

**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 SAP v3: 21 May 2019**

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

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## STATISTICAL ANALYSIS PLAN

Final Version 3.0, dated 21-May-2019

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ISN: 178-CL-206A  
EudraCT number: 2015-002876-25  
IND number: IND 69,416

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## LIST OF ABBREVIATIONS AND KEY TERMS

### List of Abbreviations

Abbreviation	Description
APEB	Astellas Pharma Europe B.V.
APGD	Astellas Pharma Global Development
ASCM	Analysis Set Classification Meeting
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC <sub>24</sub>	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 <sub>max</sub>	maximum (peak) plasma drug concentration
CRO	contract research organization
CSR	clinical study report
C <sub>trough</sub>	trough plasma concentration (measured concentration at the end of a dosing interval at steady state)
CYP	cytochrome P450
DRM	Data Review Meeting
DSMB	Data and Safety Monitoring Board
EBC	Expected Bladder Capacity
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
FSI	First Subject In
HLT	High Level Term
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISN	international study number
IUD	intrauterine device
IUS	intrauterine system
LOCF	last observation carried forward
LQTS	long QT syndrome
MCC	maximum cystometric capacity
M&S	Modeling & Simulation
NDO	neurogenic detrusor overactivity
OAB	overactive bladder
PCR	Potentially Clinically Relevant
PED	pediatric equivalent dose



<b>Abbreviation</b>	<b>Description</b>
PDAS	Pharmacodynamic Data Set
PGI-S	Patient Global Impression of Severity Scale
P-gp	P-glycoprotein
PIN-Q	Pediatric Incontinence Questionnaire
PK	Pharmacokinetic(s)
PKAS	Pharmacokinetics Analysis Set
PKDAP	Pharmacokinetic Data Analysis Plan
PKMS	Pharmacokinetics, Modeling, and Simulation
PPS	per protocol set
PR	Pulse Rate
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
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

## List of Key Terms

<b>Terms</b>	<b>Definition of terms</b>
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 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.
Treatment emergent adverse event	An adverse event observed after starting administration of the study drug.

<b>Terms</b>	<b>Definition of terms</b>
Trough sample	Pharmacokinetic sample taken just prior to the next dose of study medication.

## **1 INTRODUCTION**

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol 178-CL-206A (version 2.0, dated 02 November 2016), the current EU PIP (EMEA-000597-PIP-03-M03, EMA Decision 17 March 2017, ref. P/0056/2017) and US Written Request (NDA 202611, dated 18 March 2016), and includes detailed procedures for executing the statistical analysis of the primary and secondary endpoints and safety data.

The SAP will be finalized and signed prior to First Subject In (FSI). If needed, revisions to the approved SAP may be made prior to the database hard lock. Revisions will be version controlled.

This statistical analysis is coordinated by the responsible biostatistician of Astellas Pharma Global Development, Inc. (APGD). Any changes from the analyses planned in the SAP will be justified in the Clinical Study Report (CSR).

Prior to database hard lock, a final review of data and Tables Listings and Figures (TLFs) meeting will be held to allow a review of the clinical trial data 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 hard lock.

Pharmacokinetic (PK) analyses will be described in a separate data analysis plan (PKDAP) which will be finalized prior to the analysis commencement and will be reported separately.

A SAP for the Data and Safety Monitoring Board (DSMB) will also be provided separately and finalized prior to FSI. If needed, revisions to the approved DSMB SAP may be made prior to the database hard lock. Revisions will be version controlled.

## 2 FLOW CHART AND VISIT SCHEDULE

### 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	1 <sup>st</sup> up-titration possibility	2 <sup>nd</sup> up-titration possibility	3 <sup>rd</sup> 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 <sup>†</sup>	Visit 3	Visit 4 /TC 2 <sup>†</sup>	Visit 5	Visit 6 /TC 3 <sup>†</sup>	Visit 7	Visit 8	Visit 9 /TC 4 <sup>†</sup>	Visit 10 /EOS <sup>‡</sup>
	Screening	Start of Washout <sup>†††</sup>	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) <sup>§</sup>	X		X		X		X	X		X
Physical examination	X									X
12-lead ECG (triplicate) <sup>¶</sup>	X		X		X		X	X		X
Hematology/Biochemistry/eGFR	X		(X) <sup>††</sup>				X			X
Urinalysis	X		X		X		X	X		X
Pregnancy test <sup>††</sup>	X		X		X		X	X		X
Pharmacokinetics <sup>§§</sup>					(X)	(X)	(X)	(X)	(X)	(X)
Upper urinary tract ultrasound			X							X
Urodynamic assessments <sup>¶¶</sup>			X		X			X		
Dose-titration assessment				X	X	X				
Dispense study drug <sup>†††</sup>			X		X		X	X	(X)	
Bladder diary and collection of catheterized volume <sup>†††</sup>		X	X	X	X	X	X	X	X	X
SBPM (triplicate) <sup>§§§</sup>		X	X	X	X	X	X	X	X	X
PIN-Q, PGI-S			X					X		X
CGI-C								X		X
Acceptability questionnaires					X			X		X
Adverse events and previous and concomitant medication										

ECG: Electrocardiogram; EOS: end of study; CGI-C: Clinician Global Impression of Change scale; NDO: neurogenic detrusor overactivity; PGI-S: Patient Global Impression of Severity Scale; PIN-Q: Pediatric Incontinence Questionnaire; SBPM: self blood pressure measurement; 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).
- §§ 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 post-dose samples between 2 h and 5 h post-dose, 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 post-dose samples must occur within 1 hour after completion of breakfast [Protocol 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.
- ¶¶ Mandatory at visit 3/baseline, visit 5/week 4 and visit 8/week 24. When the urodynamic trace is believed not to be in accordance with the subject's clinical condition, it is allowed to repeat the urodynamic assessment once. Additional urodynamic assessments at other visits 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.

### **3 STUDY OBJECTIVE(S) AND DESIGN**

#### **3.1 Study Objective(s)**

##### **3.1.1 Primary Objectives**

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

##### **3.1.2 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.

#### **3.2 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.

The study consists of 3 periods:

- Pretreatment period: for a maximum of 28 days before baseline, including screening (visit 1), washout (if applicable) (visit 2) and baseline (visit 3)
- 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: From screening (visit 1) to baseline (visit 3)**

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 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 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 e-diary, catheterized volumes, questionnaires and self blood pressure measurement [SBPM]).

**Efficacy Treatment Period: From the first dose the day after baseline measurements visit 3/baseline to visit 8/week 24**

Study drug administration will begin the day after the baseline visit (i.e., on day 1). 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 (PED25).

At visit 4/week 2, visit 5/week 4 and visit 6/week 8, subjects are expected to be up-titrated to the pediatric equivalent dose of 50 mg in adults (PED50), unless:

1. The investigator considers the subject to be effectively treated with PED25, based on urodynamics and 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 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.

**Long-term Safety Period: From visit 8/week 24 to visit 10/week 52 (EOT or EOT)**

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).

### **3.3 Assignment and Allocation**

No randomization is performed for the study and all subjects will receive active mirabegron treatment (open-label).

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

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.

## 4 SAMPLE SIZE

The primary endpoint will be the change from baseline in maximum cystometric capacity (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 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  $\leq 103$  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.

## 5 ANALYSIS SETS

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

Detailed criteria for analysis sets will be laid out in Classification Specifications (CS) and the allocation of subjects to analysis sets will be determined prior to database hard lock.

### 5.1 All Screened Set

The All Screened Set will consist of all subjects for whom a valid informed consent/assent is available, as per applicable local law.

Three signatures might be available from the informed consent/assent. For calculations using the date of informed consent/assent the last available date will be used.

The All Screened Set will be used to summarize disposition of subjects who were screened.

### 5.2 All Allocated Set

The All Allocated Set will consist of all allocated subjects, i.e. all those subjects with a non-missing registration date at visit 3 (baseline).

This set will be used to summarize disposition of subjects who were allocated to mirabegron treatment.

### 5.3 Full Analysis Set (FAS)

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 post-baseline visit for the primary efficacy endpoint.

The final selection of subjects for the FAS will be confirmed in the Analysis Set Classification Meeting (ASCM) based upon a review of all the pertinent data.

The FAS will be used for primary analyses of efficacy data, for sensitivity and subgroup analyses [Sections 7.4.1.2.5 and 7.8] and for summaries of some demographic and baseline characteristics.

### 5.4 Per Protocol Set (PPS)

The per protocol set (PPS) includes 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.

The list of the protocol deviations that may result in a subject in the FAS being excluded from the PPS is provided below (Section 5.4.1). The final selection of subjects for the PPS will be confirmed in the ASCM 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.

#### 5.4.1 Reasons for Exclusion From PPS

A subject may be excluded from the PPS if there has been a deviation from the protocol sufficient to affect the assessment of the efficacy of the study drug. Such deviations may include (but are not limited to) reasons why a subject was ineligible to have been included in the study, whether there were interventions that were prohibited by the protocol, or whether the subject did not adhere adequately to the study treatment or outcome assessments.

There will be no partial exclusion (e.g. of particular timepoints only) of a subject from the PPS; all of a subject's data will be excluded.

Some reasons for exclusion of a subject from the PPS are given below; however the final decision on whether or not a particular protocol deviation (see Section 7.2.2) requires the exclusion of a subject will be confirmed at the ASCM with all reasons for the decision documented in the meeting minutes.

#### Eligibility Deviations

The inclusion and exclusion criteria for the study are detailed in Appendix 1: Inclusion and Exclusion Criteria. These are all assessed at Visit 1/screening and Visit 3/baseline.

A subject will be excluded from the PPS if:

- Any of inclusion criteria 4 or 5 are not met.
- Any of exclusion criteria 1, 3, 4, 5, 6, 7, 8, 17, or 18 are met.

Violations of other inclusion and exclusion criteria may also result in exclusion of the PPS if it is considered that there is a risk that the violation affects the assessment of the efficacy of the study drug. All such violations will be considered on an individual basis at the ASCM.

#### NDO not confirmed

A subject will be excluded from the PPS if NDO cannot be confirmed by the expert review of the urodynamic traces recorded at visit 3/baseline, whether or not it is recorded that inclusion criterion 4 has been met. However, the decision for inclusion/exclusion of the subject from the PPS will be part of the Central Review Committee Data.

#### Prohibited medications

A subject will be excluded from the PPS if he/she received prohibited medications from start of wash-out period (visit 2) to baseline and from visit 7 to visit 8. Except for Botox which is not allowed if taken from <4 months before screening and/or during the whole study period. These include, but are not limited to, the following (see Appendix 2 for a more complete list):

##### Prohibited medications:

- 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).

### **Compliance to study medication**

A subject will be excluded from the PPS for either of the reasons below based on compliance to the study medication (see Section [6.5.4](#) for details on the calculation of the compliance rate between study visits):

- Treatment stopped before the primary endpoint has been reached (MCC at visit 8/week 24);
- Treatment compliance of less than 80% between visit 7/week 12 and visit 8/week 24.

All evidence and reasons for determining a violation based on compliance to the study medication will be documented in the minutes of the ASCM.

### **Missing primary efficacy endpoint**

A subject will be excluded from the PPS if he/she does not have a valid baseline (visit 3) value and a valid visit 8 value (based on the week 24 efficacy visit windows [Day 99 to Day 237]– see Section [7.11.3](#) and not imputed from earlier weeks) of the primary efficacy variable (MCC).

### **Development of discontinuation criteria**

A subject may be excluded from PPS if they developed discontinuation criteria prior to visit 8/week 24 but were not withdrawn from the study. The decision for inclusion/exclusion of the subject from the PPS will be determined at the ASCM and documented in the minutes of this meeting.

## **5.5 Safety Analysis Set (SAF)**

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 summaries of demographic and baseline characteristics and all safety and tolerability related variables.

## **5.6 Pharmacokinetics Analysis Set (PKAS)**

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 one PK 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 Global Clinical Modeling & Simulation Lead (GCMSL). 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 GCMSL. These data points will be reported in the modeling report.

The PKAS is used for all tables and graphical summaries of the PK data.

## **5.7 Pharmacodynamic Analysis Set (PDAS)**

The PDAS is not defined for this study.

## 6 ANALYSIS VARIABLES

### 6.1 Efficacy Endpoints

#### Urodynamic assessments:

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

The following parameters will be determined:

- MCC at end of filling (mL)
- Bladder compliance
- Filling volume until first detrusor contraction (> 15 cm H<sub>2</sub>O)
- Filling volume at 20 cm, 30 cm and 40 cm H<sub>2</sub>O detrusor pressure (if reached)
- Number of overactive detrusor contractions (>15 cm H<sub>2</sub>O) until end of filling
- Detrusor pressure at end of filling
- MCC expressed as percentage of Expected Bladder Capacity (EBC)

Except for Bladder compliance and MCC expressed as % of EBC, the results of the urodynamic assessments will be entered in the eCRF. Bladder compliance will be calculated by external experts and will be obtained from an external database. MCC expressed as % of EBC will be calculated using  $EBC = 24.5 \times \text{age}(\text{years}) + 62$  (Palmer et al, 1997).

#### Bladder diary:

The bladder diary is part of the subject's e-diary. After a successful visit 1/screening, all subjects should 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 3 and discussed and confirmed with the subject or parent(s)/caregiver(s) during the (telephone) visit. If the investigator is under the impression that the subject and/or 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 completion is not considered successful, the investigator should counsel/re-train the subject or parent(s)/ caregiver(s) prior to the start of the 7-day baseline e-diary. In case the subject and/or 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/caregiver 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 (weekend e-diary):

- Catheterized volume
- Grade of leakage between CICs
- Weight of diaper/pad (visit 3/baseline and visit 8/week 24)
- Number of Leakages between CICs
- Position of measure
- Urine weight

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

### **Questionnaires:**

The following questionnaires will be used:

- The PIN-Q [Appendix 4.1] 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 4.2] will be completed on one weekend day preceding visit 3/baseline, visit 8/week 24 and visit 10/week 52 (EOT/EOS).
- The Acceptability Questionnaires [Appendix 4.3 and Appendix 4.4] will be completed on one weekend day preceding visit 5/week 4, visit 8/week 24 and visit 10/week 52 (EOT/EOS).
- The CGI-C [Appendix 4.5] will be completed at visit 8/week 24 and at visit 10/week 52 (EOT/EOS).

The PIN-Q with a Likert scale adopted for 20 measures is used. Questionnaires (i.e., PIN-Q, PGI-S and the Acceptability Questionnaires) will be provided via the e-diary. Results will be directly entered in the e-diary by the subject or subject's parent/caregiver. The CGI-C will be completed by the investigator and the results will be entered in the eCRF.

The primary and secondary variables will be calculated based on the following:

- Valid urodynamic assessments made at visit 3/baseline, visit 5/week 4 and visit 8/week 24,
- Diary data collected at each visit from Visit 3 to Visit 10/EOS. Only valid diary days from week end diary and/or week day diary as appropriate will be used.
- Quality of Life data (valid PIN-Q and PGI-S questionnaires) collected at Visits 3, 8 and 10/EOS (baseline, week 24, and week 52 respectively),
- Clinician reported Questionnaire (valid CGI-C) collected at Visit 8/Week 24 and Visit 10/Week 52).

A valid urodynamic assessment is an urodynamic assessment confirmed to be valid by central reviewers.

A valid bladder diary day in the weekday diary is any e-diary day for which at least 1 catheterization with complete date and time is recorded.

A valid bladder diary day in the weekend diary is any e-diary day for which at least one catheterized volume greater than 0 mL and complete date and time is recorded. See section [6.1.3.2](#) for calculating catheterized volume.

A valid PIN-Q questionnaire is a questionnaire with answers to at least 18 of the 20 individual items used to create the total score. A PGI-S questionnaire is considered valid when subject answer to the question “How did you feel about your bladder condition during the past 3 days?”

A CGI-C is considered valid when the physician rates the change in the subject’s overall bladder symptoms.

Analysis windows will be used, as described in section [7.11.3](#)

The efficacy endpoints are described in [Table 2](#)

A summary of the efficacy endpoints is presented in [Table 3](#)

**Table 2 Efficacy Endpoints**

<b>Endpoint Number</b>	<b>Endpoint Description</b>
<b>Primary Efficacy Endpoint based on Urodynamic Measures</b>	
1	Change from baseline in MCC at visit 8/week 24
<b>Secondary Efficacy Endpoints based on Urodynamic Measures</b>	
2	Change from baseline in MCC at visit 5/week 4
3,4	Change from baseline in Bladder compliance ( $\Delta V/\Delta P$ ) at visit 5/week 4 and visit 8/week 24
5,6	Change from baseline in number of overactive detrusor contractions (> 15 cm H <sub>2</sub> O) until end of filling at visit 5/week 4 and visit 8/week 24
7,8	Change from baseline in detrusor pressure at end of filling at visit 5/week 4 and visit 8/week 24
9,10	Change from baseline in filling volume until first overactive detrusor contraction (> 15 cm H <sub>2</sub> O) at visit 5/week 4 and visit 8/week 24
<b>Secondary Efficacy Endpoints: Bladder Volume and Leakage Measures based on 7-day diary</b>	
11	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
12	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 maximum catheterized volume
13	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 maximum catheterized daytime volume
14	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 morning catheterized volume (based on first catheterization after subject woke up)
15	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 number of leakage episodes per day (day and night time)
16	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 number of dry (leakage-free) days/7 days (day and night time)
<i>Table continued on next page</i>	

Endpoint Number	Endpoint Description
<b>Secondary Efficacy Endpoints: Subject- or Clinician reported Questionnaire Endpoints</b>	
17, 18	Change from baseline at visit 8/week 24 and visit 10/week 52 (EOT/EOS) in PIN-Q
19, 20	Change from baseline at visit 8/week 24 and visit 10/week 52 (EOT/EOS) in PGI-S
21, 22	Clinician Global Impression of Change (CGI-C) at visit 8/week 24 and visit 10/week 52 (EOT/EOS)
23, 24, 25	Acceptability at visit 5/week 4, visit 8/week 24 and visit 10/week 52 (EOT/EOS)
<b>Exploratory Efficacy Endpoints based on Urodynamic Measures</b>	
26, 27	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 <sub>2</sub> O detrusor pressure, given that those pressures are reached during the examination
28, 29	Change from baseline at visit 5/week 4 and visit 8/week 24 in MCC expressed as percentage of EBC
<b>Exploratory Efficacy Endpoints based on 7-day diary</b>	
30	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
31	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 total catheterized volume per day
32	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 number of CICs/day
33	Shift 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 Responder with respect to leakage (complete responder, partial responder, non-responder)
34	For subjects with no leakage during the sleeping time: 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 morning catheterized volume (based on first catheterization after subject woke up)
35	For subjects with leakage during the sleeping time: 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 morning catheterized volume (based on first catheterization after subject woke up)
36	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 percentage of catheterizations without intermittent leakage accident

**Table 3 Summary of Efficacy Endpoints**

Variable	Outcome	Endpoints						
		Visit 4/ week 2	Visit 5/ week 4	Visit 6/ week 8	Visit 7/ week 12	Visit 8/ week 24	Visit 9/ week 36	Visit 10/ week 52 (EOT/EOS)
<b>Primary and secondary urodynamic endpoints :</b>								
MCC	Change from baseline		2			1		
Bladder compliance	Change from baseline		3			4		
NODC*	Change from baseline		5			6		
Detrusor pressure	Change from baseline		7			8		
Filling volume	Change from baseline		9			10		
<b>Secondary bladder volume and leakage measures endpoints (7-day diary)</b>								
Average CV <sup>l</sup>	Change from baseline					11		
Maximum CV <sup>l</sup> per day	Change from baseline					12		
Maximum CV <sup>l</sup> (daytime)	Change from baseline					13		
Average CV <sup>l</sup> (morning)	Change from baseline					14		
Mean NLE <sup>8</sup> per day (day and night time)	Change from baseline					15		
Number of dry <sup>5</sup> days/7 days (day and night time)	Change from baseline					16		
<b>Secondary questionnaire endpoints</b>								
PIN-Q	Change from baseline					17		18
PGI-S	Change from baseline					19		20
CGI-C	N (%)					21		22
Acceptability (tablets and oral suspension)	N (%)		23			24		25
<b>Exploratory urodynamic and 7-day diary endpoints</b>								
Filling volume (20, 30 and 40 cm H <sub>2</sub> O)	Change from baseline		26			27		

Table continued on next page

Variable	Outcome	Endpoints						
		Visit 4/ week 2	Visit 5/ week 4	Visit 6/ week 8	Visit 7/ week 12	Visit 8/ week 24	Visit 9/ week 36	Visit 10/ week 52 (EOT/EOS)
MCC expressed as % of EBC	Change from baseline		28			29		
Mean Grade of leakage	N(%)					30		
Total CV <sup>£</sup> per 24 h	Change from baseline					31		
No of CICs/day	Change from baseline					32		
Responder with respect to leakage	Shift from baseline					33		
Subjects with no leakage during the sleeping time: Average CV <sup>£</sup> (morning)	By Visit					34		
Subjects with leakage during the sleeping time: Average CV <sup>£</sup> (morning)	By Visit					35		
Reduction in percentage of Catheterizations without intermittent leakage accident	Shift from Baseline					36		

\* Number of Overactive Detrusor Contractions (NODC); <sup>£</sup> Catheterized Volume (CV); <sup>&</sup> Number of Leakage Episodes (NLE), <sup>\$</sup> Leakage free

### 6.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be the change from baseline in MCC at visit 8/week 24 (based on filling urodynamics).

#### 6.1.1.1 Maximum Cystometric Capacity (MCC)

MCC (mL) is recorded in the “VOLUME” section of the “Urodynamic Testing” pages of the eCRF under “Volume at the end of filling”.

Baseline MCC is the MCC recorded at the baseline visit. The change from baseline at visit 8/week 24 in MCC is the MCC at the week 24 visit minus the baseline MCC.

For the primary analysis no imputation of missing data will be performed, ie, only non-missing (week 24) data will be used for analysis.

In addition, MCC will be calculated using the last observation carried forward (LOCF) method (see section 7.11.1): ie, the latest available post-baseline value from before week 24 will be carried forward and used for analysis. To calculate the change from baseline, the baseline MCC must be available and at least the visit 5/week 4 MCC, any unscheduled visit MCC before week 24, or the visit 8/week 24 MCC, else the primary efficacy variable is missing. Missing values at visit 8/week 24 will be imputed from previous post-baseline values using the last observation carried forward (LOCF) method (see section 7.11.1).

In addition, the MCC will also be calculated without using the LOCF technique, ie., only non-missing data will be used for analysis.

### 6.1.2 Primary Estimand

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

- Target population: all subjects who took at least 1 dose of the study drug, and in whom a valid non-missing MCC measurement at baseline and after administration of the study drug is available;
- Outcome measurement: MCC at visit 8/week 24;
- Intercurrent event: had the subject not discontinued the study drug for any reason;
- Population-based summary: difference of MCC at visit 8/week 24 (or prior, due to study drug discontinuation) compared to baseline.

For a single arm baseline controlled study, this “de jure” estimand is considered the appropriate choice. As some effect is expected early in the study and with continued treatment could be expected to be maintained, it’s considered appropriate to impute for subjects with missing values at visit 8/week 24 by their visit 5/week 4 value (if available).

A “de facto” estimand (treatment policy) was not chosen for this study. As this is a single arm treatment, a treatment policy estimand (which typically compares two randomized arms regardless of treatment changes) was not considered suitable for this type of study. A further reason against the use of the treatment policy estimand is the fact that subjects need to immediately start a different treatment after study drug discontinuation, which may differ

across different investigators, and is likely different from the treatment they took before entering this study. The impact of such a treatment mix on the effect of mirabegron would be difficult to interpret.

Difference of MCC at visit 8/week 24 (or prior, due to study drug discontinuation) compared to baseline is the primary estimator.

As a sensitivity analysis, Mixed-Effect Model Repeated Measure (MMRM) will be used to handle any missing endpoint at visit 8/week 24.

### **6.1.3 Secondary Efficacy Endpoints**

Secondary efficacy endpoints are described in [Table 2](#) and [Table 3](#) above.

#### **6.1.3.1 Urodynamic Measures**

For each of these endpoints, the change from baseline at the post-baseline value is the value at the post-baseline visit minus the value at the baseline visit. If either the baseline value or the post-baseline visit value is missing, the change from baseline will be missing. No imputation will be done.

##### **6.1.3.1.1 Overactive Detrusor Contractions (>15 cmH<sub>2</sub>O)**

The volume (mL) of fluid instilled until the first detrusor contraction (>15 cm H<sub>2</sub>O) is recorded in the “VOLUME” section of the “Urodynamic Testing” pages of the eCRF. If no contraction occurred, the bladder volume will be missing in the eCRF and the MCC at that visit will be used.

##### **6.1.3.1.2 Number of Overactive Detrusor Contractions and Detrusor Pressure at end of filling**

The number of overactive detrusor contractions (>15 cm H<sub>2</sub>O) until end of filling is recorded in the same section as the Overactive Detrusor Contractions of the “Urodynamic Testing” pages of the eCRF. Detrusor pressure at end of filling (cm H<sub>2</sub>O) is recorded in the same section of the eCRF.

##### **6.1.3.1.3 Bladder Compliance**

Bladder compliance ( $\Delta V/\Delta P_{det}$ ) will be assessed by the independent central reviewers and reported as annotations on the urodynamic trace and in an external database, not in the eCRF.

The calculation of the bladder compliance will be performed by the central reviewers. To standardize this calculation, the most linear part of the volume/pressure relationship will be isolated and used for calculating compliance. The values for V and P at the beginning and the end of this portion of the tracing are then used to calculate  $\Delta V/\Delta P_{det}$  [Bauer, 2015].

##### **6.1.3.2 Bladder Volume and Leakage Measures**

For each of these endpoints (see [Table 2](#) and [Table 3](#)), the change from baseline to the post-baseline value is the value at the post-baseline visit minus the value at the baseline visit. If either the baseline value or the post-baseline visit value is missing, the change from baseline will be missing. No imputation will be done.



The value calculated from the 7-day diary period before visit 3 will be regarded as the baseline value. Each post-baseline value will be calculated using the 7-day diary period before the post-baseline visit.

Catheterized volume per catheterization is not directly collected in the 7-day diary, instead the weight of the pee per catheterization is entered. If the subject recorded the presence of poo this measurement will be invalid and considered as missing for analysis purposes. Catheterized volume per catheterization [mL] will be calculated as weight of the pee per catheterization [mg], using the following conversion formula: 1 g = 1 mL.

#### **6.1.3.2.1 Average catheterized volume per catheterization (weekend diary)**

For each subject, the average catheterized volume per catheterization is calculated as the sum of all available (non-missing) catheterized volumes recorded over both of the 2 measuring days in the weekend diary, whether or not these 2 days are consecutive divided by the number of catheterizations with non-missing volumes.

If volumes are recorded on 1 single day of the weekend diary, then the average catheterized volume per catheterization is calculated using all available (non-missing) catheterized volumes recorded on that day.

If no volumes are recorded on any day of the weekend diary, then the average catheterized volume per catheterization will be missing.

#### **6.1.3.2.2 Maximum catheterized volume per day (weekend diary)**

For each subject, the maximum catheterized volume per day is calculated using all available (non-missing) catheterized volumes recorded for the 2 measuring days in the weekend e-diary, whether or not these 2 days are consecutive. The maximum value will be calculated separately for each measuring day and the mean of these two values will be used.

If volumes are recorded on 1 single day of the weekend e-diary, then the maximum catheterized volume per day is calculated using all available (non-zero) catheterized volumes recorded on that day.

If no volumes are recorded on any day of the weekend e-diary, then the maximum catheterized volume per day will be missing.

#### **6.1.3.2.3 Maximum catheterized daytime volume (weekend diary)**

For each subject, the maximum catheterized daytime volume is calculated using all available (non-missing) catheterized daytime volumes for the 2 measuring days in the weekend e-diary, whether or not these 2 days are consecutive. The maximum value will be calculated separately for each measuring day and the mean of these two values will be used.

If volumes are recorded on 1 single day of the weekend e-diary, then the maximum catheterized daytime volume is calculated using all available (non-zero) catheterized daytime volumes recorded on that day.

If no volumes are recorded on any day of the weekend e-diary, then the maximum catheterized daytime volume will be missing.

Daytime is defined as the time between wake-up time (minus 30 min) and time to sleep (plus 29 minutes) recorded in the e-diary; e.g. if the wake-up time is HH:MM=08:30 and sleep time is HH:MM=22:00, then daytime is defined from 08.00 to 22.29.

If wake up time and/or time sleeps is missing imputation rules will be applied as per section [7.11.1.2](#)

#### **6.1.3.2.4 Average morning catheterized volume (weekend diary)**

On a volume-measuring day in the e-diary, the first morning catheterized volume is the first recorded non-zero volume within or after the hour of the wake-up time, e.g. if the wake-up time is HH:MM=08:30, then the first non-zero volume recorded during the 8-9am hour period or later period is used. If the wake-up time is missing on a measuring day, the first non-zero recorded volume after 06:00 will be used. If no non-zero volume is recorded before 15:00 on a measuring day, the first morning catheterized volume will be missing for that e-diary day.

The average first morning catheterized volume is calculated as the average of the available first morning catheterized volumes recorded for the 2 measuring days in the weekend e-diary, whether or not these 2 days are consecutive.

If the first morning catheterized volume is recorded on 1 single day of the weekend e-diary, then the average morning catheterized is the first morning catheterized on that day.

If no first morning catheterized volumes are recorded on any day of the weekend e-diary, then the average first morning catheterized volume will be missing.

#### **6.1.3.2.5 Mean number of leakage episodes per day (day and night time) (weekend diary)**

For each subject, the mean number of leakage episodes per day (during day and night time) is calculated using all available (non-missing) number of leakage episodes for the 2 measuring days in the weekend diary during day and night time.

If the number of leakage episodes is recorded on 1 single day in the 7-day diary during day and night time, then the mean number of leakage episodes per day during day and night time is equal to the total number of leakage episodes recorded on that day during day and night time.

If no leakage episodes are recorded on any day of the weekend diary during day and night time, then the mean number of leakage episodes per day will be zero. If nothing is recorded, e.g., not completing the diary, the result is missing.

#### **6.1.3.2.6 Number of dry (leakage-free) days per 7 days (day and night time) (7-day diary)**

Let  $D_{dry}$  be the number of valid diary days where the response to the question 'Did you leak between this catheterization and the last one' is 'No' each time a new catheterization is entered during the day and night time period.

Let  $D_{wet}$  be the number of valid diary days where the response to the question ‘Did you leak between this catheterization and the last one’ is ‘Yes’ for at least one catheterization entered during the day and night time period.

If  $(D_{dry} + D_{wet}) > 3$ , then the number of dry days per 7 days is calculated as

$$\frac{D_{dry}}{(D_{dry} + D_{wet})} \times 7$$

Otherwise its value is missing.

#### **6.1.3.2.7 Number of dry (leakage -free) nights per 7 days**

Let  $N_{dry}$  be the number of valid diary days where the response to the question ‘Did you leak between this catheterization and the last one’ is ‘No’ each time a new catheterization is entered during the night time period.

Let  $N_{wet}$  be the number of valid diary days where the response to the question ‘Did you leak between this catheterization and the last one’ is ‘Yes’ for at least one catheterization entered during the night time period.

If  $(N_{dry} + N_{wet}) > 3$ , then the number of dry nights per 7 days is calculated as

$$\frac{N_{dry}}{(N_{dry} + N_{wet})} \times 7$$

Otherwise its value is missing.

#### **6.1.3.2.8 Identification of leakage during sleeping time**

For identification of a leakage during the sleeping time: since time for sleep and time for wake up are available, all leakages which occurred during this period are considered as ‘Sleeping time Leakages’.

For identification, at a visit, of a leakage during the sleeping time all leakages which occurred during this period are considered as ‘Sleeping time Leakages’. If there are:

- 0 leakages, the subject is considered as “Subject with no leakage” at that visit
- $\geq 1$  leakages, the subject is considered as “Subject with leakage” at the visit

#### **6.1.3.3 Subject- or Clinician-reported Questionnaire**

##### **6.1.3.3.1 Pediatric Incontinence Questionnaire (PIN-Q)**

The total PinQ score (Bower, 2006) is 20 multiplied by the average of the individual PinQ items where each of the 20 Likert scales have been converted to a score:

- For items 6 and 17; 0: “No” to 4: “Definitely” will be used; and
- For the other 18 items; 0: “No” to 4: “All the time” will be used.

It is expected that completed questionnaires will have at most a limited number of missing values; if the answers to more than two questions are missing, the total score will not be calculated and will be missing.

Individual item scores will not be directly imputed.

The change from baseline to each post-baseline visit in the total PinQ score is the value at the post-baseline visit minus the value at the baseline visit. If either the baseline value or the post-baseline visit value is missing, the change from baseline will be missing.

If change is:

- Less than 0, there is an improvement between the two time-points;
- Equal 0, there is no change between the two time-points;
- Greater than 0, there is a worsening between the two time-points.

#### **6.1.3.3.2 Patient Global Impression of Severity Scale (PGI-S)**

The Patient Global Impression of Severity Scale (PGI-S) is an answer of the question: “How did you feel about your bladder condition DURING THE PAST 3 DAYS?”

Subjects will evaluate their recent condition ticking one of the following categories: “Really Bad” (0), “Bad” (1), “Not Bad, Not Good” (2), “Good” (3) and “Really Good” (4).

PGI-S will be summarized as a continuous variable. The change from baseline to each post-baseline visit in the PGI-S score is the value at the post-baseline visit minus the value at the baseline visit. If either the baseline value or the post-baseline visit value is missing, the change from baseline will be missing.

A positive change indicates an improvement while a negative change indicates a worsening.

#### **6.1.3.3.3 Clinician Global Impression of Change (CGI-C)**

The Clinician Global Impression of Change (CGI-C) is a 7 point scale that requires the clinician to assess how much the subject’s overall bladder symptoms since the start of the study on day 1 has improved or worsened and rated as: very much improved (1); much improved (2); minimally improved (3); no change (4); minimally worse (5); much worse (6); or very much worse (7).

CGI-C will be summarized as a categorical variable.

#### **6.1.3.3.4 Acceptability (for tablets)**

Subjects will evaluate the taste of the study medication ticking one of the following categories: “Really Bad” (0), “Bad” (1), “Not Bad, Not Good” (2), “Good” (3) and “Really Good” (4).

Subjects will evaluate the swallow of the study medication ticking one of the following categories: “Really Difficult” (0), “Difficult” (1), “Not Difficult, Not Easy” (2), “Easy” (3) and “Really Easy” (4).

Taste and swallow acceptability will be summarized as categorical variables.

#### **6.1.3.3.5 Acceptability (for oral suspension)**

Subjects will evaluate the taste of the study medication ticking one of the following categories: “Really Bad” (0), “Bad” (1), “Not Bad, Not Good” (2), “Good” (3) and “Really Good” (4).

Subjects will evaluate the smell of the study medication ticking one of the following categories: “Really Bad” (0), “Bad” (1), “Not Bad, Not Good” (2), “Good” (3) and “Really Good” (4).

Subjects will evaluate the consumption of the study medication ticking one of the following categories: “Really Difficult” (0), “Difficult” (1), “Not Difficult, Not Easy” (2), “Easy” (3) and “Really Easy” (4).

Subjects will evaluate the preparation of the study medication ticking one of the following categories: “Really Difficult” (0), “Difficult” (1), “Not Difficult, Not Easy” (2), “Easy” (3) and “Really Easy” (4).

Taste, smell, consumption and preparation acceptability will be summarized as categorical variables.

#### **6.1.4 Exploratory Efficacy Endpoints**

The exploratory efficacy endpoints are summarized in [Table 2](#) and [Table 3](#).

No imputation will be done.

##### **6.1.4.1 Exploratory efficacy endpoints based on urodynamic measures**

###### **6.1.4.1.1 Filling volume at 20 cm, 30 cm and at 40 cm H<sub>2</sub>O detrusor pressure**

Bladder volumes at 20, 30 and 40 cm H<sub>2</sub>O detrusor pressure are recorded in the “VOLUME” section of the “Urodynamic Testing” pages of the eCRF. If detrusor pressure cannot be reached during the examination, the volume will be missing.

###### **6.1.4.2 Exploratory efficacy endpoints based on 7-day diary**

###### **6.1.4.2.1 MCC expressed as percentage of EBC**

MCC expressed as % of EBC will be as:

$$100\% \times \text{MCC}/\text{EBC}, \text{ where } \text{EBC} = 24.5 \times \text{age}(\text{years}) + 62.$$

###### **6.1.4.2.2 Grade of leakage (weekend diary)**

Grade of worst leakage will be assessed by answering to 1 of the 2 questions as appropriate: “How wet was your diaper/pad?” or “How wet were your clothes?”.

Subjects will evaluate the grade of leakage by ticking one of the following categories: “Fully Wet” (0), “Quite Wet” (1), “Slightly Wet” (2).

If a subject experiences leakage episodes but there is no answer to the leakage question, the leakage grade will be missing.

#### **6.1.4.2.3 Total catheterized volume per day (weekend diary)**

The total catheterized volume per 24h is calculated using all available (non-missing) catheterized volumes recorded for the 2 measuring days in the diary, whether or not these 2 days are consecutive. The total value will be calculated separately for each measuring day and the mean of these two values will be used.

If no volumes are recorded on any day of the weekend diary, then the total catheterized volume per day will be missing.

#### **6.1.4.2.4 Number of CICs/day (weekday diary)**

The number of CICs per day will be calculated as the total number of CICs reported during valid diary days in the weekday diary divided by the total number of valid weekday diary days).

#### **6.1.4.2.5 Responder in respect to leakage (weekend diary)**

The percent change from baseline to a post-baseline visit in the number of leakage episodes during the weekend diary will be calculated as follows:

$$R_x = \frac{\text{No. Leakage Epis. at Visit } x - \text{No. Leakage Epis. at baseline}}{\text{No. Leakage Epis. at baseline}} \times 100$$

A complete responder will be defined as a subject with a 100% improvement from baseline (i.e.  $R_x = -100\%$ ). A partial responder will be defined as a subject with a percent improvement from baseline  $\geq 50\%$  and  $< 100\%$  (i.e.  $-100\% < R_x \leq -50\%$ ). A non-responder will be defined as a subject with an improvement from baseline  $< 50\%$  or a worsening from baseline (i.e.  $R_x > -50\%$ ).

If the number of leakage episodes at baseline is equal to zero, a constant equal to 0.5 will be added to the baseline number of leakages to allow denominator calculation.

If the number of leakage episodes at baseline and/or at a post-baseline visit is missing then the response category in respect to leakage will be missing.

#### **6.1.4.2.6 Percentage of Catheterizations without Intermittent Leakage Accident**

For each visit the percentage of catheterizations without intermittent leakage accident is:

100% x (total number of catheterizations without intermittent leakage accident / total number of catheterizations).

For reporting 3 response criteria are defined:

- No response;  $< 50\%$  reduction from baseline;
- Partial response; 50-99% reduction from baseline; and
- Complete response; 100% reduction from baseline.

## **6.2 Safety Endpoints**

The following safety endpoints will be assessed:

**Table 4 Safety Endpoints**

<b>Endpoint Number</b>	<b>Endpoint Description</b>
<b>Safety Endpoints†</b>	
1	Incidence and severity of treatment-emergent adverse events (TEAEs)
2,3,4,5	Change from baseline in vital signs (clinic measurements): systolic blood pressure, at visit 5/week 4, visit 7/week 12, visit 8/week 24 and visit 10/week 52 (EOT/EOS)
6,7,8,9	Change from baseline in vital signs (clinic measurements): diastolic blood pressure at visit 5/week 4, visit 7/week 12, visit 8/week 24 and visit 10/week 52 (EOT/EOS)
10,11,12,13	Change from baseline in vital signs (clinic measurements): pulse rate at visit 5/week 4, visit 7/week 12, visit 8/week 24 and visit 10/week 52 (EOT/EOS)
14,15,16,17	Change from baseline in vital signs (clinic measurements): temperature at visit 5/week 4, visit 7/week 12, visit 8/week 24 and visit 10/week 52 (EOT/EOS)
18,19,20,21,22,23,24	Change from baseline in vital signs (self blood pressure measurement SBPM): systolic blood pressure 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.
25,26,27,28,29,30,31	Change from baseline in vital signs (SBPM): diastolic blood pressure 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.
32,33,34,35,36,37,38	Change from baseline in vital signs (SBPM): 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.
39,40	Change from baseline in hematology and biochemistry tests at visit 7/week 12 and visit 10/week 52 (EOT/EOS)
41,42,43,44	Change from baseline in urinalysis tests at visit 5/week 4, visit 7/week 12, visit 8/week 24 and visit 10/week 52 (EOT/EOS)
45,46,47,48	Change and categorized shift 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)
49	Categorized shift summary from baseline to visit 10/week 52 (EOT/EOS) in upper urinary tract ultrasound assessment
50,51	Change from baseline in eGFR at visit 7/week 12 and visit 10/week 52 (EOT/EOS)
<b>Exploratory Safety Endpoints</b>	
52,53	Change from baseline in body height and weight at visit 8/week 24 and visit 10/week 52 (EOT/EOS)

† Physical Examination will be analyzed as part of subject medical history or AEs depending on the time of the finding.

**Table 5 Summary of Safety Endpoints**

Variable		Endpoints						
		Week 2	Week 4	Week 8	Week 12	Week 24	Week 36	Week 52
TEAE	N (%)	1						
SBP <sup>CM</sup>	Change from baseline		2		3	4		5
DBP <sup>CM</sup>	Change from baseline		6		7	8		9
PR <sup>CM</sup>	Change from baseline		10		11	12		13
Body Temperature <sup>CM</sup>	Change from baseline		14		15	16		17
SBP <sup>SM</sup>	Change from baseline	18	19	20	21	22	23	24
DBP <sup>SM</sup>	Change from baseline	25	26	27	28	29	30	31
PR <sup>SM</sup>	Change from baseline	32	33	34	35	36	37	38
Hematology and biochemistry	Change from baseline				39			40
	Categorized shift from baseline							
Urinalysis	Change from baseline		41		42	43		44
	Categorized shift from baseline							
ECG	Change from baseline		45		46		47	48
	Categorized shift from baseline							
Upper Urinary Tract Ultrasound	Categorized shift from baseline							49
eGFR#	Change from baseline				50			51
Height and Weight	Change from baseline					52		53

<sup>CM</sup> Clinic Measurements

<sup>SM</sup> Self Measurements

# will be calculated according to the Larson Formula (Larson et al, 2004], and the modified Schwartz 2009 (for children < 12 years old) and the Cockcroft-Gault equation (for adolescents) formulas



## 6.2.1 Vital signs

### 6.2.1.1 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 measurements will be per standard clinic practices and 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.

For the purpose of the analyses of vital signs, the average per visit for vital signs measured at the clinic will be calculated as follows:

- If three or more measurements are reported, the average of all values will be used.
- If only two measurements are reported, the average of the two values will be used.
- If only one measurement is reported, it will be displayed for the average.
- If all measurements are missing, then the average will be missing.

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 6.2.3].

### 6.2.1.2 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 will be 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 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 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/caregiver in the e-diary.

*For the purpose of the analyses*, the average self-measurement vital signs will be calculated using all values from the 2-days diary collection separately for the regular measurements and the extra measurements. If all measurements are missing, then the average will be missing. However, if the extra measurements are not performed because they are covered by the regular ones, the regular measurements values will be duplicated so that they are included in both the regular and the extra analyses.

### 6.2.1.3 Conversion of Blood Pressure to Percentiles

Both the systolic and diastolic blood pressure site measurements will additionally be converted to percentiles specific to the age (years), sex and height (cm) of the subject using the following steps [NIH, 2005]:

- The height of a subject is measured at Visits 1, 3, 8, 10/EOS and, if applicable, at the Early Discontinuation Visit. As the children and adolescents in this study may be expected to increase in height during the course of the study, the height of the child at a study visit will be imputed by linearly interpolating between Visit 3 and a post-baseline visit as follow:
  - Let  $D_{\text{visit}}$  be the date of the study visit,  $H_1$  be the most recent height measurement at or prior to the study visit,  $D_1$  be the date of  $H_1$ ,  $H_2$  be the earliest height measurement at or after the study visit, and  $D_2$  be the date of  $H_2$ .
  - The height at  $D_{\text{visit}}$  is estimated as: 
$$H_{\text{visit}} = H_1 + \left( \frac{D_{\text{visit}} - D_1}{D_2 - D_1} \right) (H_2 - H_1)$$

- Let  $Z$  = the z-score (i.e. the number of standard deviations above or below the mean) of the height (cm) of the subject at the study visit relative to healthy subjects of the same age and gender using CDC growth charts [CDC, 2000]. The formula and example SAS code to calculate this are given in [Appendix 12](#)
- Let BP = the blood pressure (mmHg) that is being converted (either systolic or diastolic) and  $Y$ =the age of the child in years.
- Taking the coefficients from the appropriate column in [Table 6](#) below, compute  $Z_{BP}$ , the Z-score for the blood pressure:

$$Z_{BP} = \left[ BP - \alpha - \sum_{j=1}^4 \beta_j (Y - 10)^j - \sum_{k=1}^4 \gamma_k Z^k \right] / \sigma$$

- If  $\Phi(\cdot)$  is the area under the standard normal curve to the left of  $Z$ , calculate  $P$ , the gender, age and height specific percentile of the blood pressure as  $P = \Phi(Z_{BP}) * 100\%$ .
- The exact age at a visit will be calculated as:

$$Age = \frac{(D_V - D_B + 1)}{365.25}$$

where  $D_V$  is the visit date and  $D_B$  is the subject's date of birth. When the exact age at a visit is missing and cannot be calculated because of a missing date of birth, but where the age entered at screening is known only to be  $Y$  years (an integer), the percentile will be calculated for  $age=Y+0.5$ .

**Table 6 Coefficients for Conversion of Blood Pressure to Percentiles**

Variable	Symbol	Systolic BP		Diastolic BP		
		Male	Female	Male	Female	
Intercept	$\alpha$	102.19768	102.01027	61.01217	60.50510	
Age	(Age-10)	$\beta_1$	1.82416	1.94397	0.68314	1.01301
	(Age-10) <sup>2</sup>	$\beta_2$	0.12776	.00598	-0.09835	0.01157
	(Age-10) <sup>3</sup>	$\beta_3$	0.00249	-0.00789	0.01711	0.00424
	(Age-10) <sup>4</sup>	$\beta_4$	-0.00135	-0.00059	0.00045	-0.00137
Height	$Z$	$\gamma_1$	2.73157	2.03526	1.46993	1.16641
Z-Score	$Z^2$	$\gamma_2$	-0.19618	0.02534	-0.07849	0.12795
	$Z^3$	$\gamma_3$	-0.04659	-0.01884	-0.03144	-0.03869
	$Z^4$	$\gamma_4$	0.00947	0.00121	0.00967	-0.00079
	Standard Deviation	$\sigma$	10.7128	10.4855	11.6032	10.9573

To illustrate, a boy born on 1<sup>st</sup> January 2001 comes for a study visit on 13<sup>th</sup> January 2013. His height is measured as 159 cm and his systolic blood pressure (the mean of the triplicate) is 120 mmHg. In [Appendix 12](#) the z-score for the boy's height is worked through as an example and  $Z$  is found to equal 1.2836. The coefficients for the conversion of the blood pressure are taken from the appropriate column (systolic BP, Male) of [Table 6](#). The value of

Z<sub>BP</sub> is found to equal 0.97623 which equates to the 83.6<sup>th</sup> percentile of the standard normal curve.

#### 6.2.1.4 Pulse Rate in Relation to Age

Resting pulse rate will be compared to age-related norms [Fleming et al., 2011] according to the percentiles shown in [Table 7](#)

**Table 7 Percentiles for Resting Pulse Rate in Relation to Age and Gender**

Age	Percentile						
	1 <sup>st</sup>	10 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	90 <sup>th</sup>	99 <sup>th</sup>
3-4y	70	86	94	104	113	123	136
4-6y	65	81	89	98	108	117	131
6-8y	59	74	82	91	101	111	123
8-12y	52	67	75	84	93	103	115
12-15y	47	62	69	78	87	96	108
15-18y	43	58	65	73	83	92	104

Each value of pulse rate will be categorized as either being above the age-specific 99<sup>th</sup> percentile or below the 1<sup>st</sup> percentile.

#### 6.2.1.5 Body Temperature

Body Temperature will be compared to a reference range of 35.4 to 37.7 degrees [Kliegman et al, 2007].

### 6.2.2 Adverse Events

Collection of details of adverse events will begin at visit 1 after the signing of informed consent and will continue for all subsequent study visits. Adverse events will be evaluated during the telephone assessments at visit 2/wash-out period, visit 4/week 2, visit 6/week 8 and visit 9/week 36 and at each time the subject visits the clinic in person.

An AE with an onset date prior to the first dose of study drug is not considered treatment-emergent but rather as part of the baseline signs and symptoms of the study. These AEs will be listed in the AE listing.

A treatment-emergent adverse event (TEAE) is defined as an adverse event with date of onset occurring on or after the first dose of study medication and up to the end of study. If the adverse event occurs on Day 1 and the onset check box is marked “Onset after first dose of study drug” or the onset check box is left blank, then the adverse event will be considered treatment emergent. If the adverse event occurs on Day 1 and the onset check box is marked “Onset before first dose of study drug”, then the adverse event will not be considered treatment emergent. If a subject experiences an event both before and after the first dose of study drug, the event will be considered a TEAE only if it has worsened in severity (i.e. it is reported with a new start date). All adverse events collected that begin within 7 days after taking the last dose of study drug will also be counted as a TEAE and for Serious Adverse Events (SAE) the follow-up period will be until the end of the study.

All AEs will be compared with a list of AEs that Astellas considers to be “Always Serious” and those AEs that are on the list will be upgraded to “Serious”.

A drug-related TEAE is defined as any TEAE with at least a possible relationship to study treatment as assessed by the investigator or with a missing assessment of the causal relationship.

Common TEAEs are defined as preferred terms (PTs) that have been reported by at least 5% of the subjects.

When an AE start or stop date is missing, the date will be imputed using the rules in Section [7.11.1.3](#)

*Adverse events of interest are:*

- CV
  - Increased blood pressure
  - QT prolongation
  - Increased heart rate, tachycardia, atrial fibrillation, or palpitations  
(Note: these 3 CV events will be analyzed combined and separately)
- Urinary Tract Infection (UTI)
- Hypersensitivity reactions
- Urinary retention
- Neoplasm
- Seizure
- Syncope
- Fetal disorders after exposure during pregnancy
- Concomitant treatment with cytochrome P450 (CYP) 2D6 substrates with narrow therapeutic indices or individually dose-titrated.

AEs of interest will be identified using Standardized MedDRA queries (SMQ), version 16.0, see [Table 8](#), or sponsor-defined list of search terms, see Appendix 3.

**Table 8 Standardized MedDRA Queries, Version 16.0**

CV - Increased blood pressure	Hypertension SMQ – Narrow search
CV - QT prolongation	Torsade de pointes/QT prolongation SMQ – Broad search
CV - Increased heart rate, tachycardia, atrial fibrillation, and palpitations	Arrhythmia related investigations signs and symptoms SMQ – Broad search, Supraventricular tachyarrhythmias (SMQ) Broad search, Tachyarrhythmia terms nonspecific (SMQ) – Narrow search, Ventricular tachyarrhythmias (SMQ) - narrow search plus Ventricular tachycardia
Hypersensitivity reactions	Hypersensitivity SMQ – Narrow search
Neoplasm	Neoplasm SMQ – Narrow search
Seizure	Lower Level Term 10039906
Syncope	Syncope SMQ – Narrow search (also included as part of the CV - Increased heart rate, tachycardia, atrial fibrillation, and palpitations) PT 10042772
Fetal disorders after exposure during pregnancy	Congenital, familial and genetic disorders - SMQ Narrow Fetal disorders – SMQ Broad search Neonatal disorders – SMQ Broad search
Concomitant treatment with cytochrome P450 (CYP) 2D6 substrates with narrow therapeutic indices or individually dose-titrated	PT Drug interaction PT Potentiating drug interaction

### 6.2.3 Clinical Laboratory Variables

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 [Table 1](#)]. These data will be summarized in a table.

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).

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 of the protocol].

The laboratory parameters that will be assessed during the conduct of the study are listed in

**Table 9**

**Table 9 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

*Table continued on next page*

By Central Laboratory		
Assessment	Collecting tube	Parameters to be analyzed
Urinalysis	Dipstick	Protein Glucose pH
	Polypropylene tube	Urobilinogen Bilirubin Ketones Nitrite 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.

Blood samples for evaluation of hematology and biochemistry assessments (including liver function tests) are collected at visit 1 /screening, visit 3/baseline<sup>#</sup>, visit 5/week 4<sup>§</sup>, visit 7/week 12 and at the EOS (Visit 10).

<sup>#</sup> Additional hematology/biochemistry will be taken at baseline only if an AE related to hematology/biochemistry parameters occurred between visit 1/screening and visit 3/baseline.

<sup>§</sup> 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.

The value of each hematology and biochemistry parameter will be compared to its normal range and classified as High, Low or Normal. Urinalysis parameters will be similarly classified as either Normal or Abnormal.

When calculating changes or shifts in a result from baseline, the value from Visit 1 will be used as baseline. If the Visit 1 value is missing, the latest pre-baseline value will be used (i.e. from Visit 1 or any unscheduled visit conducted between Visit 1 and 3).

#### 6.2.4 Physical Examinations

Physical examinations will be performed at visit 1/screening and visit 10/week 52 (EoS) and will include assessments of the main body systems.



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.

### 6.2.5 12-lead Electrocardiogram (ECG)

A 12-lead ECG will be performed in triplicate one minute apart 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). The ECGs will be taken with the subject in the supine position, after the subject has been lying quietly for at least 5 minutes. ECG traces will be evaluated by the investigator who will give an overall interpretation and may leave a qualifying comment in the eCRF. The overall interpretation will be recorded as

- Normal, or
- Abnormal - not clinically significant, or
- Abnormal - clinically significant

All ECGs will be further evaluated by a cardiologist at the central laboratory. When the central laboratory cardiologist's overall interpretation is abnormal, an applicable abnormality code will be assigned. ECG abnormalities are coded for the particular class of abnormality (rhythm, QT interval, etc.) as well as the specific abnormality within each class. Details of this coding are given in [Appendix 13: ECG Abnormality Codes](#)

As well as the overall interpretation, the following ECG variables will be supplied by the central laboratory: PR Interval (msec), RR Interval (msec), QRS Duration (msec), QT Interval (msec), QTcF interval (msec) and Heart rate (HR) (beats/min). QT with Bazett correction range (QTcB interval  $\leq$  450 ms, all ages) will be only used for the inclusion criteria evaluation and won't be presented.

The mean of each triplicate of ECG measurements recorded during the study will be used for each ECG variable. If fewer or more than 3 results are recorded the mean of all available values will be used.

Let  $M_1$  and  $M_3$  equal the means of a continuous ECG variable at Visit 1 and Visit 3, respectively. The baseline value of the variable, used to assess study eligibility and all changes from baseline during the study, will equal  $(M_1 + M_3)/2$ .

### 6.2.6 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). In addition, the estimated glomerular filtration rate (eGFR) will be calculated by the central laboratory using the Larsson formula [Larsson et al, 2004]:

$$eGFR = 94.577 * [Cys C (mg/L)]^{1.2623}$$

In addition, BARC will calculate the eGFR using the modified Schwartz 2009 (for children < 12 years old) and the Cockcroft-Gault equation (for adolescents) formulas.-

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.

### 6.2.7 Height, Weight and BMI

Height and weight will be recorded at visit 1/screening, visit 3/baseline, visit 8/week 24 and at visit 10/week 52 (EOT/EOS).

As the study subjects are children and adolescents who are still growing, assessment of any effect of treatment on height and weight will be based on comparison with age (at screening) and gender norms from growth charts supplied by the Centers for Disease Control and Prevention. These charts enable the calculation of z-scores for height and weight based on the age (in months) and sex for children, adolescents and young adults up to the age of 20 years [Kuczmarski et al, 2002]. The formulae and example SAS code for the calculation of these Z-scores are given in [Appendix 12](#)

The change from baseline in the z-score for height and the z-score for weight will be calculated as the value at the relevant visit minus the baseline value. If either of these values is missing, the change from baseline will be missing.

## 6.3 Pharmacokinetic Variables

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 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., pre-dose sample).
- Sampling day 2: 1 trough and 2 post-dose samples taken between 2h and 5h post-dose, 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 on a sampling day with post-dose samples must occur within 1 hour after completion of breakfast.

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.

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

- Maximum concentration ( $C_{max}$ ) at steady state
- Time to attain  $C_{max}$  ( $t_{max}$ )

- Area under the plasma concentration–time curve (AUC) for a dose interval ( $AUC_{24}$ )
- Plasma concentration before drug administration ( $C_{trough}$ ) at steady state
- Terminal elimination half-life ( $t_{1/2}$ )
- Apparent oral clearance ( $CL/F$ )
- Apparent volume of distribution ( $V_z/F$ ).

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

Further details of the derivation of the pharmacokinetic parameters are given in the pharmacokinetics data analysis plan (PKDAP).

## 6.4 Pharmacodynamic Variables

There are no pharmacodynamic variables in this study.

## 6.5 Other Variables

### 6.5.1 Baseline Characteristics

Baseline characteristics and other variables that will be collected or derived are:

- Informed consent/assent (collected at screening);
- Demographic characteristics (collected at screening);
- Inclusion/Exclusion (collected at screening and baseline);
- Medical history (collected at screening), including a detailed NDO history;
- Current NDO medications (collected at screening and start of washout);
- Antimuscarinics medication stopped for lack of efficacy prior to start of treatment (yes/no).

If  $D_{diag}$  is the date of diagnosis and  $D_{Scr}$  is the date of last informed consent given at Screening, the years since diagnosis of NDO at Screening is

$$Y_{Diag} = \frac{(D_{Scr} - D_{Diag} + 1)}{365.25}$$

When one of these dates is partial, the rules in Section 7.11.1.2 will be used to impute it.

If  $D_B$  is the subject's date of birth, the age at Screening is

$$Age_{Scr} = \frac{(D_{Scr} - D_B + 1)}{365.25}$$

If the date of birth is not given, the age at Screening will be equal to the value recorded on the demographics page of the eCRF (an integer number of years) plus 0.5. e.g. if the age is given as 12 years in the eCRF, a value of 12.5 will be used in calculations/statistical analyses involving age (an exception to this rule is given for the conversion of blood pressure values to percentiles; see Section 6.2.1.3).

### 6.5.2 Previous and Concomitant Medications and Therapies

All treatments, both drug and non-drug therapies, whether prescribed, over the counter (OTC) or “alternative” that are used during the study will be recorded on the case report

form. Details include generic and/or brand names of medications, reason for use, route, dose, and start and end dates. This also includes drugs used on a chronic or as-needed basis.

Previous medication is defined as medication with at least one dose taken before the date of the first dose of the study drug.

Concomitant medication is defined as medication with at least one dose taken between the date of first dose (inclusive) and the date of last dose (inclusive) of the study drug.

A list of prohibited medications is given in [Appendix 2: List of Excluded Concomitant Medications](#)

When the start and stop dates of a medication or therapy are partial/missing, the dates will be imputed using the rules in Section [7.11.1.5](#)

### 6.5.3 Exposure to Study Drug

The duration of exposure to each dose of study drug (PED25 and PED50) by visit and for the whole period will also be calculated using the following information that is recorded in the eCRF:

- Overall start date and stop date of the study medication.  
The first dose of study drug is to be administered on Day 1, the day after the baseline visit (Visit 3). The initial dose will be PED25 for all subjects. The last dose of treatment is to be taken in the morning of Visit 10.
- Start date and new dose of study drug at each titration step.  
At Visits 4, 5 and 6 the dose may be up-titrated, down-titrated, or may remain the same.
- Start date and new dose of study drug after each unscheduled dose change.
- At any time during the treatment period, the subject may have an unscheduled dose interruption or reduction. At each unscheduled change in dose, the new dose, start date and reason are recorded. Dose increasing is scheduled only during time window between Visit 4/Week 2 and Visit 6/Week 8.

In addition, the return date of study medication is assumed to be the date of clinical visit.

In all cases where there is a dose change, either because of dose titration or an unscheduled dose interruption, reduction or increase, the last dose of the medication at the old level will be assumed to be the day before the given date of first dose at the new level. In this way, the subject's dosing history can be reduced to a series of unbroken intervals within each of which, the dose level is constant. From these, the subject's exposure at each dose can be calculated.

To illustrate, consider a subject with the following dose information on the eCRF:

- The dates of the very first and very last dose of the study medication given as  $D1=1\text{st July } 2016$ ,  $D_{\text{last}}=24\text{th September } 2016$ .
- Up-titration to PED50 at Visit 4. The first dose at the new level is given as  $D2=15\text{th July } 2016$ .

- Study drug interrupted at an unscheduled visit. The date of last dose at the PED 50 level is given as D3=18th July 2016
- Study drug re-started at PED25 at an unscheduled visit. The first dose at the new level is given as D4=22 July 2016.
- Remains at PED25 at Visit 5 (D5=29th July 2016). Up-titration to PED50 at Visit 6. First dose at the new level is given as D6=29th August 2016.

From these dates we calculate the following:

- The duration of exposure to the treatment can be calculated as  $ETOT = D_{last} - D1 + 1 - (D4 - D3 - 1) = 83$  days.
- Between Visits 3 and 4, the subject is on PED25. The last dose at PED25 is given on D2-1, the day before the subject has the first dose at the new level PED50. The exposure at PED25 between Visits 3 and 4 is, therefore,  $(D2 - 1) - D1 + 1 = 14$  days
- Between Visits 4 and 5, the study drug is temporarily suspended and then restarted at a new level. The subject will be considered to be exposed to the PED50 dose from D2 until D3, i.e.  $D3 - D2 + 1 = 4$  days.
- For the calculation of the exposure, suspension of the study drug is not ignored. The dose will be considered interrupted between D3 to D4-1, i.e.  $(D4 - 1) - D3 = 3$  days.
- The study drug is at PED25 from D4 to D6-1, the date of the last dose prior to Visit 6, i.e.  $(D6 - 1) - D4 + 1 = 38$  days.
- Subject is on PED50 from D6 to Dlast, a total of  $D_{last} - D6 + 1 = 27$  days.
- The total exposure at PED50 is  $EPED50 = 31$  days, at PED25 is  $EPED25 = 52$  days
- The total exposure between Visits 3 and 4 is  $E1 = 14$  days, between Visits 4 and 5 is  $E2 = 11$  days, between Visits 5 and 6 is  $E3 = 31$  days and between Visits 6 and 7 is  $E4 = 27$  days.

#### 6.5.4 Compliance to Study Drug

##### Tablet compliance

Compliance will be calculated according to the number of tablets of study medication dispensed, the number of kits used and the duration of exposure between the applicable visits and overall.

Each kit of study medication contains 35 tablets. At each dispensing visit, subjects will receive an adequate number of kits of both PED25 and PED50 as follows:

- At Visit 3, 1 kit of 25 mg and 1 kit of 50 mg will be dispensed
- At Visit 5, 2 kits of 25 mg and 2 kits of 50 mg will be dispensed
- At Visit 7, 3 kits of 25 mg or 3 kits of 50 mg will be dispensed
- At Visit 8, 7 kits of 25 mg or 7 kits of 50 mg will be dispensed

The total number of tablets used between Visits i and j ( $i < j$ ) is calculated as:

$N_{used} = \text{Total number of tablets dispensed at Visit } i - \text{Total number of tablets returned at Visit } j$

When a kit is not returned it will be assumed that all the medication from this kit was not used.

When a kit is returned late, it will be assumed that the medication was used during the study period that it was dispensed for, e.g. all the medication used from a kit dispensed at Visit 3 and returned at Visit 5 will be assumed to have been used between Visits 3 and 5.

The amount of expected study drug intake depends on the number of days of study drug treatment and the number of prescribed daily tablets. Since subjects are supposed to take 1 tablet per day, the total number of expected tablets to be used between Visits i and j is calculated as follows:

$$N_{\text{prescribed}} = (\text{Number of Exposure Days between Visit}_i \text{ and Visit}_j) \times 1 \text{ tablet,}$$

where Number of Exposure Days is calculated as: (Return date – Dispense date) + 1.

Between Visits i and j the compliance to study medication will be calculated as follows:

$$\text{Compliance} = (N_{\text{used}} / N_{\text{prescribed}}) \times 100\%.$$

To illustrate, at Visit 3 a subject was dispensed 1 kit of 25 mg and 1 kit of 50 mg. The date of first dose was 1<sup>st</sup> July 2016. When the subject returned at Visit 4 (18<sup>th</sup> July 2016), the 25 mg kit contained 20 tablets and the 50 mg kit was full (35 tablets).

$$N_{\text{used}} = (35-20) + (35-35) = 15 \text{ tablets}$$

$$\text{Number of exposure days} = (18\text{Jul}2016 - 01\text{Jul}2016) + 1\text{day} = 18 \text{ days,}$$

$$\text{Hence, } N_{\text{prescribed}} = 18 \text{ tablets}$$

$$\text{Compliance between Visits 3 and 4} = (15/18) \times 100\% = 83.3\%.$$

For the whole study period, the total amount of study drug used ( $TOTN_{\text{used}}$ ) is equal to the sum of the values of  $N_{\text{used}}$  at each applicable visit. Similarly, the total amount of study drug prescribed ( $TOTN_{\text{prescribed}}$ ) is equal to the sum of the values of  $N_{\text{prescribed}}$  at each applicable visit. Using these total values, the subject's compliance over the whole study period can be calculated as  $100\% \times (TOTN_{\text{used}} / TOTN_{\text{prescribed}})$ .

### **Suspension Compliance**

Compliance for suspension will be calculated according to:

- Number of bottles dispensed at each visit (see [Table 10](#));
- Weight of the bottles returned to the site; and
- Duration of exposure between the applicable visits and overall.

**Table 10 Number of Kits to be Dispensed at each Visit**

Dose Level	Weight	Number of kits				
		Visit 3 / Baseline	Visit 5 / Week 4	Visit 7 / Week 12	Visit 8 / Week 24	Visit 9 / Week 36
PED25	<22 kg	4	6	5	6	7
	22 - <35 kg	5	8	6	7	8
	≥ 35 kg	6	10	8	9	11
PED50	<22 kg	NA	6	8	9	11
	22 - <35 kg	NA	8	11	11	14
	≥ 35 kg	NA	10	14	15	19

NA: Not Applicable

Each kit of study medication contains a bottle with mirabegron granules. After filling the bottle containing the granules with 100 mL drinking water, the weight of the bottle with content should be 137 g.

Doses are calculated weight-based, see [Table 11](#). The body weight at Visit 3/baseline determines the weight range for the starting dose (PED25) and the up-titration dose (PED50) to be used.

**Table 11 Weight based Doses for Suspension**

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

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

† Suspension strength: 8 mg/mL

At each dispensing visit, subjects will receive an adequate number of kits of both PED25 and PED50 following the same procedure as described above for tablets.

The total dose of suspension used between Visits i and Visit j ( $i < j$ ) is calculated as:

$W_{\text{used}} = \text{Total weight of bottles dispensed at Visit } i - \text{Total weight of bottles returned at Visit } j,$   
and taking into account the suspension strength of 8 mg/mL.

where:

- Total weight dispensed = Number of kits dispensed at the Visit i x 137; and
- Total weight returned = Sum of the unused amount of study medication in each kit returned at Visit j.

When a kit is not returned it will be assumed that all the medication from this kit was not used.

When a kit is returned late, it will be assumed that the medication was used during the study

period that it was dispensed for, e.g. all the medication used from a kit dispensed at Visit 3 and returned at Visit 5 will be assumed to have been used between Visits 3 and 5.

The amount of expected study drug intake depends on the number of days of study drug treatment and the number of prescribed daily suspension pouches. Since subjects are supposed to administer 1 dose per day, the total amount of expected suspension to be used between Visit i and Visit j is calculated as follows:

$W_{\text{prescribed}} = \text{Duration in days between Visit i and Visit j times the subject's specific dose, see Table 11}$

The weight of the subject's specific dose is determined by using a conversion factor of 1 mL corresponds to 1.0216 g.

The compliance to study medication between Visits i and j will be calculated as follows:

$$\text{Compliance} = (W_{\text{used}} / W_{\text{prescribed}}) \times 100\%.$$

To illustrate, a subject, who weighted 25 kg and with dose level PED25, was dispensed with 5 kits at Visit 3. The date of first dose was 1<sup>st</sup> July 2016. When the subject returned at Visit 4 (31<sup>th</sup> July 2016), 3 kits were not used and the weight of the 2 used kits was: 32 and 124 g.

Compliance calculation:

1. Total amount of reconstituted study drug administered was resolved in  $(137-32) + (137-124) = 118$  g of suspension, which is equal to  $118/1.0216 \text{ mL} = 115.5 \text{ mL}$ .
2. Given that the solution strength is 8 mg/mL this means that in total  $115.5 \text{ mL} \times 8 \text{ mg/mL} = 924$  mg of study drug was administered to the subject.
3. Duration was 31 days (= 31 July – 1 July +1), hence expected amount of study drug to be administered is  $31 \times 4 \text{ mL} = 124 \text{ mL}$  (based on the weight of the subject the suspension volume is 4 mL, see Table 11). This results in  $124 \text{ mL} \times 8 \text{ mg/mL} = 992$  mg of study drug.
4. Compliance between Visits 3 and 4 =  $(924/992) \times 100\% = 93.15\%$ .

For the whole study period, the total amount of study drug used ( $TOTW_{\text{used}}$ ) is equal to the sum of the values of  $W_{\text{used}}$  at each applicable visit. Similarly, the total amount of study drug prescribed ( $TOTW_{\text{prescribed}}$ ) is equal to the sum of the values of  $W_{\text{prescribed}}$  at each applicable visit. Using these total values, the subject's compliance over the whole study period can be calculated as  $100\% \times TOTW_{\text{used}} / TOTW_{\text{prescribed}}$ .



## 7 STATISTICAL METHODOLOGY

### 7.1 General Considerations

All statistical analyses and summary information are to be generated according to this analysis plan. Any deviation from this plan will be documented in the final study report.

For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation, median, minimum and maximum. When needed, the use of other percentiles (e.g. 10%, 25%, 75% and 90%) will be mentioned in the relevant section.

Frequencies and percentages will be displayed for categorical data. Percentages by categories will be based on the number of subjects with no missing data, i.e. will add up to 100%.

Subjects who were screening failures or who were treated but withdrew from the study will be counted only once in summary tables. Information from both screening numbers will be shown in the individual subject listings.

Listings will be produced separately for children and adolescents, unless specified otherwise.

All statistical comparisons will be made using 2-sided tests at the  $\alpha=0.05$  significance level unless specifically stated otherwise. All summaries will be presented by age group and overall, unless specifically stated otherwise. All null hypotheses will be of no change from baseline, all alternative hypotheses will be 2-sided, unless specifically stated otherwise.

Missing primary efficacy endpoint values will be analyzed using the Last Observation Carried Forward (LOCF) method at Week 24. More details are provided in the relevant sections of this SAP.

All data processing, summaries, and analyses will be performed using SAS<sup>®</sup> Version 9.3 or higher on Unix. Specifications for table, figure, and data listing formats can be found in the TLF specifications for this study.

### 7.2 Study Population

#### 7.2.1 Disposition of Subjects

The following subject data will be presented:

- Number and percentage of subjects who
  - were included in the All Screened Set (i.e. who gave informed consent/assent);
  - were a screening failure;
  - were eligible for study drug treatment.
- Number and percentage of subjects in the All Allocated Set, FAS, PPS, SAF and PKAS;
- Number and percentage of subjects in the All Screened Set who completed or discontinued pretreatment period, by the primary reason for screening status;
- Number and percentage of subjects who completed or discontinued treatment period, by the primary reason for discontinuation, for All Allocated Set, SAF, FAS, PPS and PKAS;

- Number and percentage of subjects who completed or discontinued end of study period, by the primary reason for discontinuation, for All Allocated Set, SAF, FAS, PPS and PKAS;
- Number and percentage of subjects in the FAS who were excluded from the PPS by reason for exclusion (defined in Section 5.4.1).

The number of subjects will be tabulated by protocol version for the All Subjects Screened.

A listing of all early withdrawals, subjects who withdraw within 7 days, will be presented irrespectively whether they were dosed or not. The reason for withdrawal will be included in this listing.

A listing of screen failure with the primary screen failure reason will be provided for the screening failure subjects. In addition, disposition will be listed for All Allocated Subjects with treatment and study discontinuations.

### 7.2.2 Protocol Deviations

Protocol deviations as defined in the study protocol (see Section 8.1.6 Protocol Deviations) will be assessed for All Allocated Set.

The number and percentage of subjects with any deviation criterion will be summarized for each criterion and overall, by age group as well as by study site. Subjects deviating from a criterion more than once will be counted once for the corresponding criterion. Any subjects who have more than one protocol deviation will be counted once in the overall summary. A data listing will be provided by site and subject for the All Allocated Set.

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

† 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.

A listing of inclusion and exclusion criteria, listing of first and last evaluations as well as a listing of subjects who were excluded from at least 1 analysis set will be provided for the All Allocated Set.

### 7.2.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized by age category and overall.

Demographic and other baseline characteristics data will be provided in listing format by site and subject for the All Screened Set.

The number and percentage of subjects allocated to treatment in each region, country and site will be presented for the SAF.

Regions are defined as follows:

- Europe: Norway, Latvia, Lithuania, Denmark, Belgium, Poland, Slovakia, Romania and Serbia
- Asia and Pacific (APAC): Philippines, South Korea, Australia, Taiwan and Malaysia
- Middle East and North Africa (MENA): Turkey, Israel and Jordan
- Latin America (LatAm): Mexico and Colombia

The final list of participating/enrolling countries might be updated after end of recruitment when the list becomes final.

If sites in additional countries will be opened due to changes in recruitment strategy, these countries will be allocated respectively and reported in the CSR.

Descriptive statistics for age, height, weight, and BMI at screening will be presented as well as frequency tabulations for sex, ethnicity and race. In addition, summaries for height with respect to age- and sex-specific percentiles (Charts from the Centers for Disease Control and Prevention (CDC), See 10.6 and 10.7), and weight with respect to height- and sex- specific percentiles (CDC, See 10.8 and 10.9) will be provided. These summaries will be produced for the SAF, FAS and PPS.

Collection of date of birth depends on local regulations. Day of birth will be recorded in the eCRF as the first of the month when the day is not allowed to be collected. In cases where only year of birth is allowed to be collected, day and month will be recorded in the eCRF as the first of January. Age at Screening will be recalculated in SDTM and ADAM datasets.

Demographic characteristics of subjects on previous antimuscarinic treatment (oxybutynin at screening vs. other treatment from concomitant medications dataset) will be summarized for the FAS, PPS and SAF.

Medical history (NDO Medical History and Medical History Other than NDO) is coded in MedDRA and will be summarized by System Organ Class (SOC) and Preferred Term (PT) using SAF. Subjects will only be counted once per MedDRA level and the medical history will be sorted by descending incidence of the overall SOCs and within PTs.

The data on NDO diagnosis and history, including duration of NDO disease (at first dose of mirabegron), NDO medical condition(s), urethral sphincter activity, retardation, wheelchair bound, surgery (including for closure of spina bifida, shunt for hydrocephalus, other) and time since surgery (calculated in months) will be summarized with descriptive statistics and frequency tabulations as appropriate using SAF.

#### **7.2.4 Previous and Concomitant Medications**

Previous and concomitant medications (for NDO or other indications) will be coded with WHO-DD, and will be summarized by therapeutic subgroup (ATC 2nd level), chemical

subgroup (ATC 4th level) and preferred WHO name for the SAF. Subjects taking the same medication multiple times will be counted once per ATC level. A medication which can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups. Previous and concomitant medications will be sorted by alphabetical order by Therapeutic Subgroup and Chemical Subgroup and Preferred WHO Name.

A summary of all previous medications and concomitant medications will be produced for the NDO and non-NDO medications separately using SAF. Only the last NDO medication before start of study medication will be used for calculations.

Previous and concomitant NDO medications, non-NDO medications and non-NDO non-medication therapies will be listed using All Screened Subjects.

A listing of previous and concomitant NDO medications with ATC codes by WHO preferred name will be provided for All Screened Subjects.

### 7.3 Study Drugs

All summaries of this section will be presented by age group, dose group (see below) and overall, unless specifically stated otherwise.

#### 7.3.1 Dosing

As per study schedule (Table 1), all subjects will start with a PED equal to 25 mg of mirabegron (PED25). From visit 4/week 2 to visit 6/week 8 subjects can be:

1. up-titrated to PED50 at least once (dose group labelled “25/50”) or,
2. maintained at PED25 for any reasons for the whole study (dose group labelled “25only”).

These 2 dose groups are mutually exclusive and add up to the total number of subjects in the SAF population.

A subject who is up-titrated to PED50 can remain at that dose level, but can also experience a reduction, an interruption or a further increase of the dose. For these reasons, all subjects up-titrated to PED50 will also be categorized on the basis of the duration of their exposure to PED50 (see Section 6.5.3 for more details).

In particular, the following 2 dose groups (within the dose group “25/50”) are of interest:

- a. Subjects up-titrated to PED50 for at least of 4 weeks (28 days) [dose group labelled “50min4w”],
- b. Subjects up-titrated to PED50 for at least 2 weeks (14 days) [dose group labelled “50min2w”].

These two groups are not mutually exclusive and do not add up to the total number of subjects in the “25/50” dose group.

The following information on the study drug dose titration will be presented for the SAF:

- Number and percent of subjects in each dose group (“25/50”, “25only”, “50min4w” and “50min2w”) at each follow-up visit (Visits 4, 5, 6, 7, 8, 9 and 10),

- Number and percent of subjects with dose increases, decreases or no changes at each titration step (from Visit 4 to 6),
- Unscheduled dose changes and interruptions (will be listed only).

Details of dose calculation and drug dispensing will be listed for each subject at each visit.

### 7.3.2 Exposure

The following information on drug exposure will be presented for the SAF:

- Descriptive statistics for cumulative amount of the drug subject was exposed to and average daily dose; and

Duration of exposure will be summarized in the following ways.

- Descriptive statistics
- Exposure time will be categorized according to the following categories for both the titration period and the fixed dose period:
  - less than 14 days
  - at least 14 days, less than 28 days
  - at least 28 days, less than 56 days
  - at least 56 days
  - Unknown

and by the following categories for the whole treatment period:

- less than 84 days
- at least 84 days, less than 168 days
- at least 168 days, less than 252 days
- at least 252 days, less than 364 days
- at least 364 days
- Unknown

Counts and percentages of subjects in each of these categories will be summarized for each dose group and overall for the SAF.

### 7.3.3 Treatment Compliance

Compliance with the dosing schedule will be summarized for subjects in the SAF.

The following summaries will be produced separately for the titration period (Visit 3 to Visit 7)<sup>6</sup>, for the period between Visit 7 and Visit 8, and for the whole treatment period:

- Descriptive statistics
- Percent compliance will be categorized according to the following categories:
  - less than 70%
  - at least 70%, less than 80%
  - at least 80%, less than 120%

---

\* Period from Visit 3 to Visit 7 was chosen because no drug dispensing and collecting data is obtained at Visit 4 and Visit 6.

- at least 120%, less than 130%
- at least 130%
- Unknown.

A subject will be considered compliant if the calculated compliance over the whole treatment period is at least 70% and is additionally at least 80% between Visit 7 and Visit 8.

Treatment compliance details, including all data relevant to the calculation, will be listed by for each subject by study visit and overall.

## 7.4 Analysis of Efficacy

Efficacy data will be summarized for the FAS and the PPS for all visits.

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

Visit windows will be applied as defined in Section [7.11](#)

### 7.4.1 Analysis of Primary Endpoint

#### 7.4.1.1 Primary Analysis of Primary Endpoint/Estimand

The primary efficacy variable is the change from baseline in MCC at visit 8/week 24.

MCC and change from baseline in MCC at visit 8/week 24 will be summarized using descriptive statistics for continuous variable (n, mean, SD, min, median, and max) for the FAS. Missing MCC observations at visit 8/week 24 will be imputed using the Last Observation Carried Forward (LOCF) method.

In accordance with the definition of the estimand, the change from baseline in MCC at visit 8/week 24 will be analyzed using a paired t-test. The following hypotheses will be tested at the 2-sided significance level 0.05:

$H_0$ : Mean change from baseline in MCC at visit 8/ week 24 is equal to zero

$H_1$ : Mean change from baseline in MCC at visit 8/ week 24 in MCC is not equal to zero

The mean change from baseline estimate in MCC at visit 8/week 24, together with two-sided 95% CI and the t-test p-value will be provided using the UNIVARIATE procedure in SAS.

Example SAS code is as follows:

```
proc univariate;  
  class time;  
  var chgebc;  
run;
```

In addition to the test of the null hypothesis, it will be assessed whether the lower bound of the two-sided 95% CI excludes 0 mL. No adjustment for multiplicity will be made.

MCC at each visit and change from baseline in MCC at visit 8/week 24 (without LOCF) will be also plotted and listed for SAF and PPS.

### 7.4.1.2 Secondary Analyses of Primary Endpoint

The following secondary analyses of the primary endpoint will be produced.

#### 7.4.1.2.1 Analysis without LOCF

The same analysis described in Section 7.4.1.1 will be repeated both for FAS without imputing for missing data and for PPS.

#### 7.4.1.2.2 Analysis using Baseline Value Carried Forward

For cases where the MCC value is non-missing at baseline but missing at visit 8/week 24, the same analysis as described in Section 7.4.1.1 will be performed using a Baseline Observation Carried Forward (BOCF) approach. For this analysis the baseline value will be imputed for the missing value at Visit 8/week 24.

This analysis will be performed for the All Enrolled Subjects.

#### 7.4.1.2.3 Analysis using Repeated Measures ANCOVA

A repeated measures 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 method used in the primary model to assess the robustness of the findings. Data obtained at baseline (visit 3), at visit 5/week 4 and at visit 8/week 24 will be used. Since there are only 2 post-baseline time points in a 24 week period, the model will assume an unstructured covariance among the within subject repeated measurements. If there is a convergence problem due to the unstructured covariance matrix, the unstructured covariance matrix will be replaced by the compound symmetry covariance matrix. This analysis will be performed both for FAS and PPS.

Example SAS code is as follows:

```
proc mixed;  
  class subject agegroup visit;  
  model change = visit agegroup agegroup*visit MCC_baseline;  
  repeated visit / subject=subject type=un;  
  lsmeans visit agegroup*visit / diff cl alpha=0.05;  
run;
```

In this code the LSMEANS statement will produce least squares mean (LS mean) estimates for both age groups combined and also within each age group using a single analysis of covariance (ANCOVA) model.

Model fitting will be visually assessed. A scatter plot of residuals versus predicted values, along with histogram and normal probability plots will be produced.

#### 7.4.1.2.4 Effect of age and gender

The p-value of the change from baseline to week 24 (with and without LOCF) will be assessed using an ANCOVA model including gender, age group and a gender by age group interaction as fixed effects and the baseline MCC as a covariate.

LS mean estimates, together with 95% CIs, will be provided.

Example SAS code is as follows:

```
proc mixed;  
  class agegroup gender;  
  model change = agegroup gender agegroup*gender  
    MCC baseline;  
  lsmeans gender agegroup*gender / diff cl alpha=0.05;  
run;
```

In this code the LSMEANS statement will produce LS mean estimates for both age groups combined and also within each age group using a single ANCOVA model.

#### 7.4.1.2.5 Nonparametric Analysis of Primary Endpoint

A Wilcoxon signed-rank test will be used as a sensitivity analysis. This test is produced by the UNIVARIATE procedure in SAS and ranks the absolute values of the differences between the paired data and calculates a statistic on the number of negative and positive differences. Analysis will be done on the FAS, with (LOCF) and without imputation.

Example SAS code is as follows:

```
proc univariate;  
  var chg;  
run;
```

Box-Whisker plots of the change from baseline data will be presented for getting insight into the distribution of the data.

#### 7.4.1.2.6 Overall Impact on Primary Endpoint

For the MCC, the 95% CI will be calculated for mean change from baseline per age group, per formulation, and per dosing regimen<sup>†</sup> (with and without LOCF), using an ANCOVA model.

In addition to the hypothesis testing test, it will be assessed whether the lower bound of the two-sided 95% CI excludes 0 mL.

In addition, the nonparametric Wilcoxon signed-rank test on change from baseline data will be performed. Only statistical hypothesis testing (p-values) will be performed.

Analyses will be performed on the FAS, with (LOCF) and without imputation.

#### 7.4.1.2.7 Sensitivity Analysis of the Primary Estimand

As a sensitivity analysis for the estimand, the change from baseline to weeks 4 and 24 in MCC will be analyzed using a mixed-effect model repeated measures (MMRM) with week as fixed effect and baseline value and week by baseline interaction as covariates. The contrast between baseline and week 24 will be the primary statistical inference obtained from this model.

---

<sup>†</sup> 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.



The MMRM analysis will present the least square (LS) mean estimate, standard error (SE), and 2-sided 90% CI for change from baseline to each treatment week. The differences in the LS mean estimates will be used to obtain 1-sided P values for MCC at week 24 versus MCC at baseline.

Since there are only 2 post-baseline time points in a 24 week period, the model will assume unstructured covariance among the within subject repeated measurements. If this is not feasible, an additional covariance structure will be considered the compound symmetry covariance matrix.

#### 7.4.2 Analysis of Secondary Endpoints

Each of the secondary efficacy endpoints will be summarized with descriptive statistics (n, mean, SD, min, median, max for continuous variables; frequency and percentage for categorical variables) at each visit and for change from baseline at each visit when applicable. Each of the secondary efficacy endpoints will be plotted by visit change from baseline will also be plotted at each visit, if applicable.

The change from baseline for each continuous secondary efficacy endpoint (without LOCF) will be summarized and analyzed using the same t-test (see section 7.4.1.1) as for the primary efficacy endpoint. The mean change from baseline estimate together with 95% CI and the relative p-value will be provided using the UNIVARIATE procedure in SAS.

For the analysis of Bladder Volume until first detrusor contraction (>15 cm H<sub>2</sub>O mL) expressed as MCC, a Wilcoxon signed-rank test will be used to compare Change from Baseline at Week 4 and at Week 24 (without LOCF) with 0.

The following hypotheses will be tested:

H<sub>0</sub>: Medians of bladder volumes expressed as MCC are equal at Baseline and Week 24  
(Change from Baseline=0)

H<sub>1</sub>: Medians of bladder volumes expressed as MCC differ at Baseline and Week 24  
(Change from Baseline differs from 0)

The Wilcoxon signed-rank test p-value will be provided.

Example SAS code is as follows:

```
proc univariate;  
  class time;  
  var chgebc;  
run;
```

The medians (with first and third quartiles) of the Bladder Volumes as MCC will be presented for Baseline and Week 24. Furthermore, Box-whisker plots will be presented.

Additionally, a graph will present the Bladder Volumes as MCC (on the horizontal axis) using Detrusor Contraction as event indicator variable. The percentage of subjects will be shown on the vertical axis. Baseline and week 24 values will be overlaid on the same graph.

Example SAS code is as follows (where 'Status'=0 if the value is censored, and 1 otherwise):

```
ods trace on/listing;  
ods output ProductLimitEstimates= RiskNumbers;  
proc lifetest data=km      atrisk plots=survival (cb=hw  
    atrisk) outsurv=s1;  
    time change * Status(0);  
    strata visit ;  
run;  
ods trace off;
```

Separate analyses will be performed including and excluding subjects who had censored change from baseline.

All analyses of secondary endpoints will be produced for subjects in the FAS.

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

### 7.4.3 Analysis of Exploratory Endpoints

Each of the exploratory efficacy endpoints and changes from baseline will be summarized and plotted by visit.

The change from baseline for each continuous exploratory endpoint (without LOCF) will be summarized and analyzed using the same t-test (see section [7.4.1.1](#)) as for the primary efficacy endpoint.

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

The data will be summarized with descriptive statistics according to the nature of variables (n, mean, SD, SEM, 95% CI, min, median, max for continuous; frequency and percentage for categorical) at each visit and for change from baseline.

A listing will be presented for subjects with a filling volume of >40 cm H<sub>2</sub>O detrusor pressure at week 24. Listing will, among other, present the MCC and MCC expressed as % of EBC.

### 7.4.4 Analysis of Other Variables

There are no other efficacy endpoints in this study.

### 7.4.5 Sensitivity Analysis

Due to measurement mistakes it was found that for some assessments negative values were recorded in e-diary for the weight of urine. This affected the following parameters:

- Average catheterized volume per catheterization
- Maximum catheterized volume
- Maximum catheterized daytime volume
- Average morning catheterized volume (based on first catheterization after subject woke up)
- Total catheterized volume per day

- Average morning catheterized volume for subjects with no leakage during the sleeping time (based on first catheterization after subject woke up)
- Average morning catheterized volume for subjects with leakage during the sleeping time (based on first catheterization after subject woke up)

As a consequence of this measurement mistake a sensitivity analysis will be performed for these parameters, which will exclude all subjects with at least 1 negative value.

For each visit, the change from baseline for each efficacy endpoints will be summarized and analyzed using the same t-test (see section 7.4.1.1) as for the primary efficacy endpoint. The mean change from baseline estimate together with 95% CI and the relative p-value will be provided using the UNIVARIATE procedure in SAS.

## 7.5 Analysis of Safety

Unless specified otherwise, safety data will be summarized for the SAF.

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 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.

Summaries will be provided for the SAF unless otherwise specified, whereas listings will be provided for the All Allocated Set. Visit windows will be applied to all data except AEs, as defined in Section 7.11.3

Summaries and listings of SAEs and Serious TEAEs include SAEs upgraded by the sponsor based on review of the Sponsor's list of Always Serious terms if any upgrade was done.

### 7.5.1 Adverse Events

The MedDRA coding dictionary will be used to summarize the AEs in this study by SOC, HLT and PT.

An overview table will include the following details:

- Number of TEAEs and number and percentage of subjects with TEAEs
- Number of drug-related TEAEs and number and percentage of subjects with drug-related TEAEs
- Number of serious TEAEs and number and percentage of subjects with serious TEAEs,
- Number of serious drug-related AEs and number and percentage of subjects with serious drug-related AEs
- Number of TEAEs leading to permanent discontinuation of study drug and number and percentage of subjects with TEAEs leading to permanent discontinuation of study drug,

- Number of drug-related TEAEs leading to permanent discontinuation of study drug and number and percentage of subjects with drug-related TEAEs leading to permanent discontinuation of study drug,
- Number of TEAEs leading to death and number and percentage of subjects with TEAEs leading to death,
- Number of drug-related TEAEs leading the death and number and percentage of subjects with TEAEs leading to death
- Number and percentage of subjects who died.

The number and percentage of AEs which started after Visit 1 and before the first dose of study drug will be summarized by SOC, HLT (only for the table presenting TEAEs) and PT, as well as by worst intensity (mild, moderate or severe) using SAF.

All summaries will be sorted alphabetically by SOC and within SOC by descending frequency of PT for all subjects combined (overall), or alphabetically by SOC and within SOC by HLT (descending frequency) and within HLT by descending frequency of PT for all subjects combined (overall), the latter only for the table presenting TEAEs.

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized using SAF. Summaries will be provided for:

- TEAEs (by SOC, HLT and PT)
- Drug-related TEAEs
- Serious TEAEs
- Drug-related serious TEAEs
- TEAEs leading to permanent discontinuation of study drug
- Drug-related TEAEs leading to permanent discontinuation of study drug
- TEAEs leading to death
- Drug-related TEAEs leading to death
- TEAEs excluding serious adverse events that equal or exceed a threshold of 5.0%, regardless of dose
- TEAEs including serious adverse events that equal or exceed a threshold of 2.0%, regardless of dose

The number of TEAEs and the number and percentage of subjects with TEAEs as classified by SOC and PT will also be summarized by worst severity (mild, moderate, severe), by worst relationship to study drug (not related, possibly related, probably related) and by time intervals categories. In the subject count, if a subject has multiple TEAEs with the same SOC or PT, but with differing severity, then the subject will be counted only once with the worst severity, however, if any of the severity values are missing then the subject will be counted only once with missing severity. Similarly, in the subject count, if a subject has multiple TEAEs with the same SOC or PT, but with differing relationship, then the subject will be counted only once with the highest degree of relationship, however, if any of the relationship values are missing then the subject will be counted only once with missing relationship. If category for the same AE is missing, missing should be used, else use maximum relationship.

Time intervals are based on time from first dose of study drug and will be categorized according to the following categories:

- less than 2 weeks (i.e. less than 14 days);
- at least 2 weeks, less than 4 weeks (i.e. at least 14 days and less than 28 days);
- at least 4 weeks, less than 8 weeks (i.e. at least 28 days and less than 56 days);
- at least 8 weeks, less than 12 weeks (i.e. at least 56 days and less than 84 days);
- at least 12 weeks, less than 24 weeks (i.e. at least 84 days and less than 168 days);
- at least 24 weeks, less than 36 weeks (i.e. at least 168 days and less than 252 days);
- at least 36 weeks, less than 52 weeks (i.e. at least 252 days and less than 364 days);
- and
- at least 52 weeks (i.e. at least 364 days).

At risk denominators for summaries by time interval for onset and by time interval for prevalence will be the same across all AE categories (Overall, SOC and PT), i.e. a subject is at risk in all time period denominators up to EOS.

At risk denominators for summary by time intervals for first onset will depend on AE category and time interval according to the following algorithm:

- For each subject, day of first AE onset is determined for each AE category (Overall, SOC and PT).
- Within each AE category, a subject is at risk in all time intervals denominators up to the first AE onset.

If there is no first AE then the subject will be included in all time intervals up to EOS.

Drug related TEAEs will be presented in a similar way.

AEs of interest are described in Section [6.2.2](#) and will be summarized for PT only (no SOC).

#### **7.5.1.1 Adverse Events of Interest**

For each of the TEAEs of interest, the frequency of TEAEs will be summarized by PT.

#### **7.5.2 Clinical Laboratory Evaluation**

All laboratory data will be summarized using SAF.

The baseline visit is the last measurement taken prior to initial study drug administration.

Quantitative clinical laboratory variables, i.e. hematology, biochemistry, and urinalysis will be summarized separately using mean, standard deviation, minimum, maximum and median at each visit. Additionally, a within-subject change will be calculated as the post-baseline measurement minus the baseline measurement and summarized in the same way.

Values lower than the limit of quantification (LOQ) for laboratory parameters will be set to 0 for the calculation of descriptive statistics.

Each laboratory result will be classified as low (L), normal (N), or high (H) at each visit according to the laboratory supplied reference ranges. The number and percentage of subjects

below and above reference range will be summarized at each visit according to the laboratory supplied reference ranges.

Frequency tabulations of qualitative clinical laboratory variables (urinalysis) will be presented at each visit.

Hematology and biochemistry results will be collected at visit 1/screening, visit 3/baseline, visit 7/week 12 and visit 10/EoT visit. Shifts from Baseline to Week 12 and EoT will be summarized by two types of shift tables:

- Shift tables of reference range (low, normal, high) changes from baseline to Week 12 and EOT, and.
- Summary shifts of reference range changes from baseline to Week 12 and EOT. These shifts are categorized as:
  - “Shift to Low” : shift from normal or high to low
  - “Shift to High”: shift from normal or low to high
  - “Categorized Increase”: shift from low to normal or from normal to high
  - “Categorized No Change”: value stays in the same reference range
  - “Categorized Decrease”: shift from high to normal or from normal to low.

All clinical laboratory data collected during the study and variables derived from it will be listed using SAF.

### 7.5.2.1 Liver function tests

The following potentially clinically significant criteria for liver tests – defined as Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), total bilirubin, Aspartate Transaminase (AST) and their combination are defined. The subject’s highest value during the investigational period will be used.

<u>Parameter</u>	<u>Criteria</u>
ALT	> 3xULN > 5xULN > 10xULN > 20xULN
AST	> 3xULN > 5xULN > 10xULN > 20xULN
ALT or AST	> 3xULN
Total Bilirubin	> 2xULN
ALP	> 1.5xULN
ALT and/or AST AND Total Bilirubin *	(ALT and/or AST > 3xULN) and total bilirubin > 2xULN
ALT and/or AST AND Alkaline Phosphatase AND Total Bilirubin *	ALT and/or AST > 3xULN AND Alkaline Phosphatase < 2xULN AND Total Bilirubin > 2xULN

\*

The number and percentage of subjects with potentially clinically significant values in liver enzyme and total bilirubin tests during the investigational period will be presented

### 7.5.3 Vital Signs

#### 7.5.3.1 Clinic Measurement

Values and changes from baseline for vital signs (SBP, DBP, pulse rate and measurement for temperature) and percentiles of SBP, DBP and Pulse Rate compared to age and height norms (see section 10.6 and 10.7 for Blood Pressures and section 10.5 for Pulse Rate) will be listed and summarized at each scheduled visit using mean, standard deviation, minimum, maximum and median. The number and percentage of subjects outside reference ranges will be shown.

For shifts from baseline to each post-baseline visit the categories used for presentation were obtained from the Fourth Report (NIH, 2005), considered primary presentation, and from the 2017 (American Academy of Pediatric) Clinical Practice Guidelines, considered supportive presentation.

#### Using data from Fourth Report

For each scheduled post-baseline visit, shift tables from baseline to each post-baseline visit will be created with respect to the changes from normal blood pressure (<90<sup>th</sup> percentile): to prehypertension (for children between 90<sup>th</sup> to 95<sup>th</sup> percentile, or for adolescents if  $\geq 120/80$  mmHg, but less than the 95<sup>th</sup> percentile); to stage 1 (95<sup>th</sup> to 99<sup>th</sup> percentile + 5 mmHg); and to stage 2 (>99<sup>th</sup> percentile + 5 mmHg), using cut-points reported by the Fourth (4<sup>th</sup>) Report (NIH, 2005). For the cut-off points (90<sup>th</sup>, 95<sup>th</sup> and 99<sup>th</sup> percentiles) see Appendix 10.1 and Appendix 11.1.

#### Using data from 2017 Clinical Practice Guidelines

For each scheduled post-baseline visit, shift tables from baseline to each post-baseline visit will be presented with respect to the changes from normal blood pressure to elevated blood pressure; stage 1 HTN, or stage 2 HTN, see Table 12 For the cut-off points (90<sup>th</sup>, and 95<sup>th</sup> percentiles) see Appendix 10.2 and Appendix 11.2.

**Table 12 Definitions of Blood Pressure Categories and Stages**

<b>Children Aged 1–&lt;13 years</b>	<b>Adolescents Aged <math>\geq 13</math> years</b>
Normal BP: <90 <sup>th</sup> percentile	Normal BP: <120/<80 mm Hg
Elevated BP: $\geq 90^{\text{th}}$ percentile to <95 <sup>th</sup> percentile or 120/80 mmHg to <95 <sup>th</sup> percentile (whichever is lower)	Elevated BP: 120/<80 to 129/<80 mmHg
Stage 1 HTN: $\geq 95^{\text{th}}$ percentile to <95 <sup>th</sup> percentile + 12 mmHg, or 130/80 to 139/89 mmHg (whichever is lower)	Stage 1 HTN: 130/80 to 139/89 mmHg
Stage 2 HTN: $\geq 95^{\text{th}}$ percentile + 12 mmHg, or $\geq 140/90$ mmHg (whichever is lower)	Stage 2 HTN: $\geq 140/90$ mmHg

Table obtained from: 2017 American Academy of Pediatric Clinical Practice Guidelines, Table 3  
 Note: the age classification into children and adolescents in the Clinical Practice Guidelines (2017) differs from the definition used in the protocol

Summaries will be presented for SBP and DBP separately, overall and by age group. See further details in see Section 6.2.1.3 Conversion of Blood Pressure to Percentiles.

In addition, PR measurements will be compared to age-related norms [Fleming et al, 2011] according to the percentiles shown in Table 13. Each PR value will be categorized as either below the 1<sup>st</sup> percentile, between the 1<sup>st</sup> and 99<sup>th</sup> percentile (limits included) or above the 99<sup>th</sup> percentile. Summaries will be presented overall and by age group.

For the number of subjects with PR values below and above the normal range, the normal range is defined as: 1<sup>st</sup> – 99<sup>th</sup> percentile

**Table 13 Percentiles for Pulse Rate in Relation to Age**

Age	Percentile						
	1st	10th	25th	50th	75th	90th	99th
3-4y	70	86	94	104	113	123	136
4-6y	65	81	89	98	108	117	131
6-8y	59	74	82	91	101	111	123
8-12y	52	67	75	84	93	103	115
12-15y	47	62	69	78	87	96	108
15-18y	43	58	65	73	83	92	104

Source: web appendix to the Fleming et al article (web table 5)

**Potentially Clinically Relevant (PCR)**

[REDACTED]





### 7.5.3.2 Self-Measurements

Similarly to the clinic vital signs measurements (section 7.5.3.1), values and changes from baseline for self vital signs measurements (SBP, DBP, pulse rate) and percentiles of self-measurements SBP and DBP compared to age and gender norms will be listed and summarized at each visit using mean, standard deviation, minimum, maximum and median. The number and percentage of subjects outside reference ranges will be shown.

For shifts from baseline to each post-baseline visit the categories used for presentation were obtained from Stergiou [2007], considered primary presentation, and from the 2017 (American Academy of Pediatric) Clinical Practice Guidelines, considered supportive presentation.

#### Using data from Stergiou [2007]

For each scheduled post-baseline visit, shift tables from baseline to each post-baseline visit will be created with respect to the changes from normal blood pressure ( $\leq 95^{\text{th}}$  percentile) to abnormal blood pressure ( $> 95^{\text{th}}$  percentile), using cut-points reported in Table 14

**Table 14 Systolic and Diastolic Home Blood Pressure Values**

Height (cm)	Boys			Girls		
	n	50 <sup>th</sup> <sup>a</sup>	95 <sup>th</sup> <sup>a</sup>	n	50 <sup>th</sup> <sup>a</sup>	95 <sup>th</sup> <sup>a</sup>
120–129	23	105/64	119/76	36	101/64	119/74
130–139	51	108/64	121/77	51	103/64	120/76
140–149	39	110/65	125/77	61	105/65	122/77
150–159	41	112/65	126/78	71	108/66	123/77
160–169	45	115/65	128/78	148	110/66	124/78
170–179	91	117/66	132/78	46	112/66	125/79
180–189	57	121/67	134/79	7	114/67	128/80

<sup>a</sup> Values are systolic/diastolic blood pressure (Stergiou, 2007)

#### Using data from Clinical Practice Guidelines [2017]

For each scheduled post-baseline visit, shift tables from baseline to each post-baseline visit will be presented with respect to the changes from normal blood pressure to elevated blood

pressure; stage 1 HTN, or stage 2 HTN, see [Table 12](#) For the cut-off points (90<sup>th</sup>, and 95<sup>th</sup> percentiles) see Appendix 10.2 and Appendix 11.2.

### Potentially Clinically Relevant (PCR)

[REDACTED]

### 7.5.4 Height and Weight

Height, weight and BMI, and in addition, z-scores and percentiles compared to age and sex norms, will be listed and summarized overall for the SAF for each visit using mean, SD, 95% CI of the mean, median, minimum, and maximum.

The change from baseline to EoT in the z-score will additionally be summarized by displaying the number and percentage of subjects with changes in each of the following categories: <-1.0, >=-1.0 to <-0.5, >=-0.5 to <=0.5, >0.5 to <=1.0, >1.0.

The summary statistics for percentiles will be calculated by transforming the relevant z-score statistic to a percentile of the standard normal curve, e.g. the mean percentile will be the transformed mean z-score, rather than the mean of the individual percentiles. No estimate of SD will be calculated for the percentiles, and no summary statistics will be generated for the change from baseline in percentile.

### **7.5.5 Electrocardiograms (ECGs)**

ECG variables (QT, QTcF, HR, PR, QRS and RR) will be listed and summarized using mean, standard deviation, minimum, maximum and median at each treatment visit, including changes from baseline.

For categorical ECG variables reported by the local investigator, the worst non-missing value among the assessments will be used in the analyses. Number and percentage of subjects with normal, not clinically significant abnormal and clinically significant abnormal results as assessed by the local investigator for the 12 lead ECG will be tabulated at each visit.

Abnormal results will be presented for a certain visit if abnormal interpretation was recorded for at least one of the ECGs taken during the measurements for the particular visit.

All abnormalities will be listed together with the respective abnormality code and description.

For categorical ECG variables reported by the central laboratory, the worst non-missing value among the assessments will be used in the analysis. Number and percentage of subjects with abnormalities and number and percentage of subjects with normal and abnormal results as assessed by the central laboratory will be tabulated at each visit. Abnormal results will be presented for a certain visit if abnormal interpretation was recorded for at least one of the ECGs taken during the measurements for the particular visit.

Shift tables will be presented for changes from baseline at each visit including local interpretation categories. Shift tables will also be presented as above from baseline to worst post-baseline value during the treatment period. Similar shift tables will summarize Central Reader interpretation categories.

The corrected QT interval (i.e. QTcF) will be summarized for at each visit showing the number and percentage of subjects with a mean of the triplicate QTc values (ms) in each of the following categories:

For the children category

- > 440 ms

For the male adolescents category

- > 450 ms
- > 500 ms

For the female adolescents category

- > 480 ms
- > 500 ms

Note that these categories are cumulative in that subjects satisfying criterion for more extreme category will also be counted in each applicable less extreme category.

The corrected QT interval (i.e. QTcF) will also be summarized for each age group at each visit showing the frequencies of subjects with the following changes from baseline:  $<0$ ,  $\geq 0$  and  $<30$ ,  $\geq 30$  and  $<60$ , and  $\geq 60$  ms.

### 7.5.6 Pregnancies

A detailed listing of all pregnancies will be provided if any occur using All Screened Set.

### 7.5.7 Estimated Glomerular Filtration Rate and Upper Urinary Tract Ultrasound

Values and changes from baseline of plasma creatinine, plasma cystatin C and eGFR levels will be summarized together with the other Biochemistry variables (described in section 7.5.2). 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) using mean, standard deviation, minimum, maximum and median overall at each visit.

Number and percent of subjects with normal, not clinically significant abnormal and clinically significant abnormal ultrasound of the upper urinary tract results will be tabulated for overall at each visit. The results of the ultrasound of the upper urinary tract will be listed. Any clinically-significant abnormality should be recorded as an AE and will be included in the summaries of the AE tables.

## 7.6 Analysis of PK

### 7.6.1 Estimation of Pharmacokinetic Parameters

Pharmacokinetic data analysis will be performed by the GCMSL with mixed effects modeling using NONMEM (version 7.3 or higher, [REDACTED] USA). For the analysis, actual sampling times will be used.

Since the PK sampling is sparse and skewed towards the early phase of the profile with less information in the terminal phase, it is likely that the data from this study may be pooled with other pediatric pharmacokinetic data with richer sampling; this will support the model-based assessment of the following pharmacokinetic parameters for each subject:

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

Additional pharmacokinetic parameters may be calculated based on the model used. Further details of the derivation of the pharmacokinetic parameters are given in the PK DAP.

### 7.6.2 Statistical Analysis

Descriptive statistics (n, mean, SD, minimum, median, maximum, coefficient of variation [%CV], and geometric means) will be calculated for all plasma concentrations of mirabegron. Plasma concentration values below the limit of quantification (LOQ, 0.2 ng/mL) will be set equal to 0 in the calculation of summary statistics.

Plasma concentration data in each time window (see [Table 15](#)) will be summarized by age category (children and adolescents) and the subjects' treatment dose of mirabegron (PED25, PED50) within the age category.

**Table 15 Time Windows for Summary of Plasma Concentration Data**

Target time	Actual Time
2 trough samples	Within 1 hour prior to dosing (on sampling day 1 and 2)
2 samples between 2 h and 5 h post-dose	> 1 hour to 6 hours post-dose (with at least 1 hour in between the samples, on sampling day 2)

Note: Measurements from plasma concentrations outside the time windows will not be included in the summary of the plasma concentrations, but can still be considered for the derivation of pharmacokinetic parameters, which is based on the actual sampling time after study drug intake.

The following plots will be produced:

- Mean (+/-SD) plasma concentration-time profiles (normal scale)
- Mean plasma concentration-time profiles (semi-log scale)
- Box plots of plasma concentration-time profiles (normal scale and semi-log scale)
- Individual subject plasma concentration-time profiles (normal scale “spaghetti plots”)
- Individual subject plasma concentration-time profiles (normal scale and semi-log scale plots)

The first two plots will be produced for the PK report.

Further details will be described in the TLF specifications.

The pharmacokinetic analysis and results will be provided in a separate PK modeling report, which will supplement the CSR.

## 7.7 Analysis of PD

There are no PD data to be analyzed in this study.

## 7.8 Subgroups of Interest

The primary efficacy endpoint will be summarized descriptively with and without LOCF (unless otherwise specified) using FAS for the following subgroups:

- Age group (children vs. adolescents);
- Racial subgroups;
- Ethnicity (Hispanic or Latino / Not Hispanic or Latino)
- Formulation (tablets vs. oral suspension);
- Dosing regimen (“25/50” group vs. “25 only”, please refer to section [7.3.1](#))
- NDO medication treatment received at screening/prior to start of washout (yes vs. no);
- Stop of antimuscarinics medication specifically intended for NDO treatment (prior to study treatment) for lack of efficacy (yes vs. no [i.e., use of antimuscarinics stopped but for other reasons than for lack of efficacy]), if there are sufficient subject numbers;

- Excluding those subjects who had a positive urine culture at visit 3/baseline, visit 5/week 4, and/or visit 8/week 24 (without LOCF only), if there are sufficient subject numbers.

In addition, selected safety variables (all TEAEs and drug related TEAEs, vital signs, height and weight) will be summarized descriptively using SAF for the same subgroups.

Moreover, the selected safety variables, except for TEAEs, will be summarized with respect to age and sex-specific percentiles.

## **7.9 Other Analyses**

There are no other analyses of data in this study.

### **7.10 Interim Analysis (and Early Discontinuation of the Clinical Study)**

No interim analysis of the data for this study is planned.

However, safety data will be reviewed by an independent Drug Safety and Monitoring Board (DSMB). Details are described in the DSMB charter and the corresponding DSMB analysis plan.

### **7.11 Handling of Missing Data, Outliers, Visit Windows, and Other Information**

#### **7.11.1 Missing Data**

Missing primary efficacy endpoint values will be handled by using the Last Observation Carried Forward (LOCF) method. No values at baseline and no data from more than 5 days after the last dose of study medication will be carried forward to post-baseline visits for the analysis of the primary efficacy endpoint on the FAS.

As a general principle, no imputation of missing data for other variables will be done. Exceptions are EoT values for certain safety variables (lab values, vital signs, and ECGs), the start and stop dates of AEs and concomitant treatments, the date of diagnosis of NDO, the diary dates and the times of wake up and go to bed. Listings will present the actual partial dates/times; imputed dates/times will not be shown but derived parameters (e.g. duration of an AE) will be flagged.

##### **7.11.1.1 Imputation Rules for Missing Safety Variables**

In case subject safety data (lab values, vital signs, or ECGs) at EoT (visit 10/week 52) is missing, the LOCF method will be used for the summaries of shift from baseline to EoT only. No values at baseline and no data from more than 5 days after the last dose of study medication will be carried forward to post-baseline visits.

##### **7.11.1.2 Imputation Rules for Diary Dates**

Each item of diary data is collected with the corresponding page number of the diary on which it was recorded. This page number will be used to match “day” pages of the diary with the corresponding “night” pages. When the date for one of the two pages is missing, it will be imputed with the date from the other page.

When the dates for both pages are missing, or when the dates are present but different, the dates will be queried prior to database hard lock.

The time of waking up and going-to-bed may be imputed when they are missing to enable categorization of hour periods as “day time” or “night time”.

If the hour of the wake-up time is missing, the wake-up time will be imputed as occurring a little time prior to the first catheterization, e.g. if the first catheterization is recorded in the 09:00-10:00 hour-period, then the hour of the wake-up time will be imputed as being “09:00”. If there is no catheterization before 12:00, then the wake-up time will not be imputed.

If the hour of going-to-bed time is missing, the going-to-bed time will be imputed as occurring a short time after the last catheterization, e.g. if the last catheterization is recorded in the 20:00-21:00 hour-period, then the hour of going-to-bed will be imputed as being “21:00”. If there is no catheterization before 24:00, then the going-to-bed time will not be imputed.

If the minutes of the wake-up time or going-to-bed time are missing, they will be imputed as “00:30”.

### 7.11.1.3 Imputation Rules for Adverse Events

If there are missing or incomplete onset dates of AEs, then a worst case scenario will be used for the classification of AEs as TEAEs and for the calculation of the longest possible duration of the AE that is consistent with available information. The eCRF includes a checkbox that asks “If the onset date is the same day as study drug start date or if a complete onset date is unknown, please select one (of the following)” and the 2 options are:

3. Onset before first dose of study drug
4. Onset after first dose of the study drug

Let these 2 answers be referred to as Onset=Pre and Onset=Post respectively and also consider that the question may be unanswered (i.e. Onset=Missing).

Let the date of the first dose of study medication (not imputed) be DATE<sub>POST</sub>, and the date of onset of the AE be DATE<sub>AE</sub>.

On the assumption that inconsistencies in the data (e.g. Onset=Post, yet the year of onset is too early for this to be possible) have already been corrected, the method for imputing missing parts of a partial AE start date is as follows:

- When Onset=Pre, there will be no imputation of the AE onset date and the AE is not considered a TEAE;
- When Onset=Post, a worst case scenario will impute DATE<sub>AE</sub> to be the earliest date on or after DATE<sub>POST</sub> which is compatible with the non-missing parts of the date;
- When Onset=Missing, a worst case scenario will impute DATE<sub>AE</sub> as though Onset=Post. If no such date is possible (e.g. the year of the AE or the AE stop date are given and either are earlier than any part of the treatment period) then the AE is not considered a TEAE and no further attempt will be made to impute it.

When imputing the missing parts of a partial AE stop date, the following steps will be followed in order:

- If the year is unknown, the date will not be imputed and will be assigned a missing value;
- If the month is unknown, then assign December;
- If the day is unknown, then assign the last day of the month.

Imputation of start and/stop date should not result in having start dates after stop dates. If start date is completely missing, set it to stop date, and vice-versa.

If the AE is ongoing, the stop date will remain missing.

#### **7.11.1.4 Imputation Rules for NDO Diagnosis Onset Date**

The following steps will be followed when the onset date of NDO diagnosis is partially missing:

- Missing year, whether day and month are present or not: No imputations will occur;
- Missing day, but month and year are present: the day will be imputed as the 15th day of the month;
- Missing day and month, but year is present: the day and month will be imputed as 30 June of the year;
- If any such imputed date falls after the informed consent date, then the onset date will be taken as equal to the earliest informed consent date.

#### **7.11.1.5 Imputation Rules for Start and End Dates for Concomitant Medications and Non-Medication Therapies**

Start and stop dates for all concomitant medications and non-medication therapies are collected on the CRF. However, in case of missing or partial information in these dates, the following rules will be used:

If the start date is missing or partial:

- If the entire date is missing, use the earliest date of informed consent;
- If the year is missing, use the year of informed consent. If this makes the imputed date beyond the last visit date, reduce the year by 1;
- If the month is missing, use January;
- If the day is missing, use the first day of the month under consideration.

If the stop date is missing or partial:

- If year or the entire date is missing, no imputation is performed;
- If month is missing, use December;
- If day is missing, use the last day of the month under consideration;

Imputation of start and/stop date should not result in having start dates after stop dates.



### 7.11.2 Outliers

All values will be included in the planned analyses. A sensitivity analysis excluding outliers may be performed as an additional secondary analysis, if considered appropriate by the study statistician or the medical expert.

### 7.11.3 Visit Windows

The study protocol gives the overall study schedule and the permissible intervals for these visits expressed as the number of days relative to Visit 3 (see [Schedule of Assessments](#)).

Analyses will not exclude subject data due to the subject's failure to comply with the visit schedule; all subjects' data will be listed.

Data from screening (Visit 1) and start of washout (Visit 2), will not be windowed but assigned to the nominal visit.

Except for study dosing data, data from efficacy and some safety parameters will be assigned to windows as shown in [Table 16](#)

**Table 16 Visit Windows for Efficacy and Safety Parameters**

CRF visit	Target day relative to Baseline (Visit 3, Day -1)	Visit Window	Analysis visit
<b>CGI-C</b>			
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Upper urinary tract ultrasound</b>			
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Acceptability questionnaires</b>			
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Height and weight</b>			
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>PinQ, PGI-S</b>			
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

*Table continued on next page*

CRF visit	Target day relative to Baseline (Visit 3, Day -1)	Visit Window	Analysis visit
<b>Urodynamics</b>			
<b>SBPM and Bladder diary</b>			
<b>Vital signs, ECG, urinalysis, pregnancy test and hematology/biochemistry (except visit 8)</b>			

# Day 1 data are assumed to be prior to first dose. For the continuous ECGs, the baseline value will equal  $(M2+M3)/2$  where M2 and M3 equal the triplicate means of at Visit 2 and Visit 3. Visit 2 will windowed from Day -15 to Day -8.

\$ for hematology/biochemistry at screening. Additional hematology/biochemistry taken at baseline only if an AE related to hematology/biochemistry parameters occurred between visit 1/screening and visit 3/baseline.

\* Visit 10 may occur earlier due to early discontinuation as it is the last scheduled study visit.

For non-diary data, if a subject has more than one non-missing value in a visit window, the non-missing assessment which is closest to the target day within a window will be used. If two or more values are equally close and on different days, the latest non-missing value will be used. If two or more values are equally close and on the same day, the mean will be used for continuous variables or the worst observed case for categorical variables.

For diary data, the assessment date for the whole diary will be considered to be the date of the last valid day of the diary. If more than one diary has an assessment date within the same window, and if this results in more than one non-missing value of a diary variable, the non-missing value with the diary assessment day that is closest to the target day will be used. In case of ties on different days, the later non-missing value will be used. In case of ties located on the same side of the target day (i.e., more than one value for the same day), the mean of the values will be used for continuous variables and the worst value for categorical variables. For analyzing diary data the labels of the study visits will not be used, they will be assigned based on the dates of assessment.

A two-day window around the visit date will be applied for the assignment of study period for exposure data.

## 8 DOCUMENT REVISION HISTORY

<b>Version</b>	<b>Date</b>	<b>Changes</b>	<b>Comment/rationale for change</b>
Draft 0.1	25-MAR-2016	NA	NA
Final 1.0	21-APR-2016	Set version to Final 1.0	Finalization of document
Final 2.0	04-May-2018	Whole document	Minor textual updates/changes and typing errors are not mentioned
		Whole document	SMIP is removed from the exploratory safety endpoints. All text related to SMIP is removed from the document
		List of Tables	List of Tables was added
		List of abbreviations	List is updated
		Section <a href="#">6.1.3.1.3</a>	The calculation of bladder compliance is updated according to the central reviewers' algorithm.
		Sections <a href="#">6.2.1.1</a> and <a href="#">6.2.1.2</a>	Calculations of average vital signs are updated to align with the DSMB SAP.
		Sections <a href="#">7.5.3.1</a> and <a href="#">7.5.3.2</a>	Normal blood pressure ranges are updated to align with DSMB SAP.
		Section <a href="#">1</a>	Text is updated to include CT206. Text on PK Analysis is updated.
		<a href="#">Table 1</a>	Table 1 is updated according to protocol of CT206.
		Section <a href="#">5.3</a>	Second bullet updated: New text: Had a valid (as by the central reviewer's assessment) nonmissing MCC measurement at baseline and at a post-baseline visit for the primary efficacy endpoint. Old text: Provided both <u>valid</u> baseline and at least 1 postbaseline value for the primary efficacy endpoint (MCC)
		Section <a href="#">5.4.1</a>	Text on "Prohibited Medication" is updated with respect to Botox. New text (added text in italic): "Except for Botox which is not allowed if <i>taken from &lt;4 months before screening and/or during the whole study period.</i> "
		Section <a href="#">5.4.1</a>	Eligibility Deviations: the 2 bullets are updated
		Section <a href="#">6.1</a> Urodynamic assessments	Parameter "MCC expressed as percentage of Expected Bladder Capacity (EBC)" added plus additional text to describe the parameter
Section <a href="#">6.1</a> Questionnaires	Text from sentence below is deleted: "to be completed by the subject or the subject's parent/caregiver"		
		Section <a href="#">6.1</a> Questionnaires	Text now reads: Questionnaires (i.e., PIN-Q, PGI-S and the Acceptability Questionnaires)

<b>Version</b>	<b>Date</b>	<b>Changes</b>	<b>Comment/rationale for change</b>
			will be provided via the e-diary.
		Section <a href="#">6.1</a> Questionnaires	Sentence “Clinically relevant adverse changes will be recorded as an AE.” just above “The primary and secondary variables will be ....” is deleted
		Section <a href="#">6.1</a>	<a href="#">Table 2</a> and <a href="#">Table 3</a> are updated with respect to deleted and added variables.
		Section <a href="#">6.1.2</a>	Section on Estimand is added
		Section <a href="#">6.1.3.2.1</a> – <a href="#">6.1.3.2.4</a>	Text: “...2 days are concurrent” is replaced by “...2 days are consecutive” Note: in version 1.0 it was section 6.1.2.2.1 – 6.1.2.2.4
		Section <a href="#">6.1.3.2.2</a> and <a href="#">6.1.3.2.3</a>	Text “An alternative version of this variable will be calculated as the maximum of all the daytime values recorded over the two measuring days.” is deleted. Note: In version 1.0 it was section 6.1.2.2.2 and 6.1.2.2.3
		Section <a href="#">6.1.3.2.5</a> and <a href="#">6.1.3.2.6</a>	Section title now reads: Mean number of leakage episodes per day (day and night time) (weekend diary) In title header “day and night time” is presented instead of “night time” Note in version 1.0 it was section 6.1.2.2.5 and 6.1.2.2.6
		Section <a href="#">6.1.3.3.1</a>	Text on items of PIN-Q is updated Note in version 1.0 it was section 6.1.2.3.1
		Section <a href="#">6.1.3.3.5</a>	Section on Acceptability (for oral suspension) is added
		Section <a href="#">6.1.4.2.1</a>	Section is added to describe MCC expressed as percentage EBC
		Section <a href="#">6.1.4.2.3</a>	Last sentence: “total catheterized volume” instead of “maximum catheterized volume” Note in version 1.0 it was section 6.1.3.2.2
		Section <a href="#">6.1.4.2.6</a>	Section is added to describe “Percentage of Catheterizations without Intermittent Leakage Accident”
		Section <a href="#">6.2</a>	<a href="#">Table 5</a> footnote added
		Section <a href="#">6.2.1.2</a>	As second sentence added: “Additional SBPM will be 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.”
		Section <a href="#">6.2.1.4</a>	<a href="#">Table 7</a> is updated, now based on Fleming et al. [2011], instead of on Ostchega et al. [2011]
		Section <a href="#">6.2.2</a>	Timeframe for defining a TEAE is clarified.

<b>Version</b>	<b>Date</b>	<b>Changes</b>	<b>Comment/rationale for change</b>
			AEs of interest: First bullet (CV), the following text is added for clarification: “(Note: these 3 CV events will be analyzed combined and separately)”
		Section <a href="#">6.2.3</a>	<a href="#">Table 9</a> “Estimated glomerular filtration rate (Larsson)” is replaced by “Estimated glomerular filtration rate (Larsson, modified Schwartz and Cockcroft-Gault)”
		Section <a href="#">6.5.4</a>	Text on “Suspension Compliance” is added
		Section <a href="#">7.2.1</a>	Wash out failures summary is removed as washout failure is not defined in the protocol. Follow-up summary is replaced by end of treatment summary. Analysis Sets are added. Text added with respect to a listing of all early withdrawals and a listing of screen failures.
		Section <a href="#">7.2.3</a>	Updated countries participating in the study and added text below this paragraph to explain that countries may be added to the list
		Section <a href="#">7.4.1.1</a>	The following text is added at end of section: “MCC at each visit and change from baseline in MCC at visit 8/week 24 (without LOCF) will be also plotted and listed for SAF and PPS.”
		Section <a href="#">7.4.3</a>	The following text is added at end of section: “A listing will be presented for subjects with a filling volume of >40 cm H <sub>2</sub> O detrusor pressure at week 24. Listing will, among other, present the MCC and MCC expressed as % of EBC.”
		Section <a href="#">7.4.5</a>	Section on “Sensitivity analysis” is added. Section was added to investigate the effect of the urine measurement mistakes made.
		Section <a href="#">7.5</a>	SAEs upgraded by the Sponsor is added. This was an omission in the previous version. Text added with respect to summarizing safety parameters with respect to height- and sex-specific percentiles. Height will be summarized with respect to age- and sex-specific percentiles.
		Section <a href="#">7.5</a>	Text added: “Subgroup presentations regarding age (children and adolescents), formulation (tablets and suspension) and dosing regimen (PED25 and PED50) will be tabulated for a number of safety parameters. Added text at end of Section “For any of the subgroups specified, at least 10 subjects by stratum are required.”

<b>Version</b>	<b>Date</b>	<b>Changes</b>	<b>Comment/rationale for change</b>
		Section <a href="#">7.5.1</a>	Number and percentage of subjects who died” instead of “Number of Deaths”.
		Section <a href="#">7.5.2.1</a>	Text on “Liver Function Tests” is updated
		Sections <a href="#">7.5.3.1</a> and <a href="#">7.5.3.2</a>	Text on PCR for SBP and for DBP is updated Text on prehypertension is updated
		Section <a href="#">7.6.2</a>	<a href="#">Table 15</a> is updated to reflect the sampling strategy
		Section <a href="#">9</a>	List of References is updated.
		Section <a href="#">10.1</a>	List of In- and Exclusion criteria is updated according to protocol of 206 study”.
		Section <a href="#">10.14</a>	List of Key Contributors and Approvers is updated
Final 3.0	21-May-2019	Whole document	Typos were corrected
		Introduction	Introduction was updated to reflect it is the SAP for 206A. Reference to EU PIP, EMEA Decision, and US Written Request was added.
		Section 3.2 and 7.2.3	Deleted reference to USA
		Section 6.1	Full + Empty Bladder Pressure is deleted
		Section 6.1, Table 2 and Table 3	Tables are updated to show that change from baseline in MCC expressed as % of EBC is analyzed at Week 4 and Week 24.
		Section 6.1.2	Title updated: Estimand instead of Estimator and 1 sentence added: “Difference of MCC at visit 8/week 24 (or prior, due to study drug discontinuation) compared to baseline is the primary estimator.” Text was added why the “de facto” estimand was not chosen for this study. Last sentence of his section: to impute was changed by “to handle”
		Section 6.1.3.2.8 (new)	Added section on identification of leakage during sleeping time
		Section 6.1.3.2.8	New section added for clarification “Identification of leakage during sleeping time”
		Section 6.2.2	AEs of Interest: Deleted is: Thermogenesis (brown fat). Added are: Seizure; Syncope; Fetal disorders after exposure during pregnancy; and Concomitant treatment with cytochrome P450 (CYP) 2D6 substrates with narrow therapeutic indices or individually dose-titrated. Last sentence of Section 6.2.2: text “and AEs related to mirabegron” is deleted
		Section 6.5.4	Compliance text was updated
		Section 7.2.1	A table was added which presented the number of subjects screened under each protocol version
		Section 7.2.2	PD4: “excluded” instead of “prohibited”

<b>Version</b>	<b>Date</b>	<b>Changes</b>	<b>Comment/rationale for change</b>
			concomitant medication
		Section 7.2.3	Added Analysis Set (SAF) for summary of Medical History data.
		Section 7.3.3	Titration period: Visit 3 to Visit 7 instead of Visit 4 to Visit 6
		Section 7.4.1.1	SAS procedure TTEST was replaced by UNIVARIATE
		Section 7.4.1.2.6	Text was updated, no pooling of data from 206 and 206A and statistical method adapted.
		Section 7.4.5	Added to Average morning catheterized volume: once “for subjects with no leakage during the sleeping time” and “for subjects with leakage during the sleeping time”
		Section 7.5.1	AE will be summarized by SOC, HLT and PT instead of by SOC and PT for “All TEAEs” table only
		Section 7.5.1.2	Second paragraph is deleted
		Section 7.5.2.1	Old text replaced by standard text from SAP template
		Section 7.5.3.1	In addition to shift tables referencing to “Fourth Report” also shift table will be presented based on a more recent reference: “2017 American Academy of Pediatric Clinical Practice Guidelines”, based on FDA request. Results based on Fourth Report are considered primary, results based on other reference are considered secondary. Additional table (Table 12) was inserted. Text updated for clinical measurements and home measurements (same lay-out for both)
		Section 7.5.3.1	For presenting the number of subjects with PR values below or above the normal range, the normal range is defined. Footnote was added to Table 12 to explain that the age classification into children and adolescents in the Clinical Practice Guidelines (2017) differs from the definition used in the protocol
		Section 7.6.2	Mean plasma concentration-time profiles only on semi-log scale. Added: Box plots of plasma concentration-time profiles (normal scale and semi-log scale). And text that “First 2 plots will be produced for PK report.”
		Section 7.8	Ethnicity was added as subgroup based on request from FDA. Sentence “For any of these subgroups, at least

<b>Version</b>	<b>Date</b>	<b>Changes</b>	<b>Comment/rationale for change</b>
			10 subjects by stratum are required.” was deleted.
		Section 7.11.3	Title of table 16 was adapted and footnote was added to the table for clarification of visit 10. Two sentences were added at end of section: one to clarify that for the diary data the labels will not be used for analysis, and another one to explain for exposure data the assignment of study period
		Table 13 (new)	Table is added with data from Stergiou 2007 reference
		REFERENCES	Reference added: “2017 American Academy of Pediatric Clinical Practice Guidelines”
		Section 10: Appendices	Numbering has changed
		Section 10.1	Exclusion criteria are re-numbered, starting now at 1. To be in line with numbering in Section 5.4.1
		Section 10.3, Appendix 3.2	Section is deleted
		Sections 10.10 and 10.11	Tables with results for males and females from “2017 American Academy of Pediatric Clinical Practice Guidelines” reference are included
		Section 10.14	List of Key Contributors and Approvers is updated due to internal Astellas reorganization



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## 10 APPENDICES

### 10.1 Appendix 1: Inclusion and Exclusion Criteria

#### 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  $\geq 11$  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<sub>2</sub>O from baseline detrusor pressure, and/or a decrease in compliance leading to an increase in baseline detrusor pressure of  $> 20$  cm H<sub>2</sub>O.
5. Subject is exclusively using CIC (no voluntary voiding), starting 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 are NOT allowed.

### **Exclusion Criteria:**

Subject are 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 or during the pre-treatment period
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<sup>th</sup> percentile [Fleming et al, 2011].
10. Subject has an established hypertension and a systolic or diastolic blood pressure higher than 5 mmHg above the 99<sup>th</sup> percentile (stage 2 hypertension) or subject has a systolic or diastolic blood pressure that ranges from the 95<sup>th</sup> percentile to 5mmHg above the 99<sup>th</sup>

percentile (stage 1 hypertension) which is not well-controlled. Percentiles are determined by sex, age, and height [The Fourth Report, 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 individually dose-titrated, 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 are NOT allowed.

## 10.2 Appendix 2: List of Excluded Concomitant Medications

Any medication used for the management of NDO (including tricyclic antidepressants, 1<sup>st</sup> 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.

<b>Anticholinergics/ antimuscarinics</b>	<b>Tricyclic antidepressants</b>	<b>1st generation H1-antagonists †</b>
Darifenacin	Alimemazine / Trimipramine	Tripelennamine
Dicyclomine/Dicycloverine	Amitriptyline	Dimenhydrinate
Fesoterodine	Amoxapine	Clemastine
Flavoxate	Clomipramine	Bromazine
Isopropanolamide	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	
<b>Alpha-blockers</b>	<b>CYP2D6 with narrow therapeutic index</b>	<b>Sensitive P-gp substrates</b>
Tamsulosin	Thioridazine	Digoxin
Alfuzosin	Flecainide	Dabigatran
Doxazosin	Propafenone	
Terazosin	Imipramine	
Silodosin	Desipramine	
<b>Strong CYP3A4 inhibitors</b>	<b>Other</b>	
Itraconazole	Mirabegron (except for study drug)	
Ketoconazole	Botulinum toxin	
Ritonavir		
Clarithromycin		

† Incidental use for motion sickness is accepted.

### 10.3 Appendix 3: AEs of Interest not covered by Standard MedDRA SMQs V16.0

The following is a list of AE terms to programmatically flag subjects with AE's of interest (see Section 7.5.1.1).

Type	Term	Code	AE of Interest	MedDRA 16.0 Search Criteria
LLT	Acute retention of urine	10001055	Acute urinary retention	Selected LLT (non-SMQ)
PT	Residual urine volume	10050832	Urinary retention	Selected PT's (non-SMQ)
PT	Residual urine volume increased	10067758	Urinary retention	Selected PT's (non-SMQ)
PT	Urinary retention	10046555	Urinary retention	Selected PT's (non-SMQ)
PT	Pyelonephritis mycoplasmal	10037603	Urinary tract infection	Selected PT's (non-SMQ)
PT	Pyelonephritis viral	10065213	Urinary tract infection	Selected PT's (non-SMQ)
PT	Pyonephrosis	10037653	Urinary tract infection	Selected PT's (non-SMQ)
PT	Renal abscess	10038351	Urinary tract infection	Selected PT's (non-SMQ)
PT	Renal syphilis	10038530	Urinary tract infection	Selected PT's (non-SMQ)
PT	Renal tuberculosis	10038534	Urinary tract infection	Selected PT's (non-SMQ)
PT	Urethral abscess	10046424	Urinary tract infection	Selected PT's (non-SMQ)
PT	Urethral carbuncle	10052299	Urinary tract infection	Selected PT's (non-SMQ)
PT	Urethritis	10046480	Urinary tract infection	Selected PT's (non-SMQ)
PT	Urethritis chlamydial	10046482	Urinary tract infection	Selected PT's (non-SMQ)
PT	Urethritis gonococcal	10046483	Urinary tract infection	Selected PT's (non-SMQ)
PT	Urethritis trichomonal	10046489	Urinary tract infection	Selected PT's (non-SMQ)
PT	Urethritis ureaplasma	10046490	Urinary tract infection	Selected PT's (non-SMQ)






## 10.4 Appendix 4: Questionnaires

### Appendix 4.1 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


















### Appendix 4.2 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
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

### Appendix 4.3 Acceptability Questionnaire for Tablets

Questions				
<b>1. How was the <u>TASTE</u> of the study medication?</b>				
0	1	2	3	4
				
Really bad	Bad	Not bad, not good	Good	Really good
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>2. How was it to <u>SWALLOW</u> the study medication?</b>				
0	1	2	3	4
				
Really difficult	Difficult	Not difficult, not easy	Easy	Really easy
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

### Appendix 4.4 Acceptability Questionnaire for Oral Suspension

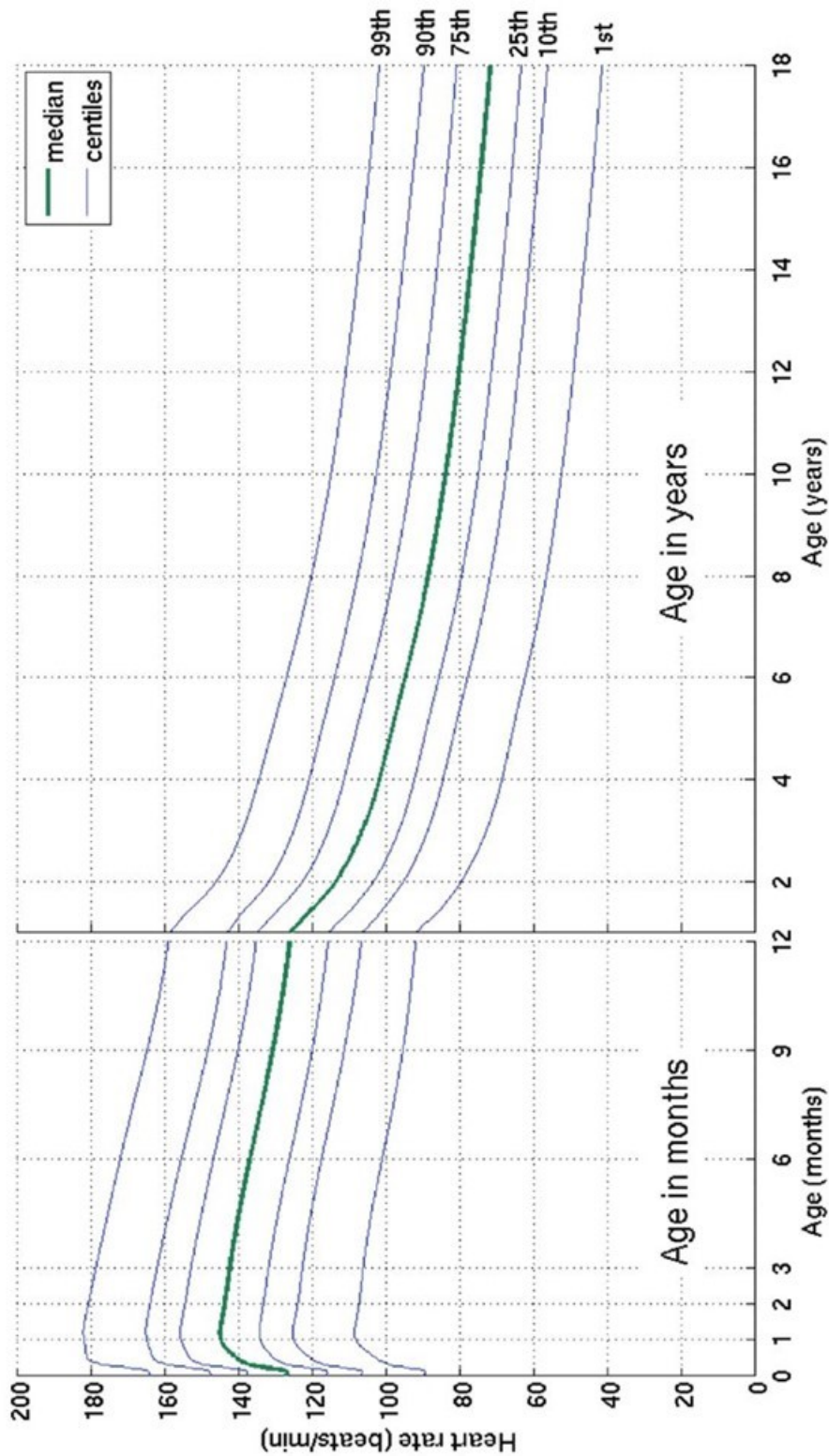
Questions				
<b>1. How was the <u>TASTE</u> of the study drug?</b>				
0	1	2	3	4
				
Really bad	Bad	Not bad, not good	Good	Really good
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>2. How was the <u>SMELL</u> of the study drug?</b>				
0	1	2	3	4
				
Really bad	Bad	Not bad, not good	Good	Really Good
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>3. How was it to <u>TAKE</u> the study drug?</b>				
0	1	2	3	4
				
Really difficult	Difficult	Not difficult, not easy	Easy	Really easy
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

### Appendix 4.5 Clinical Global Impression of Change Scale

<b>Clinical Global Impression of Change Scale</b>	
<b>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)</b>	
<input type="checkbox"/>	Very much improved
<input type="checkbox"/>	Much improved
<input type="checkbox"/>	Minimally improved
<input type="checkbox"/>	No change
<input type="checkbox"/>	Minimally worse
<input type="checkbox"/>	Much worse
<input type="checkbox"/>	Very much worse

### 10.5 Appendix 5 Centiles of heart rate for normal children from birth to 18 years of age [Fleming et al, 2011]



## 10.6 Appendix 6 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

### 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



### 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

### 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

**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

### 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)
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

### 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

## 10.7 Appendix 7 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

**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

**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



**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

**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

**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

**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

### 10.8 Appendix 8 CDC Data Table of Weight-for-age Chart for Males

Age (in months)	3rd Percentile Weight (in kilograms)	5th Percentile Weight (in kilograms)	10th Percentile Weight (in kilograms)	25th Percentile Weight (in kilograms)	50th Percentile Weight (in kilograms)	75th Percentile Weight (in kilograms)	90th Percentile Weight (in kilograms)	95th Percentile Weight (in kilograms)	97th Percentile Weight (in kilograms)
24	10.38209	10.64009	11.05266	11.78598	12.67076	13.63692	14.5834	15.18777	15.59648
24.5	10.44144	10.70051	11.1149	11.85182	12.74154	13.71386	14.66716	15.2763	15.68841
25.5	10.55847	10.81958	11.23747	11.98142	12.88102	13.8659	14.83332	15.45242	15.8717
26.5	10.6738	10.93681	11.35806	12.10889	13.01842	14.01623	14.99848	15.62819	16.05514
27.5	10.78798	11.0528	11.47728	12.23491	13.1545	14.16567	15.16351	15.8045	16.23967
28.5	10.90147	11.16803	11.59567	12.36007	13.2899	14.31493	15.32917	15.98214	16.42609
29.5	11.01466	11.28293	11.71368	12.4849	13.42519	14.46462	15.4961	16.16177	16.61508
30.5	11.12787	11.39782	11.8317	12.60983	13.56088	14.61527	15.66485	16.34395	16.8072
31.5	11.24135	11.513	11.95005	12.73523	13.69738	14.76732	15.83588	16.52915	17.00291
32.5	11.3553	11.62869	12.069	12.86144	13.83505	14.92117	16.00958	16.71773	17.2026
33.5	11.46988	11.74508	12.18875	12.9887	13.97418	15.07711	16.18624	16.91	17.40654
34.5	11.58521	11.8623	12.30948	13.11723	14.11503	15.23541	16.36612	17.10619	17.61495
35.5	11.70137	11.98046	12.43132	13.24721	14.2578	15.39628	16.5494	17.30646	17.82797
36.5	11.81842	12.09962	12.55436	13.37875	14.40263	15.55987	16.73623	17.51093	18.0457
37.5	11.93639	12.21984	12.67868	13.51197	14.54965	15.7263	16.9267	17.71965	18.26818
38.5	12.05529	12.34115	12.80431	13.64693	14.69893	15.89565	17.12085	17.93265	18.49539
39.5	12.17512	12.46354	12.93128	13.78366	14.85054	16.06797	17.3187	18.14992	18.72731
40.5	12.29587	12.58701	13.05959	13.92218	15.00449	16.24326	17.52025	18.37141	18.96385
41.5	12.41751	12.71154	13.18923	14.0625	15.16078	16.42153	17.72545	18.59705	19.20492
42.5	12.54001	12.8371	13.32017	14.20458	15.3194	16.60273	17.93424	18.82675	19.45041
43.5	12.66334	12.96366	13.45238	14.3484	15.4803	16.78682	18.14654	19.06041	19.70017
44.5	12.78746	13.09119	13.58581	14.49391	15.64343	16.97373	18.36226	19.29789	19.95407
45.5	12.91234	13.21963	13.72043	14.64105	15.80873	17.16336	18.58128	19.53907	20.21195
46.5	13.03792	13.34895	13.85618	14.78977	15.9761	17.35564	18.80348	19.78381	20.47366
47.5	13.16419	13.47911	13.99301	14.93998	16.14548	17.55044	19.02875	20.03197	20.73903
48.5	13.29111	13.61006	14.13086	15.09163	16.31677	17.74767	19.25695	20.28339	21.00793
49.5	13.41864	13.74176	14.26968	15.24463	16.48986	17.9472	19.48794	20.53795	21.28018
50.5	13.54675	13.87418	14.40943	15.39892	16.66468	18.14892	19.7216	20.79548	21.55565
51.5	13.67543	14.00727	14.55004	15.55441	16.8411	18.3527	19.95779	21.05586	21.83419
52.5	13.80466	14.14102	14.69148	15.71103	17.01904	18.55842	20.19637	21.31896	22.11568
53.5	13.93441	14.2754	14.8337	15.86872	17.19839	18.76598	20.43722	21.58464	22.39999
54.5	14.06467	14.41037	14.97666	16.0274	17.37906	18.97524	20.68022	21.8528	22.68702
55.5	14.19544	14.54593	15.12032	16.18701	17.56096	19.1861	20.92526	22.12331	22.97667
56.5	14.32672	14.68205	15.26465	16.34748	17.744	19.39846	21.17222	22.3961	23.26885
57.5	14.4585	14.81872	15.40962	16.50877	17.92809	19.6122	21.421	22.67106	23.56349
58.5	14.59079	14.95595	15.55521	16.67081	18.11316	19.82724	21.67152	22.94813	23.86054

Age (in months)	3rd Percentile Weight (in kilograms)	5th Percentile Weight (in kilograms)	10th Percentile Weight (in kilograms)	25th Percentile Weight (in kilograms)	50th Percentile Weight (in kilograms)	75th Percentile Weight (in kilograms)	90th Percentile Weight (in kilograms)	95th Percentile Weight (in kilograms)	97th Percentile Weight (in kilograms)
59.5	14.72359	15.09371	15.70139	16.83356	18.29912	20.04348	21.92369	23.22723	24.15995
60.5	14.85692	15.23202	15.84814	16.99698	18.48592	20.26086	22.17744	23.50833	24.46169
61.5	14.99078	15.37087	15.99546	17.16103	18.6735	20.47929	22.4327	23.79136	24.76575
62.5	15.1252	15.51027	16.14334	17.32567	18.8618	20.69871	22.68943	24.07632	25.07212
63.5	15.26018	15.65023	16.29176	17.49088	19.05077	20.91907	22.94758	24.36317	25.38081
64.5	15.39575	15.79076	16.44074	17.65664	19.24037	21.14031	23.20712	24.65192	25.69185
65.5	15.53193	15.93186	16.59026	17.82293	19.43058	21.36242	23.46802	24.94257	26.00527
66.5	15.66872	16.07356	16.74033	17.98974	19.62136	21.58534	23.73029	25.23514	26.32111
67.5	15.80617	16.21586	16.89096	18.15706	19.8127	21.80908	23.99391	25.52965	26.63944
68.5	15.94427	16.35879	17.04215	18.32489	20.00459	22.0336	24.2589	25.82615	26.96033
69.5	16.08306	16.50235	17.19393	18.49324	20.19703	22.25893	24.52527	26.12468	27.28386
70.5	16.22255	16.64657	17.34629	18.66211	20.39002	22.48505	24.79305	26.4253	27.6101
71.5	16.36276	16.79146	17.49926	18.83151	20.58357	22.712	25.06229	26.72807	27.93916
72.5	16.5037	16.93704	17.65285	19.00147	20.7777	22.93978	25.33302	27.03308	28.27115
73.5	16.64539	17.08332	17.80708	19.17199	20.97243	23.16845	25.6053	27.34039	28.60616
74.5	16.78785	17.23031	17.96197	19.34311	21.16779	23.39803	25.87919	27.6501	28.94432
75.5	16.93107	17.37804	18.11754	19.51485	21.36383	23.62858	26.15477	27.9623	29.28574
76.5	17.07507	17.52651	18.2738	19.68724	21.56058	23.86016	26.4321	28.27709	29.63055
77.5	17.21986	17.67574	18.43077	19.86032	21.75811	24.09284	26.71128	28.59457	29.97888
78.5	17.36543	17.82572	18.58848	20.03413	21.95645	24.32667	26.99239	28.91486	30.33083
79.5	17.5118	17.97649	18.74695	20.20871	22.15567	24.56175	27.27553	29.23806	30.68656
80.5	17.65895	18.12803	18.9062	20.38409	22.35584	24.79815	27.56081	29.56428	31.04617
81.5	17.80689	18.28036	19.06624	20.56032	22.55702	25.03598	27.84832	29.89365	31.4098
82.5	17.9556	18.43348	19.2271	20.73745	22.7593	25.27531	28.13817	30.22628	31.77756
83.5	18.10509	18.5874	19.3888	20.91553	22.96273	25.51626	28.43049	30.56228	32.14959
84.5	18.25535	18.74211	19.55136	21.0946	23.16742	25.75894	28.72538	30.90178	32.52599
85.5	18.40637	18.89763	19.71479	21.27471	23.37343	26.00344	29.02298	31.24489	32.90689
86.5	18.55813	19.05395	19.87913	21.45592	23.58086	26.24988	29.3234	31.59174	33.29238
87.5	18.71062	19.21107	20.04438	21.63828	23.78979	26.49839	29.62676	31.94243	33.68257
88.5	18.86385	19.369	20.21057	21.82185	24.00031	26.74907	29.9332	32.29708	34.07755
89.5	19.01778	19.52773	20.37771	22.00666	24.21251	27.00204	30.24283	32.65581	34.47742
90.5	19.17243	19.68727	20.54584	22.19278	24.42648	27.25743	30.55579	33.01871	34.88226
91.5	19.32776	19.84762	20.71496	22.38027	24.64231	27.51535	30.8722	33.38591	35.29215
92.5	19.48379	20.00878	20.88511	22.56917	24.8601	27.77593	31.19218	33.75749	35.70715
93.5	19.6405	20.17076	21.05629	22.75955	25.07992	28.03928	31.51586	34.13355	36.12732
94.5	19.79788	20.33357	21.22855	22.95145	25.30189	28.30554	31.84335	34.5142	36.55271
95.5	19.95594	20.4972	21.4019	23.14493	25.52607	28.5748	32.17478	34.8995	36.98338

Age (in months)	3rd Percentile Weight (in kilograms)	5th Percentile Weight (in kilograms)	10th Percentile Weight (in kilograms)	25th Percentile Weight (in kilograms)	50th Percentile Weight (in kilograms)	75th Percentile Weight (in kilograms)	90th Percentile Weight (in kilograms)	95th Percentile Weight (in kilograms)	97th Percentile Weight (in kilograms)
96.5	20.11467	20.66168	21.57637	23.34005	25.75257	28.84718	32.51025	35.28955	37.41935
97.5	20.27408	20.82702	21.75198	23.53686	25.98146	29.12281	32.84988	35.68443	37.86065
98.5	20.43418	20.99322	21.92878	23.73542	26.21284	29.40179	33.19377	36.08419	38.30731
99.5	20.59497	21.16032	22.10678	23.93579	26.44679	29.68422	33.54202	36.4889	38.75932
100.5	20.75647	21.32832	22.28602	24.13801	26.68339	29.97021	33.89472	36.89862	39.2167
101.5	20.91869	21.49726	22.46654	24.34216	26.92273	30.25986	34.25197	37.3134	39.67943
102.5	21.08166	21.66716	22.64838	24.54828	27.16489	30.55326	34.61384	37.73327	40.14749
103.5	21.2454	21.83805	22.83157	24.75645	27.40995	30.85051	34.98041	38.15826	40.62087
104.5	21.40994	22.00997	23.01617	24.9667	27.65797	31.15169	35.35176	38.58841	41.09952
105.5	21.57532	22.18296	23.20222	25.17912	27.90904	31.45689	35.72793	39.02372	41.5834
106.5	21.74156	22.35705	23.38976	25.39375	28.16324	31.76618	36.10899	39.46421	42.07247
107.5	21.90873	22.5323	23.57885	25.61067	28.42064	32.07964	36.49499	39.90987	42.56665
108.5	22.07685	22.70876	23.76955	25.82993	28.6813	32.39734	36.88596	40.36069	43.06589
109.5	22.24599	22.88648	23.96192	26.05161	28.9453	32.71933	37.28193	40.81665	43.5701
110.5	22.4162	23.06551	24.15601	26.27576	29.21271	33.04569	37.68294	41.27773	44.0792
111.5	22.58754	23.24593	24.35189	26.50246	29.48359	33.37646	38.08898	41.74388	44.5931
112.5	22.76008	23.42779	24.54962	26.73177	29.758	33.7117	38.50008	42.21507	45.11169
113.5	22.93388	23.61117	24.74929	26.96376	30.03602	34.05144	38.91622	42.69124	45.63487
114.5	23.10902	23.79613	24.95096	27.19851	30.3177	34.39573	39.33741	43.17232	46.16253
115.5	23.28558	23.98277	25.1547	27.43609	30.60311	34.7446	39.76363	43.65825	46.69454
116.5	23.46364	24.17115	25.3606	27.67657	30.8923	35.09808	40.19484	44.14895	47.23077
117.5	23.64329	24.36137	25.56874	27.92001	31.18533	35.4562	40.63103	44.64432	47.77109
118.5	23.8246	24.55351	25.77921	28.16651	31.48225	35.81896	41.07214	45.14428	48.31536
119.5	24.00769	24.74766	25.99208	28.41613	31.78312	36.1864	41.51813	45.64872	48.86343
120.5	24.19264	24.94392	26.20745	28.66894	32.08799	36.55851	41.96894	46.15753	49.41515
121.5	24.37956	25.14238	26.42541	28.92502	32.3969	36.93529	42.42452	46.6706	49.97037
122.5	24.56855	25.34314	26.64604	29.18446	32.70991	37.31675	42.88478	47.1878	50.52892
123.5	24.75971	25.54631	26.86945	29.44731	33.02704	37.70287	43.34967	47.70901	51.09064
124.5	24.95315	25.75198	27.09573	29.71365	33.34835	38.09365	43.81908	48.23408	51.65537
125.5	25.14898	25.96027	27.32496	29.98357	33.67387	38.48906	44.29292	48.76288	52.22293
126.5	25.34731	26.17126	27.55726	30.25713	34.00363	38.88907	44.77111	49.29526	52.79314
127.5	25.54826	26.38509	27.7927	30.53439	34.33766	39.29366	45.25354	49.83107	53.36584
128.5	25.75195	26.60184	28.0314	30.81543	34.67599	39.7028	45.7401	50.37016	53.94084
129.5	25.95847	26.82163	28.27343	31.10032	35.01864	40.11642	46.23066	50.91236	54.51797
130.5	26.16796	27.04457	28.51891	31.38912	35.36562	40.5345	46.72512	51.45752	55.09704
131.5	26.38051	27.27076	28.76791	31.68189	35.71695	40.95697	47.22334	52.00546	55.67787
132.5	26.59626	27.50031	29.02052	31.97868	36.07263	41.38377	47.72519	52.55602	56.26029

Age (in months)	3rd Percentile Weight (in kilograms)	5th Percentile Weight (in kilograms)	10th Percentile Weight (in kilograms)	25th Percentile Weight (in kilograms)	50th Percentile Weight (in kilograms)	75th Percentile Weight (in kilograms)	90th Percentile Weight (in kilograms)	95th Percentile Weight (in kilograms)	97th Percentile Weight (in kilograms)
133.5	26.81531	27.73332	29.27685	32.27955	36.43266	41.81484	48.23054	53.10903	56.84411
134.5	27.03777	27.96989	29.53696	32.58454	36.79704	42.2501	48.73924	53.66432	57.42915
135.5	27.26376	28.21013	29.80095	32.89371	37.16577	42.68947	49.25114	54.22171	58.01524
136.5	27.49337	28.45412	30.06888	33.20709	37.53881	43.13287	49.76611	54.78102	58.60219
137.5	27.72672	28.70197	30.34084	33.52472	37.91616	43.5802	50.28397	55.34208	59.18983
138.5	27.9639	28.95376	30.61689	33.84662	38.29777	44.03137	50.80458	55.9047	59.77799
139.5	28.20501	29.20958	30.8971	34.17281	38.68361	44.48627	51.32778	56.46873	60.3665
140.5	28.45015	29.4695	31.18151	34.5033	39.07364	44.94478	51.85339	57.03397	60.95519
141.5	28.69939	29.7336	31.4702	34.83811	39.46781	45.40679	52.38125	57.60024	61.5439
142.5	28.95283	30.00195	31.76319	35.17724	39.86604	45.87218	52.91119	58.16739	62.13246
143.5	29.21053	30.2746	32.06052	35.52066	40.26828	46.3408	53.44304	58.73522	62.72072
144.5	29.47257	30.55162	32.36224	35.86837	40.67444	46.81253	53.97661	59.30357	63.30853
145.5	29.739	30.83304	32.66834	36.22034	41.08443	47.28721	54.51174	59.87226	63.89573
146.5	30.00988	31.11891	32.97885	36.57653	41.49817	47.7647	55.04825	60.44112	64.48219
147.5	30.28525	31.40925	33.29378	36.9369	41.91555	48.24483	55.58594	61.00999	65.06776
148.5	30.56516	31.70409	33.6131	37.30138	42.33644	48.72744	56.12464	61.57871	65.65231
149.5	30.84962	32.00343	33.93681	37.66991	42.76073	49.21236	56.66416	62.1471	66.2357
150.5	31.13865	32.30727	34.26488	38.04241	43.18828	49.6994	57.20431	62.715	66.81782
151.5	31.43227	32.61561	34.59726	38.4188	43.61896	50.18839	57.74492	63.28226	67.39854
152.5	31.73046	32.92842	34.93391	38.79897	44.05259	50.67913	58.28578	63.84873	67.97776
153.5	32.03321	33.24567	35.27477	39.18281	44.48903	51.17143	58.82671	64.41424	68.55535
154.5	32.3405	33.56731	35.61976	39.5702	44.92809	51.66508	59.36752	64.97865	69.13122
155.5	32.65229	33.89329	35.96879	39.96099	45.3696	52.15987	59.90801	65.54182	69.70526
156.5	32.96852	34.22353	36.32176	40.35506	45.81336	52.65558	60.448	66.10359	70.27738
157.5	33.28913	34.55796	36.67857	40.75222	46.25917	53.152	60.98729	66.66382	70.84748
158.5	33.61404	34.89647	37.03908	41.15232	46.70681	53.64889	61.52569	67.22238	71.41549
159.5	33.94317	35.23896	37.40317	41.55516	47.15606	54.14603	62.063	67.77913	71.98133
160.5	34.27642	35.58531	37.77067	41.96056	47.60669	54.64318	62.59903	68.33393	72.5449
161.5	34.61365	35.93538	38.14143	42.3683	48.05847	55.1401	63.13359	68.88665	73.10614
162.5	34.95475	36.28902	38.51526	42.77818	48.51113	55.63653	63.66648	69.43717	73.66498
163.5	35.29956	36.64606	38.89198	43.18995	48.96443	56.13224	64.1975	69.98535	74.22134
164.5	35.64794	37.00634	39.27138	43.60337	49.4181	56.62696	64.72647	70.53106	74.77517
165.5	35.99969	37.36965	39.65325	44.01821	49.87187	57.12044	65.25318	71.07419	75.32641
166.5	36.35464	37.7358	40.03736	44.43419	50.32546	57.61241	65.77745	71.61461	75.87498
167.5	36.71259	38.10456	40.42347	44.85104	50.77859	58.10262	66.29907	72.15219	76.42083
168.5	37.07331	38.47571	40.81133	45.26849	51.23096	58.5908	66.81785	72.68681	76.9639
169.5	37.43658	38.849	41.20067	45.68625	51.68229	59.07667	67.33359	73.21836	77.50413



Age (in months)	3rd Percentile Weight (in kilograms)	5th Percentile Weight (in kilograms)	10th Percentile Weight (in kilograms)	25th Percentile Weight (in kilograms)	50th Percentile Weight (in kilograms)	75th Percentile Weight (in kilograms)	90th Percentile Weight (in kilograms)	95th Percentile Weight (in kilograms)	97th Percentile Weight (in kilograms)
170.5	37.80215	39.22417	41.59121	46.10402	52.13226	59.55998	67.84611	73.7467	78.04146
171.5	38.16976	39.60097	41.98269	46.52151	52.58059	60.04046	68.3552	74.27172	78.57582
172.5	38.53916	39.97909	42.37479	46.9384	53.02696	60.51782	68.86067	74.7933	79.10716
173.5	38.91004	40.35826	42.76722	47.35437	53.47107	60.99182	69.36233	75.3113	79.63542
174.5	39.28212	40.73817	43.15967	47.76912	53.91261	61.46217	69.85999	75.82561	80.1605
175.5	39.65509	41.11851	43.55182	48.18232	54.35128	61.92862	70.35345	76.3361	80.68236
176.5	40.02863	41.49895	43.94334	48.59365	54.78677	62.3909	70.84252	76.84263	81.2009
177.5	40.40241	41.87917	44.3339	49.00279	55.21878	62.84876	71.32701	77.34509	81.71605
178.5	40.77608	42.25882	44.72317	49.40941	55.64701	63.30195	71.80674	77.84332	82.2277
179.5	41.14932	42.63757	45.1108	49.81318	56.07116	63.75019	72.2815	78.3372	82.73579
180.5	41.52175	43.01506	45.49646	50.21378	56.49096	64.19328	72.75113	78.82659	83.24017
181.5	41.89302	43.39093	45.8798	50.61091	56.90611	64.63096	73.21544	79.31134	83.74075
182.5	42.26275	43.76482	46.26048	51.00423	57.31634	65.063	73.67424	79.7913	84.23741
183.5	42.63058	44.13638	46.63815	51.39346	57.72139	65.48919	74.12736	80.26632	84.73
184.5	42.99612	44.50523	47.01247	51.77827	58.121	65.90932	74.57462	80.73625	85.21839
185.5	43.35899	44.87102	47.3831	52.15839	58.51492	66.32318	75.01586	81.20093	85.70242
186.5	43.71882	45.23338	47.74972	52.53352	58.90293	66.73059	75.4509	81.66019	86.18192
187.5	44.07523	45.59196	48.11199	52.90339	59.2848	67.13136	75.87959	82.11386	86.65673
188.5	44.42784	45.9464	48.46959	53.26773	59.66033	67.52534	76.30176	82.56177	87.12663
189.5	44.77629	46.29635	48.82222	53.6263	60.02932	67.91236	76.71726	83.00375	87.59143
190.5	45.1202	46.64147	49.16956	53.97886	60.39159	68.29229	77.12595	83.43962	88.05093
191.5	45.45922	46.98144	49.51134	54.32518	60.74699	68.665	77.52768	83.8692	88.50487
192.5	45.79301	47.31593	49.84727	54.66505	61.09537	69.03038	77.92233	84.29229	88.95303
193.5	46.12122	47.64464	50.17709	54.99828	61.4366	69.38833	78.30977	84.70871	89.39516
194.5	46.44354	47.96727	50.50055	55.3247	61.77057	69.73878	78.68987	85.11828	89.83098
195.5	46.75967	48.28356	50.81743	55.64414	62.09719	70.08164	79.06252	85.5208	90.26024
196.5	47.06932	48.59325	51.12752	55.95647	62.41639	70.41688	79.42763	85.91607	90.68264
197.5	47.37223	48.89609	51.43062	56.26158	62.72809	70.74445	79.78509	86.30392	91.0979
198.5	47.66815	49.19189	51.72656	56.55935	63.03228	71.06433	80.13483	86.68415	91.50571
199.5	47.95687	49.48044	52.0152	56.84971	63.32892	71.37652	80.47676	87.05657	91.90578
200.5	48.23819	49.76158	52.29642	57.13261	63.61802	71.68103	80.81082	87.42099	92.29779
201.5	48.51195	50.03518	52.57011	57.408	63.89959	71.97788	81.13696	87.77725	92.68144
202.5	48.778	50.30112	52.8362	57.67589	64.17367	72.26711	81.45512	88.12516	93.05643
203.5	49.03625	50.55931	53.09465	57.93627	64.44032	72.54879	81.76528	88.46456	93.42244
204.5	49.28662	50.80971	53.34544	58.18918	64.69961	72.82297	82.06741	88.79528	93.77917
205.5	49.52905	51.05229	53.58858	58.43468	64.95165	73.08975	82.3615	89.11718	94.12633
206.5	49.76354	51.28706	53.82409	58.67285	65.19653	73.34922	82.64755	89.43011	94.46364

Age (in months)	3rd Percentile Weight (in kilograms)	5th Percentile Weight (in kilograms)	10th Percentile Weight (in kilograms)	25th Percentile Weight (in kilograms)	50th Percentile Weight (in kilograms)	75th Percentile Weight (in kilograms)	90th Percentile Weight (in kilograms)	95th Percentile Weight (in kilograms)	97th Percentile Weight (in kilograms)
207.5	49.9901	51.51404	54.05205	58.9038	65.4344	73.60152	82.92558	89.73396	94.79081
208.5	50.2088	51.73333	54.27255	59.12764	65.6654	73.84675	83.1956	90.02861	95.10761
209.5	50.4197	51.94499	54.4857	59.34454	65.8897	74.08507	83.45768	90.31396	95.41379
210.5	50.62293	52.14918	54.69165	59.55466	66.10749	74.31664	83.71185	90.58994	95.70913
211.5	50.81862	52.34603	54.89058	59.75819	66.31897	74.54164	83.9582	90.85649	95.99346
212.5	51.00695	52.53572	55.08267	59.95536	66.52437	74.76024	84.19682	91.11358	96.26661
213.5	51.18811	52.71847	55.26814	60.14639	66.7239	74.97267	84.42781	91.3612	96.52847
214.5	51.36232	52.8945	55.44723	60.33153	66.91784	75.17912	84.6513	91.59938	96.77894
215.5	51.52982	53.06406	55.6202	60.51105	67.10642	75.37983	84.86744	91.82817	97.01799
216.5	51.69086	53.2274	55.78731	60.68521	67.28993	75.57503	85.0764	92.04765	97.24564
217.5	51.84574	53.38481	55.94884	60.85431	67.46863	75.76499	85.27837	92.25795	97.46194
218.5	51.99472	53.53657	56.10508	61.01862	67.64281	75.94994	85.47356	92.45925	97.66704
219.5	52.13808	53.68296	56.25633	61.17846	67.81277	76.13018	85.66221	92.65175	97.86111
220.5	52.27612	53.82428	56.40286	61.33409	67.97877	76.30597	85.8446	92.83572	98.04443
221.5	52.40911	53.96079	56.54495	61.4858	68.14111	76.47759	86.02101	93.01148	98.21733
222.5	52.53731	54.09278	56.68288	61.63386	68.30005	76.64533	86.19177	93.17941	98.38026
223.5	52.66098	54.22046	56.81689	61.77851	68.45585	76.80948	86.35725	93.33994	98.53375
224.5	52.78032	54.34408	56.94719	61.91997	68.60872	76.97031	86.51781	93.49361	98.67844
225.5	52.89553	54.46381	57.07396	62.05842	68.75889	77.12809	86.6739	93.64099	98.81509
226.5	53.00674	54.57977	57.19732	62.19399	68.90653	77.2831	86.82597	93.78276	98.94455
227.5	53.11402	54.69205	57.31737	62.32678	69.05176	77.4356	86.97452	93.91968	99.06786
228.5	53.21739	54.80066	57.43409	62.4568	69.19467	77.5858	87.12008	94.05261	99.18615
229.5	53.31679	54.90552	57.54742	62.58399	69.33527	77.73392	87.26324	94.18252	99.30075
230.5	53.41207	55.00648	57.6572	62.70822	69.47351	77.88014	87.40462	94.31046	99.41315
231.5	53.50297	55.10328	57.76315	62.82922	69.60926	78.02461	87.54488	94.43765	99.52501
232.5	53.58913	55.19552	57.86488	62.94664	69.74228	78.16742	87.68474	94.5654	99.63819
233.5	53.67003	55.2827	57.96187	63.06	69.87224	78.30863	87.82495	94.69517	99.75477
234.5	53.74501	55.36413	58.05343	63.16863	69.99869	78.44824	87.96634	94.82857	99.87706
235.5	53.81325	55.43897	58.13869	63.27175	70.12104	78.58618	88.10976	94.96735	100.0076
236.5	53.87373	55.50617	58.21662	63.36835	70.23857	78.72234	88.25614	95.11344	100.1492
237.5	53.92519	55.56447	58.28594	63.45727	70.3504	78.8565	88.40645	95.26894	100.3048
238.5	53.96614	55.61236	58.34515	63.53709	70.45546	78.98839	88.56175	95.43613	100.4779
239.5	53.99482	55.64807	58.39247	63.60618	70.55252	79.11762	88.72311	95.61749	100.6721
240	54.00392	55.66071	58.41105	63.63611	70.59761	79.18111	88.80644	95.71431	100.7784

### 10.9 Appendix 9 CDC Data Table of Weight-for-age Chart for Females

Age (in months)	3rd Percentile Weight (in kilograms)	5th Percentile Weight (in kilograms)	10th Percentile Weight (in kilograms)	25th Percentile Weight (in kilograms)	50th Percentile Weight (in kilograms)	75th Percentile Weight (in kilograms)	90th Percentile Weight (in kilograms)	95th Percentile Weight (in kilograms)	97th Percentile Weight (in kilograms)
24	9.985668	10.21027	10.57373	11.23357	12.05504	12.98667	13.93766	14.56636	15.00156
24.5	10.04881	10.27483	10.64076	11.30567	12.13456	13.07613	14.03902	14.67659	15.11839
25.5	10.17173	10.40066	10.77167	11.44697	12.29102	13.25293	14.24017	14.89587	15.35122
26.5	10.29079	10.52274	10.89899	11.58501	12.44469	13.42753	14.43984	15.11428	15.58363
27.5	10.40664	10.64171	11.02338	11.72047	12.59622	13.60059	14.63873	15.33249	15.81632
28.5	10.5199	10.75819	11.14545	11.85392	12.74621	13.77271	14.83743	15.55113	16.0499
29.5	10.63112	10.87273	11.26575	11.98592	12.89517	13.9444	15.03646	15.7707	16.28491
30.5	10.74078	10.98581	11.38474	12.11692	13.04357	14.11611	15.23626	15.99164	16.52176
31.5	10.84935	11.09789	11.50288	12.24735	13.19181	14.28823	15.43719	16.21432	16.76085
32.5	10.95722	11.20934	11.62054	12.37757	13.34023	14.46106	15.63957	16.43904	17.00245
33.5	11.06475	11.32054	11.73806	12.50791	13.48913	14.63491	15.84365	16.66605	17.24681
34.5	11.17225	11.43177	11.85574	12.63865	13.63877	14.80998	16.04963	16.89553	17.49412
35.5	11.28	11.54332	11.97384	12.77001	13.78937	14.98647	16.25767	17.12762	17.7445
36.5	11.38824	11.65542	12.09259	12.90222	13.94108	15.16452	16.46789	17.36244	17.99807
37.5	11.49718	11.76826	12.21216	13.03542	14.09407	15.34425	16.68038	17.60006	18.25487
38.5	11.607	11.88202	12.33273	13.16977	14.24844	15.52574	16.89519	17.8405	18.51494
39.5	11.71783	11.99685	12.45442	13.30538	14.40429	15.70905	17.11235	18.08377	18.77826
40.5	11.82981	12.11284	12.57735	13.44234	14.56168	15.89422	17.33186	18.32988	19.04483
41.5	11.94304	12.23011	12.70158	13.58071	14.72064	16.08126	17.55371	18.57877	19.31458
42.5	12.05757	12.34871	12.8272	13.72054	14.88121	16.27016	17.77788	18.83042	19.58748
43.5	12.17348	12.4687	12.95423	13.86186	15.04341	16.46093	18.00432	19.08475	19.86343
44.5	12.2908	12.59011	13.08271	14.00469	15.20721	16.65353	18.23298	19.34169	20.14237
45.5	12.40954	12.71297	13.21265	14.14902	15.37263	16.84793	18.46379	19.60118	20.4242
46.5	12.52972	12.83726	13.34405	14.29485	15.53962	17.04408	18.69671	19.86313	20.70884
47.5	12.65132	12.96298	13.47689	14.44217	15.70817	17.24195	18.93166	20.12746	20.99619
48.5	12.77432	13.09012	13.61116	14.59093	15.87824	17.44149	19.16858	20.39409	21.28616
49.5	12.89869	13.21864	13.74682	14.74112	16.04978	17.64265	19.40739	20.66293	21.57866
50.5	13.02441	13.3485	13.88384	14.89269	16.22277	17.84537	19.64805	20.93393	21.8736
51.5	13.15141	13.47966	14.02217	15.0456	16.39715	18.04961	19.89048	21.20699	22.1709
52.5	13.27965	13.61206	14.16176	15.19981	16.57289	18.25533	20.13464	21.48207	22.4705
53.5	13.40907	13.74566	14.30257	15.35527	16.74994	18.46249	20.38048	21.7591	22.77232
54.5	13.53962	13.8804	14.44453	15.51193	16.92827	18.67105	20.62795	22.03803	23.07631
55.5	13.67121	14.01621	14.5876	15.66975	17.10783	18.88097	20.87704	22.31884	23.38243
56.5	13.80381	14.15303	14.73172	15.82868	17.28859	19.09224	21.1277	22.60148	23.69063
57.5	13.93732	14.29081	14.87683	15.98868	17.47052	19.30483	21.37993	22.88594	24.0009
58.5	14.0717	14.42947	15.02287	16.14971	17.65361	19.51874	21.63373	23.17222	24.31322

Age (in months)	3rd Percentile Weight (in kilograms)	5th Percentile Weight (in kilograms)	10th Percentile Weight (in kilograms)	25th Percentile Weight (in kilograms)	50th Percentile Weight (in kilograms)	75th Percentile Weight (in kilograms)	90th Percentile Weight (in kilograms)	95th Percentile Weight (in kilograms)	97th Percentile Weight (in kilograms)
59.5	14.20687	14.56897	15.16981	16.31173	17.83782	19.73395	21.88909	23.46031	24.62758
60.5	14.34277	14.70924	15.31758	16.47471	18.02314	19.95048	22.14604	23.75024	24.94401
61.5	14.47934	14.85022	15.46614	16.63861	18.20956	20.16834	22.4046	24.04202	25.26252
62.5	14.61652	14.99186	15.61545	16.80342	18.39709	20.38753	22.6648	24.3357	25.58315
63.5	14.75426	15.13412	15.76547	16.9691	18.58571	20.6081	22.92668	24.63133	25.90595
64.5	14.8925	15.27694	15.91616	17.13565	18.77545	20.83007	23.19031	24.92897	26.23096
65.5	15.03119	15.42029	16.06749	17.30305	18.96631	21.05349	23.45574	25.22868	26.55827
66.5	15.1703	15.56413	16.21943	17.4713	19.15831	21.2784	23.72305	25.53055	26.88796
67.5	15.30978	15.70843	16.37197	17.6404	19.35149	21.50486	23.99232	25.83467	27.2201
68.5	15.44961	15.85316	16.52509	17.81035	19.54588	21.73294	24.26364	26.14113	27.55481
69.5	15.58975	15.99831	16.67878	17.98118	19.74151	21.96271	24.5371	26.45005	27.8922
70.5	15.73018	16.14385	16.83304	18.15288	19.93843	22.19425	24.81282	26.76154	28.23237
71.5	15.87089	16.28977	16.98787	18.32549	20.1367	22.42763	25.09089	27.07573	28.57547
72.5	16.01186	16.43608	17.14327	18.49904	20.33636	22.66294	25.37145	27.39274	28.92162
73.5	16.1531	16.58277	17.29926	18.67356	20.53748	22.90029	25.65461	27.71272	29.27096
74.5	16.2946	16.72986	17.45586	18.84908	20.74013	23.13976	25.94051	28.0358	29.62364
75.5	16.43638	16.87736	17.61309	19.02566	20.94438	23.38146	26.22926	28.36213	29.97981
76.5	16.57843	17.02528	17.77097	19.20334	21.1503	23.6255	26.52102	28.69185	30.33962
77.5	16.7208	17.17365	17.92956	19.38217	21.35797	23.87199	26.81591	29.02513	30.70323
78.5	16.86349	17.3225	18.08887	19.56221	21.56748	24.12103	27.11407	29.36212	31.0708
79.5	17.00654	17.47187	18.24897	19.74353	21.77891	24.37274	27.41566	29.70296	31.44249
80.5	17.14998	17.6218	18.40989	19.9262	21.99235	24.62725	27.7208	30.04782	31.81846
81.5	17.29386	17.77232	18.5717	20.11027	22.20789	24.88466	28.02965	30.39685	32.19887
82.5	17.43821	17.9235	18.73445	20.29582	22.42562	25.14509	28.34233	30.75021	32.58389
83.5	17.5831	18.07539	18.89819	20.48293	22.64564	25.40866	28.659	31.10804	32.97366
84.5	17.72858	18.22805	19.063	20.67168	22.86804	25.67549	28.97979	31.47049	33.36833
85.5	17.8747	18.38153	19.22895	20.86215	23.09293	25.94569	29.30484	31.83771	33.76807
86.5	18.02152	18.53591	19.3961	21.05441	23.32039	26.21937	29.63426	32.20984	34.17302
87.5	18.16912	18.69124	19.56453	21.24855	23.55052	26.49666	29.9682	32.58701	34.5833
88.5	18.31757	18.84762	19.73432	21.44467	23.78342	26.77764	30.30677	32.96935	34.99906
89.5	18.46693	19.00511	19.90554	21.64283	24.01918	27.06244	30.65008	33.35698	35.42042
90.5	18.61729	19.16378	20.07828	21.84313	24.25789	27.35114	30.99825	33.75001	35.8475
91.5	18.76871	19.32373	20.25261	22.04564	24.49965	27.64385	31.35137	34.14856	36.2804
92.5	18.92129	19.48502	20.42863	22.25047	24.74454	27.94066	31.70954	34.55271	36.71922
93.5	19.07511	19.64775	20.6064	22.45768	24.99264	28.24165	32.07286	34.96256	37.16406
94.5	19.23024	19.81199	20.78601	22.66736	25.24403	28.54689	32.44138	35.37818	37.61498
95.5	19.38678	19.97783	20.96755	22.8796	25.4988	28.85648	32.8152	35.79964	38.07207

Age (in months)	3rd Percentile Weight (in kilograms)	5th Percentile Weight (in kilograms)	10th Percentile Weight (in kilograms)	25th Percentile Weight (in kilograms)	50th Percentile Weight (in kilograms)	75th Percentile Weight (in kilograms)	90th Percentile Weight (in kilograms)	95th Percentile Weight (in kilograms)	97th Percentile Weight (in kilograms)
96.5	19.54481	20.14535	21.15111	23.09446	25.75702	29.17046	33.19435	36.22699	38.53537
97.5	19.70442	20.31464	21.33675	23.31203	26.01874	29.4889	33.5789	36.66029	39.00492
98.5	19.86568	20.48579	21.52456	23.53237	26.28404	29.81185	33.96887	37.09956	39.48077
99.5	20.0287	20.65887	21.71462	23.75556	26.55298	30.13934	34.36431	37.54482	39.96292
100.5	20.19355	20.83397	21.907	23.98166	26.82559	30.47142	34.76522	37.99609	40.45138
101.5	20.36032	21.01117	22.10179	24.21073	27.10193	30.80811	35.17161	38.45335	40.94614
102.5	20.5291	21.19055	22.29905	24.44283	27.38203	31.14942	35.58347	38.91658	41.44718
103.5	20.69997	21.37219	22.49884	24.67802	27.66593	31.49536	36.00078	39.38577	41.95447
104.5	20.873	21.55616	22.70125	24.91634	27.95365	31.84592	36.42352	39.86086	42.46794
105.5	21.04828	21.74253	22.90633	25.15783	28.24521	32.20108	36.85164	40.34179	42.98755
106.5	21.22589	21.93138	23.11413	25.40252	28.5406	32.56084	37.28507	40.82849	43.5132
107.5	21.40589	22.12277	23.32471	25.65046	28.83984	32.92513	37.72376	41.32088	44.0448
108.5	21.58837	22.31677	23.53813	25.90167	29.14291	33.29393	38.16762	41.81885	44.58226
109.5	21.77338	22.51343	23.75442	26.15616	29.4498	33.66717	38.61656	42.32229	45.12543
110.5	21.96099	22.71282	23.97364	26.41394	29.76048	34.04479	39.07046	42.83107	45.67419
111.5	22.15126	22.91497	24.19581	26.67503	30.07493	34.4267	39.52921	43.34505	46.22839
112.5	22.34426	23.11994	24.42096	26.93942	30.39308	34.81282	39.99268	43.86408	46.78786
113.5	22.54002	23.32778	24.64912	27.20709	30.7149	35.20305	40.46071	44.38798	47.35242
114.5	22.73861	23.53851	24.88031	27.47805	31.04032	35.59726	40.93316	44.91658	47.92187
115.5	22.94006	23.75217	25.11454	27.75225	31.36928	35.99535	41.40984	45.44968	48.49603
116.5	23.14441	23.96879	25.35181	28.02968	31.70168	36.39717	41.89057	45.98708	49.07465
117.5	23.3517	24.18838	25.59214	28.31029	32.03745	36.80259	42.37517	46.52854	49.65753
118.5	23.56195	24.41097	25.83551	28.59403	32.37649	37.21144	42.86342	47.07385	50.2444
119.5	23.77519	24.63656	26.08191	28.88087	32.71868	37.62356	43.35511	47.62276	50.83502
120.5	23.99143	24.86516	26.33132	29.17072	33.06392	38.03878	43.85001	48.17501	51.42913
121.5	24.21068	25.09677	26.58372	29.46353	33.41208	38.45691	44.34788	48.73033	52.02644
122.5	24.43296	25.33137	26.83907	29.75922	33.76303	38.87775	44.84847	49.28846	52.62666
123.5	24.65826	25.56895	27.09734	30.0577	34.11663	39.30111	45.35152	49.84911	53.22951
124.5	24.88657	25.80949	27.35848	30.35888	34.47272	39.72676	45.85676	50.41198	53.83467
125.5	25.11788	26.05297	27.62244	30.66267	34.83116	40.15449	46.36392	50.97677	54.44183
126.5	25.35217	26.29934	27.88915	30.96895	35.19176	40.58407	46.87271	51.54317	55.05067
127.5	25.58941	26.54856	28.15856	31.27762	35.55437	41.01526	47.38283	52.11086	55.66086
128.5	25.82958	26.8006	28.43059	31.58856	35.9188	41.44782	47.894	52.67951	56.27207
129.5	26.07263	27.05539	28.70516	31.90163	36.28486	41.88148	48.40589	53.2488	56.88395
130.5	26.31852	27.31287	28.98218	32.21671	36.65236	42.316	48.9182	53.81837	57.49615
131.5	26.56719	27.57298	29.26156	32.53364	37.02111	42.75111	49.43061	54.3879	58.10833
132.5	26.81859	27.83564	29.54321	32.8523	37.39089	43.18655	49.9428	54.95703	58.72013

Age (in months)	3rd Percentile Weight (in kilograms)	5th Percentile Weight (in kilograms)	10th Percentile Weight (in kilograms)	25th Percentile Weight (in kilograms)	50th Percentile Weight (in kilograms)	75th Percentile Weight (in kilograms)	90th Percentile Weight (in kilograms)	95th Percentile Weight (in kilograms)	97th Percentile Weight (in kilograms)
133.5	27.07265	28.10077	29.827	33.17252	37.76149	43.62203	50.45443	55.52542	59.33118
134.5	27.3293	28.36829	30.11285	33.49415	38.1327	44.05728	50.96519	56.09271	59.94114
135.5	27.58846	28.63809	30.40062	33.81701	38.5043	44.49201	51.47473	56.65855	60.54964
136.5	27.85004	28.91009	30.69019	34.14096	38.87605	44.92595	51.98272	57.22257	61.15631
137.5	28.11395	29.18417	30.98143	34.4658	39.24775	45.3588	52.48882	57.78443	61.7608
138.5	28.38009	29.46022	31.27421	34.79137	39.61914	45.79028	52.9927	58.34376	62.36274
139.5	28.64837	29.73813	31.56838	35.11747	39.99	46.22009	53.49402	58.90022	62.96178
140.5	28.91866	30.01776	31.86381	35.44394	40.36009	46.64794	53.99244	59.45344	63.55756
141.5	29.19086	30.299	32.16034	35.77056	40.72918	47.07354	54.48762	60.00308	64.14972
142.5	29.46484	30.5817	32.45781	36.09716	41.09701	47.49661	54.97925	60.54878	64.73791
143.5	29.74046	30.86573	32.75608	36.42354	41.46336	47.91684	55.46697	61.0902	65.32179
144.5	30.0176	31.15094	33.05496	36.7495	41.82798	48.33396	55.95048	61.62701	65.90103
145.5	30.29612	31.43718	33.3543	37.07485	42.19063	48.74767	56.42944	62.15887	66.47528
146.5	30.57588	31.7243	33.65394	37.39937	42.55108	49.15771	56.90354	62.68544	67.04422
147.5	30.85671	32.01214	33.95368	37.72288	42.90909	49.56378	57.37247	63.20642	67.60754
148.5	31.13848	32.30053	34.25336	38.04517	43.26442	49.96562	57.83593	63.72148	68.16491
149.5	31.42101	32.58932	34.55281	38.36604	43.61683	50.36297	58.29361	64.23032	68.71605
150.5	31.70415	32.87832	34.85183	38.68529	43.96612	50.75555	58.74524	64.73264	69.26067
151.5	31.98774	33.16738	35.15025	39.00272	44.31204	51.14313	59.19053	65.22816	69.79847
152.5	32.27159	33.4563	35.44789	39.31812	44.65437	51.52544	59.62921	65.71661	70.32919
153.5	32.55554	33.74492	35.74455	39.63131	44.99291	51.90225	60.06103	66.19771	70.85258
154.5	32.8394	34.03306	36.04006	39.94209	45.32745	52.27334	60.48572	66.67121	71.36839
155.5	33.12301	34.32053	36.33424	40.25026	45.65777	52.63847	60.90306	67.13688	71.87638
156.5	33.40617	34.60715	36.62688	40.55564	45.98369	52.99745	61.31281	67.59448	72.37633
157.5	33.6887	34.89274	36.91782	40.85805	46.30501	53.35007	61.71477	68.04379	72.86804
158.5	33.97042	35.17711	37.20687	41.15729	46.62155	53.69614	62.10874	68.48463	73.35131
159.5	34.25114	35.46007	37.49385	41.45321	46.93314	54.03549	62.49452	68.91679	73.82597
160.5	34.53066	35.74145	37.77858	41.74562	47.23962	54.36794	62.87195	69.34011	74.29185
161.5	34.80881	36.02105	38.06087	42.03435	47.54083	54.69335	63.24088	69.75442	74.7488
162.5	35.08539	36.2987	38.34057	42.31926	47.83661	55.01159	63.60115	70.1596	75.19669
163.5	35.36022	36.57421	38.61748	42.60018	48.12685	55.32252	63.95264	70.5555	75.6354
164.5	35.63309	36.84739	38.89145	42.87697	48.41141	55.62603	64.29525	70.94203	76.06483
165.5	35.90384	37.11808	39.16232	43.14949	48.69018	55.92203	64.62889	71.31908	76.48488
166.5	36.17227	37.3861	39.42991	43.4176	48.96305	56.21044	64.95347	71.68659	76.89549
167.5	36.4382	37.65127	39.69408	43.68119	49.22993	56.49119	65.26895	72.04449	77.2966
168.5	36.70144	37.91342	39.95467	43.94012	49.49075	56.76423	65.57527	72.39275	77.68817
169.5	36.96182	38.17238	40.21154	44.1943	49.74544	57.02954	65.87243	72.73133	78.07017

Age (in months)	3rd Percentile Weight (in kilograms)	5th Percentile Weight (in kilograms)	10th Percentile Weight (in kilograms)	25th Percentile Weight (in kilograms)	50th Percentile Weight (in kilograms)	75th Percentile Weight (in kilograms)	90th Percentile Weight (in kilograms)	95th Percentile Weight (in kilograms)	97th Percentile Weight (in kilograms)
170.5	37.21916	38.428	40.46454	44.44363	49.99394	57.28708	66.16042	73.06023	78.44259
171.5	37.4733	38.68012	40.71356	44.688	50.23621	57.53687	66.43925	73.37946	78.80544
172.5	37.72405	38.92858	40.95845	44.92735	50.47222	57.77893	66.70897	73.68906	79.15873
173.5	37.97127	39.17324	41.19909	45.1616	50.70196	58.01327	66.96961	73.98906	79.50251
174.5	38.21478	39.41396	41.43538	45.39069	50.92541	58.23994	67.22127	74.27953	79.83682
175.5	38.45445	39.6506	41.66721	45.61455	51.14259	58.45903	67.46402	74.56056	80.16173
176.5	38.69012	39.88303	41.89448	45.83316	51.35353	58.67061	67.69798	74.83223	80.4773
177.5	38.92165	40.11114	42.1171	46.04647	51.55825	58.87477	67.92327	75.09468	80.78364
178.5	39.14891	40.3348	42.33498	46.25446	51.75681	59.07164	68.14006	75.34802	81.08083
179.5	39.37177	40.55392	42.54806	46.45712	51.94926	59.26135	68.3485	75.59243	81.36901
180.5	39.59012	40.76839	42.75627	46.65445	52.13568	59.44404	68.54877	75.82805	81.6483
181.5	39.80385	40.97812	42.95955	46.84646	52.31616	59.61988	68.74109	76.05507	81.91883
182.5	40.01284	41.18304	43.15786	47.03316	52.4908	59.78905	68.92566	76.2737	82.18076
183.5	40.21702	41.38308	43.35116	47.21458	52.6597	59.95173	69.10273	76.48415	82.43425
184.5	40.4163	41.57816	43.53942	47.39077	52.82299	60.10814	69.27255	76.68664	82.67946
185.5	40.6106	41.76824	43.72263	47.56176	52.98079	60.2585	69.43538	76.88142	82.91657
186.5	40.79986	41.95328	43.90078	47.72763	53.13327	60.40303	69.59151	77.06875	83.14578
187.5	40.98403	42.13324	44.07388	47.88844	53.28056	60.54199	69.74124	77.2489	83.36727
188.5	41.16306	42.3081	44.24193	48.04426	53.42284	60.67562	69.88487	77.42214	83.58126
189.5	41.33692	42.47785	44.40496	48.1952	53.56028	60.8042	70.02272	77.58878	83.78795
190.5	41.50559	42.64249	44.563	48.34134	53.69307	60.928	70.15513	77.74911	83.98755
191.5	41.66907	42.80203	44.71609	48.48279	53.82138	61.04731	70.28244	77.90345	84.18029
192.5	41.82734	42.95649	44.8643	48.61968	53.94544	61.16241	70.40499	78.05211	84.36639
193.5	41.98043	43.1059	45.00768	48.75212	54.06543	61.2736	70.52314	78.19542	84.54608
194.5	42.12835	43.25031	45.14631	48.88026	54.18158	61.3812	70.63725	78.33372	84.7196
195.5	42.27115	43.38976	45.28027	49.00422	54.29411	61.48549	70.7477	78.46734	84.88718
196.5	42.40886	43.52432	45.40964	49.12417	54.40324	61.58681	70.85484	78.59661	85.04905
197.5	42.54155	43.65406	45.53455	49.24026	54.50921	61.68546	70.95905	78.72189	85.20546
198.5	42.66928	43.77907	45.65509	49.35265	54.61224	61.78176	71.06071	78.84351	85.35663
199.5	42.79212	43.89944	45.77138	49.46152	54.71257	61.87602	71.16017	78.96181	85.50282
200.5	42.91017	44.01527	45.88355	49.56702	54.81044	61.96856	71.2578	79.07713	85.64425
201.5	43.02352	44.12666	45.99174	49.66936	54.9061	62.05968	71.35395	79.18979	85.78117
202.5	43.13227	44.23375	46.09608	49.7687	54.99978	62.1497	71.44899	79.30012	85.91379
203.5	43.23654	44.33665	46.19672	49.86524	55.09172	62.23891	71.54326	79.40845	86.04235
204.5	43.33646	44.4355	46.29382	49.95916	55.18217	62.32761	71.63707	79.51506	86.16706
205.5	43.43215	44.53044	46.38753	50.05066	55.27135	62.41609	71.73076	79.62027	86.28815
206.5	43.52374	44.62161	46.47801	50.13993	55.35951	62.50462	71.82463	79.72434	86.40583

Age (in months)	3rd Percentile Weight (in kilograms)	5th Percentile Weight (in kilograms)	10th Percentile Weight (in kilograms)	25th Percentile Weight (in kilograms)	50th Percentile Weight (in kilograms)	75th Percentile Weight (in kilograms)	90th Percentile Weight (in kilograms)	95th Percentile Weight (in kilograms)	97th Percentile Weight (in kilograms)
207.5	43.61137	44.70917	46.56543	50.22716	55.44686	62.59347	71.91896	79.82755	86.52029
208.5	43.69521	44.79326	46.64995	50.31253	55.53362	62.68289	72.01403	79.93015	86.63173
209.5	43.77538	44.87405	46.73174	50.39624	55.62001	62.77311	72.11008	80.03235	86.74034
210.5	43.85205	44.95168	46.81097	50.47847	55.70624	62.86437	72.20733	80.13439	86.84629
211.5	43.92537	45.02633	46.8878	50.5594	55.79248	62.95684	72.306	80.23643	86.94976
212.5	43.9955	45.09815	46.9624	50.63919	55.87892	63.05073	72.40626	80.33866	87.05088
213.5	44.06258	45.16729	47.03493	50.71802	55.96573	63.1462	72.50825	80.4412	87.14981
214.5	44.12679	45.23391	47.10554	50.79603	56.05305	63.24336	72.61209	80.54417	87.24667
215.5	44.18826	45.29817	47.17437	50.87336	56.141	63.34234	72.71787	80.64766	87.34157
216.5	44.24715	45.3602	47.24158	50.95014	56.2297	63.4432	72.82563	80.75172	87.43462
217.5	44.3036	45.42015	47.30728	51.02649	56.31922	63.546	72.9354	80.85638	87.5259
218.5	44.35775	45.47815	47.3716	51.10249	56.40963	63.65074	73.04714	80.96163	87.61548
219.5	44.40973	45.53431	47.43464	51.17823	56.50096	63.7574	73.1608	81.06744	87.70342
220.5	44.45965	45.58875	47.4965	51.25375	56.5932	63.86593	73.27626	81.17373	87.78975
221.5	44.50764	45.64157	47.55724	51.32908	56.68633	63.9762	73.39338	81.28039	87.87449
222.5	44.55377	45.69284	47.61693	51.40422	56.78026	64.08808	73.51197	81.3873	87.95764
223.5	44.59815	45.74262	47.67559	51.47916	56.8749	64.20136	73.63178	81.49427	88.03918
224.5	44.64082	45.79097	47.73323	51.55381	56.9701	64.3158	73.75253	81.60109	88.11907
225.5	44.68185	45.8379	47.78983	51.6281	57.06565	64.4311	73.87389	81.70752	88.19726
226.5	44.72126	45.88343	47.84535	51.70189	57.16132	64.54692	73.99546	81.81326	88.27366
227.5	44.75906	45.92751	47.89972	51.77499	57.2568	64.66283	74.1168	81.91801	88.34817
228.5	44.79521	45.97009	47.9528	51.8472	57.35176	64.77838	74.23744	82.02139	88.42066
229.5	44.82969	46.0111	48.00447	51.91825	57.44578	64.89303	74.35682	82.12303	88.491
230.5	44.8624	46.0504	48.05453	51.98781	57.5384	65.00619	74.47435	82.22248	88.55903
231.5	44.89324	46.08784	48.10274	52.05553	57.6291	65.1172	74.58939	82.31928	88.62455
232.5	44.92205	46.12322	48.14882	52.12097	57.71728	65.22534	74.70121	82.41292	88.68734
233.5	44.94866	46.1563	48.19244	52.18364	57.80227	65.32981	74.80907	82.50285	88.74718
234.5	44.97281	46.18678	48.23321	52.243	57.88334	65.42974	74.91215	82.58851	88.80382
235.5	44.99424	46.21432	48.27069	52.29842	57.95967	65.52419	75.00958	82.66927	88.85697
236.5	45.0126	46.23851	48.30438	52.34921	58.0304	65.61215	75.10041	82.74448	88.90635
237.5	45.02752	46.25891	48.3337	52.3946	58.09453	65.69252	75.18367	82.81345	88.95164
238.5	45.03852	46.27498	48.358	52.43376	58.15104	65.76413	75.25831	82.87546	88.99253
239.5	45.0451	46.28612	48.37657	52.46576	58.19877	65.82574	75.32321	82.92975	89.02867
240	45.04655	46.28963	48.38346	52.47876	58.21897	65.85238	75.35165	82.95375	89.04485



### 10.10 Blood Pressure Levels for Males by Age and Height Percentile

#### APPENDIX 10.1 Fourth (4th) Report

From Fourth (4<sup>th</sup>) Report, Males, see References

Age (years)	BP percentile	Systolic Blood Pressure (mmHg)							Diastolic Blood Pressure (mmHg)						
		Percentiles							Percentiles						
		5 <sup>th</sup>	10 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	90 <sup>th</sup>	95 <sup>th</sup>	5 <sup>th</sup>	10 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	90 <sup>th</sup>	95 <sup>th</sup>
3	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	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	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	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	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	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	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	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
11	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	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	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	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	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	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	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

## APPENDIX 10.2 2017 Clinical Practice Guidelines

From 2017 (American Academy of Pediatric) Clinical Practice Guidelines, Table 4, Males, see References

Age (years)	BP Percentile	Systolic Blood Pressure (mmHg)							Diastolic Blood Pressure (mmHg)						
		Percentiles							Percentiles						
		5 <sup>th</sup>	10 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	90 <sup>th</sup>	95 <sup>th</sup>	5 <sup>th</sup>	10 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	90 <sup>th</sup>	95 <sup>th</sup>
3	Height (cm)	92.5	93.9	96.3	99	101.8	104.3	105.8	92.5	93.9	96.3	99	101.8	104.3	105.8
	90 <sup>th</sup>	101	102	102	103	104	105	105	58	58	59	59	60	61	61
	95 <sup>th</sup>	106	106	107	107	108	109	109	60	61	61	62	63	64	64
	95th+12mmHg	118	118	119	119	120	121	121	72	73	73	74	75	76	76
4	Height (cm)	98.5	100.2	102.9	105.9	108.9	111.5	113.2	98.5	100.2	102.9	105.9	108.9	111.5	113.2
	90 <sup>th</sup>	102	103	104	105	105	106	107	60	61	62	62	63	64	64
	95 <sup>th</sup>	107	107	108	108	109	110	110	63	64	65	66	67	67	68
	95th+12mmHg	119	119	120	120	121	122	122	75	76	77	78	79	79	80
5	Height (cm)	104.4	106.2	109.1	112.4	115.7	118.6	120.3	104.4	106.2	109.1	112.4	115.7	118.6	120.3
	90 <sup>th</sup>	103	104	105	106	107	108	108	63	64	65	65	66	67	67
	95 <sup>th</sup>	107	108	109	109	110	111	112	66	67	68	69	70	70	71
	95th+12mmHg	119	120	121	121	122	123	124	78	79	80	81	82	82	83
6	Height (cm)	110.3	112.2	115.3	118.9	122.4	125.6	127.5	110.3	112.2	115.3	118.9	122.4	125.6	127.5
	90 <sup>th</sup>	105	105	106	107	109	110	110	66	66	67	68	68	69	69
	95 <sup>th</sup>	108	109	110	111	112	113	114	69	70	70	71	72	72	73
	95th+12mmHg	120	121	122	123	124	125	126	81	82	82	83	84	84	85
7	Height (cm)	116.1	118	121.4	125.1	128.9	132.4	134.5	116.1	118	121.4	125.1	128.9	132.4	134.5
	90 <sup>th</sup>	106	107	108	109	110	111	111	68	68	69	70	70	71	71
	95 <sup>th</sup>	110	110	111	112	114	115	116	71	71	72	73	73	74	74
	95th+12mmHg	122	122	123	124	126	127	128	83	83	84	85	85	86	86
8	Height (cm)	121.4	123.5	127	131	135.1	138.8	141	121.4	123.5	127	131	135.1	138.8	141
	90 <sup>th</sup>	107	108	109	110	111	112	112	69	70	70	71	72	72	73
	95 <sup>th</sup>	111	112	112	114	115	116	117	72	73	73	74	75	75	75
	95th+12mmHg	123	124	124	126	127	128	129	84	85	85	86	87	87	87
9	Height (cm)	126	128.3	132.1	136.3	140.7	144.7	147.1	126	128.3	132.1	136.3	140.7	144.7	147.1
	90 <sup>th</sup>	107	108	109	110	112	113	114	70	71	72	73	74	74	74
	95 <sup>th</sup>	112	112	113	115	116	118	119	74	74	75	76	76	77	77
	95th+12mmHg	124	124	125	127	128	130	131	86	86	87	88	88	89	89
10	Height (cm)	130.2	132.7	136.7	141.3	146.9	150.1	152.7	130.2	132.7	136.7	141.3	146.9	150.1	152.7
	90 <sup>th</sup>	108	109	111	112	113	115	116	72	73	74	74	75	75	76
	95 <sup>th</sup>	112	113	114	116	118	120	121	76	76	77	77	78	78	78
	95th+12mmHg	124	125	126	128	130	132	133	88	88	89	89	90	90	90
11	Height (cm)	134.7	137.3	141.5	145.4	151.3	155.8	158.5	134.7	137.3	141.5	145.4	151.3	155.8	158.5
	90 <sup>th</sup>	110	111	112	114	116	117	118	74	74	75	75	75	76	76
	95 <sup>th</sup>	114	114	116	118	120	123	124	77	78	78	78	78	78	78
	95th+12mmHg	126	126	128	130	132	135	136	89	90	90	90	90	90	90
12	Height (cm)	140.3	143	147.5	152.7	157.9	162.6	165.5	140.3	143	147.5	152.7	157.9	162.6	165.5
	90 <sup>th</sup>	113	114	115	117	119	121	122	75	75	75	75	75	76	76
	95 <sup>th</sup>	116	117	118	121	124	126	128	78	78	78	78	78	79	79
	95th+12mmHg	128	129	130	133	136	138	140	90	90	90	90	90	91	91

### 10.11 Blood Pressure Levels for Females by Age and Height Percentile

#### APPENDIX 11.1 Fourth (4th) Report

From Fourth (4<sup>th</sup>) Report, Females, see Reference.

Age (years)	BP percentile	Systolic Blood Pressure (mmHg)							Diastolic Blood Pressure (mmHg)						
		Percentiles							Percentiles						
		5 <sup>th</sup>	10 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	90 <sup>th</sup>	95 <sup>th</sup>	5 <sup>th</sup>	10 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	90 <sup>th</sup>	95 <sup>th</sup>
3	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	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	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	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	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	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	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	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
11	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	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	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	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	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	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	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

## APPENDIX 11.2 2017 Clinical Practice Guidelines

From 2017 (American Academy of Pediatric) Clinical Practice Guidelines, Table 5, Females, see Reference

Age (years)	BP Percentile	Systolic Blood Pressure (mmHg)							Diastolic Blood Pressure (mmHg)						
		Percentiles							Percentiles						
		5 <sup>th</sup>	10 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	90 <sup>th</sup>	95 <sup>th</sup>	5 <sup>th</sup>	10 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	90 <sup>th</sup>	95 <sup>th</sup>
3	Height (cm)	91	92.4	94.9	97.6	100.5	103.1	104.6	91	92.4	94.9	97.6	100.5	103.1	104.6
	90 <sup>th</sup>	102	103	104	104	105	106	107	60	61	61	62	63	64	65
	95 <sup>th</sup>	106	106	107	108	109	110	110	64	65	65	66	67	68	69
	95th+12mmHg	118	118	119	120	121	122	122	76	77	77	78	79	80	81
4	Height (cm)	97.2	98.8	101.4	104.5	107.6	110.5	112.2	97.2	98.8	101.4	104.5	107.6	110.5	112.2
	90 <sup>th</sup>	103	104	105	106	107	108	108	62	63	64	65	66	67	67
	95 <sup>th</sup>	107	108	109	109	110	111	112	66	67	68	69	70	70	71
	95th+12mmHg	119	120	121	121	122	123	124	78	79	80	81	82	82	83
5	Height (cm)	103.6	105.3	108.2	111.5	114.9	118.1	120	103.6	105.3	108.2	111.5	114.9	118.1	120
	90 <sup>th</sup>	104	105	106	107	108	109	110	64	65	66	67	68	69	70
	95 <sup>th</sup>	108	109	109	110	111	112	113	68	69	70	71	72	73	73
	95th+12mmHg	120	121	121	122	123	124	125	80	81	82	83	84	85	85
6	Height (cm)	110	111.8	114.9	118.4	122.1	125.6	127.7	110	111.8	114.9	118.4	122.1	125.6	127.7
	90 <sup>th</sup>	105	106	107	108	109	110	111	67	67	68	69	70	71	71
	95 <sup>th</sup>	109	109	110	111	112	113	114	70	71	72	72	73	74	74
	95th+12mmHg	121	121	122	123	124	125	126	82	83	84	84	85	86	86
7	Height (cm)	115.9	117.8	121.1	124.9	128.8	132.5	134.7	115.9	117.8	121.1	124.9	128.8	132.5	134.7
	90 <sup>th</sup>	106	106	107	109	110	111	112	68	68	69	70	71	72	72
	95 <sup>th</sup>	109	110	111	112	113	114	115	72	72	73	73	74	74	75
	95th+12mmHg	121	122	123	124	125	126	127	84	84	85	85	86	86	87
8	Height (cm)	121	123	126.5	130.6	134.7	138.5	140.9	121	123	126.5	130.6	134.7	138.5	140.9
	90 <sup>th</sup>	107	107	108	110	111	112	113	69	70	71	72	72	73	73
	95 <sup>th</sup>	110	111	112	113	115	116	117	72	73	74	74	75	75	75
	95th+12mmHg	122	123	124	125	127	128	129	84	85	86	86	87	87	87
9	Height (cm)	125.3	127.6	131.3	135.6	140.1	144.1	146.6	125.3	127.6	131.3	135.6	140.1	144.1	146.6
	90 <sup>th</sup>	108	108	109	111	112	113	114	71	71	72	73	73	73	73
	95 <sup>th</sup>	112	112	113	114	116	117	118	74	74	75	75	75	75	75
	95th+12mmHg	124	124	125	126	128	129	130	86	86	87	87	87	87	87
10	Height (cm)	129.7	132.2	136.3	141	145.8	150.2	152.8	129.7	132.2	136.3	141	145.8	150.2	152.8
	90 <sup>th</sup>	109	110	111	112	113	115	116	72	73	73	73	73	73	73
	95 <sup>th</sup>	113	114	114	116	117	119	120	75	75	76	76	76	76	76
	95th+12mmHg	125	126	126	128	129	131	132	87	87	88	88	88	88	88
11	Height (cm)	135.6	138.3	142.8	147.8	152.8	157.3	160	135.6	138.3	142.8	147.8	152.8	157.3	160
	90 <sup>th</sup>	111	112	113	114	116	118	120	74	74	74	74	74	75	75
	95 <sup>th</sup>	115	116	117	118	120	123	124	76	77	77	77	77	77	77
	95th+12mmHg	127	128	129	130	132	135	136	88	89	89	89	89	89	89
12	Height (cm)	142.8	145.5	149.9	154.8	159.6	163.8	166.4	142.8	145.5	149.9	154.8	159.6	163.8	166.4
	90 <sup>th</sup>	114	115	116	118	120	122	122	75	75	75	75	76	76	76
	95 <sup>th</sup>	118	119	120	122	124	125	126	78	78	78	78	79	79	79
	95th+12mmHg	130	131	132	134	136	137	138	90	90	90	90	91	91	91

## 10.12 Appendix 12: Calculation of Z-Scores for Height, Weight and BMI for Age and Sex Norms

The Centers for Disease Control and Prevention have provided growth charts that enable the calculation of z-scores for height, weight and BMI based on the age (in months) and sex for children, adolescents and young adults upto the age of 20 years [Kuczmarski et al, 2002].

On the basis that a 12-month year consists of 365.25 days,  $A_m$ , the age in months of a child at a study visit, equals (date of visit – date of birth)/30.4375. This age should not be rounded to the nearest month in the calculation of the z-score.

For each gender, separate formulae for the height, weight and BMI norms curves are supplied for each month in a child’s age with integer values of the age at the mid-point of each interval, e.g there are separate curves for 30.5-<31.5, 59.5-<60.5 months etc.

For a curve where the mid-point of the age interval is A whole months (e.g. for a child of 30.85 or 31.36 months,  $A=31$ ), the formula of the curve relies on six constants,  $L_1$ ,  $M_1$ ,  $S_1$ ,  $L_2$ ,  $M_2$  and  $S_2$ .

For a child aged  $A_m$  months, the z-score (Z) for height can be derived as follows (z-scores for weight and BMI follow similar steps):

- Let  $r = (A_m - A + 0.5)$
- Let  $L = L_1 + (L_2 - L_1) * r$ ,  $M = M_1 + (M_2 - M_1) * r$ , and  $S = S_1 + (S_2 - S_1) * r$
- If  $-0.01 < L < 0.01$  then  $Z = \left(\frac{1}{S}\right) \log\left(\frac{\text{height}}{M}\right)$

$$\text{otherwise } Z = \left(\frac{1}{LS}\right) \left(\left(\frac{\text{height}}{M}\right)^L - 1\right)$$

Formula are also given for if a z-score indicates a “biologically infeasible value” (BIV):

- Let  $LO = 0.5 * (M - M(1 - 2LS)^{\frac{1}{L}})$
- Let  $HI = 0.5 * (M(1 + 2LS)^{\frac{1}{L}} - M)$
- If  $\text{height} < M$  then  $\text{flag} = (\text{height} - M) / LO$ , otherwise  $\text{flag} = (\text{height} - M) / HI$
- If  $\text{flag} < -5$  or  $\text{flag} > 3$  then the height is a BIV.

To illustrate, a boy born on the 1<sup>st</sup> January 2001 comes for a visit on 13<sup>th</sup> January 2013 and his height is measured as 159 cm. The steps for calculating Z are as follows:

- The boy is 4395 days old at the visit, which gives  $A_m = 4395 / 30.4375 = 144.3943$
- As 144.3943 is in the interval (143.5, 144.5),  $A = 144$

- $R=144.3943-144+0.5=0.8943$
- The curve for  $A=144$  has  $L_1=0.416777012$ ,  $M_1=148.7917006$ ,  $S_1=0.04987865$ ,  $L_2=0.420919142$ ,  $M_2=149.3088178$  and  $S_2=0.049947823$  (see example SAS code below).
- The values of L,M and S are calculated to be  $L=0.420481$ ,  $M=149.254$ , and  $S=0.0499478$ .
- $$Z = \left( \frac{1}{0.420481 * 0.0499478} \right) \left( \left( \frac{159}{149.254} \right)^{0.420481} - 1 \right) = 1.283576$$
- $LO=7.23925$ ,  $HI=7.67069$  and, as  $height > M$ ,  $flag = (height - M) / HI = 1.27053$ . This does not represent a BIV

Example SAS code for the creation of the Z-Score and BIV flag is as follows:

```
*input dataset is called DATAIN and has at least the following variables;
*AGEMOS : Age in months;
*SEX : 1=male, 2=female;
*HEIGHT : standing height in cm;
*WEIGHT : weight in kg;
*BMI : BMI in kg/m^2;

**DATA FILE FOR HEIGHT-FOR-AGE;

data htrcv;
  infile cards pad;
  input sex _age _LH1 _MH1 _SH1 _LH2 _MH2 _SH2;
cards;
1 24 0.875839864 86.042792680 0.040247430 1.007208070 86.861609340 0.040395626
1 25 1.007208070 86.861609340 0.040395626 0.837251351 87.652472820 0.040577525
1 26 0.837251351 87.652472820 0.040577525 0.681492975 88.423264340 0.040723122
1 27 0.681492975 88.423264340 0.040723122 0.538779654 89.175492280 0.040833194
1 28 0.538779654 89.175492280 0.040833194 0.407697153 89.910408530 0.040909059
1 29 0.407697153 89.910408530 0.040909059 0.286762453 90.629077620 0.040952433
1 30 0.286762453 90.629077620 0.040952433 0.174489485 91.332423790 0.040965330
1 31 0.174489485 91.332423790 0.040965330 0.069444521 92.021271670 0.040949976
1 32 0.069444521 92.021271670 0.040949976 -0.029720564 92.696379460 0.040908737
1 33 -0.029720564 92.696379460 0.040908737 -0.124251789 93.358465460 0.040844062
1 34 -0.124251789 93.358465460 0.040844062 -0.215288396 94.008229230 0.040758431
1 35 -0.215288396 94.008229230 0.040758431 -0.303854340 94.646369810 0.040654312
1 36 -0.303854340 94.646369810 0.040654312 -0.390918369 95.273591060 0.040534120
1 37 -0.390918369 95.273591060 0.040534120 -0.254801167 95.914749290 0.040572876
1 38 -0.254801167 95.914749290 0.040572876 -0.125654535 96.547343280 0.040616910
1 39 -0.125654535 96.547343280 0.040616910 -0.003167350 97.171913090 0.040666414
1 40 -0.003167350 97.171913090 0.040666414 0.112912210 97.788977270 0.040721467
1 41 0.112912210 97.788977270 0.040721467 0.222754969 98.399028300 0.040782045
1 42 0.222754969 98.399028300 0.040782045 0.326530126 99.002543380 0.040848042
1 43 0.326530126 99.002543380 0.040848042 0.424361560 99.599977000 0.040919281
1 44 0.424361560 99.599977000 0.040919281 0.516353108 100.191764000 0.040995524
1 45 0.516353108 100.191764000 0.040995524 0.602595306 100.778319800 0.041076485
1 46 0.602595306 100.778319800 0.041076485 0.683170764 101.360041100 0.041161838
1 47 0.683170764 101.360041100 0.041161838 0.758158406 101.937305800 0.041251224
1 48 0.758158406 101.937305800 0.041251224 0.827636736 102.510473500 0.041344257
1 49 0.827636736 102.510473500 0.041344257 0.891686306 103.079885200 0.041440534
1 50 0.891686306 103.079885200 0.041440534 0.950391530 103.645864000 0.041539635
1 51 0.950391530 103.645864000 0.041539635 1.003830006 104.208713000 0.041641136
1 52 1.003830006 104.208713000 0.041641136 1.052135690 104.768725600 0.041744602
1 53 1.052135690 104.768725600 0.041744602 1.095366900 105.326163800 0.041849607
```

1	54	1.095366900	105.326163800	0.041849607	1.133652119	105.881282300	0.041955723
1	55	1.133652119	105.881282300	0.041955723	1.167104213	106.434314600	0.042062532
1	56	1.167104213	106.434314600	0.042062532	1.195845353	106.985476900	0.042169628
1	57	1.195845353	106.985476900	0.042169628	1.220004233	107.534968000	0.042276619
1	58	1.220004233	107.534968000	0.042276619	1.239715856	108.082969500	0.042383129
1	59	1.239715856	108.082969500	0.042383129	1.255121285	108.629645700	0.042488804
1	60	1.255121285	108.629645700	0.042488804	1.266367398	109.175144100	0.042593311
1	61	1.266367398	109.175144100	0.042593311	1.273606657	109.719595400	0.042696342
1	62	1.273606657	109.719595400	0.042696342	1.276996893	110.263113600	0.042797615
1	63	1.276996893	110.263113600	0.042797615	1.276701119	110.805796700	0.042896877
1	64	1.276701119	110.805796700	0.042896877	1.272887366	111.347726500	0.042993904
1	65	1.272887366	111.347726500	0.042993904	1.265728536	111.888969400	0.043088503
1	66	1.265728536	111.888969400	0.043088503	1.255402281	112.429576100	0.043180513
1	67	1.255402281	112.429576100	0.043180513	1.242090871	112.969582700	0.043269806
1	68	1.242090871	112.969582700	0.043269806	1.225981067	113.509010800	0.043356287
1	69	1.225981067	113.509010800	0.043356287	1.207263978	114.047867800	0.043439893
1	70	1.207263978	114.047867800	0.043439893	1.186140222	114.586148600	0.043520597
1	71	1.186140222	114.586148600	0.043520597	1.162796198	115.123831500	0.043598407
1	72	1.162796198	115.123831500	0.043598407	1.137442868	115.660886200	0.043673359
1	73	1.137442868	115.660886200	0.043673359	1.110286487	116.197269100	0.043745523
1	74	1.110286487	116.197269100	0.043745523	1.081536236	116.732925000	0.043815003
1	75	1.081536236	116.732925000	0.043815003	1.051403740	117.267787900	0.043881929
1	76	1.051403740	117.267787900	0.043881929	1.020102497	117.801781900	0.043946461
1	77	1.020102497	117.801781900	0.043946461	0.987847213	118.334821500	0.044008785
1	78	0.987847213	118.334821500	0.044008785	0.954853043	118.866812300	0.044069112
1	79	0.954853043	118.866812300	0.044069112	0.921334742	119.397652000	0.044127675
1	80	0.921334742	119.397652000	0.044127675	0.887505723	119.927230900	0.044184725
1	81	0.887505723	119.927230900	0.044184725	0.853577030	120.455433000	0.044240532
1	82	0.853577030	120.455433000	0.044240532	0.819756239	120.982136200	0.044295379
1	83	0.819756239	120.982136200	0.044295379	0.786246296	121.507213600	0.044349559
1	84	0.786246296	121.507213600	0.044349559	0.753244292	122.030534200	0.044403374
1	85	0.753244292	122.030534200	0.044403374	0.720940222	122.551963400	0.044457130
1	86	0.720940222	122.551963400	0.044457130	0.689515708	123.071364500	0.044511135
1	87	0.689515708	123.071364500	0.044511135	0.659142731	123.588599000	0.044565693
1	88	0.659142731	123.588599000	0.044565693	0.629997853	124.103531200	0.044621104
1	89	0.629997853	124.103531200	0.044621104	0.602203984	124.616016100	0.044677662
1	90	0.602203984	124.616016100	0.044677662	0.575908038	125.125918200	0.044735646
1	91	0.575908038	125.125918200	0.044735646	0.551231340	125.633101200	0.044795322
1	92	0.551231340	125.633101200	0.044795322	0.528279901	126.137431900	0.044856941
1	93	0.528279901	126.137431900	0.044856941	0.507143576	126.638780400	0.044920730
1	94	0.507143576	126.638780400	0.044920730	0.487895344	127.137021700	0.044986899
1	95	0.487895344	127.137021700	0.044986899	0.470590753	127.632036200	0.045055632
1	96	0.470590753	127.632036200	0.045055632	0.455267507	128.123710400	0.045127088
1	97	0.455267507	128.123710400	0.045127088	0.441945241	128.611938300	0.045201399
1	98	0.441945241	128.611938300	0.045201399	0.430625458	129.096622000	0.045278671
1	99	0.430625458	129.096622000	0.045278671	0.421291648	129.577672300	0.045358979
1	100	0.421291648	129.577672300	0.045358979	0.413909588	130.055010100	0.045442372
1	101	0.413909588	130.055010100	0.045442372	0.408427813	130.528566900	0.045528869
1	102	0.408427813	130.528566900	0.045528869	0.404778262	130.998285700	0.045618459
1	103	0.404778262	130.998285700	0.045618459	0.402877077	131.464121800	0.045711105
1	104	0.402877077	131.464121800	0.045711105	0.402625561	131.926043900	0.045806742
1	105	0.402625561	131.926043900	0.045806742	0.403911270	132.384034800	0.045905281
1	106	0.403911270	132.384034800	0.045905281	0.406609232	132.838092000	0.046006604
1	107	0.406609232	132.838092000	0.046006604	0.410583274	133.288229100	0.046110573
1	108	0.410583274	133.288229100	0.046110573	0.415687443	133.734475900	0.046217028
1	109	0.415687443	133.734475900	0.046217028	0.421767514	134.176880100	0.046325790
1	110	0.421767514	134.176880100	0.046325790	0.428662551	134.615507600	0.046436662
1	111	0.428662551	134.615507600	0.046436662	0.436206531	135.050443300	0.046549430
1	112	0.436206531	135.050443300	0.046549430	0.444230000	135.481792500	0.046663871
1	113	0.444230000	135.481792500	0.046663871	0.452561760	135.909681300	0.046779748
1	114	0.452561760	135.909681300	0.046779748	0.461030578	136.334257700	0.046896817
1	115	0.461030578	136.334257700	0.046896817	0.469466904	136.755692300	0.047014827
1	116	0.469466904	136.755692300	0.047014827	0.477704608	137.174179400	0.047133525
1	117	0.477704608	137.174179400	0.047133525	0.485582720	137.589937800	0.047252654
1	118	0.485582720	137.589937800	0.047252654	0.492947182	138.003211400	0.047371961
1	119	0.492947182	138.003211400	0.047371961	0.499652617	138.414270300	0.047491194
1	120	0.499652617	138.414270300	0.047491194	0.505564115	138.823411400	0.047610108
1	121	0.505564115	138.823411400	0.047610108	0.510559047	139.230959200	0.047728463
1	122	0.510559047	139.230959200	0.047728463	0.514528903	139.637266300	0.047846030
1	123	0.514528903	139.637266300	0.047846030	0.517381177	140.042714000	0.047962592
1	124	0.517381177	140.042714000	0.047962592	0.519041285	140.447712700	0.048077942

1	125	0.519041285	140.447712700	0.048077942	0.519454524	140.852702200	0.048191889
1	126	0.519454524	140.852702200	0.048191889	0.518588072	141.258151500	0.048304259
1	127	0.518588072	141.258151500	0.048304259	0.516433004	141.664559200	0.048414893
1	128	0.516433004	141.664559200	0.048414893	0.513006312	142.072452000	0.048523648
1	129	0.513006312	142.072452000	0.048523648	0.508352901	142.482385200	0.048630402
1	130	0.508352901	142.482385200	0.048630402	0.502547502	142.894940300	0.048735050
1	131	0.502547502	142.894940300	0.048735050	0.495696454	143.310724100	0.048837504
1	132	0.495696454	143.310724100	0.048837504	0.487939275	143.730366300	0.048937694
1	133	0.487939275	143.730366300	0.048937694	0.479449924	144.154516700	0.049035564
1	134	0.479449924	144.154516700	0.049035564	0.470437652	144.583841400	0.049131073
1	135	0.470437652	144.583841400	0.049131073	0.461147305	145.019019200	0.049224189
1	136	0.461147305	145.019019200	0.049224189	0.451858946	145.460735900	0.049314887
1	137	0.451858946	145.460735900	0.049314887	0.442886661	145.909678400	0.049403145
1	138	0.442886661	145.909678400	0.049403145	0.434576385	146.366527800	0.049488934
1	139	0.434576385	146.366527800	0.049488934	0.427302633	146.831951300	0.049572216
1	140	0.427302633	146.831951300	0.049572216	0.421464027	147.306592900	0.049652935
1	141	0.421464027	147.306592900	0.049652935	0.417477538	147.791063500	0.049731004
1	142	0.417477538	147.791063500	0.049731004	0.415771438	148.285929400	0.049806300
1	143	0.415771438	148.285929400	0.049806300	0.416777012	148.791700600	0.049878650
1	144	0.416777012	148.791700600	0.049878650	0.420919142	149.308817800	0.049947823
1	145	0.420919142	149.308817800	0.049947823	0.428606007	149.837639100	0.050013518
1	146	0.428606007	149.837639100	0.050013518	0.440218167	150.378426700	0.050075353
1	147	0.440218167	150.378426700	0.050075353	0.456097443	150.931333100	0.050132858
1	148	0.456097443	150.931333100	0.050132858	0.476536014	151.496388700	0.050185471
1	149	0.476536014	151.496388700	0.050185471	0.501766234	152.073489700	0.050232532
1	150	0.501766234	152.073489700	0.050232532	0.531951655	152.662387800	0.050273285
1	151	0.531951655	152.662387800	0.050273285	0.567179725	153.262681900	0.050306885
1	152	0.567179725	153.262681900	0.050306885	0.607456565	153.873812400	0.050332406
1	153	0.607456565	153.873812400	0.050332406	0.652704121	154.495058000	0.050348860
1	154	0.652704121	154.495058000	0.050348860	0.702759868	155.125536500	0.050355216
1	155	0.702759868	155.125536500	0.050355216	0.757379106	155.764208600	0.050350423
1	156	0.757379106	155.764208600	0.050350423	0.816239713	156.409885800	0.050333444
1	157	0.816239713	156.409885800	0.050333444	0.878947416	157.061241500	0.050303283
1	158	0.878947416	157.061241500	0.050303283	0.945053486	157.716828900	0.050259018
1	159	0.945053486	157.716828900	0.050259018	1.014046108	158.375092900	0.050199837
1	160	1.014046108	158.375092900	0.050199837	1.085383319	159.034399000	0.050125062
1	161	1.085383319	159.034399000	0.050125062	1.158487278	159.693050100	0.050034180
1	162	1.158487278	159.693050100	0.050034180	1.232768816	160.349316800	0.049926861
1	163	1.232768816	160.349316800	0.049926861	1.307628899	161.001458600	0.049802977
1	164	1.307628899	161.001458600	0.049802977	1.382473225	161.647751500	0.049662610
1	165	1.382473225	161.647751500	0.049662610	1.456720479	162.286511900	0.049506051
1	166	1.456720479	162.286511900	0.049506051	1.529810247	162.916120200	0.049333801
1	167	1.529810247	162.916120200	0.049333801	1.601219573	163.535045000	0.049146553
1	168	1.601219573	163.535045000	0.049146553	1.670433444	164.141848600	0.048945190
1	169	1.670433444	164.141848600	0.048945190	1.736995571	164.735219900	0.048730749
1	170	1.736995571	164.735219900	0.048730749	1.800483802	165.313975500	0.048504404
1	171	1.800483802	165.313975500	0.048504404	1.860518777	165.877071500	0.048267442
1	172	1.860518777	165.877071500	0.048267442	1.916765525	166.423608700	0.048021230
1	173	1.916765525	166.423608700	0.048021230	1.968934444	166.952835400	0.047767192
1	174	1.968934444	166.952835400	0.047767192	2.016781776	167.464146600	0.047506783
1	175	2.016781776	167.464146600	0.047506783	2.060109658	167.957081400	0.047241456
1	176	2.060109658	167.957081400	0.047241456	2.098765817	168.431317500	0.046972650
1	177	2.098765817	168.431317500	0.046972650	2.132642948	168.886664400	0.046701759
1	178	2.132642948	168.886664400	0.046701759	2.161677790	169.323054800	0.046430122
1	179	2.161677790	169.323054800	0.046430122	2.185849904	169.740535100	0.046159004
1	180	2.185849904	169.740535100	0.046159004	2.205180153	170.139255000	0.045889585
1	181	2.205180153	170.139255000	0.045889585	2.219728869	170.519456700	0.045622955
1	182	2.219728869	170.519456700	0.045622955	2.229593700	170.881464000	0.045360101
1	183	2.229593700	170.881464000	0.045360101	2.234907144	171.225671700	0.045101913
1	184	2.234907144	171.225671700	0.045101913	2.235833767	171.552534500	0.044849174
1	185	2.235833767	171.552534500	0.044849174	2.232567138	171.862557600	0.044620566
1	186	2.232567138	171.862557600	0.044620566	2.225326500	172.156286500	0.044362674
1	187	2.225326500	172.156286500	0.044362674	2.214353232	172.434298300	0.044129985
1	188	2.214353232	172.434298300	0.044129985	2.199905902	172.697193500	0.043904897
1	189	2.199905902	172.697193500	0.043904897	2.182262864	172.945589800	0.043687723
1	190	2.182262864	172.945589800	0.043687723	2.161704969	173.180112000	0.043478698
1	191	2.161704969	173.180112000	0.043478698	2.138524662	173.401389600	0.043277987
1	192	2.138524662	173.401389600	0.043277987	2.113023423	173.610051800	0.043085685
1	193	2.113023423	173.610051800	0.043085685	2.085490286	173.806717900	0.042901835
1	194	2.085490286	173.806717900	0.042901835	2.056219500	173.991999800	0.042726424
1	195	2.056219500	173.991999800	0.042726424	2.025496648	174.166495100	0.042559396



1	196	2.025496648	174.166495100	0.042559396	1.993598182	174.330785500	0.042400652
1	197	1.993598182	174.330785500	0.042400652	1.960789092	174.485434400	0.042250063
1	198	1.960789092	174.485434400	0.042250063	1.927320937	174.630985600	0.042107465
1	199	1.927320937	174.630985600	0.042107465	1.893430240	174.767961700	0.041972676
1	200	1.893430240	174.767961700	0.041972676	1.859337259	174.896863400	0.041845488
1	201	1.859337259	174.896863400	0.041845488	1.825245107	175.018169100	0.041725679
1	202	1.825245107	175.018169100	0.041725679	1.791339209	175.132334500	0.041613015
1	203	1.791339209	175.132334500	0.041613015	1.757787065	175.239792600	0.041507249
1	204	1.757787065	175.239792600	0.041507249	1.724738292	175.340954000	0.041408129
1	205	1.724738292	175.340954000	0.041408129	1.692324905	175.436207100	0.041315398
1	206	1.692324905	175.436207100	0.041315398	1.660661815	175.525919100	0.041228796
1	207	1.660661815	175.525919100	0.041228796	1.629847495	175.610435800	0.041148060
1	208	1.629847495	175.610435800	0.041148060	1.599964788	175.690083000	0.041072931
1	209	1.599964788	175.690083000	0.041072931	1.571081817	175.765167100	0.041003150
1	210	1.571081817	175.765167100	0.041003150	1.543252982	175.835975700	0.040938463
1	211	1.543252982	175.835975700	0.040938463	1.516519998	175.902778800	0.040878617
1	212	1.516519998	175.902778800	0.040878617	1.490912963	175.965829300	0.040823368
1	213	1.490912963	175.965829300	0.040823368	1.466451429	176.025364100	0.040772475
1	214	1.466451429	176.025364100	0.040772475	1.443145460	176.081605000	0.040725706
1	215	1.443145460	176.081605000	0.040725706	1.420996665	176.134759300	0.040682834
1	216	1.420996665	176.134759300	0.040682834	1.399999187	176.185020800	0.040643640
1	217	1.399999187	176.185020800	0.040643640	1.380140651	176.232570700	0.040607913
1	218	1.380140651	176.232570700	0.040607913	1.361403047	176.277578100	0.040575448
1	219	1.361403047	176.277578100	0.040575448	1.343763564	176.320200800	0.040546051
1	220	1.343763564	176.320200800	0.040546051	1.327195355	176.360586400	0.040519532
1	221	1.327195355	176.360586400	0.040519532	1.311668242	176.398872500	0.040495713
1	222	1.311668242	176.398872500	0.040495713	1.297149359	176.435187400	0.040474421
1	223	1.297149359	176.435187400	0.040474421	1.283603728	176.469651000	0.040455493
1	224	1.283603728	176.469651000	0.040455493	1.270994782	176.502375100	0.040438773
1	225	1.270994782	176.502375100	0.040438773	1.259284830	176.533464000	0.040424111
1	226	1.259284830	176.533464000	0.040424111	1.248435461	176.563015300	0.040411366
1	227	1.248435461	176.563015300	0.040411366	1.238407910	176.591119700	0.040400405
1	228	1.238407910	176.591119700	0.040400405	1.229163362	176.617862100	0.040391101
1	229	1.229163362	176.617862100	0.040391101	1.220663228	176.643321900	0.040383334
1	230	1.220663228	176.643321900	0.040383334	1.212869374	176.667572900	0.040376990
1	231	1.212869374	176.667572900	0.040376990	1.205744310	176.690684400	0.040371962
1	232	1.205744310	176.690684400	0.040371962	1.199251356	176.712721000	0.040368149
1	233	1.199251356	176.712721000	0.040368149	1.193354770	176.733743000	0.040365456
1	234	1.193354770	176.733743000	0.040365456	1.188019859	176.753807000	0.040363795
1	235	1.188019859	176.753807000	0.040363795	1.183213059	176.772965700	0.040363080
1	236	1.183213059	176.772965700	0.040363080	1.178901998	176.791268700	0.040363233
1	237	1.178901998	176.791268700	0.040363233	1.175055543	176.808762200	0.040364179
1	238	1.175055543	176.808762200	0.040364179	1.171643828	176.825489500	0.040365850
1	239	1.171643828	176.825489500	0.040365850	1.168638270	176.841491400	0.040368180
2	24	1.093625008	84.553793340	0.040723061	1.051272912	85.397316900	0.040859727
2	25	1.051272912	85.397316900	0.040859727	1.041951175	86.290263180	0.041142161
2	26	1.041951175	86.290263180	0.041142161	1.012592236	87.157141820	0.041349399
2	27	1.012592236	87.157141820	0.041349399	0.970541909	87.996018400	0.041500428
2	28	0.970541909	87.996018400	0.041500428	0.921129988	88.805511500	0.041610508
2	29	0.921129988	88.805511500	0.041610508	0.868221392	89.584766890	0.041691761
2	30	0.868221392	89.584766890	0.041691761	0.814544130	90.333417220	0.041753680
2	31	0.814544130	90.333417220	0.041753680	0.761957977	91.051543600	0.041803562
2	32	0.761957977	91.051543600	0.041803562	0.711660228	91.739635200	0.041846882
2	33	0.711660228	91.739635200	0.041846882	0.664323379	92.398544290	0.041887626
2	34	0.664323379	92.398544290	0.041887626	0.620285102	93.029453920	0.041928568
2	35	0.620285102	93.029453920	0.041928568	0.579556310	93.633822780	0.041971514
2	36	0.579556310	93.633822780	0.041971514	0.541980940	94.213357090	0.042017509
2	37	0.541980940	94.213357090	0.042017509	0.511429832	94.796432390	0.042104522
2	38	0.511429832	94.796432390	0.042104522	0.482799937	95.373919180	0.042199507
2	39	0.482799937	95.373919180	0.042199507	0.455521041	95.946926770	0.042300333
2	40	0.455521041	95.946926770	0.042300333	0.429150288	96.516449120	0.042405225
2	41	0.429150288	96.516449120	0.042405225	0.403351725	97.083372110	0.042512706
2	42	0.403351725	97.083372110	0.042512706	0.377878239	97.648480700	0.042621565
2	43	0.377878239	97.648480700	0.042621565	0.352555862	98.212465790	0.042730809
2	44	0.352555862	98.212465790	0.042730809	0.327270297	98.775930690	0.042839638
2	45	0.327270297	98.775930690	0.042839638	0.301955463	99.339397350	0.042947412
2	46	0.301955463	99.339397350	0.042947412	0.276583851	99.903312200	0.043053626
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run;
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2	56	-3.284099963	15.184797990	0.081392203	-3.304814150	15.175128710	0.081912623
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2	58	-3.321596954	15.167028110	0.082464661	-3.334615646	15.160470680	0.083047295
2	59	-3.334615646	15.160470680	0.083047295	-3.344047622	15.155431070	0.083659478
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2	62	-3.352893805	15.149804790	0.084968200	-3.352691376	15.149168250	0.085662539
2	63	-3.352691376	15.149168250	0.085662539	-3.349664380	15.149949840	0.086382035
2	64	-3.349664380	15.149949840	0.086382035	-3.343998803	15.152125850	0.087125591
2	65	-3.343998803	15.152125850	0.087125591	-3.335889574	15.155671860	0.087892047
2	66	-3.335889574	15.155671860	0.087892047	-3.325522491	15.160564190	0.088680264
2	67	-3.325522491	15.160564190	0.088680264	-3.313078460	15.166779470	0.089489106
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2	78	-3.109557879	15.296759670	0.098464710	-3.084290931	15.316066440	0.099426955
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2 219	-2.315651874	21.328054890	0.147349514	-2.321217310	21.353425630	0.147411215
2 220	-2.321217310	21.353425630	0.147411215	-2.326481911	21.378124620	0.147487979
2 221	-2.326481911	21.378124620	0.147487979	-2.331428139	21.402145890	0.147580453
2 222	-2.331428139	21.402145890	0.147580453	-2.336038473	21.425483510	0.147689289
2 223	-2.336038473	21.425483510	0.147689289	-2.340295450	21.448131560	0.147815150
2 224	-2.340295450	21.448131560	0.147815150	-2.344181703	21.470084120	0.147958706
2 225	-2.344181703	21.470084120	0.147958706	-2.347680000	21.491335290	0.148120633
2 226	-2.347680000	21.491335290	0.148120633	-2.350773286	21.511879180	0.148301619
2 227	-2.350773286	21.511879180	0.148301619	-2.353444725	21.531709890	0.148502355
2 228	-2.353444725	21.531709890	0.148502355	-2.355677743	21.550821550	0.148723546
2 229	-2.355677743	21.550821550	0.148723546	-2.357456070	21.569208240	0.148965902
2 230	-2.357456070	21.569208240	0.148965902	-2.358763788	21.586864060	0.149230142
2 231	-2.358763788	21.586864060	0.149230142	-2.359585369	21.603783090	0.149516994
2 232	-2.359585369	21.603783090	0.149516994	-2.359905726	21.619959390	0.149827195
2 233	-2.359905726	21.619959390	0.149827195	-2.359710258	21.635387000	0.150161492
2 234	-2.359710258	21.635387000	0.150161492	-2.358980464	21.650061260	0.150520734
2 235	-2.358980464	21.650061260	0.150520734	-2.357714508	21.663972700	0.150905439



```

2 236 -2.357714508 21.663972700 0.150905439 -2.355892424 21.677117360 0.151316531
2 237 -2.355892424 21.677117360 0.151316531 -2.353501353 21.689489350 0.151754808
2 238 -2.353501353 21.689489350 0.151754808 -2.350528726 21.701082880 0.152221086
2 239 -2.350528726 21.701082880 0.152221086 -2.346962247 21.711892250 0.152716206
;
run;

data curves;
  merge htcrv wtcrv bmicrv;
  by sex _age;
run;

data test;
  set datain;
  _age=int(agemos+0.5);          *age rounded to nearest month;
  _id=_N_;
run;

proc sort data=test out=test2;
  by sex _age _id;
run;

data test2;
  merge test2(in=a) curves(in=b);
  by sex _age;
  if a;

  if height lt 45 or height gt 300 then _ht=.;          *implausible height;
  else _ht=height;
  if weight lt 10 or weight gt 150 then _wt=.;          *implausible weight;
  else _wt=weight;
  if bmi lt 10 or bmi gt 45 then _bmi=.;                *implausible bmi;
  else _bmi=bmi;

  _r=(agemos-_age+0.5);

  ***HEIGHT***;
  if _ht eq . then do;
    _ZH=.; _BIVH=.;
  end;
  else do;
    _LH = _LH1+ _r*( _LH2-_LH1);
    _MH = _MH1+ _r*( _MH2-_MH1);
    _SH = _SH1+ _r*( _SH2-_SH1);
    if ( _LH gt -0.01 and _LH lt 0.01) then _ZH=log(_ht/_MH)/_SH;
    else _ZH=((_ht/_MH)**_LH-1)/(_LH*_SH);
    _LOH=((_MH-_MH*(1-2*_LH*_SH)**(1/_LH))/2);
    _HIH=((_MH*(1+2*_LH*_SH)**(1/_LH)-_MH)/2);
    if _ht lt _MH then flagH=( _ht-_MH)/_LOH;
    else flagH=( _ht- _MH)/_HIH;
    if flagH eq . then _BIVH=.;
    else if flagH lt -5 then _BIVH=1;          *implausibly low value;
    else if flagH gt 3 then _BIVH=2;          *implausibly high value;
    else _BIVH=0;          *acceptable value;
  end;

  ***WEIGHT***;
  if _wt eq . then do;
    _ZW=.; _BIVW=.;
  end;
  else do;
    _LW = _LW1+ _r*( _LW2-_LW1);
    _MW = _MW1+ _r*( _MW2-_MW1);
    _SW = _SW1+ _r*( _SW2-_SW1);
    if ( _LW gt -0.01 and _LW lt 0.01) then _ZW=log(_wt/_MW)/_SW;
    else _ZW=((_wt/_MW)**_LW-1)/(_LW*_SW);
    _LOW=((_MW-_MW*(1-2*_LW*_SW)**(1/_LW))/2);
    _HIW=((_MW*(1+2*_LW*_SW)**(1/_LW)-_MW)/2);
    if _wt lt _MW then flagW=( _wt-_MW)/_LOW;
    else flagW=( _wt- _MW)/_HIW;
    if flagW eq . then _BIVW=.;
  end;

```

```
        else if flagW lt -5 then BIVW=1; *implausibly low value;
        else if flagW gt 5 then BIVW=2; *implausibly high value;
        else _BIVW=0; *acceptable value;
    end;

    end;

    ***BMI***;
    if _bmi eq . then do;
        _ZB=.; _BIVB=.;
    end;
    else do;
        _LB = _LB1+ _r*( _LB2-_LB1);
        _MB = _MB1+ _r*( _MB2-_MB1);
        _SB = _SB1+ _r*( _SB2-_SB1);
        if (_LB gt -0.01 and _LB lt 0.01) then _ZB=log(_bmi/_MB)/_SB;
        else ZB=(( bmi/ MB)** LB-1)/( LB* SB);
        _LOB=(( MB- MB*(1-2* LB* SB)**(1/ LB))/2);
        _HIB=(( _MB*(1+2* LB* SB)**(1/ LB)-_MB)/2);
        if _bmi lt _MB then flagB=( _bmi-_MB)/_LOB;
        else flagB=( bmi- MB)/ HIB;
        if flagB eq . then _BIVB=.;
        else if flagB lt -4 then BIVB=1; *implausibly low value;
        else if flagB gt 5 then _BIVB=2; *implausibly high value;
        else _BIVB=0; *acceptable value;
    end;
    keep _id _zh _bivh _zw _bivw _zb _bivb;
run;

*output dataset contains original data plus Z scores and BIV flags for height, weight and
BMI;

proc sort data=test2;
    by _id;
run;

data dataout(drop=_id);
    merge test(drop=_age) test2;
        by _id;
run;
```

### 10.13 Appendix 13: ECG Abnormality Codes

ECG abnormalities are coded according to the class of the abnormality and specific type. Each type of abnormality is given a particular abnormality code. The classes of abnormality and the form of the abnormality codes for each class are as follows:

Abnormality Class	Form of Abnormality Code
Rhythm	1xy or 1xy.z
PR Intervals	3xy or 3xy.z
QT Intervals	4xy or 4xy.z
P Wave	6xy or 6xy.z
QRS Complex	7xy or 7xy.z
ST Segment	8xy or 8xy.z
T Wave	90x or 90x.y
Other	98x or 98x.y

Specific abnormalities coded in each class are as follows:

#### Class: Rhythm

Abnormality Code	Abnormality Text
101	Sinus Tachycardia
102	Sinus Bradycardia
103	Atrial Tachycardia - Without Block
104	Atrial Tachycardia - With Block
105	Atrial Flutter
106	Atrial Fibrillation
106.5	Ectopic Atrial Rhythm
107	PSVT(Paroxysmal Supraventricular Tachycardia)
108	Variable Atrial Pacemaker
109	Junctional Rhythm without Aberrancy
110	Junctional Rhythm with Aberrancy
110.4	Junctional Tachycardia
110.5	Junctional Rhythm
111	Ventricular Rhythm
112	Ventricular Tachycardia
112.1	Sustained Ventricular Tachycardia
112.2	Non-sustained Ventricular Tachycardia
112.4	Torsades de Pointes

Abnormality Code	Abnormality Text
112.5	Idioventricular Rhythm
113	Accelerated AV Conduction Pattern
113.5	Short PR Interval without Ventricular Pre-Excitation
114	Wolff - Parkinson - White Pattern
115	Supraventricular Ectopic Beats
115.2	Frequent Atrial Premature Complexes (>3)
115.3	Atrial Premature Complexes
115.4	Supraventricular Tachycardia
115.5	Ectopic Supraventricular Rhythm
116	Ventricular Ectopic Beats – Unifocal
117	Ventricular Ectopic Beats – Multifocal
118	Pacemaker Rhythm
119	Ventricular Fibrillation
119.4	Frequent Ventricular Premature Complexes (>2)
119.5	Ventricular Premature Complexes
120	Sinus Arrest
120.5	Sinus Pause
121	Sinus Arrhythmia
122	Nodal Tachycardia
123	LGL Syndrome
124	Junctional Escape Complexes
125	Sino - Atrial Block
199.4	Ectopy Other
199.5	Rhythm Other

**Class: PR Intervals**

Abnormality Code	Abnormality Text
301	First Degree AV Block
302	Second Degree AV Block - Mobitz I
303	Second Degree AV Block - Mobitz II
304	Complete AV Block
304.5	2:1 AV Block
399.5	Conduction Other

**Class: QT Intervals**

Abnormality Code	Abnormality Text
401	Prolonged QT Interval
402	Prolonged QTc interval

**Class: P Wave**

Abnormality Code	Abnormality Text
601	Right Atrial Enlargement
602	Left Atrial Enlargement
602.5	Borderline Left Atrial Enlargement
603	P-Wave Abnormality

**Class: QRS Complex**

Abnormality Code	Abnormality Text
701	AV Dissociation
702	Left Anterior Hemiblock
703	Left Posterior Hemiblock
704	Right Bundle Branch Block
705	Incomplete Right Bundle Branch Block
706	Left Bundle Branch Block
707	Incomplete Left Bundle Branch Block
708	Nonspecific Intraventricular Conduction Delay
709	Bifascicular Block
710	Left Axis Deviation
711	Right Axis Deviation
712	Abnormal QRS Axis
712.5	Indeterminate Axis
713	Left Ventricular Hypertrophy
714	Left Ventricular Hypertrophy by Voltage Only
714.4	Left Atrial Abnormality
714.5	Left Ventricular Hypertrophy with Strain
715	Right Ventricular Hypertrophy
715.5	Right Atrial Abnormality
716	Old Myocardial Infarction: Antero Septal
716.4	Septal MI V1, V2, (V3)
716.5	Antero Septal MI V1-V4

Abnormality Code	Abnormality Text
717	Old Myocardial Infarction: Antero Lateral
717.4	Extensive Anterior MI 1, L, V1-V6
717.5	Antero Lateral MI V3-V6
718	Old Myocardial Infarction: Infero Lateral
718.5	Anterior MI V3, V4
719	Old Myocardial Infarction: Infero Posterior
719.5	Inferior MI (2), 3, F
720	Old Myocardial Infarction: Postero Lateral
721	Old Myocardial Infarction: Lateral
721.4	Lateral MI 1, L, V5, V6
721.5	High Lateral MI 1, AVL
722	Low Voltage QRS Complex
723	Poor R-Wave Progression
724	Late R-Wave Transition
725	Early Repolarization - Normal Variant
726	Early R-Wave Transition
799.4	Morphology Other
799.5	Myocardial Infarction Other

**Class: ST Segment**

Abnormality Code	Abnormality Text
801	New Myocardial Infarction: Antero Septal
802	New Myocardial Infarction: Antero Lateral
803	New Myocardial Infarction: Infero Lateral
804	New Myocardial Infarction: Infero Posterior
805	New Myocardial Infarction: Postero Lateral
806	New Myocardial Infarction: Lateral
807	Myocardial Infarction - Nontransmural -Acute or Evolving
808	ST Elevation Consistent with Ischaemia: Anterior
809	ST Elevation Consistent with Ischaemia: Septal
810	ST Elevation Consistent with Ischaemia: Lateral
811	ST Elevation Consistent with Ischaemia: Inferior
812	ST Elevation Consistent with Ischaemia: Posterior
813	ST Elevation Consistent with Ischaemia: High Lateral
814	ST Elevation Consistent with Pericarditis
814.5	ST Segment Elevated
815	Non-Specific ST-T Change

Abnormality Code	Abnormality Text
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816	ST-T Changes - Consistent with Drug Effects
817	ST Depression: Anterior
818	ST Depression: Septal
819	ST Depression: Lateral
820	ST Depression: Inferior
821	ST Depression: Posterior
822	ST Depression: High Lateral
823	ST Depression - Non-Specific
823.5	ST Segment Depressed
899.5	ST Segment Other

**Class: T Wave**

Abnormality Code	Abnormality Text
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901	T-Wave Inversion Suggestive of Non-Q-Wave MI
902	T-Wave Flattening or Inversion in Two or More Leads
902.4	T-Wave Flat
902.5	T-Wave Inverted
903	Non-Specific T-Wave Changes
904	T-Wave Inversion Suggestive of Ischaemia
905	T-Wave Peaking
905.5	T Wave Other

**Class: Other**

Abnormality Code	Abnormality Text
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998	U-Wave Abnormality
998.5	U-Wave Other
999	Other





## Author and Approver Signatories

(E-signatures are attached at end of document)

