STATISTICAL ANALYSIS PLAN

A Randomized, Assessor-Blind, Multicenter, Dose-Ranging Study Comparing the Safety and Efficacy of Prepopik™ versus Polyethylene Glycol Preparation (Local Standard of Care) in Children Aged 9 Years to 16 Years

000103

Investigational Product:	PREPOPIK (sodium picosulfate, magnesium oxide, and anhydrous citric acid)
Indication:	Bowel preparation for pediatric colonoscopy
Phase:	Phase I/II-Post Approval Pediatric Study
Author:	[redacted]
Date of issue:	16 February 2017
Version:	Final 2.0

Change log

Version No.	Effective Date	Reason for the Change / Revision	Supersedes
2.0	16Feb2017	In addition to the pre-specified 95% confidence intervals (CIs), 90% CIs will also be produced. Summaries for pre-specified orthostatic changes in vital signs are added. Additional clarity on what is considered a major protocol deviation is added. Summary table and listing for the pharmacokinetic concentration data is added.	1.0

Signed Agreement on Statistical Analysis Plan

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1 Introduction

This document describes the planned statistical analyses for Trial 00103 based on protocol version 3, dated 8 July 2013, protocol version 4, dated 21 Aug 2013 and protocol version 5, dated 28 July 2014.

1.1 Definitions/ Abbreviations

1.1.1 Definition of Terms

Terms	Definitions
Analysis set	Data included in a specific analysis
Aronchick Scale	see Protocol section 7.1
Baseline	The last observed value collected prior to the start of treatment
Change from baseline	Difference between a data value at an analysis time point minus the corresponding baseline value
Concomitant medications	Medication taken during the study
Percent change from baseline	Numerical percent difference between baseline value and post-baseline value at a given study visit
Preparation	In this study, this term and the term “treatment,” which is generally used in clinical trials, may be used interchangeably
Prior medications	Medications taken before entering the study
Randomization	The unpredictable allocation of a subject to a particular treatment (or preparation) in a clinical trial
Randomized	Subject randomized to trial treatment
Responder	A responder will be defined for the Aronchick Scale as subject rated as excellent or good during the colonoscopy
Screened	Subject who enters Screening
Screening	Questions and assessments performed to determine if a person qualifies to enter a clinical trial
TEAE	Any adverse event that occurs during or after the start of treatment or begins prior to preparation and increases in intensity during and/or after the start of preparation

1.1.2 Abbreviations

Abbreviations	Meaning of abbreviations in document
AE	adverse event
ATC	Anatomic-Therapeutic-Chemical
CI	confidence interval
CRF	case report form
IMP	investigational medicinal product
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
PEG	polyethylene glycol
PK	pharmacokinetic
PP	per-protocol
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SD	standard deviation
TEAE	treatment-emergent adverse event
US	United States
V	visit
WHO	World Health Organization

2 Trial Objectives and Endpoints

2.1 Objectives

2.1.1 Primary Objective

- To describe the efficacy of the Prepopik in children aged 9 years to 16 years for overall colon cleansing in preparation for colonoscopy based on the Aronchick scale by including oral polyethylene glycol (PEG) based preparation/local standard of care as a reference group

2.1.2 Secondary Objectives

- To describe the safety of Prepopik in children aged 9 years to 16 years through the collection of adverse events (AEs), clinical laboratory tests, and physical examination
- To describe the completion of prep as directed to colon cleansing by Prepopik in preparation from colonoscopy in children aged 9 years to 16 years
- To describe the tolerability and satisfaction of colon cleansing by Prepopik in preparation for colonoscopy in children aged 9 years to 16 years as assessed by a standardized subject questionnaire administered at the study site before colonoscopy
- To evaluate pharmacokinetic (PK) characteristics of Prepopik in children aged 9 years to 16 years

2.2 Endpoints

2.2.1 Primary Endpoint

- Proportion of subjects classified as success defined by “excellent” or “good” in the Aronchick scale

2.2.2 Secondary Endpoints

- Incidence of adverse events and abnormal findings in clinical laboratory test and physical examination
- Proportion of subjects who took the assigned dose for the IMP [investigational medicinal product]
- Frequency of each category of the Tolerability and Satisfaction Questionnaire
- PK exposure will be assessed utilizing a sparse sampling of subjects (Sparse sampling means no need for special PK time)

3 Trial Design

This study is a randomized, assessor-blind, multicenter, dose-ranging study. Subjects undergoing an elective complete colonoscopy will randomly receive one of the following products:

- Prepopik: 2 divided doses given the night before (first dose) and approximately 5 hours prior (second dose) to procedure. A dose is defined for one subset of subjects aged 9 years to 12 years as ½ sachet, for another subset of subjects aged 9 years to 12 years per randomization as 1 sachet and for subjects aged 13 to 16 years as 1 sachet.
- Oral PEG based preparation/local standard of care per appropriate label and/or institutional instructions.

See Section 3.1.1 of the protocol for the trial design diagram.

3.1 General Design Considerations

This is an age-stratified, parallel-group design with three treatment arms in the younger ages and two treatment arms in the older ages as shown in Table 1.

Table 1 Overview of Study Treatment Groups by Age

Treatment Group	Age Group		Total
	9-12 years	13-16 years	
Prepopik: ½ sachet	15	0	15
Prepopik: 1 sachet	15	15	30
Standard of care	15	15	30
Total subjects	45	30	75

3.1.1 Dosage Selection

Selection of doses for this study are based on current dosages in Canada and the European Union. In Canada, current pediatric dosage is ½ sachet (x2) for ages 9-12 years and 1 sachet (x2) for ages 13-18 years. This dosage has been studied in a well-controlled trial from the Toronto Hospital for Sick Children. It aimed to compare bowel preparation for colonoscopy in children with PicoSalax or PEG with electrolyte solution. Thirty five of PicoSalax patients (81%) were satisfied or very satisfied with the clean out compared with 19 (48%) in the PEG group (p=.001).7 The current dosages used in pediatrics in the European Union for ages 9-18 years is 1 sachet (x2). Therefore, in our study, the younger group (ages 9-12 years) will compare adult dose (1 sachet x2 as in the European Union) and ½ the adult dose (1/2 sachet x2, Canadian dose) while the older group (ages 13-16 years) will use the adult dose.

3.1.2 Blinding

Blinding treatment to the endoscopist and his/her assistant(s) assessing the efficacy of the tested preparations removes possible bias. A placebo-controlled design would not be practical or ethical in this study as subjects would be required to have a second colonoscopy.

The integrity of blinding will be further preserved by requiring each subject or parent/guardian and the unblinded coordinator to sign a nondisclosure affidavit form instructing subjects/parents/guardians and the unblinded coordinator not to disclose the treatment groups.

3.2 Determination of Sample Size

Approximately 6-8 sites in the US are planned. A sufficient number of subjects will be screened to ensure up to approximately 75 (~15 subjects per treatment arm).

A total of at least 45 subjects will be exposed to Prepopik. In the two Phase 3 studies for adults, 83% and 84.2% of subjects were classified as success after bowel preparation with Prepopik. With 45 subjects, if 80% of subjects are classified as success in this study, the exact 95% confidence interval of the success rate will be calculated as 65% - 90%.

4 Subject Disposition

All subjects screened will be accounted for. The number of subjects screened but not randomized/allocated to treatment will be presented with the reason(s) for screen failure in a data listing.

The number and percentage of subjects randomized, beginning treatment, having a colonoscopy, completing, and withdrawing from the study will be tabulated for each treatment group, overall and by age group. The denominator for the percentages is the total number of subjects in the given treatment group, or the combined sample as appropriate. Reasons for early withdrawal will be tabulated by treatment group. Individual subject listings of study completion information will be produced, including the reason for early withdrawal.

The number of subjects included and excluded from safety and efficacy populations will be summarized for each treatment group. In addition, the reason(s) for exclusion from each population will be summarized. Individual subject listings of reasons for exclusion from the analysis populations will be produced. In addition, a separate subject listing of any eligibility violations will be produced.

The number and percentage of subjects randomized, treated, completing/withdrawing from the study and included/excluded from safety and efficacy populations will also be tabulated by study site.

5 Protocol Deviations

Major and minor protocol deviations will be defined and documented prior to database lock. Major protocol deviations which exclude the subject from the PP analysis set will include the following:

- Key violations of the protocol inclusion or exclusion criteria
- Significant violation of the dosing regimen as recorded on the eCRF including the amount of study preparation, and timing of receiving study medication
- Receiving study medication other than randomized assignment
- Taking exclusionary medications during the study and/or prior to the procedure, as described in the protocol. Exclusionary medications include:
    - Lithium
    - Laxatives (suspended for 24 hours prior to procedure)
    - Constipating drugs (suspended for 2 days prior to procedure)
    - Antidiarrheals (suspended for 72 hours prior to procedure)
    - Oral iron preparations (suspended for 1 week prior to procedure)

6 Analysis Sets

6.1 Intention-To-Treat Analysis Set

The ITT analysis set will include all subjects who are randomized independent of whether or not the subject receives study treatment dose. Subjects who do not have an efficacy assessment for the data (Aronchick Scale) will be scored as a non-responder. Analyses for the ITT will be conducted according to the randomized treatment.

6.2 Per Protocol Analysis Set

Subjects with major protocol deviations that potentially impact efficacy will be excluded from the PP (per-protocol) analysis set. Subjects not taking the study medication in the prescribed time intervals will be excluded from the PP analysis set. These subjects will be identified prior to breaking the study blind. Analyses for the PP will be conducted according to the randomized treatment.

6.3 Safety Analysis Set

All subjects consuming at least one dose of study medication will be included in the Safety Analysis Set. Analyses for the Safety Dataset will be conducted according to the treatment actually received.

6.4 Pharmacokinetics Analysis Set

The pharmacokinetic (PK) analysis set will include all subjects from whom PK samples are obtained.

7 Trial Population

7.1 Demographics and Other Baseline Characteristics

Descriptive statistics of demographics, and other baseline characteristics will be presented for the ITT, PP and safety populations by treatment group, overall and by age group. For quantitative variables, all summaries will include the sample size, mean, median, standard deviation, minimum, and maximum. For the qualitative variables, the summaries will include the number and percentage of subjects for each outcome.

7.1.1 Demographics

The demographics variables to be summarized are: age in years, age group (9-12, 13-16), race, ethnicity, child-bearing potential, height and weight.

7.1.2 Vital Signs at Baseline

Baseline vital signs include systolic and diastolic blood pressure and pulse in the supine and standing positions. The change from supine to standing in systolic and diastolic blood pressures will also be presented as a measure of orthostatic change.

7.1.3 Laboratory Parameters at Baseline

The baseline laboratory parameter assessments include the blood chemistry, hematology, and coagulation test values.

7.2 Medical History

Medical history will be coded using MedDRA version 16.1 or later. Summaries will be presented by preferred term within System Organ Class for each treatment group, overall and by age group.

7.3 Prior and Concomitant Medications and Other Safety Evaluations

Prior and concomitant medications will be coded using the latest version of the World Health Organization (WHO) Drug Reference List. Summaries will be presented by preferred terms within Anatomic-Therapeutic-Chemical (ATC) class 1 and 2 for each treatment group, overall and by age group.

Separate summaries will be generated for prior medications and concomitant medications. Prior medications and concomitant medications are defined as follows:

- *Prior medications* are medications taken exclusively before receipt of study treatment. That is, the stop date of the medication is before the date of first study treatment administration.
- *Concomitant medications* are medications taken during the treatment period. That is, the medication was not stopped before the date of first study treatment administration AND was not started after the last visit date (i.e., visit 6).

If the timing of the dose of a medication cannot be established in relation to the start of study treatment administration, it will be considered as concomitant medication.

7.4 Physical Examination

Physical examination findings (normal, abnormal; clinically significant or not) will be summarized by treatment group, overall and by age group.

8 Exposure and Treatment Compliance

The date and time of each dose of study treatment, the number of glasses of liquid, the number of glasses of water and whether the doses were administered within the correct time frame will be listed.

8.1.1 Extent of Exposure

The number and percentage of subjects receiving each dose of study treatment will be summarized by treatment group, overall and by age group for the Safety analysis set.

8.1.2 Treatment Compliance

The number and percentage of subjects taking each dose within the specified time frame, as well as the required number of glasses of liquid will be summarized by treatment group, overall and by age group. The number of glasses of liquid and number of glasses of water will be summarized by the number of non-missing values, mean, median, minimum, maximum, and standard deviation by treatment group, overall and by age group.

9 Efficacy

9.1 General Considerations

For quantitative variables, all summaries will include the sample size, mean, median, standard deviation, minimum, and maximum. For the qualitative variables, the summaries will include the number and percentage of subjects for each outcome.

Nominal p-values and confidence intervals will be presented to aid in interpretation of the summary of data.

SAS® (version 9.2) will be used for generation of analyses.

9.2 Primary Endpoint(s)

The number and percentage of subjects with each category of the Aronchick scale will be displayed by treatment group, overall and by age group. In addition, the number and percentage of subjects classified as a responder (Excellent or Good rating) will be included in the summary. Specifically, for the overall summaries, the Prepopik 1 sachet and the standard of care groups for the two age groups will be combined; and, all Prepopik groups will be combined.

The treatment group difference will be assessed by constructing the 90% and 95% confidence intervals (CIs) of the difference in proportions between each Prepopik group and standard of care within each age group. Additionally, the 90% and 95% CIs of the difference in proportions between the following combined groups will be constructed:

- Prepopik 1 sachet versus combined standard of care
- All Prepopik groups combined versus combined standard of care

The 90% and 95% confidence intervals will be multiplied by 100 so as to present the resulting interval as percentages.

The analyses will be performed for the ITT and PP populations. The ITT population is the primary population and the PP population is supportive.

9.3 Secondary Endpoint(s)

The following secondary endpoints will be summarized in the same manner as the primary endpoint:

- proportion of subjects who completed colon cleansing
- proportion of subjects who completed the colonoscopy procedure
- proportion of subjects with responses to the individual questions on the Tolerability and Satisfaction Questionnaire

Additionally, based on the individual questions subjects responses will be categorized as tolerable and as satisfactory according to the following algorithms:

- Tolerable is defined as a response of 1 (Never) or 2 (Rarely) to the five items specified in question 3.
- Satisfactory is defined as a response of 1(Very Easy) or 2 (Easy) on question 1 and a response of 1 (Very Well) or 2 (Well) on question 2.

9.4 Pharmacokinetic Endpoints

For subjects that participated in the pharmacokinetic sub-study, the picosulfate and magnesium plasma concentrations will be summarized for the Prepopik treatment groups, overall and by age group. The summary will include the mean, median, standard deviation, minimum, maximum, coefficient of variation, geometric mean and geometric mean coefficient of variation. A listing of the concentration data will also be produced.

Analysis of the population pharmacokinetic endpoints is described in a separate document.

10 Safety

10.1 General Considerations

Safety parameters will be evaluated for the safety analysis data set. Subjects will be summarized by actual treatment received.

10.2 Adverse Events

All AEs will be coded using MedDRA version 16.1 or later. The relation between AEs and study medication will be characterized as having a reasonable possibility or not. The intensity of AEs will be characterized as mild, moderate, or severe.

Treatment-emergent AEs are those adverse events which begin after the start of study treatment or which worsen after the start of study medication. Any event with partial date information reported on or after the date of the first dose of study treatment will be considered treatment-emergent. Only treatment-emergent AEs will be summarized.

Written narratives will be issued for all serious AEs (including deaths) and AEs leading to withdrawal.

10.2.1 Overview of Treatment-Emergent Adverse Events

An AE overview summary table will be prepared including the number of subjects reporting an AE, the percentage of subjects (%) with an AE, and the number of events (E) reported, for the following categories:

- Treatment-emergent adverse events
- Deaths
- Serious adverse events
- Adverse events leading to withdrawal
- Severe and life threatening adverse events
- Adverse drug reactions

10.2.2 Incidence of Adverse Events

The number and percentage of patients experiencing a specific TEAE, as well as the number of events reported, will be tabulated by SOC, preferred term, and treatment group, overall and by age group. Additional summary tables will be provided for AEs by maximum intensity and by relationship to study treatment. Additional summaries for related AEs, serious AEs, AEs leading to withdrawal, and AEs leading to death will be generated. Non-serious AEs with an incidence of 5% or greater in any treatment group will also be summarized.

10.2.3 Data Listings

Supportive data listings will be provided for:

- All adverse events
- Serious adverse events
- Adverse events leading to death
- Adverse events leading to withdrawal

A mapping of adverse event verbatim terms to MedDRA preferred terms and system organ class will also be created.

10.3 Safety Laboratory Variables

Baseline for all laboratory analyses will be the values obtained at the last assessment prior to the first dose of study treatment. Treatment-emergent laboratory data will include tests completed after the first dose of study treatment through the residual time of drug effect. End of trial will include the last post-baseline observations during the trial.

10.3.1 Summary Statistics

At each nominal time point, the actual value and change from baseline (pre-treatment) will be summarized using the number of non-missing observations, mean, median, minimum, maximum and standard deviation for each treatment group, overall and by age group.

10.3.2 Laboratory Variable Changes Relative to Normal Range

Changes relative to normal ranges will be presented with shift tables showing the total number of subjects, and number and percentage of subjects who experienced a shift from baseline. The following categories for shift tables are defined:

- Low: Values which are below the lower reference range limit;
- Normal: Values which are within the lower and upper reference range;
- High: Values which are above the upper reference range limit.

For all haematology and clinical chemistry variables, shift tables will be prepared to compare baseline values to the worst post-treatment value.

10.3.3 Markedly Abnormal Changes

A summary table will be prepared that displays for each laboratory variable the number and percentage of subjects with normal baseline values who had at least one pre-specified markedly abnormal value anytime during the treatment period. The summary table will be presented by treatment group, overall and by age group. Pre-specified markedly abnormal criteria for laboratory tests are given in Appendix 1.

10.3.4 Data Listings

All clinical laboratory values outside normal range will be listed separately by subject number, including demographic information and abnormal flag values.

10.4 Vital Signs

Baseline for all vital signs analyses will be the values obtained at the last assessment prior to the first dose of study treatment. Treatment-emergent vital signs data will include tests completed after the first dose of study treatment through the time of residual drug effect. End of trial will include the last post-baseline observation during the trial.

10.4.1 Summary Statistics

At each nominal time point, the actual value and change from baseline (pre-treatment) will be summarized using the number of non-missing observations, mean, median, minimum, maximum and standard deviation for each treatment group, overall and by age group. In this study, blood pressure and pulse are first measured after at least 5 minutes resting in supine position and after 3 minutes in standing position. Summaries will be provided for vital signs recorded in the supine and standing positions, as well as the change from supine to standing (orthostatic measurement).

10.4.2 Markedly Abnormal Changes

Summary tables will be prepared displaying the number and percentage of subjects with normal baseline values who had one or more pre-specified markedly abnormal treatment-emergent values. Summaries will be provided by treatment group, overall and by age group. Pre-specified markedly abnormal criteria for vital signs are given in Appendix 1.

For orthostatic changes in blood pressure and pulse rate, the following criteria are suggestive of fluid volume depletion [1]:

- a decrease in systolic blood pressure greater than or equal to 20 mmHG within 3 minutes of standing,
- a decrease in diastolic blood pressure greater than or equal to 10 mmHG within 3 minutes of standing, or
- an increase in heart rate (pulse rate) greater than or equal to 30 beats per minute (bpm) in the presence of a drop in blood pressure (systolic, diastolic or both).

The number and percentage of subjects whose changes meet these pre-specified criteria will be summarized by treatment group, overall and by age group.

10.4.3 Data Listings

Data listings will be prepared for all subjects, including flags for any abnormal vital signs value or abnormal orthostatic measure at any time-point.

10.5 Physical Examination

The number and percentage of subjects having an abnormal physical exam at Screening, or with a change from Screening, will be summarized by body system for each treatment group, overall and by age group.

Physical examination findings at each evaluation will be listed for the safety dataset. Subjects with abnormal findings will be noted on the data listings.

11 Interim Analyses

No interim analyses are planned for this study.

12 Deviations from Protocol Analysis

The following are a list of changes and/or additions from the protocol specified analyses:

- In addition to the pre-specified 95% CIs, 90% CIs will also be computed and displayed.
- Additional summaries for pre-specified orthostatic changes in blood pressure will be provided.
- Pharmacokinetic concentration summaries and listings will be provided.

13 References

[1] Clinical Practice Guideline: Orthostatic vital sings full version. Emergency Nurses Association. December 2011.

14 Tables, Listings and Figures

The document with tables, listings, and figures (TLF) shells is presented in a separate document.

Appendix 1 Markedly Abnormal Laboratory Safety Values and Vital Signs

HEMATOLOGY				
Variable	**Units**	**Age**	**Markedly Abnormal Criteria**	
			Low (≤)	**High (≥)**
Hemoglobin	g/dL	6 mo-18 yr	8	18
RBC	$x10^6/mm^3$	6 mo-18 yr	3.5	6
Hematocrit	%	6 mo-18 yr	30	50
Reticulocytes	%	6 mo to 12 yr > 12 yr:	NA NA	1 2
MCV	Fl	6 mo-18 yr	70	100
MCH	pg	6 mo-18 yr	20	35
MCHC	g/dL	6 mo-18 yr	30	NA
Leukocytes	$x10^3/mm^3$	6 mo to 18 yr	4	20
Neutrophils	$x10^3/mm^3$	6 mo-18 yr	1	10
Lymphocytes	$x10^3/mm^3$	2-18 yr	1	10
Eosinophils	%*	All ages	NA	5
Monocytes	%*	6 mo-18 yr	NA	5
Basophils	%*	6 mo-18 yr	NA	1
Platelets	$x10^3/mm^3$	6 mo-18 yr	50	750

*The percentage indicates the relative number of each type of leucocytes in the blood. The absolute count is calculated by multiply the relative value (%) by the total leukocyte count/100.

CHEMISTRY				
Variable	**Units**	**Age**	**Markedly Abnormal Criteria**	
			Low	**High**
ALT	U/L	1-19yr	Not applicable	≥ 3x NL
AST	U/L	1-19yr	Not applicable	≥ 3x NL
Total protein	g/L	> 1yr	≤ 40	≥80
Albumin	g/L	All	≤ 25	> 60
Alkaline phosphatase	U/L	All	Not applicable	≥ 3x NL
Total bilirubin	µmol/L	> 5d	Not applicable	≥ 34*
C-reactive protein	mg/L	All	Not applicable	≥ 10
Total cholesterol	mmol/L	All	Not applicable	≥ 6
Trygliceride s	mmol/l	All	Not applicable	≥ 1.9
Creatinin	µmol/L	24m-11yr 12-18yr	Not applicable	≥100 ≥120
Glucose	mmol/L	24m-11yr 12-18yr	≤ 2.5 ≤2.8	> 8 > 10
GGT	U/L	All	Not applicable	≥ 3x NL
Creatine kinase	U/L	> 3m	Not applicable	≥ 300
LDH	U/L	All	Not applicable	≥ 700
Urea nitrogen	Mmol/L	All	Not applicable	≥ 8.0
Uric acid	µmol/L	6-11yr 12-19yr: **M** **F**	Not applicable	≥ 500 **M** ≥ 600 **F** ≥ 500
Potassium	mmol/L	> 2m	≤3	≥6
Sodium	mmol/L	All	≤ 130	≥ 150
Calcium total	mmol/L	All	≤1.8	≥ 3
Chloride	mmol/L	All	≤90	≥115
Phosphorus, inorganic	mmol/L	4-11yr 12-15yr 16-19yr	≤ 0.9 ≤ 0.9 ≤ 0.6 ≤ 0.6	≥ 2.8 ≥ 2.5 ≥ 2.2

HEMOSTASIS AND COAGULATION				
Variable	**Units**	**Age**	**Markedly Abnormal Criteria**	
			Low	**High**
Coagulation factor VIII	% of normal ranges U/dl	All All	≤ 30 ≤ 30	Not applicable
Coagulation factor IX	% of normal ranges U/dl	All All	≤ 30 ≤ 30	Not applicable
Von Willebrand protein	VWF:RCo activity(%)	All	≤ 20	Not applicable
Fibrinogen	g/L	All	Not applicable	≥ 5
Prothrombin Time (PT)	seconds	All	NA	≥ 20
Partial Thromboplastin Time (APTT)	seconds	6 mo-18 yr	≤20	≥ 50

* Applicable only for term healthy newborns

ECG		
Variable	**Baseline Normal Value**	**Markedly Abnormal Treatment-Emergent Value**
Duration of PR interval	3-8 yr: 90-160 9-16 yr: 90-180	3-8 yr ≥ 180 msec 9-16 yr ≥ 200 msec
Duration of QRS interval	3-8 yr: ≤ 100 9-16 yr: ≤110	3-8 yr ≥ 110 msec 9-16 yr ≥120
Duration of QTc interval	Not applicable*	≥ 450 msec
Duration of QTc interval	Not applicable	Increase from baseline of ≥ 30 msec

* We do not list a lower limit of normal but the literature often defines the short QT syndrome as a QTc <300 ms.

PULSE RATE		
	Markedly Abnormal Criteria	
Age	**Low**	**High**
7 years ≤ x < 9 years	≤66	≥114
9 years ≤ x < 11 years	≤66	≥114
11 years ≤ x < 13 years girls 11 years ≤ x < 13 years boys	≤66 ≤61	≥114 ≥109
13 years ≤ x < 15 years girls 13 years ≤ x < 15 years boys	≤61 ≤56	≥109 ≥104
15 years ≤ x < 17 years girls 15 years ≤ x < 17 years boys	≤56 ≤51	≥104 ≥99

RESPIRATORY RATE (breaths/min)		
	Markedly Abnormal Criteria	
Age	**Low**	**High**
5 years <= x < 12 years	≤10	≥40
12 years <= x < 16 years	≤7	≥40
16 years <= x	≤7	≥30

Markedly abnormal blood pressure levels for BOYS by age (height fixed at 50% percentile)

Age (years)	Unit	SBP Lower limit (≤)	SBP Upper limit (≥)	DBP Lower limit (≤)	DBP Upper limit (≥)
8 years <= x < 9 years	mm Hg	74	124	32	86
9 years <= x < 10 years	mm Hg	76	125	33	87
10 years <= x < 11 years	mm Hg	77	127	34	88
11 years <= x < 12 years	mm Hg	79	129	35	89
12 years <= x < 13 years	mm Hg	81	131	35	89
13 years <= x < 14 years	mm Hg	84	134	36	90
14 years <= x < 15 years	mm Hg	86	136	36	90
15 years <= x < 16 years	mm Hg	89	139	37	91
16 years <= x < 17 years	mm Hg	92	141	39	93

Markedly abnormal blood pressure levels for GIRLS by age (Height fixed at 50 % percentile)

Age (years)	Unit	SBP Lower limit (≤)	SBP Upper limit (≥)	DBP Lower limit (≤)	DBP Upper limit (≥)
8 years <= x < 9 years	mm Hg	74	123	33	84
9 years <= x < 10 years	mm Hg	76	124	34	85
10 years <= x < 11 years	mm Hg	78	126	35	86
11 years <= x < 12 years	mm Hg	80	128	36	87
12 years <= x < 13 years	mm Hg	81	130	37	88
13 years <= x < 14 years	mm Hg	83	132	38	89
14 years <= x < 15 years	mm Hg	85	134	39	90
15 years <= x < 16 years	mm Hg	86	135	40	91
16 years <= x < 17 years	mm Hg	87	136	41	92