 SBPM.

- Change from baseline in hematology and biochemistry tests at visit 7/week 12 and visit 10/week 52 (EOT/EOS) and urinalysis tests at visit 5/week 4, visit 7/week 12, visit 8/week 24 and visit 10/week 52 (EOT/EOS)
- Change from baseline in ECG parameters at visit 5/week 4, visit 7/week 12, visit 8/week 24 and visit 10/week 52 (EOT/EOS)
- Change from baseline to visit 10/week 52 (EOT/EOS) in upper urinary tract ultrasound assessment
- Change from baseline in eGFR at visit 7/week 12 and visit 10/week 52 (EOT/EOS)

Pharmacokinetics of mirabegron

- C_{max}, t_{max}, AUC_{24}, C_{trough}, CL/F and V_z/F.
- Additional pharmacokinetic parameters may be calculated based on the model used.

Exploratory:

Efficacy:

Based on filling urodynamics:

Change from baseline at visit 5/week 4 and visit 8/week 24 in:

- Filling volume at 20 cm, 30 cm and at 40 cm H_2O detrusor pressure, given that the pressures are reached during the examination.

Based on e-diary:

Change from baseline at visit 4/week 2, visit 5/week 4, visit 6/week 8, visit 7/week 12, visit 8/week 24, visit 9/week 36 and visit 10/week 52 (EOT/EOS) in:

- Mean grade of leakage
- Total catheterized volume per day
- Change from baseline in SMIP-derived bladder compliance
- Number of CICs/day
- Responder in respect to leakage (complete, partial, no response)

Safety:

Intravesical pressure (SMIP):

- Change from baseline at visit 4/week 2, visit 5/week 4, visit 6/week 8, visit 7/week 12, visit 8/week 24, visit 9/week 36 and visit 10/week 52 (EOT/EOS).

Body weight and height:

- Change from baseline at visit 8/week 24 and visit 10/week 52 (EOT/EOS).

Assessments:

Urodynamic Assessments:

Subjects will undergo urodynamic assessment at baseline, visit 5/week 4 and visit 8/week 24. Additional urodynamic assessments can be performed at visit 10/week 52 (EOT/EOS), or at any other time point when deemed necessary by the investigator.

Patient-reported Outcome Data:

The following information will be collected and entered by the subject or the subject's parent(s)/caregiver(s) at home in the e-diary during the week preceding the visits as indicated in the Schedule of Assessments.

- Bladder diary:
  - Each day for 7 days: time of CICs
  - Each day for 7 days: presence of leakage between CICs

- Each day for 7 days: sleep time and wake-up time
- On the 2 weekend days: catheterized volume
- On the 2 weekend days: SMIP (if applicable)
- On the 2 weekend days: grade and number of leakages between CICs
- On the 2 weekend days (visit 3/baseline and visit 8/week 24): weight of diaper/pad

- SBPM (blood pressure and pulse rate):
  - On the 2 weekend days: triplicate measurements in the morning and evening
  - On 2 consecutive 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.
- Questionnaires: on 1 weekend day at selected visits
  - PIN-Q
  - PGI-S
  - Acceptability
- Confirmation of study drug intake: daily

The Investigator must guide the subject and subject's parent(s)/caregiver(s) to ensure that on the evening before and during the two weekend days of collection of catheterized volume and SMIP (if applicable), the subject's fluid intake should be regulated to an appropriate level taking 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.

At the screening visit, detailed on-site training of the e-diary and the assessments and a booklet with operating instructions in local language will be provided to the subject and the subject's parent(s)/caregiver(s).

Pharmacokinetics:

When the subject reached steady state of her/his optimal dose, a total of 4 pharmacokinetic samples will be collected divided over 2 sampling days:

- Sampling day 1: 1 sample prior to dosing (i.e., trough sample).
- Sampling day 2: 1 trough and 2 postdose samples between 2h and 5h postdose, with at least 1 hour in between the samples.

On visit days where a pharmacokinetic sample is planned in the clinic, completion of breakfast and study drug dosing should occur in the clinic. Dosing must occur within 1 hour after completion of breakfast. Dosing time on the sampling day and dosing time of the previous day will be collected. In addition to the dosing time, the time of completion of breakfast, and type of breakfast will be collected in the eCRF on the sampling day with postdose sampling.

Safety:

During the study collection of adverse events (AEs), vital signs, body temperature, laboratory tests, ECG parameters, renal function, and height and weight will take place.

Statistical Methods:

Sample size justification:

In order to allow the detection of a statistically significant change from baseline in MCC in the overall NDO with CIC study population with 90% power, 44 evaluable subjects for the assessment of the endpoint need to be enrolled, i.e., subjects with a valid (as by the central reviewer's assessment) nonmissing MCC measurement at baseline and at a postbaseline visit. The power calculation is based upon a paired t-test with a 2-sided significance level of 0.05, an expected change from baseline of at least 52 mL and a SD of not larger than 103 mL. Assuming 30% of enrolled subjects will not be evaluable, a total of approximately 63 subjects may need to be enrolled.

Four analysis populations will be defined: the safety analysis set (SAF), full analysis set (FAS), per protocol set (PPS), and pharmacokinetics analysis set (PKAS) for pharmacokinetic population analysis.

Efficacy:

The primary analysis will be a paired t-test for the change from baseline to visit 8/week 24 for subjects included in the FAS to test the hypothesis that the change from baseline in MCC is not equal to zero with a 2-sided alpha level of 0.05. A 95% CI will be calculated for mean change from baseline and it will be assessed whether the estimated lower bound of the interval is greater than zero. Additionally 95% CIs per age group will be presented.

Continuous secondary efficacy variables will be analyzed in the same way as the primary efficacy variable. Discrete secondary efficacy variables will be analyzed descriptively.

Pharmacokinetics:

Pharmacokinetic parameters will be summarized for the PKAS using descriptive statistics.

Pharmacodynamics:

Not applicable.

Safety:

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

Other Analyses:

Descriptive statistics will be used to explore whether there is an association between certain subject characteristics (such as medical history) and the final titrated mirabegron doses. Collected data on study drug compliance rates and maintenance of treatment will be analyzed using descriptive statistics

Interim analyses:

Not applicable.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart

Study Period (56 weeks)									
Pretreatment Period (4 weeks)			**Efficacy Treatment Period † (24 weeks)**					**Long-term Safety Period ‡ (28 weeks)**	
Visit 1	**Visit 2/TC 1**	**Visit 3**	**Visit 4/TC 2 Week 2**	**Visit 5 Week 4**	**Visit 6/TC 3 Week 8**	**Visit 7 Week 12**	**Visit 8 Week 24**	**Visit 9/TC 4 Week 36**	**Visit 10/EOS Week 52**
Screening	Group A & B §: Review of 2-day e-diary Group B: Start washout on day -15	Baseline	1st up-titration possibility	2nd up-titration possibility	3rd up-titration possibility	Fixed dose	Fixed dose	Fixed dose	End of Study

TC: telephone contact; EOS: end of study

† The efficacy treatment period begins with the first dose, the day after baseline measurements on visit 3/baseline.

‡ The long-term safety period begins immediately after visit 8/week 24.

§ Group A: Subjects who are currently not receiving any prohibited medication including any oral drug treatment to manage their NDO, or when botulinum toxin is no longer considered effective. Group B: Subjects who currently are receiving oral drug treatment to manage their NDO or receive any other prohibited medication.

Table 1 Schedule of Assessments

Assessments	Visit 1	Visit 2 /TC 1 †	Visit 3	Visit 4 /TC 2 †	Visit 5	Visit 6 /TC 3 †	Visit 7	Visit 8	Visit 9 /TC 4 †	Visit 10 /EOS ‡
	Screening	Start of Washout †††	Baseline	Week 2	Week 4	Week 8	Week 12	Week 24	Week 36	Week 52
	Day -28 to Day -15	Day -15 to Day -8	Day -1	Day 14 (+3 days)	Day 28 (+3 days)	Day 56 (±7 days)	Day 84 (±7 days)	Day 168 (±7 days)	Day 252 (±14 days)	Day 364 (±14 days)
Signing informed consent form	X									
Inclusion/Exclusion criteria	X		X							
Demographics	X									
Height & weight	X		X					X		X
Medical history (including NDO)	X									
Current NDO medications	X	X								
Vital signs (triplicate) and body temperature (ear) §	X		X		X		X	X		X
Physical examination	X									X
12-lead ECG (triplicate) ¶	X		X		X		X	X		X
Hematology/Biochemistry/eGFR	X		(X) ††		(X) ††		X			X
Urinalysis	X		X		X		X	X		X
Pregnancy test ‡‡	X		X		X		X	X		X
Pharmacokinetics §§					(X)	(X)	(X)	(X)	(X)	(X)
Upper urinary tract ultrasound			X							X
Urodynamic assessments ¶¶			X		X			X		
Dose-titration assessment				X	X	X				
Dispense study drug †††			X		X		X	X	(X)	
Bladder diary, SMIP and collection of catheterized volume ‡‡‡		X	X	X	X	X	X	X	X	X
SBPM (triplicate) §§§		X	X	X	X	X	X	X	X	X
PIN-Q, PGI-S			X					X		X
CGI-C								X		X
Acceptability questionnaire					X			X		X
Adverse events and previous and concomitant medication	●									●

ECG: Electrocardiogram; EOS: end of study; CGI-C: Clinician Global Impression of Change scale; DSMB: Data and Safety Monitoring Board; NDO: neurogenic detrusor overactivity; PGI-S: Patient Global Impression of Severity Scale; PIN-Q: Pediatric Incontinence Questionnaire; SBPM: self blood pressure measurement; SMIP: self-measurement of intravesical pressure; TC: telephone contact.

Table footnotes continued on next page

† For the visits where a TC is indicated there is no need for the subject to visit the clinic, provided that the e-diary data is reviewed by the investigator prior to the TC and discussed and confirmed with the subject or the subject's parent(s)/caregiver(s) during the TC.

‡ Subjects who withdraw early from the study after having received study drug should complete the EOS visit. If the final dose is reached before the last possibility for up-titration at 8 weeks, the fixed-dose treatment period will be extended to keep the entire treatment period 364 days as a minimum. The maximum is 378 days in order to allow for visit windows.

§ Triplicate vital signs with an interval of approximately 2 minutes 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. Clinic measurements will be used to assess eligibility. Single measurements for body temperature must be performed with an ear thermometer.

¶ Triplicate 12-lead ECG with an interval of about 30 seconds to 5 minutes in the supine position (when possible, but always in the same position). Subject should have been calm and without distress for at least 5 minutes.

†† Additional hematology/biochemistry taken at baseline only if an AE related to hematology/biochemistry parameters occurred between visit 1/screening and visit 3/baseline. The first group of subjects (minimum of 5, maximum of 10) who reach study visit 5/week 4 will have an additional blood draw for a DSMB-mandated interim safety check at this visit. For sampling, preferably the left arm should be used. Blood sampling should occur after vital signs and ECG measurements.

‡‡ Pregnancy test in female subjects of childbearing potential in serum (if blood is drawn) or urine (at other visits).

§§ If the subject reached steady state of her/his optimal dose, a total of 4 pharmacokinetic samples will be collected, divided over 2 sampling days. Sampling day 1: 1 trough sample; Sampling day 2: 1 trough and 2 postdose samples between 2 h and 5 h postdose, with at least 1 hour in between the samples. These 2 sampling days do not have to be in a specific order and can be selected from the given options. To allow for an early assessment of the dose-response relationship by the DSMB, it is preferred the pharmacokinetic sampling takes place as early in the study as possible. Dosing on a sampling day with postdose samples must occur within 1 hour after completion of breakfast [Section 5.3.4. On days where a pharmacokinetic visit is planned in the clinic, breakfast and dosing should occur in the clinic. Blood sampling should occur after vital signs and ECG measurements.

¶¶ Additional urodynamic assessments may be performed if deemed necessary by the investigator.

††† Daily study drug administration will begin on Day 1 (the day after visit 3/baseline). Due to shelf-life limitations, an additional dispensing visit is foreseen at visit 9/week 36 for subjects receiving mirabegron oral suspension. This dispensing visit does not need to be accompanied by the subject.

‡‡‡ After a successful screening visit, all subjects start with the completion of a 2-day weekend e-diary visit to get acquainted with the e-diary and the assessments. Completion of this diary should start in the weekend prior to visit 2. Completion of subsequent bladder diaries should start approximately
7 days prior to the indicated visit (or TC). If successful completion of the 2-day weekend e-diary is confirmed at visit 2, subjects from group A start with collection of the 7-day baseline e-diary, followed by the baseline visit. Subjects in group B start with a 14-day washout. In the second week of the washout period, collection of their 7-day baseline e-diary starts, followed by the baseline visit.

§§§ Triplicate SBPM will be performed in the morning and evening during the 2-day weekend e-diary collection period and on 2 consecutive 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. Measurements to be taken with an interval of approximately 2 minutes in the sitting position (when possible, otherwise supine, but always in the same position). Preferably the right arm should be used. Morning measurements should be taken after waking-up, before breakfast and before study drug intake, evening measurements prior to bedtime. Subject should have been calm and without distress for at least 5 minutes.

1 INTRODUCTION

1.1 Background

Protocol 178-CL-206A is part of the Sponsor's clinical program to develop mirabegron for neurogenic detrusor overactivity (NDO) and overactive bladder (OAB) in pediatric patients. In the EU the development of mirabegron for the indication of NDO is outlined in the pediatric investigation plan (PIP) for mirabegron and approved by the Pediatric Committee (PDCO).

In the US, the protocol 178-CL-206 is planned to fulfill the Pediatric Research Equity Act (PREA) requirement commitment and the Proposed Pediatric Study Request (PPSR).

Protocol 178-CL-206A will start in the regions as mentioned in the synopsis. Protocol 178-CL-206 will start later in the US after review and approval of further mirabegron data by the FDA. Protocol 178-CL-206A and 178-CL-206 will be kept identical and subject data from both protocols will be pooled and analyzed as outlined in the statistical section of the protocol [see Section 7].

The population for this pediatric clinical efficacy study with mirabegron is children and adolescents with NDO who require clean intermittent catheterization (CIC). NDO is defined by the International Children's Continence Society as detrusor overactivity when there is a relevant neurologic condition. "Detrusor overactivity is the occurrence of involuntary detrusor contractions during filling cystometry. They may be spontaneous or provoked and produce a waveform of variable duration and amplitude. Contractions may be phasic or terminal. Symptoms of urgency and/or urgency incontinence may or may not occur" [Austin et al, 2014].

NDO can develop as a result of a lesion at any level in the nervous system, including the cerebral cortex, spinal cord, or peripheral nervous system. In 85% of the children with NDO, the condition is caused by myelomeningocoele (spina bifida) [Bauer et al, 2012]. In a subset of NDO patients (typically patients who suffer from detrusor sphincter dyssynergia [DSD] or have a surgically repaired underactive sphincter), treatment requires constant and fastidious bladder management from shortly after birth, including performance of CIC [Bauer et al, 2012]. Performance of CIC ensures that bladder volumes are regularly reduced to zero, thereby decreasing end-filling bladder pressure.

In the population of NDO patients requiring CIC, the medical need for treatment is the highest, due to the underlying pathophysiology of the urinary tract. In these patients, the overactive detrusor contracts against a closed or partially closed sphincter instead of a relaxed sphincter, due to DSD and/or sphincter surgery. The consequence is that these children cannot void normally, but instead leak when the pressure in the bladder exceeds the sphincter pressure (incontinence). This is independent of age and bladder training.

If left untreated, NDO leads to deterioration of urinary tract function at early age. Kidney function deteriorates from hydronephrosis due to backpressure caused by high (end-filling) bladder pressure. Further renal damage can occur from ascending urinary tract infections

(UTIs) resulting from vesico-urethral reflux. Fibrosis of the bladder wall, induced by strong and uninhibited overactive contractions and frequent UTIs, contributes to the development of a noncompliant bladder (loss of expansile capability; high pressures at low volumes). In a noncompliant bladder, the critical level of detrusor pressure is reached at lower filling volumes, further predisposing the patient to kidney damage.

Current drug therapy consists of oral antimuscarinics or botulinum toxin injected into the bladder wall. The drug therapy decreases end-filling pressure, overactive contractions and increases bladder capacity and as such protects against kidney damage and deterioration of bladder wall. Although to date, the vast majority (approximately 90%) of patients can be treated successfully with the gold standard treatment of oxybutynin (oral or intravesical) and CIC [Verpoorten et al, 2008], development of alternative therapy is desirable because of insufficient efficacy and/or the side effects of antimuscarinics; dry mouth, constipation, blurred vision, headache, tiredness (somnolence), impaired school performance, facial flushing, gastrointestinal discomfort, and dry itchy skin [Rawashdeh et al, 2012] and the invasive administration of botulinum toxin, which is bothersome for the patient.

Mirabegron, a beta-3 adrenergic receptor agonist, represents a new class of drugs for treatment of OAB. The use of mirabegron as an alternative therapy to control detrusor overactivity in patients with NDO has not yet been established, although some reports of a positive effect of mirabegron on urodynamic parameters in patients with NDO have been published [Wöllner et al, 2015; Wada et al, 2015; Skobejko 2014].

1.2 Nonclinical and Clinical Data

Detailed information on studies conducted with mirabegron can be found in the most recent pediatric mirabegron Investigator's Brochure (IB). Nonclinical and clinical data are also summarized in the package insert for mirabegron (current locally-available product information for mirabegron).

Summaries of findings from nonclinical and clinical studies with mirabegron which have relevance for the current study are presented below.

1.2.1 Nonclinical Data

The primary pharmacology studies showed that mirabegron induced bladder relaxation during the filling phase and inhibited the frequency of nonvoiding activity. Other pharmacological effects, such as the glucogenolytic effects of mirabegron in rodents, did not translate to any effect in adult humans.

The safety pharmacology and toxicological studies showed that the safety profile of mirabegron, when administered to achieve exposures similar to those seen at the maximum recommended human dose, compares favorably with the currently approved antimuscarinic drug therapies indicated for the treatment of OAB.

The 39 toxicology studies that have been conducted with mirabegron in adult mice, rats, rabbits, dogs and cynomolgus monkeys support the safety of mirabegron for the treatment of OAB in adults and adolescents. The ages of the rats and monkeys that were used in the

nonclinical repeated-dose toxicity studies were 8 weeks and 3 to 4 years old, respectively, which corresponds to a human age of 12 to 13 years. In support of clinical trials in children from 6 months of age and older, 2 repeated-dose toxicity studies were conducted in 10-day-old juvenile rats (postnatal day 10 [PND10]): a 14-day oral dose range-finding study (Study 178-TX-054) and a 13-week oral repeated dose toxicity study with a 4-week recovery period (Study 178-TX-055).

Modest elevation of alanine aminotransferase (ALT) was observed in monkeys, but the changes observed were below the level of toxicological significance, and there were no changes in liver histopathology. There were no significant changes in liver enzymes or liver histopathology in dogs. In the toxicology studies in juvenile rats, increased activities in aspartate aminotransferase (AST) and ALT were noted in male rats at doses of 30 mg/kg (22-fold higher than the maximum recommended human dose). Modest (less than 2-fold) increases in plasma alkaline phosphatase (ALP) were observed at high doses (72-fold higher than the maximum recommended human dose), together with reversible changes in hepatocytes. Single and repeated dose toxicology studies in dogs, monkeys and rats demonstrated cardiovascular changes at high doses (please refer to the mirabegron IB).

In rodents, beta 3-agonists have an anti-obesity effect due to an increase in metabolic rate due to the activation of thermogenesis in brown adipocytes and to lipolysis in white adipocytes [Lafontan & Berlan, 1993]. In adult and juvenile rats treated with > 10 mg/kg mirabegron, decreased lipid droplets were observed in the brown adipose tissues and white adipose tissues. In addition, behavioral effects like decreased activity, which could be related to an increased body temperature, were also observed in juvenile rats in males and females in the 10 and 30 mg/kg groups. However, no comparable effect in primates was seen. In clinical studies with mirabegron in adults no effects on weight or body temperature have been observed. In healthy subjects, neither single nor repeat dose administration affected mean blood glucose, C-peptide, triglyceride, insulin levels or oral temperature compared with placebo, suggesting that mirabegron does not affect lipid or glucose metabolism in healthy subjects. In subjects with type 2 diabetes mellitus, mirabegron induced no substantial changes from baseline in body weight or oral temperature. However, since brown adipose tissue is more prevalent in children than in adults, it could be that brown adipose tissue has a greater physiological role in children than in adults. Therefore, it cannot be excluded that administration of mirabegron has an effect on body weight and/or body temperature in young children.

In the toxicology studies, increased activities in aspartate aminotransferase (AST) and ALT were noted in male rats at doses of 30 mg/kg (22-fold higher than the maximum recommended human dose). Modest (less than 2-fold) increases in plasma alkaline phosphatase (ALP) were observed at high doses (72-fold higher than the maximum recommended human dose), together with reversible changes in hepatocytes.

Mirabegron was not found to be genotoxic, carcinogenic, or teratogenic in the battery of in vitro and in vivo studies. The in vitro oxidative metabolism of mirabegron in human liver microsomes is primarily mediated by cytochrome P450 (CYP) 3A4, but a possible role for

CYP2D6 could not be excluded. In vitro CYP inhibition studies suggest that mirabegron is a moderate and time-dependent inhibitor of CYP2D6 and a weak inhibitor of CYP3A4.

Exposure levels in juvenile (PND10) rats were 5-fold to 10-fold increased compared to adult rats (PND100). The exposure levels of mirabegron in young (PND21) and adolescent (PND45) rats were 2-fold to 5-fold lower than the exposures observed in the adult rats (PND100). The increased exposure levels of mirabegron on PND10 and decreased exposure levels on PND21 and PND45 are in line with the knowledge on the ontogeny of drug metabolizing (phase I and phase II) enzymes and (efflux) transporters in rats [de Zwart et al, 2008; Saghir et al, 2012]. This could translate into differences in exposures between adults/adolescents and pediatric subjects, in which the phase I (until 2 years of age) and/or phase II (until 11 years of age) enzymes are still maturing.

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 2].

Table 2 Overview of Current Supporting Mirabegron Studies in the Pediatric Clinical Development Program for NDO and OAB

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 neurogenic detrusor overactivity (NDO) or overactive bladder (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 neurogenic detrusor overactivity (NDO) or overactive bladder (OAB).	Ongoing
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	Ongoing

The results of studies 178-CL-201 and 178-CL-202 are reported in the most recent version of the pediatric IB. The data from these studies 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 less or because they cannot swallow tablets, an oral suspension with a strength of 2 mg/mL was developed. The relative bioavailability was assessed in healthy subjects (178-CL-201) to be 53.44% lower compared to tablets. The results of this study and study 178-CL-202 was used to support the use of the 2 mg/mL in study 178-CL-203.

That study is a single dose phase 1 study with mirabegron oral suspension in pediatric subjects from 3 to less than 12 years of age with NDO and in pediatric subjects from 5 to less than 12 years of age with OAB. This study is currently ongoing with 6 of 9 planned subjects having completed the study. Single doses of mirabegron are administered that are predicted to result in an exposure comparable to that in adults when dosed with 50 mg mirabegron tablets once daily at steady-state (188 ng·h/mL). Subjects received mirabegron oral suspension within 1 hour after a light breakfast. Doses were compensated for the lower bioavailability of suspension versus tablets (see above). This study is ongoing but the preliminary results are provided below.

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, three period cross over design in healthy subjects. Subjects received the following three treatments in random order: 1) 11mL 8 mg/mL oral suspension of mirabegron under fasted conditions, 2) 11mL 8 mg/mL oral suspension of mirabegron under fed conditions and 3) 44 mL 2 mg/mL oral suspension of mirabegron under fasted conditions. This study is ongoing, but a summary of the preliminary results is provided below.

Exposure:

The single doses of the 2 mg/mL oral suspension for Study 178-CL-203 were predicted using a population pharmacokinetic (popPK) model developed on pharmacokinetic data obtained in Study 178-CL-201, with food, dose, and formulation effects on the bioavailability, and was validated on data from Study 178-CL-202. The observed exposures were in line with the target exposure of 188 ng·h/mL; the median AUC_{24} was 207 ng·h/mL (n=6, mean (SD): 226.4 (152.3), range: 39.7-467). These preliminary results suggest that the use of the popPK model is appropriate for dose selection. The model predictions of the PED50 doses at a strength of 2 mg/mL would require large volumes of oral suspension every day (up to 44 mL). Therefore, to reduce the volume, a higher strength oral suspension was developed.

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 3].

Table 3 178-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)

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} (n•.h/mL)	**234**	**232**	**100.9**	**(90.6, 112.4)**
C_{max} (ng/mL)	**12.1**	**11.3**	**106.7**	**(84.2, 135.2)**

CI: confidence interval; LS: least squares.

The analysis was performed on log-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.

The information obtained in studies 178-CL-203 and 178-CL-208 was taken into account when predicting the doses for this study as outlined in Section 2.2.2 of this protocol.

The doses described in Section 2.2.2 suggest tablets for pediatric subjects with a body weight of ≥ 35 kg, and the 8 mg/mL oral suspension for children with a body weight between 11 and 35 kg, or for those subjects with a body weight ≥ 35 kg who do not want to or are unable to take tablets.

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 6 subjects who completed the study (3 with NDO and 3 with OAB) 1 treatment emergent adverse event (TEAE) was reported: pyrexia on day 1 in a 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 QTcF values > 450 ms and no QTc prolongation > 30 ms versus baseline was observed (mean of triplicates).

Increases in vital signs have been observed but these were not considered clinically significant per investigator's assessment.

A 24-hour Holter recording was recorded in all subjects on a reference day and on the dosing day. The main objective of the Holter 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 has been observed. This was not considered as

clinically relevant taken into account the multiple blood draws, the low number of subjects and the absence of a placebo 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. 20 AEs were considered not related; 2 were considered possibly related (dizziness, mild and orthostatic dizziness mild).

1.3 Summary of Key Safety Information for Study Drugs

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

For further information reference is made to the most recent version of the pediatric IB for mirabegron, and current locally-available product information for mirabegron.

Mirabegron has been approved in more than 65 countries worldwide. In adults, the safety of mirabegron treatment has been well characterized in 5863 subjects (95% with overactive bladder) 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, UTI, fetal disorders after exposure during pregnancy and events induced by concomitant treatment with 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.

1.4 Risk-Benefit Assessment

Mirabegron tablets have a favorable risk-benefit profile in adults in the indication OAB. 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.

Successful management of NDO prevents the occurrence of progressive kidney impairment and decrease in bladder compliance in subjects with NDO. As such, the benefit of successful treatment in this subject population is large, and is expected to be larger than in subjects suffering from OAB, provided that mirabegron is effective and has an acceptable safety profile in this population.

The use of mirabegron as an alternative therapy to control detrusor contraction in subjects with NDO has not yet been established. However some reports have been published showing a positive effect of mirabegron on urodynamic parameters in patients with NDO [Wöllner et

al, 2015; Wada et al, 2015; Skobejko 2014]. Beneficial effects are also expected on gaining continence.

The major risk in this study is periods of uncontrolled high end-filling detrusor pressure. This risk is monitored on a regular basis and can be mitigated by the investigator as follows:

- A washout period is necessary to achieve an adequate baseline. The washout period has been restricted to 2 weeks in order to prevent renal damage and minimize the burden for the subject. At baseline a urodynamic investigation is planned, allowing the investigator to judge the risk to the subject in case mirabegron would not be efficacious. At this stage the risk can be mitigated by increasing the CIC frequency.
- The initial dose of mirabegron will be based on the subject's weight, and predicted to achieve plasma concentrations equivalent to the steady state exposures expected with 25 mg mirabegron administered once daily in adults (pediatric equivalent dose [PED] 25). This low dose is chosen considering possible beta-adrenergic side effects of mirabegron.
- After 2 weeks on PED25 all subjects will be up-titrated to PED50 unless there is a safety issue with mirabegron or the investigator considers that with the low mirabegron dose full efficacy has been reached. By striving to get an efficacious dose of mirabegron early after start of dosing, the risk for bladder and kidney damage is mitigated.
- At 4 weeks of therapy, a second urodynamic investigation allows the investigator to judge and mitigate the risk by increasing the dose in subjects without prior dose increase or, in subjects on the maximum dose, by increasing the CIC frequency or by withdrawal of the subject.
- Additional urodynamic assessments may be performed at any time in the study if deemed necessary by the investigator.

Concerning drug safety, important identified or potential risks in adults and their monitoring in this study are listed below:

- Increased heart rate and tachycardia is monitored in this study by at-home measurement of vital signs and measurement of vital signs at the study visits at the center;
- Hypersensitivity reactions (immediate or nonimmediate and cutaneous or noncutaneous) are monitored in this study by AE monitoring;
- Increased blood pressure is monitored in this study by at-home measurement of vital signs and measurement of vital signs at the study visits at the center;
- Urinary retention does not apply in children on CIC;
- Potential QT prolongation is monitored by ECG at each visit at the center;
- Potential urinary tract infection is monitored by urine analysis at each visit in the center;
- Potential fetal disorders after exposure during pregnancy is mitigated by the inclusion criteria;
- Potential events by concomitant treatment with CYP2D6 substrates with narrow therapeutic index is mitigated by excluding these medications;
- Although not observed in adults, the potential activation of thermogenesis will be monitored by temperature measurement. Weight loss due to activation of thermogenesis in brown fat will be monitored by regular weight measurements.

Regarding the formulations to be administered: 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 of the United Nations (FAO) and the World Health Organization (WHO) (JECFA) [FAO 2015].

The protocol is designed to minimize the burden to the subject by restricting the number of urodynamic investigations, the number of blood draws (safety and pharmacokinetic sampling) and the number of study visits to a minimum.

The use of popPK for the analysis of the pharmacokinetic profile of mirabegron allows reducing the number of blood draws for pharmacokinetic analysis to 4. Butterfly needles can be used and are allowed to stay in place to reduce the number of punctures.

The blood draws for safety assessment have been reduced by omitting a baseline safety blood draw in subjects where the hematology and biochemistry results obtained at the screening visit did not show significant abnormalities and no AEs occurred after the screening visit that could influence the hematology/biochemistry results.

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. The investigator should not include any subject for whom it is expected that their condition will not allow protocol compliance.

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.

Data and Safety Monitoring Board (DSMB) assessment including review of safety and efficacy (no, or insufficient efficacy is a safety risk) is planned after the first 5 subjects have reached visit 5/week 4 allowing a risk /benefit assessment early after start of the study. In case the DSMB cannot reach a verdict based on the safety samples of these 5 subjects, this group will be increased with 5 more subjects, to obtain a maximum of 10 visit 5/week 4 safety samples for early DSMB assessment. In the DSMB charter detailed information can be found. In view of the above considerations, the risk-benefit ratio for this study is considered to be acceptable for the subjects that will participate in this study.

2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objectives:

- To evaluate the efficacy of mirabegron after multiple-dose administration in the pediatric population.

2.1.2 Secondary Objectives:

- To evaluate the safety and tolerability of mirabegron after multiple-dose administration in the pediatric population.
- To evaluate the pharmacokinetics of mirabegron after multiple-dose administration in the pediatric population.

2.2 Study Design and Dose Rationale

2.2.1 Study Design

This is a phase 3, open-label, baseline-controlled, multicenter study in male and female children and adolescents aged 3 to less than 18 years of age with NDO on CIC. Approximately 50 enrolling study centers in Europe, Latin America, Africa, Middle East and Asia-Pacific are planned.

At least 44 evaluable subjects (estimate of 63 enrolled), with at least 10 subjects from each age group (children aged 3 to less than 12 years of age; adolescents aged 12 to less than 18 years of age) are planned. A subject is considered being evaluable if the subject has a valid (as by the central reviewer's assessment) nonmissing maximum cystometric capacity (MCC) measurement at baseline and at a postbaseline visit. An enrolled subject withdrawing or discontinuing before dosing will be replaced. A subject discontinuing treatment after dosing can be replaced at the discretion of the Sponsor. The study is conducted under the aegis of a DSMB.

The study will consist of 3 periods:

- Pretreatment period: for a maximum of 28 days before baseline, including screening, washout (if applicable) and baseline
- Efficacy treatment period: beginning the day after baseline and continuing to visit 8/week 24
- Long-term safety period: beginning after visit 8/week 24 and continuing to visit 10/week 52 (end of study [EOS]), or to the end of treatment (EOT).

2.2.1.1 Pretreatment Period

After informed consent and visit 1/screening, subjects are grouped according to their current NDO therapy and/or other medication:

- Group A: Subjects who are currently not receiving any prohibited medication including any oral drug treatment to manage their NDO, or when botulinum toxin is no longer considered effective.

- Group B: Subjects who currently are receiving oral drug treatment to manage their NDO or receive any other prohibited medication.

After the screening visit, a 2-day weekend e-diary has to be completed by the subjects to get acquainted with the e-diary and the home assessments:

- Group A: Following successful completion of the first 2-day weekend e-diary, confirmed at visit 2, the subjects will start to complete the 7-day baseline e-diary followed by the baseline visit (visit 3).
- Group B: Following successful completion of the first 2-day weekend e-diary, confirmed at visit 2, the subjects will start their 2-week washout period. In the second week of their washout period, they will complete the 7-day baseline e-diary followed by the baseline visit (visit 3).

If a subject is suffering from a symptomatic UTI at visit 1/screening or is diagnosed with one between visit 1/screening and visit 3/baseline, the UTI should be treated successfully (clinical recovery) prior to baseline. If a symptomatic UTI is present at or just before visit 3/baseline, all baseline assessments should be postponed with a maximum of 7 days until the UTI is successfully treated (clinical recovery). The 7-day baseline e-diary does not have to be repeated if at least the 2-day weekend e-diary and 1 day of the weekday e-diary were completed while the subject did not suffer from a symptomatic UTI.

Subjects will enter the efficacy treatment period if they meet the eligibility criteria and satisfactorily complete the pretreatment period (ability to complete bladder diary, catheterized volumes and questionnaires).

In case the subject or the subject's parent(s)/caregiver(s) are not able or willing to perform the SMIP, the measuring device is not available at the site, or there is a technical problem, the SMIP may be omitted.

2.2.1.2 Efficacy Treatment Period

Study drug administration will begin on the day after the baseline visit (i.e., on day 1). The initial dose of mirabegron is predicted to achieve plasma concentrations equivalent to the steady state exposures expected with 25 mg mirabegron administered once daily in adults (PED25).

At visit 4/week 2, visit 5/week 4 or visit 6/week 8, subjects must be up-titrated to the pediatric equivalent dose of 50 mg in adults (PED50), based on the given dose titration criteria [see Section 5.1.2].

At visit 8/week 24, the primary efficacy endpoint will assessed, which is the change from baseline in MCC.

If a subject is suffering from a symptomatic UTI in the week prior to any (un)scheduled urodynamic investigation (e.g., visit 5/week 4, visit 8/week 24), the UTI should be treated successfully first (clinical recovery). To allow for treatment of the UTI, these visits may be postponed with an additional maximum of 7 days on top of the already existing visit window.

The 7-day e-diary does not have to be repeated if at least the 2-day weekend e-diary and 1 day of the weekday e-diary were completed while the subject did not suffer from a symptomatic UTI.

If a subject suffers from a symptomatic UTI in the week prior to any other study visit, these visits do not need to be postponed and the 7-day e-diary does not have to be repeated.

2.2.1.3 Long-term Safety Period

For long-term safety evaluation, following visit 8/week 24, subjects will stay on their individual dose level until visit 10/week 52 (EOT/EOS).

2.2.2 Dose Rationale

The target exposures of 69 and 188 ng·h/mL for pediatric equivalent dose 25 mg (PED25) and pediatric equivalent dose 50 mg (PED50) were derived from the adult phase 3 program and are the mean steady state AUC_{tau} values following 25 and 50 mg prolonged-release tablets once daily in adults.

A population pharmacokinetic model was used to predict the PED for subjects in the 178-CL-206A study. In brief, this popPK 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; IND 58135), 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 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. Subjects with a body weight < 35 kg cannot be dosed with the 25 and 50 mg tablets because that would result in higher than 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 11 kg (the approximate body weight of a 3-year-old child, according to the NHANES 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. Suspension dosing for body weights ≥ 35 kg was also determined for cases in which a pediatric subject in that weight category does not want or would be unable to swallow a tablet. The simulation resulted in the 3 body weight categories that can be found in the dosing schedule (see [Section 5.1.1]).

2.3 Endpoints

2.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be the change from baseline in MCC after 24 weeks of treatment (based on filling urodynamics).

2.3.2 Secondary Efficacy Endpoints

2.3.2.1 Urodynamic Measures

Secondary efficacy endpoints will include the change from baseline in the following urodynamic measures:

- MCC at visit 5/week 4
- Bladder compliance (ΔV/ΔP) at visit 5/week 4 and visit 8/week 24
- Number of overactive detrusor contractions (> 15 cm H_20) until end of filling at visit 5/week 4 and visit 8/week 24
- Detrusor pressure at end of filling at visit 5/week 4 and visit 8/week 24
- Filling volume until first overactive detrusor contraction (> 15 cm H_20) at visit 5/week 4 and visit 8/week 24

2.3.2.2 Bladder Volume and Leakage Measures

The following endpoints will be obtained from the e-diary and be analyzed as the change from baseline at visit 4/week 2, visit 5/week 4, visit 6/week 8, visit 7/week 12, visit 8/week 24, visit 9/week 36 and visit 10/week 52 (EOT/EOS).

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

For this study the first morning catheterization after waking up is regarded as part of the ‘night’, whilst the last evening catheterization before sleep time is part of the ‘day’.

The collected urine volume will be weighed by the subject or subject's parent(s)/caregiver(s) and the results will be entered in the e-diary. The conversion factor used for weight-to-volume is 1g = 1mL.

2.3.2.3 Patient- or Clinician-reported Questionnaire Endpoints

The following endpoints will be obtained from patient- or clinician-reported questionnaires.

- Change from baseline at visit 8/week 24 and visit 10/week 52 (EOT/EOS) in PIN-Q
- Change from baseline at visit 8/week 24 and visit 10/week 52 (EOT/EOS) in PGI-S
- Clinician Global Impression of Change (CGI-C) at visit 8/week 24 and visit 10/week 52 (EOT/EOS)
- Acceptability at visit 5/week 4, visit 8/week 24 and visit 10/week 52 (EOT/EOS)

2.3.3 Safety Endpoints

The following safety endpoints will be assessed:

- Incidence and severity of TEAEs
- Change from baseline in vital signs (clinic measurements): systolic blood pressure, diastolic blood pressure, pulse rate and temperature at visit 5/week 4, visit 7/week 12, visit 8/week 24 and visit 10/week 52 (EOT/EOS)
- Change from baseline in vital signs (self blood pressure measurement [SBPM]): systolic blood pressure, diastolic blood pressure, pulse rate at visit 4/week 2, visit 5/week 4, visit 6/week 8, visit 7/week 12, visit 8/week 24, visit 9/week 36 and visit 10/week 52 (EOT/EOS) and on 2 consecutive days at around 1 and 2 weeks after start of dosing with PED25 (day 1) and after up-titration to PED50 (visit 4/week 2, visit 5/week 4 or visit 6/week 8), if not already covered by the scheduled visit 4/week 2 and/or visit 5/week 4 SBPM.
- Change from baseline in hematology and biochemistry tests at visit 7/week 12 and visit 10/week 52 (EOT/EOS) and urinalysis tests at visit 5/week 4, visit 7/week 12, visit 8/week 24 and visit 10/week 52 (EOT/EOS)
- Change from baseline in ECG parameters at visit 5/week 4, visit 7/week 12, visit 8/week 24 and visit 10/week 52 (EOT/EOS)
- Change from baseline to visit 10/week 52 (EOT/EOS) in upper urinary tract ultrasound assessment
- Change from baseline in eGFR at visit 7/week 12 and visit 10/week 52 (EOT/EOS)

2.3.4 Pharmacokinetics

The following pharmacokinetic parameters will be determined for each individual:

- C_{max}, t_{max}, AUC_{24}, C_{trough}, CL/F and V_z/F

Additional pharmacokinetic parameters may be calculated based on the model used.

2.3.5 Exploratory Endpoints

2.3.5.1 Exploratory Efficacy Endpoints

The following efficacy endpoints will be examined:

- Change from baseline at visit 5/week 4 and visit 8/week 24 in filling volume at 20 cm, 30 cm and at 40 cm H_2O detrusor pressure, given that those pressures are reached during the examination
- Change from baseline at visit 4/week 2, visit 5/week 4, visit 6/week 8, visit 7/week 12, visit 8/week 24, visit 9/week 36 and visit 10/ week 52 (EOT/EOS), as determined from the e-diary entries in:
  - Mean grade of leakage
  - Total catheterized volume per day
  - Change from baseline in SMIP-derived bladder compliance
  - Number of CICs/day
  - Responder in respect to leakage (complete, partial, no response)

2.3.5.2 Exploratory Safety Endpoints

- Change from baseline in intravesical pressure (SMIP) at visit 4/week 2, visit 5/week 4, visit 6/week 8, visit 7/week 12, visit 8/week 24, visit 9/week 36 and visit 10/ week 52 (EOT/EOS)
- Change from baseline in body height and weight at visit 8/week 24 and visit 10/week 52 (EOT/EOS)

3 STUDY POPULATION

3.1 Selection of Study Population

The study population will be male and female child and adolescent subjects aged 3 to less than 18 years of age with NDO on CIC. The age of the subjects at the date of signing the informed consent or assent form at visit 1/screening will determine the age of the subject for inclusion into the study.

Re-screening is not allowed.

3.2 Inclusion Criteria

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

1. Independent Ethics Committee (IEC)/Institutional Review Board (IRB)-approved written Informed Consent and privacy language as per national regulations must be obtained from the subject and/or from the subject's parent(s) or legal guardian(s) prior to any study-related procedures (including discontinuation of prohibited medication, if applicable); assent by the subject is given as required by local law.

2. Subject is male or female from 3 to less than 18 years of age.

3. Subject has a body weight of ≥ 11 kg.

4. Subject suffers from NDO confirmed by urodynamic investigation at baseline. The diagnosis of NDO must be confirmed by the presence of at least 1 involuntary detrusor contraction > 15 cm H_2O from baseline detrusor pressure, and/or a decrease in compliance leading to an increase in baseline detrusor pressure of > 20 cm H_2O.

5. Subject has been using CIC for at least 4 weeks prior to visit 1/screening.

6. Subject has a current indication for drug therapy to manage NDO.

7. Subject is able to take the study drug in accordance with the protocol.

8. Female subject must either:

- Be of nonchildbearing potential:
  - Clearly premenarchal or in the judgment of the investigator is premenarchal,
  - Documented surgically sterile,
- Or, if of childbearing potential:
  - Agree not to try to become pregnant during the study and for 28 days after the final study drug administration,
  - And have a negative pregnancy test at visit 1/screening and at baseline,
  - And, if sexually active must agree to use a highly effective method of birth control, which includes established use of oral, injected or implanted hormonal methods of contraception, OR placement of an intrauterine device (IUD) or intrauterine system (IUS). Birth control must be practiced from visit 1/screening and continuing throughout the study period, and for 28 days after the final study drug administration.

9. Male subject and their female spouse/partner who are of childbearing potential must be using a highly effective method of birth control, which includes established use of oral, injected or implanted hormonal methods of contraception, placement of an IUD or IUS. Birth control must be practiced from visit 1/screening and continuing throughout the study period, and for 28 days after the final study drug administration.

10. Female subject must not be breastfeeding from visit 1/screening until 28 days after last study drug administration.

11. Subject and subject's parent(s)/legal guardian(s) agree that the subject will not participate in another interventional study while participating in the study.

12. 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.

Waivers to the inclusion criteria will NOT be allowed.

3.3 Exclusion Criteria

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

1. Subject has a known genitourinary condition (other than NDO) that may cause overactive contractions or incontinence (e.g., bladder extrophy, urinary tract obstruction, urethral diverticulum or fistula) or kidney/bladder stones or another persistent local pathology that may cause urinary symptoms.

2. Subject has one of the following gastrointestinal problems: partial or complete obstruction, decreased motility such as paralytic ileus, subjects at risk of gastric retention.

3. Subject has a urinary indwelling catheter within 4 weeks prior to visit 1/screening

4. Subject has a surgically treated underactive urethral sphincter

5. Subject has vesico-ureteral reflux grade 3 to 5.

6. Subject has undergone bladder augmentation surgery.

7. Subject receives electrostimulation therapy, if started within 30 days before visit 1/screening or is expected to start during the study period. Subjects who are on an established regimen may remain on this for the duration of the study.

8. Subject suffers from a symptomatic UTI at baseline (symptomatic is defined as pain, fever, hematuria, new onset foul-smelling urine). If present at visit 1/screening or diagnosed between visit 1/screening and visit 3/baseline, the UTI should be treated successfully (clinical recovery) prior to baseline. If a symptomatic UTI is present at baseline, all baseline assessments should be postponed for a maximum of 7 days until the UTI is successfully treated (clinical recovery).

9. Subject has a (mean) resting pulse rate > 99^{th} percentile [Fleming et al, 2011].

10. Subject has an established hypertension and a systolic or diastolic blood pressure greater than the 99th percentile of the normal range determined by sex, age and height, plus 5 mmHg [NIH 2005].

11. Subject has a risk of QT prolongation (e.g., hypokalemia, long QT syndrome [LQTS]; or family history of LQTS, exercise-induced syncope).

12. Subject has severe renal impairment (eGFR according to Larsson equation < 30 mL/min).

13. Subject's AST or ALT is greater than or equal to 2 times the upper limit of normal (ULN) or total bilirubin (TBL) greater than or equal to 1.5 times the ULN according to age and sex.

14. Subject has a history or presence of any malignancy prior to visit 1/screening.

15. Subject has known or suspected hypersensitivity to mirabegron, any of the excipients used in the current formulations or previous severe hypersensitivity to any drug.

16. Subject has participated in another clinical trial (and/or has taken an investigational drug) within 30 days (or 5 half-lives of the drug, or the limit set by national law, whichever is longer) prior to visit 1/screening.

17. Subject uses any of the following prohibited medications (after start of washout):

- Any medication, other than the study drug used, for the management of NDO;
- Any drugs that are sensitive CYP2D6 substrates with a narrow therapeutic index or sensitive P-glycoprotein (P-gp) substrates
- Any strong CYP3A4 inhibitors if the subject has a mild to moderate renal impairment (eGFR 30 – 89 mL/min).

18. Subject has been administered intravesical botulinum toxin; except if given > 4 months prior to visit 1/screening and the subject experiences symptoms comparable to those existing prior to the botulinum toxin injections.

19. Subject has any other condition, which in the opinion of the Investigator, precludes the subject's participation in the study.

20. Subject's parent/legal guardian is an employee of the Astellas Group, the Contract Research Organization (CRO) involved, or the investigator site executing the study.

Waivers to the exclusion criteria will NOT be allowed.

For exclusion criterion 9 please refer to Appendix 12.9 and for exclusion criterion 10 please refer to Appendix 12.10, Appendix 12.11, Appendix 12.12 and Appendix 12.13.

4 TREATMENTS

4.1 Identification of Investigational Products

4.1.1 Test Drug

Mirabegron prolonged-release (or extended-release) tablets were approved in Japan in 2011, and to date have been approved in more than 65 countries worldwide; trade names include Betanis®, Betmiga® and Myrbetriq®. 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.

For detailed information on mirabegron prolonged-release tablets and mirabegron granules for oral suspension, please refer to the applicable Investigational Medicinal Product Dossier (IMPD).

Mirabegron tablets are supplied as prolonged-release tablets containing 25 mg or 50 mg of active ingredient.

For the oral suspension, mirabegron prolonged-release granules are supplied and will be reconstituted with water to prepare an oral suspension of 8 mg/mL. Detailed information on the preparation of the mirabegron oral suspension will be provided to the subject and

subject's parent(s)/caregiver(s) in local language. Due to shelf-life limitations, an additional dispensing visit is foreseen at visit 9/week 36 for subjects receiving mirabegron oral suspension. This dispensing visit does not need to be accompanied by the subject.

4.1.2 Comparative Drug(s)

Not applicable.

4.2 Packaging and Labeling

All study drugs used in this study will be prepared, packaged, and labeled under the responsibility of qualified staff 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 Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable local laws/regulations.

Each study drug 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 study drugs according to Directive 2003/94/EC annex 13.

4.3 Study Drug Handling

Current ICH GCP Guidelines require the investigator to ensure that study drug deliveries from the Sponsor are received by the investigator/or designee and

- That such deliveries are recorded,
- That study drug is handled and stored according to labeled storage conditions,
- That study drug is with appropriate expiry/retest and is only dispensed to study subjects in accordance with the protocol, and
- That any unused study drug is returned to the Sponsor.

Drug inventory and accountability records for the study drugs will be kept by the investigator/ or designee. Study drug accountability throughout the study must be documented and reconciled. The following guidelines are therefore pertinent:

- The investigator agrees not to supply study drugs to any persons except the subject or subject's parent(s)/caregiver(s) of the eligible subjects in this study in accordance with the protocol.
- The investigator or designee will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these test drugs.
- A study drug inventory will be maintained by the investigator or designee. The inventory will include details of material received and a clear record of when they were dispensed and to which subject.

- At the conclusion or termination of this study, the investigator or designee agrees to conduct a final drug supply inventory and to record the results of this inventory on the drug accountability record. It must be possible to reconcile delivery records with those of used and/or returned study drugs. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility.
- The site must return study drug to the Sponsor or designee at the end of the study or upon expiration. If due to institutional policy or local law, used drug cannot be returned to the Sponsor or designee the drug may be destroyed according to local law.

4.4 Blinding

This section is not applicable as this is an open-label study.

4.5 Assignment and Allocation

All subjects will receive active mirabegron treatment (open-label).

Subject number assignment will be coordinated centrally by using an interactive response system.

4.5.1 Subject Numbering

Subjects will be assigned a subject number at study entry. The full subject number will consist of 10 digits; 5 for the site number (provided by the Sponsor) and 5 for the consecutive subject number.

4.5.2 Subject Replacement

An enrolled subject who withdraws or discontinues before dosing will be considered a screening failure and will be replaced. If a subject discontinues treatment after dosing, this subject will be replaced at the discretion of the Sponsor.

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drug

5.1.1 Dose/Dose Regimen and Administration Period

The initial dose will be PED25 [Section 2.2.2]. The dose must be up-titrated to PED50 according to the titration criteria. Study drug will be taken orally, once a day in the morning around the same time of day and around time of food intake (i.e., within 1 hour before or after breakfast).

On visit days where a pharmacokinetic sample is planned in the clinic, completion of breakfast and study drug dosing should occur in the clinic and dosing will be done under supervision of the investigator.

Mirabegron tablets will be taken with a sip of water. The tablet should be taken as a whole and should not be chewed, divided or crushed.

Mirabegron prolonged-release granules will be reconstituted with water to prepare a mirabegron oral suspension of 8 mg/mL. Administration will be via an oral syringe with a sip of water afterwards. Detailed information on the preparation of the suspension will be provided to the subject and subject's parent(s)/caregiver(s) in local language. For subjects receiving mirabegron oral suspension, an additional (optional) dispensing visit is scheduled at visit 9/week 36.

Selection of the formulation:

Subjects with a body weight < 35 kg: mirabegron oral suspension.

Subjects with a body weight ≥ 35 kg: mirabegron tablets.

Selection of the dose:

Doses are calculated weight-based. The bodyweight at visit 3/baseline determines the weight range for the starting dose (PED25) and the up-titration dose (PED50) to be used [Table 4].

Table 4 Weight-based Doses for Tablets or Suspension

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

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

† Suspension strength: 8 mg/mL

Further dosing information:

- For subjects with a body weight ≥ 35 kg who do not want to or are unable to take tablets, the oral suspension can be supplied.
- At visit 8/week 24 subjects on mirabegron oral suspension may switch to tablets if the body weight turns to be ≥ 35 kg.
- Subjects receiving mirabegron tablets can switch to mirabegron oral suspension (and vice versa) for acceptability reasons after Sponsor's prior approval and on a case-by-case basis.

5.1.2 Increase or Reduction in Dose of the Study Drug(s)

The aim is to obtain a safe low pressure bladder, to inhibit overactive detrusor contractions and to reach continence. Subject discontinuation rules apply (see [Section 6.1]).

Dose up-titration to PED50 must be performed at visit 4/week 2, visit 5/week 4 or visit 6/week 8, unless:

1. The investigator considers the subject to be effectively treated with PED25, based on urodynamics and the e-diary;
2. There are safety or tolerability issues with PED25.

Dose down-titration to PED25 can be performed at any time if there is a safety issue.

If an insufficient control of the NDO is observed at the highest tolerated mirabegron dose due to insufficient effect (based on, for example, ultrasound showing upper tract dilation; the appearance of a high grade reflux; high intravesical pressures; high detrusor pressures or high amplitude overactive contractions), the investigator should reconsider the subject's further participation in the study and consider an alternative treatment.

5.1.3 Previous and Concomitant Treatment (Medication and Nonmedication Therapy)

Please refer to [Appendix 12.1] for drug classes or specific medications that are prohibited during participation in the study.

5.1.4 Treatment Compliance

The investigator or designee should instruct the subject and/or subject's parent(s)/caregiver(s) to meet 100% compliance with study drug intake throughout the entire study period. If compliance is around 80% or 120%, the investigator or designee is to counsel the subject and/or subject's parent(s)/caregiver(s) and ensure steps are taken to improve compliance.

Compliance of the study drug taken outside the clinic will be monitored at each subsequent visit at the clinic by the accounting of used and unused study drugs returned by the subject.

Subjects and their parent(s)/caregiver(s) will be clearly instructed to return all study drugs to the clinic at each clinic visit. This includes empty study drug containers.

5.1.5 Restrictions for Foods and Drinks During the Study

Restrictions for foods and drinks are not applicable. On visit days where a pharmacokinetic sample is planned in the clinic, completion of breakfast and study drug dosing should occur in the clinic.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

Demographics and baseline characteristics will be collected at visit 1/screening. Demographics will include date of birth (or year depending on the country), age, sex and race/ethnicity.

Measurements for height and weight will be taken at visit 1/screening, visit 3/baseline, visit 8/week 24 and at visit 10/week 52 (EOT/EOS).

5.2.2 Medical History

A complete medical history including a detailed NDO history will be collected at visit 1/screening. All relevant past and present conditions, as well as prior surgical procedures will be recorded for the main body systems.

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

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

5.3 Efficacy and Pharmacokinetics Assessment

5.3.1 Urodynamic Assessments

Urodynamic assessments will be performed at visit 3/baseline, and at visit 5/week 4, visit 8/week 24.

Additional urodynamic assessments can be performed at e.g. visit 10/week 52 (EOT/EOS), or at any other time point when deemed necessary by the investigator.

Computerized urodynamic equipment should be used to allow central analysis. A manual with detailed SOPs will be provided to the investigators to ensure standardization of the procedure. On-site assessment and evaluation of the urodynamic assessments are to be conducted by a medically qualified & trained person.

Every effort should be taken to ensure that the rectum is free of stool. The evening before the urodynamic investigation, bowel preparation should be performed with the existing bowel regimen or when a subject is not an a bowel management program a suppository or enema should be applied to cleanse the rectum and increase accuracy of rectal pressure recordings [Bauer et al, 2015]. If digital evacuation of stool is required for the subject, this should be performed prior to the procedure.

The subject is placed in a stable position. The position should be the same for all procedures throughout the study. The bladder is then filled with room-warm saline via a pump with a filling rate of 10% of the mean of the catheterized volumes collected in the bladder diary prior to baseline. All urodynamic investigations in each subject should be done at the same filling rate for all visits. If the filling rate was accidentally too high or too low at the baseline visit, that same filling rate should be used throughout the study for this individual subject. Minor deviations in the filling rate (no more than 1 or 2 mL/min) caused by inaccuracy of the pump are accepted.

The following parameters will be determined:

- MCC at end of filling
- Bladder compliance
- Filling volume until first detrusor contraction (> 15 cm H_2O)
- Filling volume at 20 cm, 30 cm and 40 cm H_2O detrusor pressure (if reached)
- Number of overactive detrusor contractions (> 15 cm H_2O) until end of filling
- Detrusor pressure at end of filling

Filling will be stopped (end of filling) when:

- Major leakage occurs (the rate of leakage exceeds the rate of infusion)
- 135% of maximum catheterized volume has been reached
- The subject experiences pain or discomfort at filling which does not resolve after temporary stop of filling
- The detrusor pressure exceeds 100 cm H_20 or is considered dangerously high by the investigator or urodynamicist (for instance a prolonged passive detrusor pressure > 40 cm H_2O).

The results of the urodynamic assessments, including the position of the subject during the assessments will be entered in the eCRF.

5.3.2 Bladder 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 visit 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 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. 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 this is not the case, the investigator should counsel/re-train the subject or the subject's parent(s)/caregiver(s) prior to the start of the 7-day baseline e-diary. In case the subject and/or the subject's parent(s)/caregiver(s) are still not able to complete the 7-day baseline e-diary satisfactorily, the subject should be excluded from further participation in the study.

If successful completion of the 2-day weekend e-diary is confirmed at visit 2:

- Subjects from group A start with collection of the 7-day baseline e-diary, followed by visit 3/baseline.
- Subjects in group B start with a 14-day washout. In the second week of the washout period collection of their 7-day baseline e-diary starts, followed by visit 3/baseline.

Subsequent bladder diaries will be completed by the subject or the subject's parent(s)/caregiver(s) in the week prior to visit 4/week 2, visit 5/week 4, visit 6/week 8, visit 7/week 12, visit 8/week 24, visit 9/week 36 and visit 10/week 52 (EOT/EOS). Completion of 7-day bladder diaries should start approximately 7 days prior to the indicated visit (or telephone contact).

The following information will be collected in the bladder diary.

Daily during the 7-day period:

- Time of CICs
- Presence of leakage between CICs
- Sleep time and wake-up time

On 2 consecutive weekend days within the 7-day period:

- Catheterized volume
- Grade of leakage between CICs
- Weight of diaper/pad (visit 3/baseline and visit 8/week 24)
- SMIP [Section 5.4.6]

The Investigator must guide the subject and subject's parent(s)/caregiver(s) to ensure that on the evening before and during the two weekend days of collection of catheterized volume and SMIP, the subject's fluid intake should be regulated to an appropriate level taking 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. Detailed on-site training of the bladder diary and a booklet with operating instructions in local language will be provided to the subject and subject's parent(s)/caregiver(s).

To ensure consistency in collection of the data and subject's routine, assessments must be performed over the weekend and by the same person. As an exception, it is possible to perform the weekend assessments on 2 other days in the collection week (e.g., during a holiday period) if the subject can maintain his/her standard weekend routine for catheterizations and fluid intake.

Results will be directly entered by the subject or subject's parent(s)/caregiver(s) in the e-diary [Section 8.1.1].

5.3.3 Questionnaires

Questionnaires will be completed as described below.

The following questionnaires will be used:

- The PIN-Q [Appendix 12.4] will be completed on one weekend day preceding visit 3/baseline, visit 8/week 24 and visit 10/week 52 (EOT/EOS).
- The PGI-S [Appendix 12.5] will be completed on one weekend day preceding visit 3/baseline, visit 8/week 24 and visit 10/week 52 (EOT/EOS).
- The Acceptability Questionnaire [Appendix 12.6] will be completed on one weekend day preceding at visit 5/week 4, visit 8/week 24 and visit 10/week 52 (EOT/EOS). For each formulation a separate questionnaire is available [Appendix 12.6 and Appendix 12.7].
- The CGI-C [Appendix 12.8] will be completed at visit 8/week 24 and at visit 10/week 52 (EOT/EOS).

The PIN-Q was chosen as the most appropriate cross-cultural pediatric quality of life measurement tool in this population. A Likert scale adopted for 20 measures is used [Bower et al, 2006].

Questionnaires to be completed by the subject or the subject's parent(s)/caregiver(s) (i.e., PIN-Q, PGI-S and the Acceptability Questionnaire) will be available 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) [Section 8.1.1].

The CGI-C will completed by the investigator and the results will be entered in the eCRF. Clinically relevant adverse changes will be recorded as an AE [Section 5.5.1].

5.3.4 Pharmacokinetics

Samples of venous blood for pharmacokinetic assessments will be taken when the subject has reached steady state at the optimal dose (considered to be reached after 10 days of daily dosing). A total of 4 pharmacokinetic samples will be collected, divided over 2 sampling days. These 2 days can be selected from any of the options given in the schedule of assessments (i.e., on visit 5/week 4, visit 6/week 8, visit 7/week 12, visit 8/week 24, visit 9/week 36, or visit 10/week 52) and do not have to be in a specific (consecutive) order:

- Sampling day 1: 1 trough sample (i.e., predose sample).
- Sampling day 2: 1 trough and 2 postdose samples taken between 2h and 5h postdose, with at least 1 hour in between the samples.

To allow for an early assessment of the dose-response relationship by the DSMB, it is preferred the pharmacokinetic sampling takes place as early in the study as possible.

On visit days where a pharmacokinetic sample is planned in the clinic, completion of breakfast and study drug dosing should occur in the clinic. Dosing on a sampling day with postdose samples must occur within 1 hour after completion of breakfast.

In case there is a dose change within 10 days prior to a planned pharmacokinetic sampling visit, the subject is not considered to be at steady state, and samples should be postponed to another visit as per the schedule of assessments.

Trough samples must be taken within 1 hour prior to dosing. Dosing time on the sampling day and dosing time of the previous day will be collected in the eCRF/e-diary respectively. Postdose samples must be taken between 2h and 5h postdose, with at least 1 hour in between the samples. In addition to the dosing time, the time of completion of breakfast, and type of breakfast will be collected in the eCRF on this sampling day.

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.

Operational aspects of sample collection, storage and shipment of frozen samples are described in the protocol [Section 5.6] and in the laboratory manual.

5.4 Safety Assessments

5.4.1 Vital Signs

5.4.1.1 Clinic Measurement of Vital Signs

Triplicate blood pressure and pulse measurements and single body temperature measurements (ear thermometer) will be performed at visit 1/screening, visit 3/baseline, and on visit 5/week 4, visit 7/week 12, visit 8/week 24 and visit 10/week 52 (EOT/EOS). Clinic measurements of vital signs at visit 1/screening and visit 3/baseline will be used to assess eligibility.

The preferred method of measurement is via the auscultatory technique. If this method is not available at the site, measurements will be per standard clinic practices. The method for measuring vital signs should be consistent for all visits. For each subject the correct size of the blood pressure cuff must be determined and used when assessing blood pressures. Blood pressure and pulse will be measured with approximately 2-minute intervals, after the subject has been calm and without distress for at least 5 minutes.

The subject should be seated with the back supported, feet on the floor and right arm supported, legs uncrossed and the cubital fossa at heart level. If sitting is not possible, supine is allowed, but measurements should always be taken in the same position. The subject should not move and should remain silent during the reading, as moving and talking can affect the reading.

The right arm is preferred in repeated measures of blood pressure for consistency and comparison to standard tables. The same arm should be used throughout the study whenever possible. Vital sign measurements should be performed prior to blood sampling.

The method of body temperature measurement is via an ear thermometer and should be consistent for all visits.

Clinically relevant adverse changes in vital signs will be recorded as an AE [Section 5.5.1].

5.4.1.2 Self-measurement of Vital Signs

Triplicate SBPM (blood pressure and pulse rate) will be performed on the 2 weekend days prior to each visit. Additional SBPM is done on 2 consecutive days at around 1 and 2 weeks after start of dosing with PED25 (day 1) and after up-titration to PED50 (visit 4/week 2, visit 5/week 4 or visit 6/week 8), if not already covered by the scheduled visit 4/week 2 and/or visit 5/week 4 SBPM.

Following successful completion [see Section 5.3.2] of the first 2-day weekend e-diary, confirmed at visit 2, subsequent measurements will be performed in the weekend preceding visit 3/baseline, visit 4/week 2, visit 5/week 4, visit 6/week 8, visit 7/week 12, visit 8/week 24, visit 9/week 36 and visit 10/week 52 (EOT/EOS).

Devices for measuring blood pressure and pulse rate 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)/caregiver(s).

For each subject the correct cuff size will be determined by the investigator by measuring the circumference of the subject's upper arm in order to give the subject the device with the best cuff type. Ideally, the bladder length of the cuff should be 80% to 100% of the arm's circumference and the width of the bladder approximately 40% (the bladder is the inflatable part of the cuff). The cuff should be put on according to the instructions given by investigator.

Morning measurements should be taken after waking up, before breakfast and before study drug intake, evening measurements should be taken prior to bedtime. If deemed necessary by the Investigator, subjects may be asked to perform additional measurements.

Self-measurements should, where possible, be performed in the same position as the clinic measurements for vital signs.

Results will be directly entered by the subject or subject's parent(s)/caregiver(s) in the e-diary [Section 8.1.1].

5.4.2 Adverse Events

AEs will be collected from visit 1/screening until visit 10/week 52 (EOT/EOS). See [Section 5.5] for information regarding AE collection and data handling.

5.4.2.1 Adverse Events of Possible Hepatic Origin

See [Appendix 12.2] for detailed information on monitoring and assessment of suspected liver abnormalities, if an AE for a subject enrolled in a study and receiving study drug is due to circulating liver enzymes (AST, ALT, ALP) or bilirubin, or if the AE is suspected to be due to hepatic dysfunction.

Subjects with AEs of hepatic origin accompanied by liver function test (LFT) abnormalities should be carefully monitored.

5.4.3 Laboratory Assessments

Hematology and biochemistry assessments will be taken at visit 1/screening, visit 7/week 12 and visit 10/week 52 (EOT/EOS). In the event that an AE related to hematology/biochemistry parameters is found at visit 1/screening, an additional hematology/biochemistry assessment is to be taken at visit 3/baseline.

Urinalysis is to be assessed at visit 1/screening, at visit 3/baseline, and at visit 5/week 4, visit 7/week 12, visit 8/week 24 and visit 10/week 52 (EOT/EOS).

To allow for an early DSMB safety assessment, the first 5-10 subjects who reach study visit 5/week 4 will have an additional blood draw at this visit [see Section 1.4].

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.

All safety laboratory assessments will be performed at a central laboratory, except for urine pregnancy testing, which is done locally. Pregnancy test in female subjects of childbearing potential will be performed in serum (if blood is drawn for hematology/biochemistry) or urine (at the other visits).

Specimen collection and shipping procedures will be described in a laboratory manual. All laboratory results, including ULNs used in exclusion and discontinuation criteria, will be compared to age-appropriate norms. The investigator may decide to repeat the safety laboratory assessments, should the results be important for safety reasons and considered clinically relevant. Repeating safety laboratory assessments for re-screening is not allowed.

The clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator/sub-investigator who is a qualified physician. Clinically significant adverse changes will be recorded as an AE [Section 5.5.1].

The laboratory parameters that will be assessed during the conduct of the study are listed in [Appendix 12.3].

5.4.4 Physical Examination

Physical examinations will be performed at visit 1/screening and at visit 10/week 52 (EOT/EOS).

The physical examination will be performed per clinic standards and clinically significant findings at screening will be recorded as part of the subject's medical history. Clinically significant findings discovered after visit 1/screening will be recorded as an AE [Section 5.5.1].

5.4.5 Electrocardiograms

Triplicate 12-lead ECG will be performed at visit 1/screening, visit 3/baseline, visit 5/week 4, visit 7/week 12, visit 8/week 24 and at visit 10/week 52 (EOT/EOS).

ECGs will be taken in the supine position (when possible, but always in the same position), after the subject has been lying quietly for at least 5 minutes. ECG machines will be provided to the site by a central laboratory to allow for central reading (ECG recordings will be performed according to ICH guidelines E14 [CPMP/ICH/2711/99] to make them readable and interpretable for potential later assessment by an independent cardiologist).

ECGs will be recorded with an interval of about 30 seconds to 5 minutes between each ECG. Recordings will be made at a speed of 25 mm/s and all leads have to include at least 4 complexes. This is according to the standard settings on the machines. The ECGs should be transmitted from the machine to the central laboratory (following the steps indicated in the user manual). In addition, 2 prints of the original ECG traces should be made on normal, nonheat sensitive paper. These should be clearly marked with the subject identification number (in such a way that they are anonymized), include date and time, and should be kept with the source documents.

The ECG machine will produce automatically calculated interval duration measurements for intervals of QT, QTcB, QTcF, etc., and an evaluation on the printed ECG. For a final safety assessment the manually read analysis reports of the central ECG readings (from cardiologists) will be made available to the investigators within 72 hours. The final ECG reports sent by the central laboratory must be reviewed by the investigator since there might be relevant differences from the initial analysis produced by the ECG machines.

For analysis the mean values of the triplicate readings will be used (not the highest or lowest value). In case of incomplete triplicates, mean values of the available ECG readings will be taken.

Please refer to [Section 6.1] for discontinuation criteria based on centrally read results from the QTcB mean from the visit 1 and visit 3 ECG triplicates (at least 2 ECGs of each triplicate reading must be available).

The ECG report itself will not be captured on the electronic case report from (eCRF), but will be captured in the central ECG laboratory database. Only the visit, ECG date and time, overall ECG interpretation and relevant comments will be captured in the eCRF. If specific concerns regarding the cardiac safety of a subject exist, a dual approach is recommended:

- On-site evaluation of the ECGs are to be conducted by a medically qualified person.
- In addition, the central ECG laboratory can be contacted (24 hours a day) to provide the final centrally read ECG analysis results within a shorter timeframe than the usual 72 hours (for contact details see the ECG Study Manual provided by the central ECG laboratory).

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. Clinically significant abnormalities should be reported as an AE [Section 5.5.1].

Detailed instructions and procedures for ECG recordings will be described in a separate manual.

5.4.6 Self-measurement of Intravesical Pressure

SMIP will be performed as part of the bladder diary [Section 5.3.2]. In case the measuring device is not available/approved for use at the site, the subject or parent(s)/caregiver(s) are not able or willing to perform the SMIP, or there is a technical problem, the SMIP may be omitted.

Following successful completion of the first 2-day weekend e-diary, confirmed at visit 2, subsequent measurements will be performed in the weekend preceding visit 3/baseline, visit 4/week 2, visit 5/week 4, visit 6/week 8, visit 7/week 12, visit 8/week 24, visit 9/week 36 and visit 10/week 52 (EOT/EOS).

SMIP is a method to measure the intravesical pressure at home. The pressure in the bladder can be measured by the subject or subject's parent(s)/caregiver(s) at the moment the subject catheterizes him/herself in the course of using CIC as a therapeutic intervention. Measurements will be performed on a full and emptied bladder.

The aim of this method is to verify that the intravesical pressure is in a safe range and particularly if the pressure at the time of CIC (the end-filling pressure), where intravesical pressure can be expected to be at its greatest, is at an acceptable level.

To start measurements, the SMIP device is connected to a CIC catheter with a 3-way stopcock via an air tube. By switching the handle on the stopcock, a closed circuit can be established between the SMIP device and the CIC catheter. The urine from the subject exerts pressure to the trapped air in the closed circuit and this pressure is transferred to a sensor in the SMIP device. The signal from the sensor is interpreted by a microprocessor which then displays the pressure numerically in centimeters H_2O. The zero is set to atmospheric pressure.

Once a stable read-out has been obtained, the handle on the stopcock can be switched again and the urine can now flow out of the catheter attached to the other outlet of the 3-way stopcock.

After the bladder has been emptied, the intravesical pressure is measured a second time by switching the handle of the stopcock again, establishing a closed circuit between the SMIP catheter and the SMIP device.

Devices (Peritron+, [redacted] for measuring intravesical pressure will be provided to subjects along with required auxiliaries such as special catheters and connectors (Air Trap Tubing, [redacted] Detailed on-site training of the SMIP and a booklet with operating instructions in local language will be provided to the subject and the subject's parent(s)/caregiver(s).

Results will be entered by the subject or subject's parent(s)/caregiver(s) in the e-diary [Section 8.1.1].

5.4.7 Estimated Glomerular Filtration Rate and Upper Urinary Tract Ultrasound

Renal function will be assessed via monitoring plasma creatinine and cystatin C levels at visit 1/screening, visit 7/week 12 and visit 10/week 52 (EOT/EOS).

The presence or absence of structural abnormalities of the urinary tract, upper tract dilation, vesicoureteral reflux, or obstruction at the ureterovesical or ureteropelvic junction will be assessed with an ultrasound of the upper urinary tract at visit 3/baseline, and at visit 10/week 52 (EOT/EOS).

For the first group of subjects (minimum of 5, maximum of 10) who reach study visit 5/week 4, the renal function will also be determined at visit 5/week 4 to allow for the early DSMB safety assessment.

Clinically significant abnormalities should be reported as an AE [Section 5.5.1].

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a subject administered a study drug or has undergone study procedures and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Some countries may have additional local requirements for events that are required to be reported as AEs or in an expedited manner similar to a serious adverse event (SAE). In these cases, it is the investigator's responsibility to ensure these AEs or other reporting requirements are followed and the information is appropriately recorded in the eCRF accordingly.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets 1 of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study drug intake
- The abnormality or investigational value is clinically significant in the opinion of the investigator.

5.5.2 Definition of Serious Adverse Events

An AE is considered "serious" if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- 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 or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other medically important events

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, should also

usually be 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.

Safety events of interest on the medicinal products administered to the subject as part of the study (e.g., study drug, comparator, background therapy) that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of the medicinal product(s)
- Suspected abuse/misuse of the medicinal product(s)
- Inadvertent or accidental exposure to the medicinal product(s)
- Medication error involving the medicinal product(s) (with or without subject exposure to the Sponsor medicinal product, e.g., name confusion)

All of the events of interest noted above should be recorded on the eCRF. Any situation involving these events of interest that also meets the criteria for an SAE should be recorded on the AE page of the eCRF and marked 'serious' and the SAE worksheet.

The Sponsor has a list of events that they classify as "always serious" events. If an AE is reported that is considered to be an event per this classification as "always serious", additional information on the event may be requested.

5.5.3 Criteria for Causal Relationship to the Study Drug

AEs that fall under either "Possible" or "Probable" should be defined as "AEs whose relationship to the study drugs could not be ruled out".

Causal relationship to the study drug	**Criteria for causal relationship**
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re- administration (rechallenge) or withdrawal (dechallenge).

5.5.4 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

5.5.5 Reporting of Serious Adverse Events

In the case of an SAE, the investigator must contact the CRO by telephone or fax/e-mail immediately (within 1 working day of awareness).

The investigator should complete and submit an SAE Worksheet containing all information that is required by the Regulatory Authorities to CRO by fax/e-mail immediately (within 1 working day of awareness). If the faxing/e-mailing of an SAE Worksheet is not possible or is not possible within 1 working day, the local drug safety contact should be informed by phone. Within 1 working day during weekdays or within 60 hours during weekends, whatever is shorter, after receipt of the information, the CRO will forward the SAE details to the Sponsor.

SAEs must be reported up to 28 days after the EOS visit or up to 28 days after early discontinuation of dosing.

For contact details, see [Section II] Contact Details of Key Sponsor's Personnel. Please fax/email to:

[redacted]

Safety & Pharmacovigilance

Please use the country specific toll-free fax number provided on the SAE Fax cover sheet.

In case of fax failure, email: [redacted]

If there are any questions, or if clarification is needed regarding the SAE, please contact the Sponsor's Medical Monitor/Expert or his/her designee (Section II).

Follow-up information for the event should be sent promptly (within 7 days of the initial notification).

Full details of the SAE should be recorded on the medical records and on the eCRF.

The following minimum information is required:

- International Study Number (ISN)
- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event) and
- Causal relationship to the study drug

Where required by local requirements, the Sponsor or Sponsor's designee will submit expedited safety reports (e.g., IND Safety Reports) to the regulatory agencies (e.g., FDA) as necessary, and will inform the investigators of such regulatory reports. Investigators must

submit safety reports as required by their IEC/IRB within timelines set by regional regulations (i.e., EU, (e)CTD, FDA). Documentation of the submission to and receipt by the IEC/IRB of expedited safety reports should be retained by the site.

The delegated CRO will notify all investigators responsible for ongoing clinical studies with the study drug of all SAEs which require submission per local requirements.

The investigators should provide written documentation of IEC/IRB notification for each report to the Sponsor, where required by local requirements.

You may contact the Sponsor's Medical Monitor/Expert for any other problem related to the safety, welfare, or rights of the subject.

5.5.6 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.

If during AE follow-up, the AE progresses to an SAE, or if a subject experiences a new SAE, the investigator must immediately report the information to the Sponsor.

Please refer to [Appendix 12.2] for detailed instructions on Drug Induced Liver Injury.

5.5.7 Monitoring of Common Serious Adverse Events

Common serious adverse events are SAEs commonly anticipated to occur in the study population independent of drug exposure. For this protocol, there is no list of common serious adverse events that the Sponsor considers to be associated with the disease state being studied for which a single occurrence will be excluded from safety reporting.

5.5.8 Procedure in Case of Pregnancy

If a female subject or partner of a male subject becomes pregnant during the study dosing period or within 28 days from the discontinuation of dosing, the investigator should report the information to the CRO as if it is an SAE. 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.

The investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE and will report the outcome to the Sponsor.

When the outcome of the pregnancy falls under the criteria for SAEs [spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including anomaly in a miscarried fetus)], the investigator should respond in accordance with the report procedure for SAEs.

Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below.

- "Spontaneous abortion" includes miscarriage, abortion and missed abortion

- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug
- If an infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as "possible" by the investigator
- In the case of a delivery of a living newborn, the "normality" of the infant is evaluated at the birth
- 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

5.5.9 Emergency Procedures and Management of Overdose

In the event of suspected mirabegron overdose, the subject should receive supportive care and monitoring. Heart rate, blood pressure and ECG monitoring are recommended. The Medical Monitor/Expert should be contacted as applicable.

5.5.10 Supply of New Information Affecting the Conduct of the Study

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

5.6 Test Drug Concentration

Samples will be collected as per local standards, however a topical anesthetic cream or plaster must be offered at the point of venipuncture to minimize distress of the subject. Venous blood (2 mL) for bioanalysis of mirabegron will be collected in properly labeled tubes containing sodium-heparin as anticoagulant and sodium fluoride as stabilizer.

Blood samples will be kept on melting-ice until ready for centrifugation, which must be done within 30 minutes after collection. Blood samples will be centrifuged at 1500 g for 10 minutes at ambient temperature in order to obtain plasma. Plasma will be harvested and transferred into a properly labeled polypropylene tube and stored at -20°C or below (preferably at -70°C) within 30 minutes after centrifugation.

Plasma samples will be sent to the central laboratory, packed with sufficient dry ice, to keep the samples frozen during shipment. Bioanalysis of mirabegron in plasma will be done at a designated CRO using a validated liquid chromatography-tandem mass spectrometry method.

5.7 Other Measurements, Assessments or Methods

If deemed relevant, the remaining plasma may be used for retrospective mirabegron metabolite profiling, identification and/or quantification studies. Analysis of these metabolites will be done at Astellas or at a designated CRO using LC-MS/MS or other appropriate analytical techniques. The results from these tests will be described in (a) separate report(s) and will not be incorporated in the integrated clinical study report.

5.8 Total Amount of Blood

The total amount of blood that is to be taken as foreseen over the entire study period is approximately 25 to 30 mL per subject [Table 5]:

Table 5 Total Amount of Blood Volume per Subject During the Study Period

Amount for pharmacokinetic sampling (2.0 mL/sample x 4 samples)	8 mL
Amount for safety hematology & biochemistry † (5.5 mL/sample x 3‡ samples)	16.5 mL
Total §	24.5 mL

† If applicable, pregnancy test will be done from the same sample; no additional blood is required.

‡ The first group of subjects (minimum of 5, maximum of 10) who reach study visit 5/week 4 will have an additional blood draw of about 5 mL at study visit 5/week 4 for DSMB safety monitoring. The total amount of blood drawn from these subjects will thus be approximately 30.0 mL

§ Volume does not take any unscheduled visits or re-tests into account (e.g., follow-up of AEs)

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

A discontinuation is a subject who received study drugs and for whom study treatment is permanently discontinued prematurely 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 terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

If a subject is discontinued from the study with an ongoing AE or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until the condition stabilizes or no longer is clinically significant.

Discontinuation criteria from treatment for individual subjects:

- If, within 7 days of the first dose of mirabegron:
  - The centrally read urodynamic trace reveals no evidence of NDO
  - The centrally read ECG has an average QTcB interval greater than 450 ms, based on the QTcB mean from the visit 1 and visit 3 ECG triplicates
- If signs or symptoms of hypersensitivity to mirabegron are observed (e.g., anaphylactic reaction, erytheme multiforme or exfoliative dermatitis).
- Discontinuation of 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%).
- In addition, if close monitoring for a subject with moderate or severe hepatic laboratory tests is not possible, the drug should be discontinued.

6.2 Discontinuation of the Site

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

6.3 Discontinuation of the Study

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.

7 STATISTICAL METHODOLOGY

The statistical analysis will be coordinated by the responsible biostatistician of Astellas. A Statistical Analysis Plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures (TLFs) to be produced. The SAP will be finalized before the database soft lock at the latest. Any changes from the analyses planned in SAP will be justified in the clinical study report (CSR).

Prior to database lock, a final meeting will be held to allow a review of the clinical trial data and (TLFs) and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed and documented. A meeting to determine analysis set classifications may also be held prior to database lock.

In general, all data will be summarized with descriptive statistics (number of subjects, mean, standard deviation, minimum, median and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints.

7.1 Sample Size

The primary endpoint will be the change from baseline in MCC after 24 weeks of mirabegron treatment. There are data from previous studies that indicate the effect size that can be expected as a result of the treatment with mirabegron. Franco et al. (2005) analyzed 2 age groups (1 to 5 years, and 6 to 15 years) and reported mean (SD) MCC changes from baseline of 71.5 (88) mL and 75.4 (102.7) mL respectively after 24 weeks treatment with oxybutynin. Goessl et al. (2000) reported an increase of 52.8 mL after 3 months treatment with tolterodine. Cartwright et al. (2009) reported an increase of 98 mL after 14 weeks treatment with oxybutynin and a corresponding SD of 87 mL.

A study with 44 evaluable subjects who have valid (as by the central reviewer's assessment) nonmissing MCC measurements at visit 8/week 24 and at baseline would have a 90 percent power to detect a statistical significant change from baseline, if the real change from baseline in the subject population is at least 52 mL and the real SD for change from baseline is ≤ 103 mL. The power calculation was done assuming a paired t-test with 2-sided significance level of 0.05.

Assuming 30% of enrolled subjects will discontinue or will not be evaluable for the primary endpoint, a total of approximately 63 subjects may need to be enrolled so that 44 subjects are evaluable in total.

These sample size considerations should allow sufficient precision for the assessment of the primary objective in this nonrandomized pediatric trial.

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 hard-lock.

7.2 Analysis Set

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 hard-lock.

7.2.1 Full Analysis Set

The full analysis set (FAS) will consist of all subjects who:

- Took at least 1 dose of study drug, and
- Had a valid (as by the central reviewer's assessment) nonmissing MCC measurement at baseline and at a postbaseline visit for the primary efficacy endpoint.

The FAS will be used for primary analyses of efficacy data, for sensitivity and subgroup analyses [Section 7.4.1.3] and for summaries of some demographic and baseline characteristics.

7.2.2 Per Protocol Set

The per protocol set (PPS) will include all subjects of the FAS who fulfill the protocol in terms of their eligibility, interventions and outcome assessments, and for whom valid MCC measurements at visit 3/baseline and at visit 8/week 24 are reported.

A list of the protocol deviations that may result in a subject in the FAS being excluded from the PPS will be provided in the SAP. The final selection of subjects for the PPS will be confirmed in the Analysis Set Classification Meeting based upon a review of all the pertinent data.

The PPS will be used for secondary analyses of efficacy data. Also, selected demographic and baseline characteristics may also be summarized for the PPS.

7.2.3 Safety Analysis Set

The safety analysis set (SAF) will consist of all subjects who took at least 1 dose of study drug.

The SAF will be used for all summaries of demographic and baseline characteristics and all safety and tolerability related variables.

7.2.4 Pharmacokinetics Analysis Set

The pharmacokinetics analysis set (PKAS) consists of the subset of subjects of the SAF for whom plasma concentration data are available to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of last dose prior to sampling is known.

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.

Since the actual bioanalytical results may only become available after the data review meeting, additional data points may be excluded at the time of pharmacokinetic analysis at the discretion of the pharmacokineticist. These data points will be reported in the CSR.

7.3 Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized by using descriptive statistics. Summaries of demographic data will be provided for each analysis set within and across age groups.

7.4 Analysis of Efficacy

Efficacy analysis will be conducted on the FAS. The interpretation of results from statistical tests 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.

7.4.1 Analyses of Primary Endpoint

7.4.1.1 Primary Analysis

Baseline for efficacy variables is the last assessment made prior to the first intake of study drug at visit 3 (day -1).

The primary efficacy variable is change from baseline in MCC after 24 weeks of treatment (based on filling urodynamics). The primary analysis will be a paired t-test for the change from baseline to week 24 to test the hypothesis that the change from baseline in MCC is not equal to zero with a 2-sided alpha level of 0.05. A 95% CI will be calculated for mean change from baseline. It will be assessed whether the estimated lower bound of the 95% CI excludes 0 mL. No adjustment for multiplicity will be made.

Missing MCC observations at visit 8/week 24 will be imputed using the last observation carried forward method (LOCF). The data will be summarized with descriptive statistics as a continuous variable (n, mean, SD, SEM, 95% CI, min, median, max).

7.4.1.2 Secondary Analyses

A repeat of the primary analysis will be performed on the FAS without imputing missing data as well as based on the PPS.

A repeated measures analysis of covariance (ANCOVA) will be performed considering the change from baseline (without LOCF) and baseline MCC. This analysis will serve as a sensitivity analysis to the LOCF methods used in the primary model to assess robustness of those findings. For this analysis, data will be windowed according to predefined study visit windows.

Details of these analyses, including study visit windows, will be provided in the SAP.

7.4.1.3 Subgroup and Sensitivity Analyses of Primary Endpoint

For the primary efficacy endpoint, MCC, 95% CI will be calculated for mean change from baseline per age group, per formulation, and per dosing regimen (with and without LOCF).

Dosing regimen here refers to whether the subjects had been up-titrated to PED50 at least once or maintained at PED25 for safety reasons at least until visit 8/week 24.

A subgroup analysis of the primary efficacy endpoint by whether NDO medication treatment was received at screening/prior to start of washout for both groups of subjects will be performed if there are sufficient subject numbers (with and without LOCF) on the FAS.

A subgroup analysis of the primary efficacy endpoint of subjects with insufficient efficacy under antimuscarinics specifically intended for NDO treatment (i.e. stopping the medication for lack of efficacy prior to start of treatment) will be performed if there are sufficient subject numbers (with and without LOCF) on the FAS.

The following sensitivity analyses of the primary efficacy endpoint will be performed if there are sufficient subject numbers (without LOCF only) on the FAS:

- Excluding those subjects who had a positive urine culture at visit 3/baseline and/or visit 8/week 24.
- For any of the subgroups specified, at least 10 subjects by stratum are required.

7.4.2 Analysis of Secondary Endpoints

Each of the secondary efficacy endpoints will be summarized and, if applicable, plotted by visit.

The change from baseline for secondary endpoint based on urodynamic assessments, the subject's e-diary (including bladder diary) and questionnaires will be summarized and analyzed using similar primary statistical methods as for the primary endpoint, where appropriate.

CGI-C and acceptability results will be tabulated per time point of assessment.

These analyses of secondary endpoints will be produced for subjects in the FAS. Details of these analyses and of any further analyses will be defined in the SAP.

7.4.3 Analysis of Exploratory Endpoints

Each of the exploratory efficacy endpoints will be summarized and analyzed in the same way as the secondary efficacy endpoints [Section 7.4.2].

Details of these analyses and of any further analyses will be defined in the SAP.

7.5 Analysis of Safety

The baseline for safety variables is the last assessment made prior to first intake of study drug (visit 3/day -1).

For safety variables relating to the ECG intervals, baseline values are taken from the mean of the visit 1 and visit 3 mean values.

All safety data will be summarized descriptively based on the SAF. The continuous safety data will be summarized using the following descriptive statistics: n, mean, SD, min, median, max, at each time point and for change from baseline. Categorical data will be summarized by absolute and relative frequencies. All safety data from subjects in the SAF will be listed.

Safety parameters such as vital signs and weight will also be summarized with respect to height- and sex-specific percentiles. Height will also be summarized with respect to age- and sex-specific percentiles.

Subgroup presentations regarding age (children and adolescents), formulation (tablets and suspension) and dosing regimen (PED25 and PED 50) will be tabulated for the following parameters: AEs, vital signs and ECGs. For any of the subgroups specified, at least 10 subjects by stratum are required.

7.5.1 Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline by treatment group and time. 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.

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].

7.5.2 Adverse Events

AEs will be coded using MedDRA. The number and percentage of AEs, SAEs, AEs leading to discontinuation, and AEs related to study drug will be summarized by system organ class and preferred term. The number and percentage of AEs by severity will also be summarized.

7.5.3 Laboratory Assessments

For quantitative laboratory measurements descriptive statistics will be used to summarize results and change from baseline time point. Shifts relative to normal ranges from baseline to each time point during treatment period in lab tests will also be tabulated.

7.5.4 Physical Examination

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

7.5.5 Electrocardiograms

12-lead ECG parameters (QT, QT interval corrected by Fridericia's formula [QTcF], HR, PR, QRS and RR) and their changes from baseline will be summarized with descriptive statistics by visit. The following thresholds will be used to characterize an individual subject's QTcF data: QTcF interval > 440 ms for children, and QTcF interval > 450 ms and >500 ms for male adolescents and >480 ms and >500 ms for female adolescents. These categories are cumulative in that subjects satisfying criterion for a more extreme category will also be counted in each applicable less extreme category. A summary of normal, abnormal not clinical significant and abnormal clinical significant findings will be provided.

In addition for QTcF, the impact of concomitant medications potentially prolonging QTc will be evaluated.

To perform this analysis, all QTcF post-baseline values will be presented (regardless of time point). If anomalies occur, an additional presentation will be provided using only QTcF values not under the influence of respective concomitant medications.

Details on how these will be derived, will be described in the SAP.

7.5.6 Estimated Glomerular Filtration Rate and Upper Urinary Tract Ultrasound

For eGFR and upper urinary tract ultrasound, descriptive statistics will be used to summarize results and change from baseline by time point. The eGFR results will be summarized based upon the Larsson, the modified Schwartz 2009 (for children < 12 years old) and the Cockcroft-Gault equation (for adolescents).

7.5.7 Analysis of Exploratory Endpoints

Each of the exploratory safety endpoints will be summarized and analyzed in the same way as the safety endpoints [Sections 7.5.1 to 7.5.6]. For SMIP descriptive statistics will be used to summarize results and change from baseline by time point.

All analyses of exploratory safety endpoints will be produced for subjects in the SAF.

Details of these analyses and of any further analyses will be defined in the SAP.

7.6 Analysis of Pharmacokinetics

Descriptive statistics (N, mean, SD, minimum, median, maximum, coefficient of variation and geometric mean) will be provided for plasma concentration data. Further details will be specified in the SAP.

7.6.1 Estimation of Pharmacokinetic Parameters

The plasma concentrations will be analyzed with nonlinear mixed effects modeling (population pharmacokinetics) using NONMEM (version 7.3 or higher, [redacted] USA).

The following plasma pharmacokinetic parameters of mirabegron will be calculated for each subject:

- C_{max}, t_{max}, AUC_{24}, C_{trough}, CL/F and V_z/F.

7.7 Protocol Deviations and Other Analyses

Protocol deviations as defined in [Section 8.1.6] will be summarized for all subjects by site. A data listing will be provided by site and subject.

The protocol deviation criteria will be uniquely identified in the summary table and listing. The unique identifiers will be as follows:

PD1 - Entered into the study even though they 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.

Descriptive statistics will be used to explore whether there is an association between certain subject characteristics (such as medical history) and the final titrated mirabegron doses. Collected data on study drug compliance rates and maintenance of treatment will be analyzed using descriptive statistics.

7.8 Interim Analysis (and Early Discontinuation of the Clinical Study)

No formal interim analysis is planned.

7.9 Handling of Missing Data, Outliers, Visit Windows, and Other Information

As a general principle, no imputation of missing data (with exception of visit 8/week 24, LOCF analysis for MCC) will be performed. Values lower than the limit of quantification for laboratory parameters will be set to 0 for the calculation of descriptive statistics.

See the SAP for details of the definitions for windows to be used for analyses by visit.

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 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 site designee should record data (including laboratory values, if applicable) in the eCRF within 5 working days after the subject visit.

The investigator or site designee is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents should be appropriately maintained by the site.

The monitor should verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them.

Laboratory tests (except for the locally performed pregnancy tests) are performed at a central laboratory and results are visible for the site shortly after analysis has been completed. Laboratory data will be transferred electronically to the Sponsor or designee at predefined intervals during the study. The laboratory will provide the Sponsor or designee with a complete and clean copy of the data.

ECG analysis and interpretation are performed at a central ECG reading vendor and results are visible for the site shortly after analysis has been completed. Central ECG read data will be transferred electronically to the Sponsor or designee at predefined intervals during the study. The central ECG vendor will provide the Sponsor or designee with a complete and clean copy of the data.

For Screen failures the demographic data, reason for failing, informed consent, inclusion and exclusion criteria and AEs will be collected in the eCRF and listed.

8.1.1.1 Electronic Patient Reported Outcomes

Subject bladder diaries, questionnaires and other data completed by the subject or the subject's parent(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 completion before each planned visit of the subject (on site or phone visit) and discuss the results or retrain the subject and/or subject's parent(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 [Section 5.5.1].

The bladder 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.

For this study the following information will be collected and entered by the subject or subject's parent(s)/caregiver(s) in the e-diary (see [Sections 5.3.2, 5.3.3, and 5.4.1.2] for detailed information per visit):

- Bladder diary:
  - Each day for 7 days: time of CICs
  - Each day for 7 days: presence of leakage between CICs
  - Each day for 7 days: sleep time and wake-up time
  - On the 2 weekend days: catheterized volume
  - On the 2 weekend days: SMIP (if applicable)
  - On the 2 weekend days: grade and number of leakages between CICs
  - On the 2 weekend days (selected visits): weight of diaper/pad
- SBPM (blood pressure and pulse rate):
  - On the 2 weekend days: triplicate measurements in the morning and evening
  - On 2 consecutive 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.
- Questionnaires: on 1 weekend day at selected visits
  - PIN-Q
  - PGI-S
  - Acceptability
- Confirmation of study drug intake: daily

The Investigator must guide the subject and subject's parent(s)/caregiver(s) to ensure that on the evening before and during the two weekend days of collection of catheterized volume and SMIP (if applicable), the subject's fluid intake should be regulated to an appropriate level taking 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.

8.1.2 Specification of Source Documents

Source data must be available at the site to document the existence of the study 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.

The following information should be included in the source medical records (not exhaustive):

- Demographic data (e.g., date of birth/age, sex, race/ethnicity, height and body weight)
- Subject number
- Inclusion and exclusion criteria details
- Participation in study and original signed and dated informed consent forms (ICFs)
- Visit dates
- Dispensing and return of study drug details
- Medical history and physical examination details
- Key efficacy and safety data (as specified in the protocol)

- AEs and concomitant medication
- Results of relevant examinations (e.g., ECG printouts, physical examination)
- Laboratory printouts
- Reason for premature discontinuation (if applicable)

8.1.3 Clinical Study Monitoring

The Sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the investigator/sub-investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The Sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

8.1.4 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the Sponsor or delegated CRO as well as inspections from the IEC/IRB and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents [Section 8.1.2] when they are requested by the Sponsor monitors and auditors, the IEC/IRB, or regulatory authorities. The confidentiality of the subjects' identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

8.1.5 Data Management

Data Management will be coordinated by the Global Data Science Department of the Sponsor in accordance with the SOPs for data management. All study-specific processes and definitions will be documented by Data Management. eCRF completion will be described in the eCRF instructions. Coding of medical terms and medications will be performed using MedDRA and the World Health Organization Drug Dictionary respectively.

8.1.6 Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. 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 welfare 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 trial subjects.

A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

For the purposes of this protocol, deviations requiring notification to Sponsor are defined as any subject who:

- Entered into the study even though they did not satisfy entry criteria†
- Developed withdrawal criteria during the study and not withdrawn
- Received wrong treatment or incorrect dose
- Received excluded concomitant treatment

† Subjects who are discontinued within the first 7 days of dosing, after the centrally read urodynamic trace or the ECG results from visit 3/baseline show the subject is no longer fulfilling the eligibility criteria, will not result in a protocol deviation.

When a 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.

If a deviation impacts the safety of a subject, the investigator must contact the Sponsor immediately.

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

NOTE: Other deviations outside of the categories defined above will be reported to the IEC/IRB as required in accordance with local requirements, as applicable.

8.1.7 End of Trial in All Participating Countries

The end of trial in all participating countries is defined as the last subject's last visit.

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 Independent Ethics Committee/Competent Authorities

GCP requires that the clinical protocol, any protocol amendments, the IB, the informed consent/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 IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent/assent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any substantial amendments to the protocol will require IEC/IRB approval prior to implementation of the changes made to the study design at the site. The investigator will be required to submit, maintain and archive study essential documents according to ICH-GCP.

Any SAEs that meet reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH

Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to Sponsor.

If required by local regulations, the investigator shall make accurate and adequate written progress reports to the IEC/IRB at appropriate intervals, not exceeding 1 year. The investigator shall make an accurate and adequate final report to the IEC/IRB within 1 year after last subject out or termination of the study.

8.2.2 Ethical Conduct of the Study

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

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

For this pediatric study in subjects aged 3 to less than 18 years, in addition to information sheets and consent/assent forms for subjects (according to applicable local regulations), parent/legal guardian information sheets and consent forms will also be prepared.

Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the subject's parent(s) or legal guardian(s), the person who administered the informed consent/assent, and any other signatories according to local requirements.

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

- The investigator/sub-investigator is responsible for explaining the nature and purpose of the study as well as other study-related matters to subjects and their parents or legal guardians, using the written information, and for obtaining the child's assent and the parent(s)'/guardian(s)' full understanding and written consent 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 trial at any time, this will have to be considered by the investigator, even if consent 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 should be obtained from the subject and his/her parent(s)/legal guardian(s), before start of pre-investigational period. Assent and consent 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/sub-investigator, collaborators, or the Sponsor from liability for negligence.

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

8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

- The investigator or his/her representative will immediately inform the subject or subject's parent(s)/guardian(s) orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue to participate in the study (e.g., report of serious drug adverse drug reaction). The communication must be documented in the subject's medical records and must document whether the subject is willing to remain in the study or not.
- The investigator must update their ICF and submit it for approval to the IEC/IRB. The investigator or his/her representative must obtain written informed consent from the subject on all updated ICFs throughout their participation in the study. The investigator or his/her designee must reconsent subjects with the updated ICF even if relevant information was provided orally. The investigator or his/her representative who obtained the written informed consent and the subject should sign and date the informed consent form. A copy of the signed ICF 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 re-consent process.

8.2.4 Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the subject to the subject's physician 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 clinical study without justifiable reasons.

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

The Sponsor will ensure that the use and disclosure of protected health information obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information.

8.3 Administrative Matters

8.3.1 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, the IB 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 clinical 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 clinical 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 Clinical Study Agreement.

8.3.2 Documents and Records Related to the Clinical Study

The investigator will archive all study data (e.g., Subject Identification Code List, source data, CRFs, and Investigator's File) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation (for US sites, 2 years after approval of the NDA or discontinuation of the IND). The Sponsor will notify the site/investigator if the MAA is approved or if the IND/IMPD 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 subjects' medical records and/or study progress notes. All data will be entered on the eCRFs supplied for each subject.

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.

8.3.3 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 IEC/IRB, Competent Authority approval or notification may be required. The changes will become effective only after the approval of the Sponsor, the investigator, the regulatory authority, and the IEC/IRB (if applicable).

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

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

8.3.4 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.

8.3.5 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final study report which 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 Coordinating Investigator(s) or the Principal Investigator(s) will be selected from the participating investigators by the Sponsor prior to database lock.

9 QUALITY ASSURANCE

The Sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

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

10 STUDY ORGANIZATION

10.1 Independent Data-Monitoring Committee | Data and Safety Monitoring Board | Monitoring Committee | Other Evaluation Committee(s)

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

Subject safety 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.

10.2 Other Study Organization

Not applicable.

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12 APPENDICES

12.1 List of Excluded Concomitant Medications

Any medication used for the management of NDO (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.

Strong CYP3A4 inhibitors are excluded for subjects with mild to moderate renal impairment (mild: eGFR 60 to 89 mL/min; moderate: eGFR 30 to 59 mL/min).

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 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	
Strong CYP3A4 inhibitors	**Other**	
Itraconazole	Mirabegron (except for study drug)	
Ketoconazole	Botulinum toxin	
Ritonavir		
Clarthromycin		

† Incidental use for motion sickness is accepted.

12.2 Liver Safety Monitoring and Assessment

Any subject enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases to > 3 × ULN, or bilirubin > 2 × ULN, should undergo detailed testing for liver enzymes (including at least ALT, AST, ALP) and TBL. Testing should be repeated within 48-72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central lab regarding moderate and severe liver abnormality to inform the investigator, study monitor and study team. Subjects or his/her parent(s)/caregiver(s) 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:

	ALT or AST		Total Bilirubin
Moderate	> 3× ULN	or	> 2× ULN
Severe*	> 3× ULN	and	> 2× ULN

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 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%).

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 laboratory tests. The site should complete the Liver Abnormality Case Report Form (LA-CRF) that has been developed globally and can be activated for any study or an appropriate document. Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal LFTs should be repeated 2-3 times weekly then weekly or less frequently if abnormalities stabilize or the study drug 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 an SAE.

The Sponsor should be contacted and informed of all subjects for whom severe hepatic liver function abnormalities possibly attributable to study drug 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 should be recorded as 'adverse events' on the AE page of the eCRF. 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 aminotransferase 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, including dose, should be entered on the concomitant medication page of the eCRF. 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 laboratory tests including INR, 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 Discontinuation

In the absence of an explanation for increased LFTs, such as viral hepatitis, pre-existing or acute liver disease or exposure to other agents associated with liver injury, the subject may be discontinued from the study. The investigator may determine that it is not in the subject's best interest to continue study enrollment. Discontinuation of 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%).

In addition, if close monitoring for a subject with moderate or severe hepatic laboratory tests is not possible, the drug 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 10–50% 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 transaminase elevations higher 3 times the upper limit of normal ("2 x ULN elevations are too common in treated and untreated subjects to be discriminating");

2) Cases of increased bilirubin (at least 2 x ULN) with concurrent transaminase elevations at least 3x ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's syndrome [Temple 2006].

Reference

Guidance for Industry titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" issued by FDA on July 2009.

12.3 Laboratory Assessments

By Central Laboratory		
Assessment	**Collecting tube**	**Parameters to be analyzed**
Hematology	EDTA tube	HbA1c Hemoglobin Hematocrit Platelets Red blood cells White blood cells Differential white blood cell count
Biochemistry	Serum tube	Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Calcium Chloride Creatine phosphokinase Creatinine Cystatin C Estimated glomerular filtration rate (Larsson, modified Schwartz and Cockcroft-Gault) Gamma-glutamyl transaminase Glucose hCG † Lactate dehydrogenase Potassium Sodium Total bilirubin Total protein Urea Uric acid
Urinalysis	Dipstick	Protein Glucose pH Urobilinogen Bilirubin Ketones Nitrite
	Polypropylene tube	Casts Crystals Bacteria Epithelial cells Small round cells Yeasts Red blood cells White blood cells ‡
Done Locally		
Pregnancy	Urine	hCG †

HbA1c: glycosylated hemoglobin A1c; hCG: human chorionic gonadotropin;

† Only in female subjects of childbearing potential

‡ If white blood cell count is >100/µL (or '++' for semi-quantitative results) a urine culture will be done including an antibiotic sensitivity test.

12.4 Pediatric Incontinence Questionnaire

1. I get shy because of my bladder problem
□ No □ Hardly ever □ Sometimes □ Often □ All the time
2. People in my family treat me in a different way because of my bladder problem
□ No □ Hardly ever □ Sometimes □ Often □ All the time
3. I am worried that people might think my clothes smell of wee
□ No □ Hardly ever □ Sometimes □ Often □ All the time
4. I think that my bladder problem won't get better
□ No □ Hardly ever □ Sometimes □ Often □ All the time
5. Mum and Dad worry about me because of my bladder problem
□ No □ Hardly ever □ Sometimes □ Often □ All the time
6. I would feel better about myself if I didn't have a bladder problem
□ No □ Maybe □ Probably □ Yes □ Definitely
7. My bladder problem makes me feel nervous
□ No □ Hardly ever □ Sometimes □ Often □ All the time
8. Mum or Dad sometimes seem a bit cranky because of my bladder problem
□ No □ Hardly ever □ Sometimes □ Often □ All the time
9. My bladder problem stops me going on sleepovers or holidays
□ No □ Hardly ever □ Sometimes □ Often □ All the time
10. My bladder problem makes me feel bad about myself
□ No □ Hardly ever □ Sometimes □ Often □ All the time
11. I wake up during my sleep because of my bladder problem
□ No □ Hardly ever □ Sometimes □ Often □ All the time
12. I miss out on doing things because of my bladder problem
□ No □ Hardly ever □ Sometimes □ Often □ All the time
13. I feel unhappy because of my bladder problem
□ No □ Hardly ever □ Sometimes □ Often □ All the time
14. My bladder problem makes me feel sad
□ No □ Hardly ever □ Sometimes □ Often □ All the time
15. I think about my bladder problem when choosing which sport to play
□ No □ Hardly ever □ Sometimes □ Often □ All the time
16. I have to go to the toilet when I'm watching a movie
□ No □ Hardly ever □ Sometimes □ Often □ All the time
17. If my bladder problem was fixed I would invite more friends to my house
□ No □ Maybe □ Probably □ Yes □ Definitely
18. I choose hobbies that won't be spoiled by stopping to go to the toilet
□ No □ Hardly ever □ Sometimes □ Often □ All the time
19. My bladder problem makes me feel different to other people
□ No □ Hardly ever □ Sometimes □ Often □ All the time
20. I miss out on being with friends because of my bladder problem
□ No □ Hardly ever □ Sometimes □ Often □ All the time

PINQ (UK-English) Astellas Pharma Europe Ltd FINAL V1 Oxford, Version 30NOV2011

12.5 Patient Global Impression of Severity Scale

How did you feel about your bladder condition <u>DURING THE PAST 3 DAYS?</u>

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

12.6 Acceptability 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
☐	☐	☐	☐	☐

12.7 Acceptability 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
☐	☐	☐	☐	☐

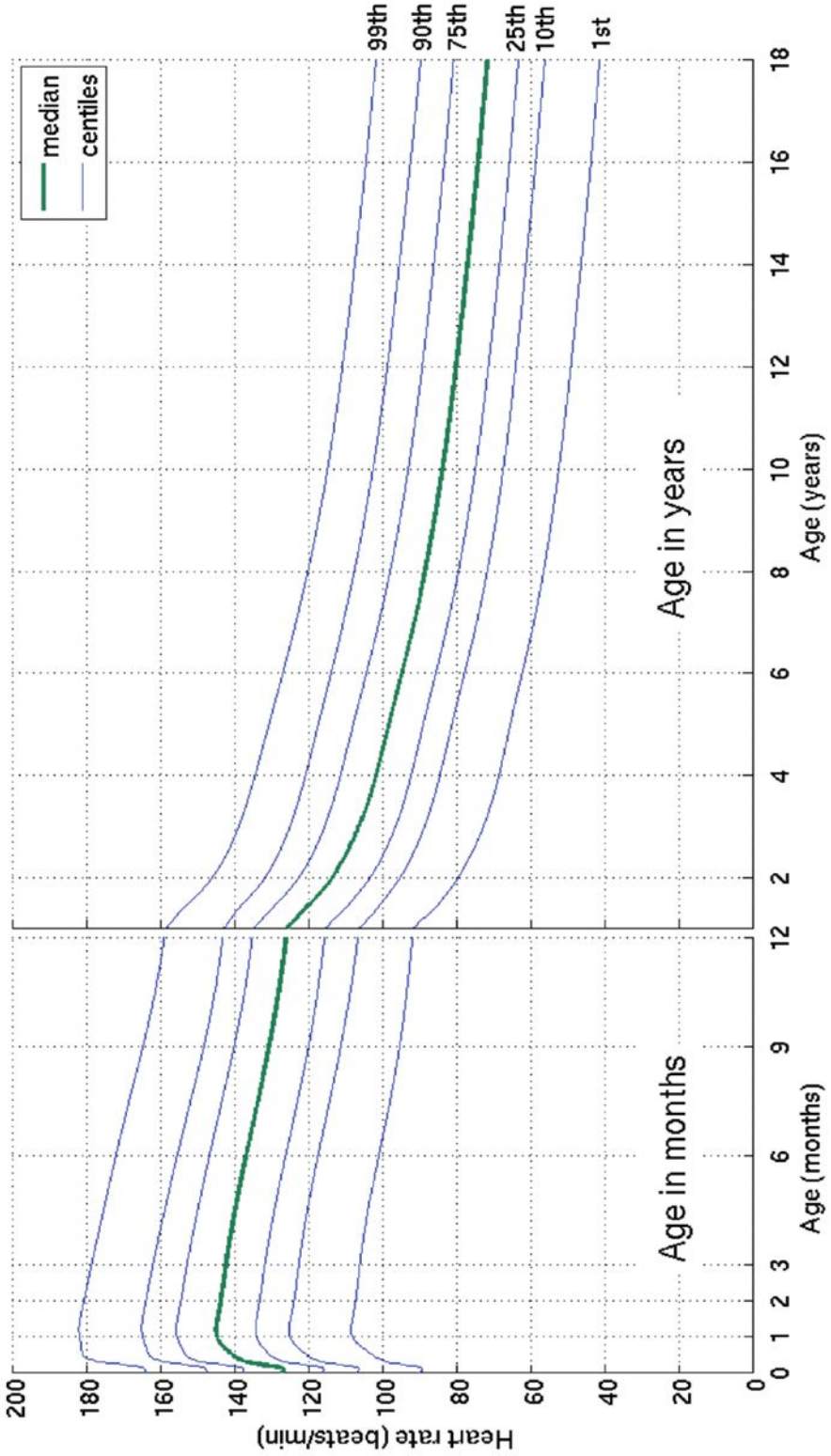
4. How was it to <u>PREPARE</u> the study drug?

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

12.8 Clinical Global Impression of Change Scale

Clinical Global Impression of Change Scale
Please rate the degree of change in the subject's overall bladder symptoms since the start of the study on day 1 (tick 1 box)
☐ Very much improved
☐ Much improved
☐ Minimally improved
☐ No change
☐ Minimally worse
☐ Much worse
☐ Very much worse

12.9 Centiles of heart rate for normal children from birth to 18 years of age [Fleming et al, 2011]



12.10 CDC 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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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)
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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12.11 CDC 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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12.12 Blood Pressure Levels for Boys by Age and Height Percentile [NIH 2005]

Blood Pressure Levels for Boys by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90

Blood Pressure Levels for Boys by Age and Height Percentile (Continued)

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

For research purposes, the standard deviations in Appendix Table B–1 allow one to compute BP Z-scores and percentiles for boys with height percentiles given in Table 3 (i.e., the 5th,10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28%; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in Appendix B. For children with height percentiles other than these, follow steps 1–4 as described in Appendix B.

12.13 Blood Pressure Levels for Girls by Age and Height Percentile [NIH 2005]

Blood Pressure Levels for Girls by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88

Blood Pressure Levels for Girls by Age and Height Percentile (Continued)

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

For research purposes, the standard deviations in Appendix Table B–1 allow one to compute BP Z-scores and percentiles for girls with height percentiles given in Table 4 (i.e., the 5th,10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28%; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in Appendix B. For children with height percentiles other than these, follow steps 1–4 as described in Appendix B.

13 ATTACHMENT 1: SUBSTANTIAL AMENDMENT 1

I. The purpose of this amendment is:

Substantial Changes
1. Add Mirabegron Oral Suspension as a Formulation of the Study Drug
DESCRIPTION OF CHANGE:
Mirabegron oral suspension (8 mg/mL) is added to the protocol as a second study drug formulation.
RATIONALE:
As part of the pediatric mirabegron development program, a suspension formulation of the study drug has been developed. This is to ensure availability of an appropriate formulation for smaller children or children who have difficulties with swallowing tablets. This formulation is now available to be included into the study.
2. Update of Inclusion Criterion 3
DESCRIPTION OF CHANGE:
The lower weight range for inclusion of subjects in the study is updated to ≥ 11 kg.
RATIONALE:
Due to the addition of mirabegron oral suspension to the protocol, subjects below 35 kg can now be included. Based on the dose prediction performed, the minimum body weight for inclusion of subjects in the study is updated to 11 kg.
3. Update of the Age Range for the Study Population
DESCRIPTION OF CHANGE:
The age range for the study population to enter the study is updated to male and female children from 3 to less than 18 years of age.
RATIONALE:
This study is targeted to fulfill both the EMA and FDA requirements related to the conduct of pediatric trials. A "Written Request" received from the FDA includes a stipulation to decrease the lower limit of the age range from 5 to 3 years of age. Therefore, in order to ensure that the current study meets the needs of both the FDA and the EMA, the age range is adjusted. Lowering the age range from 5 to 3 years is possible because dose predictions in this study cover doses from a body weight of 11 kg onwards. The cut-off of 11 kg body weight is considered appropriate for the age range of 3 to less than 18 years old.

4. Add Extra Self Blood Pressure Measurements
DESCRIPTION OF CHANGE:
Extra Self Blood Pressure Measurements (SBPM) are included at week 1 and 2 after the start of dosing and after a dose escalation.
RATIONALE:
The EMA and FDA requested additional blood pressure measurements to be performed. This change implements additional SBPM done around 1 and 2 weeks after start of mirabegron (PED25) treatment and after up-titration from PED25 to PED50 (if not already covered by the scheduled SBPM). Triplicate home measurements will be taken in the morning and in the evening.

Non-Substantial Changes
1. Remove IND Number on Cover Page
The IND number on the cover page of the protocol is removed.
RATIONALE:
The study is not conducted under IND. The IND reference number was cited on the cover page of the protocol in error.
2. Update Available Clinical Data
DESCRIPTION OF CHANGE:
Preliminary data of ongoing studies 178-CL-203 and 178-CL-208 are included in the protocol. Data from completed study 178-CL-202 are moved to the Investigator's Brochure.
RATIONALE:
After the finalization of the protocol new data from mirabegron studies within the pediatric program has become available. This preliminary data has now been included in the introduction of the protocol to support dosing in children/adolescents with a body weight < 35 kg. Since the protocol was finalized, the final clinical study report for Study 178-CL-202 has become available and so this information has been removed from the protocol and has been incorporated in the Investigator's Brochure.
3. Update Mirabegron Approval Information
DESCRIPTION OF CHANGE:
The number of countries that Mirabegron has been approved in is updated.
RATIONALE:

The pediatric Investigator's Brochure has been updated and this change makes the two documents consistent.
4. Remove SMIP Measurement as a Dose Titration Criteria
DESCRIPTION OF CHANGE:
The Self Measurement of Intravesical Pressure (SMIP) is removed from the dose titration criteria.
RATIONALE:
The SMIP was intended to be included as a safety parameter to assess the intravesical pressure in an at-home situation. In the FDA Advice Letter the Sponsor was asked to exclude the results of SMIP as a basis for dose titration in this study.
5. Correct Exploratory Efficacy Endpoints
DESCRIPTION OF CHANGE:
For the e-Diary, the maximum confirmed daytime dry period is removed as an exploratory endpoint and for the endpoints on total catheterized volume an explanation is included on how catheterizations are assigned to a certain period of the day.
RATIONALE:
The maximum confirmed daytime dry period and the maximum confirmed dry daytime period/7 days were included to take into account the intervals between the catheterizations. It was deleted to reduce the number of exploratory parameters. To ensure a correct assignment of the catheterization times to daytime and/or night-time, a clarification is included to explain that the first morning catheterization after waking up is regarded as part of the 'night', whilst the last evening catheterization before sleep time is part of the 'day'.
6. Include Missing Variable for Bladder Diary
DESCRIPTION OF CHANGE:
The number of leakages between CICs is included in the sections on collected Patient Reported Outcome data in the protocol.
RATIONALE:
The number of leakages between CICs is used in the calculation of secondary and exploratory endpoints. The collection of this variable is included in the eDiary and its' submitted documentation, but was not correctly specified as a collected variable in the protocol.

7. Include Preferred Method for Clinic Vital Signs Measurements
DESCRIPTION OF CHANGE:
Auscultation is included in the protocol as the preferred method for measuring vital signs in the clinic.
RATIONALE:
The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents, which is used as the basis for the blood pressure percentiles used in this study states that "*The BP tables are bases on auscultatory measurements, therefore the preferred measurement is auscultation"* †. This method has been included in the protocol as the preferred method for measuring vital signs. † *The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. U.S. Department of Health and Human Services, National Institutes of Health National Heart, Lung, and Blood Institute. NIH Publication No. 05-5267 Originally printed September 1996 (96-3790) Revised May 2005*
8. Add Conversion Factor for Urine Weight-to-Volume
DESCRIPTION OF CHANGE:
A gram-to-milliliter conversion factor is included in the protocol to calculate urine volume based on the subject's reported urine weight in the eDiary.
RATIONALE:
The protocol did not include the conversion factor to calculate the urine volume based on the urine weight that is reported by the subject in the eDiary.
9. Add eGFR Parameters
DESCRIPTION OF CHANGE:
Two additional eGFR parameters are included for reporting in the Clinical Study Report. For subjects from 3 to 12 years of age, the modified Schwartz formula (2009) is added and for subjects from 12 to 18 years of age, the Cockcroft-Gault equation.
RATIONALE:
The calculation of eGFR according to both the modified Schwartz formula and the Cockcroft-Gault Equation will be summarized in line with a request form the FDA. No additional assessment or increase in collected blood volume is required. Both parameters will be derived based on already collected biochemistry results.

10. Amend Text for Start of Adverse Event Collection
DESCRIPTION OF CHANGE:
The text on the start of adverse event collection is updated to avoid any misunderstanding.
RATIONALE:
The current text in the protocol was ambiguous, possibly leading to confusion on when the collection of AEs start. The sentence has been re-worded to provide clarity.
11. Correct Text for Safety Reporting
DESCRIPTION OF CHANGE:
The text related to the safety reporting timeline between the CRO and the Sponsor is updated from 24 hours, to 1 working day.
RATIONALE:
In line with ICH-GCP E6, chapter 5.2, Astellas has outsourced the safety reporting process for sites to the CRO [redacted]). The ultimate responsibility for safety reporting will remain with the Sponsor, as will be the responsibility for adhering to the reporting timelines according to section 5.1.5 of the EU guideline "Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use" (CT3). Instead of a reporting timeline of 1 working day between receipt of the SAE worksheet at the CRO and forwarding of this worksheet to the Sponsor, the protocol listed a 24 hour reporting timeline. This has been corrected. For the Sponsor's reporting obligations, the clock starts at the time the CRO has first knowledge of the minimum criteria for expedited reporting. This correction will not affect the regulatory reporting timelines.
12. Add SAE Reporting Procedure after End of Treatment
DESCRIPTION OF CHANGE:
Timelines for SAE reporting after End of Study are included in the protocol.
RATIONALE:
The protocol did not mention the cut-off timelines for reporting of new SAEs occurring after the End of Study visit. This timeline is 28 days and the information has now been included into the protocol.
13. Amend Text for Pharmacokinetic Sampling Times
DESCRIPTION OF CHANGE:
The preferred timing of pharmacokinetic sampling is added to the protocol.
RATIONALE:
To allow for an early assessment of the dose-response relationship by the Data Safety

Monitoring Board (DSMB), it is preferred the pharmacokinetic sampling takes place as early in the study as possible.
14. Addition of Subgroup Analyses
DESCRIPTION OF CHANGE:
Subgroup analyses for selected safety parameters are added to the statistical section of the protocol.
RATIONALE:
Subgroup analyses related to formulation (tablet or suspension) and dosing regimen (PED25 or PED50) for selected safety parameters have been added to further characterize the safety profile.
15. Administrative-type Changes
DESCRIPTION OF CHANGE:
Various edits related to consistency, formatting and numbering are made throughout the protocol.
RATIONALE:
To provide clarification to the protocol and to ensure complete understanding of the study procedures.

II. Amendment Summary of Changes: Substantial

Cover Page, 2 Investigator's Signature and IV Synopsis, Title of Study and Study Population
WAS:
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 5 to Less Than 18 Years of Age With Neurogenic Detrusor Overactivity (NDO) on Clean Intermittent Catheterization (CIC)
IS AMENDED TO:
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 ~~5~~ **3** to Less Than 18 Years of Age ~~W~~**w**ith Neurogenic Detrusor Overactivity (NDO) on Clean Intermittent Catheterization (CIC)

IV Synopsis, Number of Subjects to be Enrolled/Randomized and 2 Study Objectives(s), Design, and Endpoints
2.2.1 Study Design

WAS:
At least 44 evaluable subjects (estimate 63 enrolled), with at least 10 subjects from each age group (children aged 5 to less than 12 years of age; adolescents aged 12 to less than 18 years of age) are planned. A subject is considered being evaluable if the subject has a nonmissing maximum cystometric capacity (MCC) measurement at baseline and at a postbaseline visit.
IS AMENDED TO:
At least 44 evaluable subjects (estimate 63 enrolled), with at least 10 subjects from each age group (children aged ~~5~~ **3** to less than 12 years of age; adolescents aged 12 to less than 18 years of age) are planned. A subject is considered being evaluable if the subject has a **valid (as by the central reviewer's assessment)** nonmissing maximum cystometric capacity (MCC) measurement at baseline and at a postbaseline visit.

IV Synopsis, Inclusion/Exclusion Criteria, 2 Study Objectives(s), Design, and Endpoints, 3 Study Population and 8 Operational and Administrative Considerations *2.2.1 Study Design, 3.1 Selection of Study Population, 3.2 Inclusion Criteria and 8.2.3.1 Subject Information and Consent*
WAS:
2. Subject is male or female from 5 to less than 18 years of age.
IS AMENDED TO:
2. Subject is male or female from ~~5~~ **3** to less than 18 years of age.

IV Synopsis, Inclusion/Exclusion Criteria and 3 Inclusion/Exclusion Criteria *3.2 Inclusion Criteria*
WAS:
3. Subject has a body weight of ≥ 35 kg.
IS AMENDED TO:
3. Subject has a body weight of ≥ ~~35~~**11** kg.

IV Synopsis, Investigational Product(s)
WAS:
Investigational Product(s)**:** Mirabegron tablets, strengths 25 mg and 50 mg **Dose(s):** The initial dose will be PED25. The dose may be up-titrated to PED50 according to the dose-titration criteria. **Mode of Administration:** Study drug will be taken orally, once a day in the morning around the same time of day and around time of food intake (i.e., within 1 hour before or after breakfast). Tablet to be taken with a sip of water (tablet should be taken as a whole and should not be chewed, divided or

crushed).

On visit days where a pharmacokinetic sample is planned in the clinic, completion of breakfast and study drug dosing should occur in the clinic.

IS AMENDED TO:

Investigational Product~~(s)~~:
Mirabegron **prolonged-release** tablets, strengths 25 mg and 50 mg
Mirabegron oral suspension, strength 8 mg/mL

Dose~~(s)~~:
~~The initial dose will be PED25. The dose may be up-titrated to PED50 according to the dose-titration criteria.~~

Selection of the formulation:
Subjects with a body weight < 35 kg: mirabegron oral suspension.
Subjects with a body weight ≥ 35 kg: mirabegron tablets.

Selection of the dose:
Doses are calculated weight-based. The bodyweight at visit 3/baseline determines the weight range for the starting dose (PED25) and the up-titration dose (PED50) to be used in the table below:

Weight-based Doses for Tablets or Suspension

PED	Weight Range	Suspension Volume †	Tablet Dose
PED25	11 - < 22 kg	3 mL	-
	22 - < 35 kg	4 mL	-
	≥ 35 kg	6 mL	25 mg
50	11 - < 22 kg	6 mL	-
	22 - < 35 kg	8 mL	-
	≥ 35 kg	11 mL	50 mg

PED25: Pediatric equivalent dose 25 mg; PED50: Pediatric equivalent dose 50 mg
† Suspension strength: 8 mg/mL

Further dosing information:
- **For subjects with a body weight ≥ 35 kg who do not want to or are unable to take tablets, the oral suspension can be supplied.**
- **At visit 8/week 24 subjects on mirabegron oral suspension may switch to tablets if the body weight turns to be ≥ 35 kg.**
- **Subjects receiving mirabegron tablets can switch to mirabegron oral suspension (and vice versa) for acceptability reasons after Sponsor's prior approval and on a case-by-case basis.**

Mode of Administration:
Study drug will be taken orally, once a day in the morning around the same time of day and around time of food intake (i.e., within 1 hour before or after breakfast).

Mirabegron ~~T~~tablet**s** ~~to~~ **will** be taken with a sip of water (tablet should be taken as a whole and should not be chewed, divided or crushed).

Mirabegron oral suspension will be administered via an oral syringe with a sip of water afterwards.

On visit days where a pharmacokinetic sample is planned in the clinic, completion of breakfast and study drug dosing should occur in the clinic.

IV Synopsis, Endpoints for Evaluation and 2 Study Objectives(s), Design, and Endpoints
2.3.2.3 Patient- or Clinician-reported Questionnaire Endpoints
WAS:
Based on questionnaires: • Acceptability questionnaire at visit 8/week 24 and visit 10/week 52 (EOT/EOS)
IS AMENDED TO:
Based on questionnaires: • Acceptability questionnaire at **visit 5/week 4,** visit 8/week 24 and visit 10/week 52 (EOT/EOS)

IV Synopsis, Endpoints for Evaluation, safety, Assessments, 2 Study Objective(s), Design, and Endpoints and 5 Treatments and Evaluation
2.3.3 Safety Endpoints and 5.4.1.2 Self-measurement of Vital Signs
WAS:
• Change from baseline in vital signs (SBPM): systolic blood pressure, diastolic blood pressure, pulse rate at visit 4/week 2, visit 5/week 4, visit 6/week 8, visit 7/week 12, visit 8/week 24, visit 9/week 36 and visit 10/week 52 (EOT/EOS)
IS AMENDED TO:
• Change from baseline in vital signs (**self blood pressure measurement [**SBPM**]**): systolic blood pressure, diastolic blood pressure, pulse rate at visit 4/week 2, visit 5/week 4, visit 6/week 8, visit 7/week 12, visit 8/week 24, visit 9/week 36 and visit 10/week 52 (EOT/EOS) **and on 2 consecutive days at around 1 and 2 weeks after start of dosing with PED25 (day 1) and after up-titration to PED50 (visit 4/week 2, visit 5/week 4 or visit 6/week 8), if not already covered by the scheduled visit 4/week 2 and/or visit 5/week 4 SBPM.**

1 Introduction
1.4 Risk-Benefit Assessment
WAS:
Mirabegron has a favorable risk-benefit profile in adults in the indication OAB. In the pediatric phase 1 study executed thus far, mirabegron has an acceptable safety profile and was well tolerated.
IS AMENDED TO:
Mirabegron **tablets** has~~s~~ **have** a favorable risk-benefit profile in adults in the indication OAB. **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 stud~~y~~**ies** executed thus far, mirabegron **tablets and mirabegron oral suspension** ha~~s~~**d** an acceptable safety profile and w~~as~~**ere** well tolerated.

1 Introduction

1.4 Risk-Benefit Assessment

WAS:

Regarding the formulation to be administered: the tablets are the same as used in adults. All excipients are pharmaceutical materials and are considered safe for the intended pediatric population.

IS AMENDED TO:

Regarding the formulation**s** to be administered: ~~the tablets are the same as used in adults.~~ **for both the tablet and the suspension formulation,** ~~A~~**a**ll excipients are pharmaceutical **grade** materials and are considered safe for the intended pediatric population.

2 Study Design and Dose Rationale

2.2.2 Dose Rationale

WAS:

The approved posology in adults for the treatment of OAB is either once daily 25 or 50 mg prolonged-release tablets. In children, the dosing strategy is based on extrapolation of efficacious doses in adults. Based on data obtained from adult and pediatric subjects following tablet and oral suspension dosing, a popPK model of steady state exposures will be used to predict the pediatric doses equivalent to 25 and 50 mg mirabegron administered once daily in adults. The target exposures for these pediatric equivalent doses (PED25 and PED50) are 69 ng·h/mL and 188 ng·h/mL, respectively. The popPK model indicates that pediatric subjects with a body weight of 35 kg or above can safely be dosed with the available tablets.

For pediatric subjects with a weight too low for dosing with tablets, or who cannot swallow the tablets, an oral suspension is under development. All subjects will start with the PED25 dose. Based on the criteria as described in [Section 5.1.2], the dose will be up-titrated to PED50 or will remain at PED25.

IS AMENDED TO:

~~The approved posology in adults for the treatment of OAB is either once daily 25 or 50 mg prolonged-release tablets. In children, the dosing strategy is based on extrapolation of efficacious doses in adults. Based on data obtained from adult and pediatric subjects following tablet and oral suspension dosing, a popPK model of steady state exposures will be used to predict the pediatric doses equivalent to 25 and 50 mg mirabegron administered once daily in adults. The target exposures for these pediatric equivalent doses (PED25 and PED50) are 69 ng·h/mL and 188 ng·h/mL, respectively. The popPK model indicates that pediatric subjects with a body weight of 35 kg or above can safely be dosed with the available tablets.~~

~~For pediatric subjects with a weight too low for dosing with tablets, or who cannot swallow the tablets, an oral suspension is under development. All subjects will start with the PED25 dose. Based on the criteria as described in [Section 5.1.2], the dose will be up-titrated to PED50 or will remain at PED25.~~

The target exposures of 69 and 188 ng·h/mL for pediatric equivalent dose 25 mg (PED25) and pediatric equivalent dose 50 mg (PED50) were derived from the adult phase 3 program and are the mean steady state AUC_{tau} values following 25 and 50 mg prolonged-release tablets once daily in adults.

A population pharmacokinetic model was used to predict the PED for subjects in the 178-CL-206A study. In brief, this popPK 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; IND 58135), 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 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. Subjects with a body weight < 35 kg cannot be dosed with the 25 and 50 mg tablets because that would result in higher than 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 11 kg (the approximate body weight of a 3-year-old child, according to the NHANES 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. Suspension dosing for body weights ≥ 35 kg was also determined for cases in which a pediatric subject in that weight category does not want or would be unable to swallow a tablet. The simulation resulted in the 3 body weight categories that can be found in the dosing schedule (see [Section 5.1.1]).

4 Treatment(s)
4.1.1 Test Drug

WAS:

For detailed information on mirabegron tablets, please refer to the Investigational Medicinal Product Dossier (IMPD) or IND.

Mirabegron is supplied as tablets containing 25 mg or 50 mg of active ingredient.

IS AMENDED TO:

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

For detailed information on mirabegron **prolonged-release** tablets and **mirabegron granules for oral suspension**, please refer to the **applicable** Investigational Medicinal Product Dossier (IMPD) ~~or IND~~.

Mirabegron **tablets are** ~~is~~ supplied as **prolonged-release** tablets containing 25 mg or 50 mg of active ingredient.

For the oral suspension, mirabegron prolonged-release granules are supplied and will be reconstituted with water to prepare an oral suspension of 8 mg/mL. Detailed information on the preparation of the mirabegron oral suspension will be provided to the subject and subject's parent(s)/caregiver(s) in local language. Due to shelf-life limitations, an additional dispensing visit is foreseen at visit 9/week 36 for subjects receiving mirabegron oral suspension. This dispensing visit does not need to be accompanied by the subject.

5 Treatments and Evaluation
5.1.1 Dose/Dose Regimen and Administration Period

WAS:

Each tablet is to be taken with a sip of water. The tablet should be taken as a whole and should not be chewed, divided or crushed.

IS AMENDED TO:

~~Each~~ **Mirabegron** tablet**s** ~~is to~~ **will** be taken with a sip of water. The tablet should be taken as a whole and should not be chewed, divided or crushed.

Mirabegron prolonged-release granules will be reconstituted with water to prepare a mirabegron oral suspension of 8 mg/mL. Administration will be via an oral syringe with a sip of water afterwards. Detailed information on the preparation of the suspension will be provided to the subject and subject's parent(s)/caregiver(s) in local language. For subjects receiving mirabegron oral suspension, an additional (optional) dispensing visit is scheduled at visit 9/week 36.

Selection of the formulation:
Subjects with a body weight < 35 kg: mirabegron oral suspension.
Subjects with a body weight ≥ 35 kg: mirabegron tablets.

Selection of the dose:
Doses are calculated weight-based. The bodyweight at visit 3/baseline determines the

weight range for the starting dose (PED25) and the up-titration dose (PED50) to be used [Table 4].

Table 4 Weight-based doses for tablets or suspension

	Weight Range	Suspension Volume †	Tablet Dose
PED25	**11 - < 22 kg**	**3 mL**	**-**
	22 - < 35 kg	**4 mL**	**-**
	≥ 35 kg	**6 mL**	**25 mg**
PED50	**11 - < 22 kg**	**6 mL**	**-**
	22 - < 35 kg	**8 mL**	**-**
	≥ 35 kg	**11 mL**	**50 mg**

PED25: Pediatric equivalent dose 25 mg; PED50: Pediatric equivalent dose 50 mg
† Suspension strength: 8 mg/mL

Further dosing information:

- **For subjects with a body weight ≥ 35 kg who do not want to or are unable to take tablets, the oral suspension can be supplied.**
- **At visit 8/week 24 subjects on mirabegron oral suspension may switch to tablets if the body weight turns to be ≥ 35 kg.**
- **Subjects receiving mirabegron tablets can switch to mirabegron oral suspension (and vice versa) for acceptability reasons after Sponsor's prior approval and on a case-by-case basis.**

5 Treatments and Evaluation

5.3.3 Questionnaires

WAS:

- The PIN-Q [Appendix 12.4] will be administered on one weekend day preceding visit 3/baseline, visit 8/week 24 and visit 10/week 52 (EOT/EOS).
- The PGI-S [Appendix 12.5] will be administered on one weekend day preceding visit 3/baseline, visit 8/week 24 and visit 10/week 52 (EOT/EOS).
- The Acceptability Questionnaire [Appendix 12.6] will be administered on one weekend day preceding visit 8/week 24 and at visit 10/week 52 (EOT/EOS).
- The CGI-C [Appendix 12.7] will be administered at visit 8/week 24 and at visit 10/week 52 (EOT/EOS).

IS AMENDED TO:

- The PIN-Q [Appendix 12.4] will be ~~administered~~ **completed** on one weekend day preceding visit 3/baseline, visit 8/week 24 and visit 10/week 52 (EOT/EOS).
- The PGI-S [Appendix 12.5] will be ~~administered~~ **completed** on one weekend day preceding visit 3/baseline, visit 8/week 24 and visit 10/week 52 (EOT/EOS).
- The Acceptability Questionnaire ~~[Appendix 12.6]~~ will be ~~administered~~ **completed** on one weekend day preceding **visit 5/week 4,** visit 8/week 24 and ~~at~~ visit 10/week 52 (EOT/EOS). **For each formulation a separate questionnaire is available [Appendix 12.6 and Appendix 12.7**].

- The CGI-C [Appendix **12.~~7~~8**] will be ~~administered~~ **completed** at visit 8/week 24 and at visit 10/week 52 (EOT/EOS).

11 References

ADDED:

McDowell MA, Fryar CD, Ogden CL, Flegal KM. Anthropometric reference data for children and adults: United States, 2003–2006. Natl Health Stat Report. 2008;22(10):1-48.

Momper JD, Mulugeta Y, Green DJ, Karesh A, Krudys KM, Sachs HC, et al. Adolescent Dosing and Labeling Since the Food and Drug Administration Amendments Act of 2007. JAMA Pediatr. 2013;167(10):926-932. doi:10.1001/jamapediatrics.2013.465.

12 Appendices

ADDED:

12.7 Acceptability Questionnaire for Oral Suspension

Questions

3. How was the TASTE of the study drug?

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

4. How was the SMELL of the study drug?

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

5. How was it to TAKE the study drug?

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

6. 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
☐	☐	☐	☐	☐

III. Amendment Summary of Changes: Non-Substantial

Cover Page
DELETED:
~~IND 69,416~~

IV. Synopsis *<u>Study Design Overview</u>*
WAS:
If a symptomatic UTI is present at baseline, all baseline assessments are allowed to be postponed for a maximum of 7 days until the UTI is successfully treated.
IS AMENDED TO:
If a symptomatic UTI is present at baseline, all baseline assessments ~~are allowed to~~ **should** be postponed for a maximum of 7 days until the UTI is successfully treated **(clinical recovery). The 7-day baseline e-diary does not have to be repeated if at least the 2-day**

weekend e-diary and 1 day of the weekday e-diary were completed while the subject did not suffer from a symptomatic UTI.

IV. Synopsis
Study Design Overview
ADDED:
The 7-day e-diary does not have to be repeated if at least the 2-day weekend e-diary and 1 day of the weekday e-diary were completed while the subject did not suffer from a symptomatic UTI. **If a subject suffers from a symptomatic UTI in the week prior to any other study visit, these visits do not need to be postponed and the 7-day e-diary does not have to be repeated.**

IV Synopsis, Study Design Overview and 2 Study Objective(s), Design, and Endpoints
2.2.1.1 Pretreatment Period
WAS:
Subjects will enter the efficacy treatment period if they meet the eligibility criteria and satisfactorily complete the pretreatment period (ability to complete bladder diary, catheterized volumes, self-measurement of intravesical pressures [SMIP], questionnaires and self blood pressure measurement [SBPM]).
IS AMENDED TO:
Subjects will enter the efficacy treatment period if they meet the eligibility criteria and satisfactorily complete the pretreatment period (ability to complete bladder diary, catheterized volumes, ~~self-measurement of intravesical pressures [SMIP],~~ **and** questionnaires).

IV Synopsis, Dose Titration and 5 Treatments and Evaluation
5.1.2 Increase or Reduction in Dose of the Study Drug(s)
WAS:
1. The investigator considers the subject to be effectively treated with PED25, based on urodynamics, e-diary and SMIP (if available);
IS AMENDED TO:
1. The investigator considers the subject to be effectively treated with PED25, based on urodynamics~~,~~ **and** the e-diary ~~and SMIP (if available)~~;

IV. Synopsis, Exploratory Efficacy and 2 Study Objective(s), Design, and Endpoints
2.3.5.1 Exploratory Efficacy Endpoints
WAS:

Based on e-diary: Change from baseline at visit 4/week 2, visit 5/week 4, visit 6/week 8, visit 7/week 12, visit 8/week 24, visit 9/week 36 and visit 10/week 52 (EOT/EOS) in: • Mean grade of leakage • Total catheterized volume per 24 h • Maximum confirmed daytime dry period/24 h • Maximum confirmed daytime dry period/7 days • Change from baseline in SMIP-derived bladder compliance • Number of CICs/day • Responder in respect to leakage (complete, partial, no response)
IS AMENDED TO:
Based on e-diary: Change from baseline at visit 4/week 2, visit 5/week 4, visit 6/week 8, visit 7/week 12, visit 8/week 24, visit 9/week 36 and visit 10/week 52 (EOT/EOS) in: • Mean grade of leakage • Total catheterized volume per ~~24 h~~**day** • ~~Maximum confirmed daytime dry period/24 h~~ • ~~Maximum confirmed daytime dry period/7 days~~ • Change from baseline in SMIP-derived bladder compliance • Number of CICs/day • Responder in respect to leakage (complete, partial, no response)

IV Synopsis, Assessments and 5 Treatments and Evaluation *5.3.1 Urodynamic Assessments*
WAS:
Additional urodynamic assessments can be performed at visit 10/week 52 (EOT/EOS), or at any other time point when deemed necessary by the investigator (e.g., confirmatory urodynamic assessments at visit 7/week 12 if up-titration or down-titration was done at visit 6/week 8, or when the SMIP was not performed).
IS AMENDED TO:
Additional urodynamic assessments can be performed at visit 10/week 52 (EOT/EOS), or at any other time point when deemed necessary by the investigator ~~(e.g., confirmatory urodynamic assessments at visit 7/week 12 if up-titration or down-titration was done at visit 6/week 8, or when the SMIP was not performed~~**)**.

IV. Synopsis, Patient Reported Outcome Data and 8 Operational and Administrative Considerations *8.1.1.1 Electronic Patient Reported Outcomes*
WAS:
• Bladder diary: o Each day for 7 days: time of CICs o Each day for 7 days: presence of leakage between CICs o Each day for 7 days: sleep time and wake-up time

o On the 2 weekend days: catheterized volume o On the 2 weekend days: SMIP (if applicable) o On the 2 weekend days: grade of leakage between CICs o On the 2 weekend days (visit 3/baseline and visit 8/week 24): weight of diaper/pad • SBPM (blood pressure and pulse rate): o On the 2 weekend days: triplicate measurements in the morning and evening • Questionnaires: on 1 weekend day at selected visits o PIN-Q o PGI-S o Acceptability • Confirmation of study drug intake: daily
IS AMENDED TO:
• Bladder diary: o Each day for 7 days: time of CICs o Each day for 7 days: presence of leakage between CICs o Each day for 7 days: sleep time and wake-up time o On the 2 weekend days: catheterized volume o On the 2 weekend days: SMIP (if applicable) o On the 2 weekend days: grade **and number** of leakage**s** between CICs o On the 2 weekend days (visit 3/baseline and visit 8/week 24): weight of diaper/pad • SBPM (blood pressure and pulse rate): o On the 2 weekend days: triplicate measurements in the morning and evening o **On 2 consecutive 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.** • Questionnaires: on 1 weekend day at selected visits o PIN-Q o PGI-S o Acceptability • Confirmation of study drug intake: daily **The Investigator must guide the subject and subject's parent(s)/caregiver(s) to ensure that on the evening before and during the two weekend days of collection of catheterized volume and SMIP (if applicable), the subject's fluid intake should be regulated to an appropriate level taking 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.**

IV. Synopsis, Statistical Methods
WAS:
Sample size justification: In order to allow the detection of a statistically significant change from baseline in MCC in the overall NDO with CIC study population with 90% power, 44 evaluable subjects for the assessment of the endpoint need to be enrolled, i.e., subjects with a nonmissing MCC measurement at baseline and at a postbaseline visit. The power calculation is based upon a paired t-test with a 2-sided significance level of 0.05, a real change from baseline of at least 52 mL and a SD of not larger than 103 mL. Assuming 30% of enrolled subjects will not be

evaluable, a total of approximately 63 subjects may need to be enrolled. Four analysis populations will be defined: the safety analysis set (SAF), full analysis set (FAS), per protocol set (PPS), and pharmacokinetic analysis set (PKAS) for pharmacokinetic population analysis.
IS AMENDED TO:
Sample size justification: In order to allow the detection of a statistically significant change from baseline in MCC in the overall NDO with CIC study population with 90% power, 44 evaluable subjects for the assessment of the endpoint need to be enrolled, i.e., subjects with a **valid (as by the central reviewer's assessment)** nonmissing MCC measurement at baseline and at a postbaseline visit. The power calculation is based upon a paired t-test with a 2-sided significance level of 0.05, a**n** ~~real~~ **expected** change from baseline of at least 52 mL and a SD of not larger than 103 mL. Assuming 30% of enrolled subjects will not be evaluable, a total of approximately 63 subjects may need to be enrolled. Four analysis populations will be defined: the safety analysis set (SAF), full analysis set (FAS), per protocol set (PPS), and pharmacokinetic**s** analysis set (PKAS) for pharmacokinetic population analysis.

V Flowchart and Schedule of Assessments *Table 1: Schedule of Assessments*
See next page.

WAS:

Assessments	Visit 1	Visit 2 /TC 1 †	Visit 3	Visit 4 /TC 2 †	Visit 5	Visit 6 /TC 3 †	Visit 7	Visit 8	Visit 9 /TC 4 †	Visit 10 /EOS ‡
	Screening	Start of Washout †††	Baseline	Week 2	Week 4	Week 8	Week 12	Week 24	Week 36	Week 52
	Day -28 to Day -15	Day -15 to Day -8	Day -1	Day 14 (±3 days)	Day 28 (±3 days)	Day 56 (±7 days)	Day 84 (±7 days)	Day 168 (±7 days)	Day 252 (±14 days)	Day 364 (±14 days)
Signing informed consent form	X									
Inclusion/Exclusion criteria	X		X							
Demographics	X									
Height & weight	X		X					X		X
Medical history (including NDO)	X									
Current NDO medications	X	X								
Vital signs (triplicate) and body temperature (ear) §	X		X		X		X	X		X
Physical examination	X									X
12-lead ECG (triplicate) ¶	X		X		X		X	X		X
Hematology/Biochemistry/eGFR	X		(X) ††		(X) ††		X			X
Urinalysis	X		X		X		X	X		X
Pregnancy test ‡‡	X		X		X		X	X		X
Pharmacokinetics §§					(X)	(X)	(X)	(X)	(X)	(X)
Upper urinary tract ultrasound			X							X
Urodynamic assessments ¶¶			X		X			X		
Dose-titration assessment				X	X	X				
Dispense study drug †††			X		X		X	X		
Bladder diary, SMIP and collection of catheterized volume ‡‡‡		X	X	X	X	X	X	X	X	X
SBPM (triplicate) §§§		X	X	X	X	X	X	X	X	X
PIN-Q, PGI-S			X					X		X
CGI-C								X		X
Acceptability questionnaire								X		X
Adverse events and previous and concomitant medication	●									●

ECG: Electrocardiogram; EOS: end of study; CGI-C: Clinician Global Impression of Change scale; DSMB: Data and Safety Monitoring Board; NDO: neurogenic detrusor overactivity; PGI-S: Patient Global Impression of Severity Scale; PIN-Q: Pediatric Incontinence Questionnaire; SBPM: self blood pressure measurement; SMIP: self-measurement of intravesical pressure; TC: telephone contact.

See Footnotes on next page

† For the visits where a TC is indicated there is no need for the subject to visit the clinic, provided that the e-diary data is reviewed by the investigator prior to the TC and discussed and confirmed with the subject or parent(s)/caregiver(s) during the TC.

‡ Subjects who withdraw early from the study after having received study drug should complete the EOS visit. If the final dose is reached before the last possibility for up-titration at 8 weeks, the fixed-dose treatment period will be extended to keep the entire treatment period 364 days as a minimum. The maximum is 378 days in order to allow for visit windows.

§ Triplicate vital signs with an interval of approximately 2 minutes 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. Clinic measurements will be used to assess eligibility. Single measurements for body temperature must be performed with an ear thermometer.

¶ Triplicate 12-lead ECG with an interval of about 30 seconds to 5 minutes in the supine position (when possible, but always in the same position). Subject should have been calm and without distress for at least 5 minutes.

†† Additional hematology/biochemistry taken at baseline only if an AE related to hematology/biochemistry parameters occurred between visit 1/screening and visit 3/baseline. The first group of subjects (minimum of 5, maximum of 10) who reach study visit 5/week 4 will have an additional blood draw for a DSMB-mandated interim safety check at this visit. For sampling, preferably the left arm should be used. Blood sampling should occur after vital signs and ECG measurements.

‡‡ Pregnancy test in female subjects of childbearing potential in serum (if blood is drawn) or urine (at other visits).

§§ If the subject reached steady state of her/his optimal dose, a total of 4 pharmacokinetic samples will be collected, divided over 2 sampling days. Sampling day 1: 1 trough sample; Sampling day 2: 1 trough and 2 postdose samples between 2 h and 5 h postdose, with at least 1 hour in between the samples. These 2 sampling days do not have to be in a specific order and can be selected from the given options. Dosing on a sampling day with postdose samples must occur within 1 hour after completion of breakfast [Section 5.3.4]. On days where a pharmacokinetic visit is planned in the clinic, breakfast and dosing should occur in the clinic. Blood sampling should occur after vital signs and ECG measurements.

¶¶ Additional urodynamic assessments may be performed if deemed necessary by the investigator (e.g., if SMIP is not performed at visit 4/week 2, confirmatory urodynamic assessments at visit 7/week 12 if up-titration or down-titration was done at visit 6/week 8, or an additional urodynamic assessment at visit 10/week 52 [EOT/EOS]).

††† Daily study drug administration will begin on Day 1 (the day after visit 3/baseline).

‡‡‡ After a successful screening visit, all subjects start with the completion of a 2-day weekend e-diary visit to get acquainted with the e-diary and the assessments. Completion of this diary should start in the weekend prior to visit 2. Completion of subsequent bladder diaries should start approximately 7 days prior to the indicated visit (or TC). If successful completion of the 2-day weekend e-diary is confirmed at visit 2, subjects from group A start with collection of the 7-day baseline e-diary, followed by the baseline visit. Subjects in group B start with a 14-day washout. In the second week of the washout period, collection of their 7-day baseline e-diary starts, followed by the baseline visit.

§§§ Triplicate SBPM will be performed in the morning and evening during the 2-day weekend e-diary collection period. Measurements to be taken with an interval of approximately 2 minutes in the sitting position (when possible, otherwise supine, but always in the same position). Preferably the right arm should be used. Morning measurements should be taken after waking-up, before breakfast and before study drug intake, evening measurements prior to bedtime. Subject should have been calm and without distress for at least 5 minutes.

IS AMENDED TO:

Assessments	Visit 1	Visit 2 /TC 1 †	Visit 3	Visit 4 /TC 2 †	Visit 5	Visit 6 /TC 3 †	Visit 7	Visit 8	Visit 9 /TC 4 †	Visit 10 /EOS ‡
	Screening	Start of Washout †††	Baseline	Week 2	Week 4	Week 8	Week 12	Week 24	Week 36	Week 52
	Day -28 to Day -15	Day -15 to Day -8	Day -1	Day 14 (±3 days)	Day 28 (±3 days)	Day 56 (±7 days)	Day 84 (±7 days)	Day 168 (±7 days)	Day 252 (±14 days)	Day 364 (±14 days)
Signing informed consent form	X									
Inclusion/Exclusion criteria	X		X							
Demographics	X									
Height & weight	X		X					X		X
Medical history (including NDO)	X									
Current NDO medications	X	X								
Vital signs (triplicate) and body temperature (ear) §	X		X		X		X	X		X
Physical examination	X									X
12-lead ECG (triplicate) ¶	X		X		X		X	X		X
Hematology/Biochemistry/eGFR	X		(X) ††		(X) ††		X			X
Urinalysis	X		X		X		X	X		X
Pregnancy test ‡‡	X		X		X		X	X		X
Pharmacokinetics §§					(X)	(X)	(X)	(X)	(X)	(X)
Upper urinary tract ultrasound			X							X
Urodynamic assessments ¶¶			X		X			X		
Dose-titration assessment				X	X	X				
Dispense study drug †††			X		X		X	X	**(X)**	
Bladder diary, SMIP and collection of catheterized volume ‡‡‡		X	X	X	X	X	X	X	X	X
SBPM (triplicate) §§§		X	X	X	X	X	X	X	X	X
PIN-Q, PGI-S			X					X		X
CGI-C								X		X
Acceptability questionnaire					**X**			X		X
Adverse events and previous and concomitant medication	●									●

ECG: Electrocardiogram; EOS: end of study; CGI-C: Clinician Global Impression of Change scale; DSMB: Data and Safety Monitoring Board; NDO: neurogenic detrusor overactivity; PGI-S: Patient Global Impression of Severity Scale; PIN-Q: Pediatric Incontinence Questionnaire; SBPM: self blood pressure measurement; SMIP: self-measurement of intravesical pressure; TC: telephone contact.

See Footnotes on next page

† For the visits where a TC is indicated there is no need for the subject to visit the clinic, provided that the e-diary data is reviewed by the investigator prior to the TC and discussed and confirmed with the subject or **the subject's** parent(s)/caregiver(s) during the TC.

‡ Subjects who withdraw early from the study after having received study drug should complete the EOS visit. If the final dose is reached before the last possibility for up-titration at 8 weeks, the fixed-dose treatment period will be extended to keep the entire treatment period 364 days as a minimum. The maximum is 378 days in order to allow for visit windows.

§ Triplicate vital signs with an interval of approximately 2 minutes 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. Clinic measurements will be used to assess eligibility. Single measurements for body temperature must be performed with an ear thermometer.

¶ Triplicate 12-lead ECG with an interval of about 30 seconds to 5 minutes in the supine position (when possible, but always in the same position). Subject should have been calm and without distress for at least 5 minutes.

†† Additional hematology/biochemistry taken at baseline only if an AE related to hematology/biochemistry parameters occurred between visit 1/screening and visit 3/baseline. The first group of subjects (minimum of 5, maximum of 10) who reach study visit 5/week 4 will have an additional blood draw for a DSMB-mandated interim safety check at this visit. For sampling, preferably the left arm should be used. Blood sampling should occur after vital signs and ECG measurements.

‡‡ Pregnancy test in female subjects of childbearing potential in serum (if blood is drawn) or urine (at other visits).

§§ If the subject reached steady state of her/his optimal dose, a total of 4 pharmacokinetic samples will be collected, divided over 2 sampling days. Sampling day 1: 1 trough sample; Sampling day 2: 1 trough and 2 postdose samples between 2 h and 5 h postdose, with at least 1 hour in between the samples. These 2 sampling days do not have to be in a specific order and can be selected from the given options. **To allow for an early assessment of the dose-response relationship by the DSMB, it is preferred the pharmacokinetic sampling takes place as early in the study as possible.** Dosing on a sampling day with postdose samples must occur within 1 hour after completion of breakfast [Section 5.3.4]. On days where a pharmacokinetic visit is planned in the clinic, breakfast and dosing should occur in the clinic. Blood sampling should occur after vital signs and ECG measurements.

¶¶ Additional urodynamic assessments may be performed if deemed necessary by the investigator ~~(e.g., if SMIP is not performed at visit 4/week 2, confirmatory urodynamic assessments at visit 7/week 12 if up-titration or down-titration was done at visit 6/week 8, or an additional urodynamic assessment at visit 10/week 52 [EOT/EOS])~~.

††† Daily study drug administration will begin on Day 1 (the day after visit 3/baseline). **Due to shelf-life limitations, an additional dispensing visit is foreseen at visit 9/week 36 for subjects receiving mirabegron oral suspension. This dispensing visit does not need to be accompanied by the subject.**

‡‡‡ After a successful screening visit, all subjects start with the completion of a 2-day weekend e-diary visit to get acquainted with the e-diary and the assessments. Completion of this diary should start in the weekend prior to visit 2. Completion of subsequent bladder diaries should start approximately 7 days prior to the indicated visit (or TC). If successful completion of the 2-day weekend e-diary is confirmed at visit 2, subjects from group A start with collection of the 7-day baseline e-diary, followed by the baseline visit. Subjects in group B start with a 14-day washout. In the second week of the washout period, collection of their 7-day baseline e-diary starts, followed by the baseline visit.

§§§ Triplicate SBPM will be performed in the morning and evening during the 2-day weekend e-diary collection period **and on 2 consecutive 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**. Measurements to be taken with an interval of approximately 2 minutes in the sitting position (when possible, otherwise supine, but always in the same position). Preferably the right arm should be used. Morning measurements should be taken after waking-up, before breakfast and before study drug intake, evening measurements prior to bedtime. Subject should have been calm and without distress for at least 5 minutes.

1 Introduction

1.2.2 Clinical Data

WAS:

The global pediatric development program for mirabegron in NDO and OAB currently consists of 8 studies in various stages of completion.
The first available clinical data of mirabegron in children comes from study 178-CL-202: a single ascending dose phase 1 study with mirabegron tablets in pediatric subjects diagnosed with OAB or NDO.
Cohort 1: male and female adolescents (12 to less than 18 years); low dose and fed
Cohort 2: male and female children (5 to less than 12 years); low dose and fed
Cohort 3: male and female adolescents (12 to less than 18 years); high dose and fed
Cohort 4: male and female children (5 to less than 12 years); high dose and fed
Cohort 5: male and female children (5 to less than 12 years); high dose and fasted
Fed: within one hour after a light breakfast
Low dose: single oral doses that are predicted to result in an exposure comparable to that in adults when dosed with 25 mg mirabegron tablets once daily at steady-state (69 ng.h/mL).
High dose: single oral doses that are predicted to result in an exposure comparable to that in adults when dosed with 50 mg mirabegron tablets once daily at steady-state (188 ng.h/mL).
The doses in Study 178-CL-202 were predicted applying an allometric scaling approach of the data obtained in adults under non standardized food conditions.
A dose escalation committee including a pediatric nephrologist and pediatric cardiologist has reviewed the data obtained in these cohorts and concluded that mirabegron exposure was within the predicted target ranges for all cohorts and that mirabegron showed an acceptable safety profile at the doses tested.
5 TEAEs were reported: 'vomiting'(2x), 'fever', 'mean QT interval corrected by Bazett's formula (QTcB) of 452 ms' and 'QTcB prolongation'. The intensity for all TEAEs was mild and only one (QTcB prolongation versus baseline) was judged by the investigator to be possibly related to study drug. No QTc prolongation > 60 ms versus baseline was observed (mean of triplicates).
No clinically significant increases in vital signs have been observed. Increases in pulse rate were observed across all cohorts but these were not considered clinically significant/relevant per investigator's assessment.
The centrally read Holter observations in cohort 4 and 5 showed a trend towards 2 episodes of a mean and median increase in mean hourly heart rate; the first one starting 4 to 6 hours postdose and reaching the highest values at 6 to 8 hours after dosing and the second one starting 10-12h after dosing and continuing until the end of the recording, without a change in circadian rhythm. This was not considered as clinically relevant by the dose escalation committee.
For pediatric subjects an oral suspension is under development.

IS AMENDED TO:

~~The global pediatric development program for mirabegron in NDO and OAB currently consists of 8 studies in various stages of completion.~~
~~The first available clinical data of mirabegron in children comes from study 178-CL-202: a single ascending dose phase 1 study with mirabegron tablets in pediatric subjects diagnosed with OAB or NDO.~~

- ~~Cohort 1: male and female adolescents (12 to less than 18 years); low dose and fed~~
- ~~Cohort 2: male and female children (5 to less than 12 years); low dose and fed~~
- ~~Cohort 3: male and female adolescents (12 to less than 18 years); high dose and fed~~
- ~~Cohort 4: male and female children (5 to less than 12 years); high dose and fed~~
- ~~Cohort 5: male and female children (5 to less than 12 years); high dose and fasted~~

~~Fed: within one hour after a light breakfast~~
~~Low dose: single oral doses that are predicted to result in an exposure comparable to that i adults when dosed with 25 mg mirabegron tablets once daily at steady-state (69 ng.h/mL).~~
~~High dose: single oral doses that are predicted to result in an exposure comparable to that i adults when dosed with 50 mg mirabegron tablets once daily at steady-state (188 ng.h/mL)~~

~~The doses in Study 178-CL-202 were predicted applying an allometric scaling approach of the data obtained in adults under non standardized food conditions.~~

~~A dose escalation committee including a pediatric nephrologist and pediatric cardiologist has reviewed the data obtained in these cohorts and concluded that mirabegron exposure was within the predicted target ranges for all cohorts and that mirabegron showed an acceptable safety profile at the doses tested.~~

~~5 TEAEs were reported: 'vomiting'(2x), 'fever', 'mean QT interval corrected by Bazett's formula (QTcB) of 452 ms' and 'QTcB prolongation'. The intensity for all TEAEs was mild and only one (QTcB prolongation versus baseline) was judged by the investigator to be possibly related to study drug. No QTc prolongation > 60 ms versus baseline was observed (mean of triplicates).~~

~~No clinically significant increases in vital signs have been observed. Increases in pulse rate were observed across all cohorts but these were not considered clinically significant/ relevant per investigator's assessment.~~

~~The centrally read Holter observations in cohort 4 and 5 showed a trend towards 2 episodes of a mean and median increase in mean hourly heart rate; the first one starting 4 to 6 hours postdose and reaching the highest values at 6 to 8 hours after dosing and the second one starting 10-12h after dosing and continuing until the end of the recording, without a change in circadian rhythm. This was not considered as clinically relevant by the dose escalation committee.~~

~~For pediatric subjects an oral suspension is under development.~~

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 2].

Table 2 Overview of Current Supporting Mirabegron Studies in the Pediatric Clinical Development Program for NDO and OAB

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**	**Completed**

	female subjects.	
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 neurogenic detrusor overactivity (NDO) or overactive bladder (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 neurogenic detrusor overactivity (NDO) or overactive bladder (OAB).**	**Ongoing**
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**	**Ongoing**

The results of studies 178-CL-201 and 178-CL-202 are reported in the most recent version of the pediatric IB. The data from these studies 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 less or because they cannot swallow tablets, an oral suspension with a strength of 2 mg/mL was developed. The relative bioavailability was assessed in healthy subjects (178-CL-201) to be 53.44% lower compared to tablets. The results of this study and study 178-CL-202 were used to support the use of the 2 mg/mL in study 178-CL-203.
That study is a single dose phase 1 study with mirabegron oral suspension in pediatric subjects from 3 to less than 12 years of age with NDO and in pediatric subjects from 5 to less than 12 years of age with OAB. This study is currently ongoing with 6 of 9 planned subjects having completed the study. Single doses of mirabegron are administered that are predicted to result in an exposure comparable to that in adults when dosed with 50 mg mirabegron tablets once daily at steady-state (188 ng·h/mL). Subjects received mirabegron oral suspension within 1 hour after a light breakfast. Doses were compensated for the lower bioavailability of suspension versus tablets (see above). This study is ongoing but the preliminary results are provided below.
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, three period cross over design in healthy subjects. Subjects received the following three treatments in

random order: 1) 11mL 8 mg/mL oral suspension of mirabegron under fasted conditions, 2) 11mL 8 mg/mL oral suspension of mirabegron under fed conditions and 3) 44 mL 2 mg/mL oral suspension of mirabegron under fasted conditions. This study is ongoing, but a summary of the preliminary results is provided below.

Exposure:

The single doses of the 2 mg/mL oral suspension for Study 178-CL-203 were predicted using a population pharmacokinetic (popPK) model developed on pharmacokinetic data obtained in Study 178-CL-201, with food, dose, and formulation effects on the bioavailability, and was validated on data from Study 178-CL-202. The observed exposures were in line with the target exposure of 188 ng·h/mL; the median AUC24 was 207 ng·h/mL (n=6, mean (SD): 226.4 (152.3), range: 39.7-467). These preliminary results suggest that the use of the popPK model is appropriate for dose selection. The model predictions of the PED50 doses at a strength of 2 mg/mL would require large volumes of oral suspension every day (up to 44 mL). Therefore, to reduce the volume, a higher strength oral suspension was developed.

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 3].

Table 3 178-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)

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)

CI: confidence interval; LS: least squares.

The analysis was performed on log-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.

The information obtained in studies 178-CL-203 and 178-CL-208 was taken into account when predicting the doses for this study as outlined in Section 2.2.2 of this protocol. The doses described in Section 2.2.2 suggest tablets for pediatric subjects with a body weight of ≥ 35 kg, and the 8 mg/mL oral suspension for children with a body weight between 11 and 35 kg, or for those subjects with a body weight ≥ 35 kg who do not want to or are unable to take tablets.

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 6 subjects who completed the study (3 with NDO and 3 with OAB) 1

treatment emergent adverse event (TEAE) was reported: pyrexia on day 1 in a 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 QTcF values > 450 ms and no QTc prolongation > 30 ms versus baseline was observed (mean of triplicates).
Increases in vital signs have been observed but these were not considered clinically significant per investigator's assessment.
A 24-hour Holter recording was recorded in all subjects on a reference day and on the dosing day. The main objective of the Holter 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 has been observed. This was not considered as clinically relevant taken into account the multiple blood draws, the low number of subjects and the absence of a placebo 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. 20 AEs were considered not related; 2 were considered possibly related (dizziness, mild and orthostatic dizziness mild).

1 Introduction and 4 Treatment(s)

1.3 Summary of Key Safety Information for Study Drugs and 4.1.1 Test Drug

WAS:

Mirabegron has been approved in more than 50 countries including the US, Japan and the EU.

IS AMENDED TO:

Mirabegron has been approved in more than ~~50~~ **65** countries ~~including the US, Japan and the EU~~ **worldwide**.

1 Introduction

1.4 Risk-Benefit Assessment

WAS:

- Beyond 4 weeks of therapy, repeated home measurements of the intravesical pressure and at least 1 urodynamic investigation allow the investigator to adapt the CIC-regimen or to withdraw the subject if considered necessary. If SMIP evaluations are not done, the investigator can perform additional urodynamic assessments if deemed necessary.

IS AMENDED TO:

- ~~Beyond 4 weeks of therapy, repeated home measurements of the intravesical pressure and at least 1 urodynamic investigation allow the investigator to adapt the CIC-regimen or to withdraw the subject if considered necessary. If SMIP evaluations are not done, the investigator can perform additional urodynamic assessments if deemed necessary.~~

- **Additional urodynamic assessments may be performed at any time in the study study if deemed necessary by the investigator.**

2 Study Objective(s), Design, and Endpoints

2.3.2.2 Bladder Volume and Leakage Measures

ADDED:

For this study the first morning catheterization after waking up is regarded as part of the 'night', whilst the last evening catheterization before sleep time is part of the 'day'. The collected urine volume will be weighed by the subject or subject's parent(s)/caregiver(s) and the results will be entered in the e-diary. The conversion factor used for weight-to-volume is 1g = 1mL.

2 Study Objective(s), Design, and Endpoints

2.3.3 Safety Endpoints

WAS:

- Change from baseline in ECG parameters at visit 5/week 4 and visit 10/week 52 (EOT/EOS)

IS AMENDED TO:

- Change from baseline in ECG parameters at visit 5/week 4**, visit 7/week 12, visit 8/week 24,** and visit 10/week 52 (EOT/EOS)

2 Study Objective(s), Design and, Endpoints

2.3.4 Pharmacokinetics

WAS:

The following pharmacokinetic parameters will be determined at visit 5/week 4, visit 6/week 8, visit 7/week 12, visit 8/week 24 and/or visit 9/week 36:

- C_{max}, t_{max}, AUC_{24}, C_{trough}, CL/F and V_z/F

Additional pharmacokinetic parameters as may be calculated based on the model used.

IS AMENDED TO:

The following pharmacokinetic parameters will be determined **for each individual** ~~at visit 5/week 4, visit 6/week 8, visit 7/week 12, visit 8/week 24 and/or visit 9/week 36~~:

- C_{max}, t_{max}, AUC_{24}, C_{trough}, CL/F and V_z/F

Additional pharmacokinetic parameters ~~as~~ may be calculated based on the model used.

3 Study Population

3.3 Exclusion Criteria

WAS:
1. Subject has a known genitourinary condition (other than NDO) that may cause overactive contractions or incontinence (e.g., bladder extrophy, urinary tract obstruction, urethral diverticulum or fistula) or kidney/bladder stones or another persistent urinary tract pathology that may cause symptoms.
IS AMENDED TO:
1. Subject has a known genitourinary condition (other than NDO) that may cause overactive contractions or incontinence (e.g., bladder extrophy, urinary tract obstruction, urethral diverticulum or fistula) or kidney/bladder stones or another persistent **local** ~~urinary tract~~ pathology that may cause **urinary** symptoms.

3 Study Population
3.3 Exclusion Criteria
ADDED:
For exclusion criterion 9 please refer to Appendix 12.9 and for exclusion criterion 10 please refer to Appendix 12.10, Appendix 12.11, Appendix 12.12 and Appendix 12.13.

5 Treatments and Evaluation
5.3.4 Pharmacokinetics
WAS:
These 2 days can be selected from the options given in the schedule of assessments (i.e., on visit 5/week 4, visit 6/week 8, visit 7/week 12, visit 8/week 24 or visit 9/week 36) and do not have to be in a specific (consecutive) order:
IS AMENDED TO:
These 2 days can be selected from **any of** the options given in the schedule of assessments (i.e., on visit 5/week 4, visit 6/week 8, visit 7/week 12, visit 8/week 24**,** ~~or~~ visit 9/week 36**, or visit 10/week 52**) and do not have to be in a specific (consecutive) order:

5 Treatments and Evaluation
5.3.4 Pharmacokinetics
ADDED:
To allow for an early assessment of the dose-response relationship by the DSMB, it is preferred the pharmacokinetic sampling takes place as early in the study as possible.

5 Treatments and Evaluations
5.4.1.1 Clinic Measurement of Vital Signs
WAS:
The measurements will be per standard clinic practices and should be consistent for all visits.

IS AMENDED TO:
The **preferred method of measurement is via the auscultatory technique. If this method is not available at the site,** measurements will be per standard clinic practices. **The method for measuring vital signs** ~~and~~ should be consistent for all visits.

5 Treatments and Evaluation *5.4.2 Adverse Events*
WAS:
AEs will be collected from visit 1/screening until visit 10/week 52 (EOT/EOS). See [Section 5.5] for information regarding AE collection and data handling. Collection of AEs will start once the ICF is signed.
IS AMENDED TO:
AEs will be collected from visit 1/screening until visit 10/week 52 (EOT/EOS). See [Section 5.5] for information regarding AE collection and data handling. ~~Collection of AEs will start once the ICF is signed.~~

5 Treatments and Evaluation *5.4.6 Self-measurement of Intravesical Pressure*
WAS:
SMIP will be performed as part of the bladder diary [Section 5.3.2].
IS AMENDED TO:
SMIP will be performed as part of the bladder diary [Section 5.3.2]. **In case the measuring device is not available/approved for use at the site, the subject or parent(s)/caregiver(s) are not able or willing to perform the SMIP, or there is a technical problem, the SMIP may be omitted.**

5 Treatments and Evaluation *5.5.5 Reporting of Serious Adverse Events*
WAS:
In the case of an SAE, the investigator must contact the CRO by telephone or fax/e-mail immediately (within 24 hours of awareness). The investigator should complete and submit an SAE Worksheet containing all information that is required by the Regulatory Authorities to CRO by fax/e-mail immediately (within 24 hours of awareness). If the faxing/e-mailing of an SAE Worksheet is not possible or is not possible within 24 hours, the local drug safety contact should be informed by phone. Within 24 hours after receipt of the information, the CRO will forward the SAE details to the Sponsor.
IS AMENDED TO:
In the case of an SAE, the investigator must contact the CRO by telephone or fax/e-mail immediately (within ~~24 hours~~ **1 working day** of awareness).

The investigator should complete and submit an SAE Worksheet containing all information that is required by the Regulatory Authorities to CRO by fax/e-mail immediately (within ~~24 hours~~ **1 working day** of awareness). If the faxing/e-mailing of an SAE Worksheet is not possible or is not possible within ~~24 hours~~ **1 working day**, the local drug safety contact should be informed by phone. Within ~~24 hours~~ **1 working day during weekdays or within 60 hours during weekends, whatever is shorter,** after receipt of the information, the CRO will forward the SAE details to the Sponsor. **SAEs must be reported up to 28 days after the End of Study visit or up to 28 days after early discontinuation of dosing.**

7 Statistical Methodology *7.1 Sample Size*
WAS:
A study with 44 evaluable subjects who have MCC measurements at treatment week 24 and at baseline would have a 90 percent power to detect a statistical significant change from baseline, if the real change from baseline in the subject population is at least 52 mL and the real SD for change from baseline is ≤ 103 mL.
IS AMENDED TO:
A study with 44 evaluable subjects who have **valid (as by the central reviewer's assessment) nonmissing** MCC measurements at ~~treatment~~ **visit 8**/week 24 and at baseline would have a 90 percent power to detect a statistical significant change from baseline, if the real change from baseline in the subject population is at least 52 mL and the real SD for change from baseline is ≤ 103 mL.

7 Statistical Methodology *7.2.1 Full Analysis Set*
WAS:
The full analysis set (FAS) will consist of all subjects who: • Took at least 1 dose of study drug, and • Provided both valid baseline and at least 1 postbaseline value for the primary efficacy endpoint (MCC).
IS AMENDED TO:
The full analysis set (FAS) will consist of all subjects who: • Took at least 1 dose of study drug, and • ~~Provided both~~ **Had a** valid **(as by the central reviewer's assessment) nonmissing MCC measurement at** baseline and at ~~least 1~~ **a** post baseline ~~value~~ **visit** for the primary efficacy endpoint ~~(MCC)~~.

7 Statistical Methodology *7.2.4 Pharmacokinetics Analysis Set*

WAS:
Since the actual bioanalytical results from the last treatment group may only become available after the data review meeting, additional data points may be excluded at the time of pharmacokinetic analysis at the discretion of the pharmacokineticist.
IS AMENDED TO:
Since the actual bioanalytical results ~~from the last treatment group~~ may only become available after the data review meeting, additional data points may be excluded at the time of pharmacokinetic analysis at the discretion of the pharmacokineticist.

7 Statistical Methodology

7.4.1.3 Subgroup and Sensitivity Analyses of Primary Endpoint

WAS:

For the primary efficacy endpoint, MCC, 95% CI will be calculated for mean change from baseline per age group.

A subgroup analysis of the primary efficacy endpoint by whether NDO medication treatment was received at screening/prior to start of washout for both groups of subjects will be performed if there are sufficient subject numbers (with and without LOCF) on the FAS.

A subgroup analysis of the primary efficacy endpoint of patients with insufficient efficacy under antimuscarinics specifically intended for NDO treatment (i.e. stopping the medication for lack of efficacy prior to start of treatment) will be performed if there are sufficient subject numbers (with and without LOCF) on the FAS.

The following sensitivity analyses of the primary efficacy endpoint will be performed if there are sufficient subject numbers (without LOCF only) on the FAS:

- Excluding those subjects who had a positive urine culture at visit 3/baseline and/or visit 8/week 24.

IS AMENDED TO:

For the primary efficacy endpoint, MCC, 95% CI will be calculated for mean change from baseline per age group**, per formulation, and per dosing regimen (with and without LOCF)**.

Dosing regimen here refers to whether the subjects had been up-titrated to PED50 at least once or maintained at PED25 for safety reasons at least until visit 8/week 24.

A subgroup analysis of the primary efficacy endpoint by whether NDO medication treatment was received at screening/prior to start of washout for both groups of subjects will be performed if there are sufficient subject numbers (with and without LOCF) on the FAS.

A subgroup analysis of the primary efficacy endpoint of ~~patients~~ **subjects** with insufficient efficacy under antimuscarinics specifically intended for NDO treatment (i.e. stopping the medication for lack of efficacy prior to start of treatment) will be performed if there are sufficient subject numbers (with and without LOCF) on the FAS.

The following sensitivity analyses of the primary efficacy endpoint will be performed if there are sufficient subject numbers (without LOCF only) on the FAS:

● Excluding those subjects who had a positive urine culture at visit 3/baseline and/or visit 8/week 24. ● **For any of the subgroups specified, at least 10 subjects by stratum are required.**

7 Statistical Methodology *7.4.2 Analysis of Secondary Endpoints*
WAS:
The change from baseline for secondary endpoint based on urodynamic assessments, the subject's e-diary (including bladder diary) and questionnaires will be summarized and analyzed using similar statistical methods as for the primary endpoint, where appropriate.
IS AMENDED TO:
The change from baseline for secondary endpoint based on urodynamic assessments, the subject's e-diary (including bladder diary) and questionnaires will be summarized and analyzed using similar **primary** statistical methods as for the primary endpoint, where appropriate. **CGI-C and acceptability results will be tabulated per time point of assessment.**

7 Statistical Methodology *7.5 Analysis of Safety*
WAS:
Safety parameters such as vital signs, height and weight will also be summarized with respect to age- and sex-specific percentiles.
IS AMENDED TO:
Safety parameters such as vital signs~~, height~~ and weight will also be summarized with respect to ~~age~~**height**- and sex-specific percentiles. **Height will also be summarized with respect to age- and sex-specific percentiles.** **Subgroup presentations regarding age (children and adolescents), formulation (tablets and suspension) and dosing regimen (PED25 and PED50) will be tabulated for the following parameters: AEs, vital signs and ECGs. For any of the subgroups specified, at least 10 subjects by stratum are required.**

7 Statistical Methodology *7.5.1 Vital Signs*
WAS:
Descriptive statistics will be used to summarize vital sign results and changes from baseline by treatment group and time. Z-scores and percentiles for SBP and DBP will be calculated and summarized based on a comparison with age and sex norms supplied by the Center for Disease Control and Prevention.

IS AMENDED TO:
Descriptive statistics will be used to summarize vital sign results and changes from baseline by treatment group and time. **For clinic measurements** Z-scores and percentiles for SBP and DBP will be calculated and summarized based on a comparison with age and ~~sex~~**height** norms supplied by the Center for Disease Control and Prevention. **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].**

7 Statistical Methodology *7.5.2 Adverse Events*
WAS:
AEs will be coded using MedDRA. The number and percentage of AEs, SAEs, AEs leading to discontinuation, and AEs related to study drug will be summarized by system organ class, preferred term and treatment group. The number and percentage of AEs by severity will also be summarized.
IS AMENDED TO:
AEs will be coded using MedDRA. The number and percentage of AEs, SAEs, AEs leading to discontinuation, and AEs related to study drug will be summarized by system organ class~~,~~ **and** preferred term ~~and treatment group~~. The number and percentage of AEs by severity will also be summarized.

7 Statistical Methodology *7.5.3 Laboratory Assessments*
WAS:
For quantitative laboratory measurements descriptive statistics will be used to summarize results and change from baseline by treatment group and time point. Shifts relative to normal ranges from baseline to each time point during treatment period in lab tests will also be tabulated.
IS AMENDED TO:
For quantitative laboratory measurements descriptive statistics will be used to summarize results and change from baseline by ~~treatment group and~~ time point. Shifts relative to normal ranges from baseline to each time point during treatment period in lab tests will also be tabulated.

7 Statistical Methodology *7.5.5 Electrocardiograms*
WAS:
12-lead ECG parameters (QT, QTc, QT interval corrected by Fridericia's formula [QTcF], QTcB, HR, PR, QRS and RR) and their changes from baseline will be summarized with descriptive statistics by visit. The following thresholds will be used to characterize an

individual subject's QTc data: QTc interval > 450 ms for children, and QTc interval > 450 ms and >500 ms for male adolescents and >480 ms and >500 ms for female adolescents. These categories are cumulative in that subjects satisfying criterion for a more extreme category will also be counted in each applicable less extreme category. Similar tables will be provided for QTcF and QTcB as well. A summary of normal, abnormal not clinical significant and abnormal clinical significant findings will be provided.
IS AMENDED TO:
12-lead ECG parameters (QT, ~~QTc,~~ QT interval corrected by Fridericia's formula [QTcF], ~~QTcB,~~ HR, PR, QRS and RR) and their changes from baseline will be summarized with descriptive statistics by visit. The following thresholds will be used to characterize an individual subject's QTc**F** data ~~(QTcB and QTcF)~~: QTc**F** interval > 45~~4~~0 ms for children, and QTc**F** interval > 450 ms and >500 ms for male adolescents and >480 ms and >500 ms for female adolescents. These categories are cumulative in that subjects satisfying criterion for a more extreme category will also be counted in each applicable less extreme category. ~~Similar tables will be provided for QTcF and QTcB as well.~~ A summary of normal, abnormal not clinical significant and abnormal clinical significant findings will be provided. **In addition for QTcF, the impact of concomitant medications potentially prolonging QTc will be evaluated.** **To perform this analysis, all QTcF post-baseline values will be presented (regardless of time point). If anomalies occur, an additional presentation will be provided using only QTcF values not under the influence of respective concomitant medications.** **Details on how these will be derived, will be described in the SAP.**

7 Statistical Analyses *7.5.6 Estimated Glomerular Filtration Rate and Upper Urinary Tract Ultrasound*
WAS:
For eGFR and upper urinary tract ultrasound, descriptive statistics will be used to summarize results and change from baseline by time point.
IS AMENDED TO:
For eGFR and upper urinary tract ultrasound, descriptive statistics will be used to summarize results and change from baseline by time point. **The eGFR results will be summarized based upon the Larsson, the modified Schwartz 2009 (for children < 12 years old) and the Cockcroft-Gault equation (for adolescents).**

7 Statistical Methodology *7.6 Analysis of Pharmacokinetics*
WAS:
Descriptive statistics (N, mean, SD, minimum, median, maximum, coefficient of variation and geometric mean) will be provided for plasma concentration data and derived pharmacokinetic parameters. Further details will be specified in the SAP.

IS AMENDED TO:
Descriptive statistics (N, mean, SD, minimum, median, maximum, coefficient of variation and geometric mean) will be provided for plasma concentration data ~~and derived pharmacokinetic parameters~~. Further details will be specified in the SAP.

7 Statistical Methodology
7.6.1 Analysis of Pharmacokinetics
WAS:
Noncompartmental methods will be used to derive the PK parameters using WinNonlin software ([redacted] USA). The following plasma PK parameters of mirabegron will be calculated for each individual: C_{max}, t_{max}, AUC_{24}, C_{trough}, CL/F and V_z/F.
IS AMENDED TO:
~~Noncompartmental methods will be used to derive the PK parameters using WinNonlin software ([redacted] USA).~~ **The plasma concentrations will be analyzed with nonlinear mixed effects modeling (population pharmacokinetics) using NONMEM (version 7.3 or higher, [redacted] USA).** The following plasma ~~PK~~ **pharmacokinetic** parameters of mirabegron will be calculated for each ~~individual~~ **subject**: C_{max}, t_{max}, AUC_{24}, C_{trough}, CL/F and V_z/F.

8 Operational and Administrative Considerations
8.1.1 Data Collection
WAS:
For Screen failures the demographic data, reason for failing, informed consent, inclusion and exclusion criteria and AEs will be collected in the eCRF.
IS AMENDED TO:
For Screen failures the demographic data, reason for failing, informed consent, inclusion and exclusion criteria and AEs will be collected in the eCRF **and listed**.

11 References
WAS:
U.S. Department of Health and Human Services, National Institutes of Health. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Available from: https://www.nhlbi.nih.gov/files/docs/resources/heart/hbp_ped.pdf [Accessed 25 November 2015]

IS AMENDED TO:
~~U.S. Department of Health and Human Services, National Institutes of Health.~~ The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. **U.S. Department of Health and Human Services, National Institutes of Health National Heart, Lung, and Blood Institute. NIH Publication No. 05-5267 Originally printed September 1996 (96-3790) Revised May 2005.** Available from: https://www.nhlbi.nih.gov/files/docs/resources/heart/hbp_ped.pdf ~~[Accessed 25 November 2015]~~

11 References
ADDED:
Cockcroft DW, Gault MH (1976). Prediction of creatinine clearance from serum creatinine. Nephron. 16 (1): 31–41. doi:10.1159/000180580. PMID 1244564.
Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New Equations to Estimate GFR in Children with CKD. J Am Soc Nephrol. 2009;20:629–37.

12.3 Laboratory Assessments *Biochemistry*
WAS:
Estimated glomerular filtration rate (Larsson)
IS AMENDED TO:
Estimated glomerular filtration rate (Larsson**, modified Schwartz and Cockcroft-Gault**)

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