1VIT18045 Efficacy and Safety of Intravenous Ferric Carboxymaltose in Pediatric Patients With Iron Deficiency Anemia and Unsatisfactory Response Oral Iron Under Study Protocol 1VIT17044 NCT04269707

03DEC2019

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Statistical Analysis Plan

Protocol No.: 1VIT18045

Evaluating the Efficacy and Safety of Intravenous Ferric Carboxymaltose in Pediatric Patients with Iron Deficiency Anemia and an Unsatisfactory Response to Oral Iron under Study Protocol 1VIT17044

Sponsor:	American Regent, Inc.
Version:	Version 1.0
Issue Date:	12 August 2020

STATISTICAL ANALYSIS PLAN APPROVAL

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LIST OF ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CHr	Reticulocyte Hemoglobin Content
CTCAE	Common Terminology Criteria for Adverse Events
dL	Deciliter
eCRF	Electronic Case Report Form
e.g.	For Example
EOS	End of Study
FCM	Ferric Carboxymaltose
FDA	Food and Drug Administration
Fe	Iron
g	Gram
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
Hct	Hematocrit
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Viral Antibody
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonisation
IDA	Iron-deficiency Anemia
i.e.	That Is
IND	Investigational New Drug Application
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous
Kg	Kilogram
L	Liter
LDH	Lactate Dehydrogenase
MCH	Mean Cell Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
m	Meter
mg	Milligrams
mL	Milliliter
NCI	National Cancer Institute
ng	Nanogram
PCS	Potentially Clinically Significant
PE	Physical Examination

PT	Preferred Term
RBC	Red Blood Cells
RDW	Red Cell Distribution Width
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treament Emergent Adverse Event
TIBC	Total Iron Binding Capcacity
TSAT	Transferrin Saturation
US	United States
WBC	White Blood Cells
WHO	World Health Organization

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Protocol 1VIT18045 (Administrative Change 1 Date: 03 December 2019). This SAP should be read in conjunction with the corresponding clinical study protocol and electronic case report forms (eCRFs).

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

The primary objective of this study is to evaluate the efficacy and safety of intravenous (IV) Ferric Carboxymaltose (FCM) in pediatric participants who have iron deficiency anemia (IDA).

1.2 STUDY ENDPOINTS

1.2.1 Primary Efficacy Endpoint

The primary endpoint is the change in hemoglobin (Hgb) from baseline to Day 35.

1.2.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Change in ferritin from baseline to Day 35
- Change in transferrin saturation (TSAT) from baseline to Day 35
- Changes from baseline in Hgb, ferritin, TSAT, and reticulocyte hemoglobin content (CHr) throughout the study.

1.2.3 Safety Endpoints

Safety endpoints include:

- Extent of exposure
- Adverse events
- Laboratory assessments
- Vital signs
- Physical examinations

1.3 SUMMARY OF THE STUDY DESIGN

1.3.1 General Study Design and Plan

This is a single arm, open-label, multi-center, multi-national, non-randomized study that will evaluate the efficacy and safety of a one course treatment with FCM in participants who had an unsatisfactory response to oral iron in study 1VIT17044.

Subjects will have an EOS Visit (Day 35) from the 1VIT17044 study to qualify for entry. Subjects will then be screened, meet all inclusion criteria, no exclusion criteria and have a baseline evaluation. Based on the successful completion of the baseline evaluations, subjects will be enrolled and will receive the first dose of FCM (Day 0). The second FCM dose should occur 7 days from the first dose. Subjects will return to the clinic 14 and 28 days post their first dose for laboratory and safety assessments, and at 35 days post the first dose, participants will return to the clinic for final safety and efficacy assessments. Once all assessments are complete the participant will exit the study.

An **unsatisfactory response** to oral iron (i.e., an increase in Hgb of <1 g/dL from baseline) will be defined as non-responders to oral iron treatment. Non-responders who continue to meet all inclusion criteria (including Hgb <11 g/dL) and none of the exclusion criteria will receive 1 course of FCM.

Table 1: Schedule of Activities

Procedures	Screening[1] Day -7 to -1	Enrollment Visit 1, Day 0	Study Visit 2 Day 7 ± 1 day	Study Visit 3 Day 14 ± 1 day	Study Visit 4 Day 28 ± 1 day	Study Visit 5 Day 35 ± 1 day
Informed Consent / Assent	X					
Medical History	X					
Physical Exam		X				X
Inclusion/Exclusion Criteria	X	X				
IRT	X	X				X
Vital Signs	X	X	X	X	X	X
Weight	X	X				
Height	X					
Temperature		X	X			
Blood sampling for Hematology, Chemistry and Iron Indices (5.5 mL) [1]	X	X	X	X	X	X
Blood sampling for Serum Pregnancy Test (1.5 mL), if applicable	X					X
Concomitant Medications	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X
FCM Dosing		X	X			

1. Note that there will be a 7 ± 1 day waiting period between 1VIT17044 end of study and extension screening
2. For a full description of central laboratory assessments, refer to Protocol Section 6.4.

1.3.2 Stratification/Randomization

This is a non-randomized, single arm study.

1.3.3 Sample Size and Statistical Power Considerations

There were no sample size estimations for this study. The current study is a rollover for study 1VIT17044. There will be a maximum of approximately 36 participants from study 1VIT17044 who had an unsatisfactory response to oral iron or required an intervention.

2. STATISTICAL METHODS

2.1 GENERAL CONSIDERATIONS

Analysis datasets will be produced according to CDISC standards. All study-collected data will be summarized in tables or graphs. Listing will be produced when appropriate and all ICH-required listings will be produced.

Continuous variables will be summarized in terms of the number of observations (n), mean, standard deviation (SD), median, quartiles (Q1 and Q3), minimum (min), and maximum (max) values. Other descriptive statistics (e.g., coefficient of variation) may be reported when appropriate. Analysis of categorical variables will include frequency counts and percentages. Unknown and missing data may be presented as a separate category and the denominator will include unknown or missing values as appropriate. If applicable, hypothesis testing will be carried out at the two-sided α=0.05 level unless otherwise specified; 2-sided 95% confidence intervals (CIs) will be presented, where specified.

Generally, data will be summarized by nominal visit. However, data from both unscheduled and scheduled will be used for determination of last observed value, and in worst- or best-case changes and/or shifts from baseline. Assessment windows will not be defined for the purpose of classifying measurements obtained outside scheduled assessment times.

2.1.1 Reporting Precision

Summary statistics will be presented to the following degree of precision, unless otherwise specified:

Statistics	Degree of Precision
Mean, Geometric mean, Median, Quartiles, Confidence limit boundaries	One decimal place more than the raw data.
Standard deviation, Standard error	Two decimal places more than the raw data.
Minimum, Maximum	The same as the raw data.
p-value	Rounded to 4 decimal places and therefore presented as 0. xxxx; p-values smaller than

	0.0001 as '<0.0001'; p-values greater than 0.9999 as '>0.9999'.
Percentage	One decimal place. A percentage of 100% will be reported as 100%. Percentages of zero will be reported as 0.

For weight and height, one decimal place will be used for summary statistics. Fractional numeric values will be presented with a zero to the left of the decimal point (for example, 0.12 – 0.30).

2.2 DEFINITIONS OF ANALYSIS POPULATIONS (ANALYSIS SETS)

2.2.1 Safety Population

The safety population will consist of all participants who received at least one dose of study drug (IV FCM).

2.3 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

2.3.1 Baseline Definition

For evaluations collected at multiple time points, the baseline will be defined as the last value obtained before the first dose of study drug.

2.3.2 Study Day

Study Day will be calculated relative to the day of first dose (defined as Day 1).

If the assessment (or event) date falls on or after the date of first dose then

Study Day = Assessment Date – Date of First Dose + 1

If assessment date falls before the date of first dose then

Study Day = Assessment Date – Date of First Dose

In the case of adverse events or concomitant medications where the assessment date is partially or completely missing, Study Day and any corresponding durations will follow the conventions given in Section 2.3.4.

2.3.3 Time Windows for Analysis

No assessment windows will be defined for the purpose of classifying measurement obtained outside scheduled assessment times. The summary by visit will be based on the observations at scheduled visits only. Data from both unscheduled and scheduled will be used for determination of last observed value, and in worst- or best-case changes and/or shifts from baseline.

2.3.4 Handling of Missing Data

A participant who withdraws from the study for any reason will be included in the analyses regardless of time on study. Methods for handling withdrawals and missing data will be specific to each endpoint to be analyzed. Missing data will not be imputed for descriptive statistical summaries in safety or efficacy.

For statistical inferential (paired t-tests) analyses, missing data will be imputed using last observation carried forward (LOCF) method for hemoglobin and other efficacy endpoints. e.g. for primary endpoint, hemoglobin, when Day 35 data is missing (subject has discontinued before Day 35, or measurement not taken at Day 35 though subject was not discontinued), Day 28 or last unscheduled result will be carried forward. If there is no post-baseline value observed, the worst value obtained from Day 35 of all subjects in the safety population will be used. The worst value is defined as the lowest value for hemoglobin, ferritin, TSAT and reticulocyte hemoglobin content.

Dates missing the day or both day and month of the year will adhere to the following conventions to classify TEAE and to classify prior/concomitant medications.

- A medication with a completely missing start date will be considered a prior medication. A medication with a completely missing stop date will be considered a concomitant medication.

- If complete AE onset date is missing and AE end date is on or after the first dose date then it will be counted as a treatment emergent AE (TEAE) for the study. If complete AE onset date is missing and AE end date is before the first dose date then it will not be counted as a TEAE for the study.

- If an AE or a medication has a partial missing start or stop date, the following rules will be used for imputation:

    - If year is present but month and day are missing, impute start date as January 1 of that year or first dose date if the year is the same as the year of first dose date and impute stop date as December 31 of that year.

    - If year and day are present but month is missing, impute start month as January or the month of the first dose date if the year is the same as the year of first dose date and impute stop month as December.

    - If year and month are present but day is missing, impute start date as first day of that month or first dose date if the year and month are the same as the year and month of first dose date and impute stop date as last day of that month.

2.4 POOLING OF CENTERS

The study centers are not planned to be used as a stratification factor nor a covariate in the statistical modeling and testing, therefore it is not necessary to pool small centers together.

2.5 ANALYSIS SOFTWARE

All summaries and statistical analyses will be generated using SAS® version 9.4 or higher.

3. STUDY SUBJECTS

3.1 DISPOSITION OF SUBJECTS

Disposition will be summarized for all screened subjects and the number of subjects in Safety Population will be summarized in each investigative site.

The disposition will include the following:

- Participants who are screened
- Participants who are included in Safety Population
- Participants who complete the study
- Participants who discontinue the study

The number and percent of subjects will be summarized for each reason for premature discontinuation.

3.2 PROTOCOL DEVIATIONS

The clinical team will identify deviations and the deviations will be identified in the database. The number and percent of participants with clinically important protocol deviations will be summarized for each type of deviation based on the safety population.

4. DEMOGRAPHY AND BASELINE CHARACTERISTICS

4.1 DEMOGRAPHY AND BASELINE CHARACTERISTICS

Demography data such as sex, age, age group (1 to <12 and ≥12 to 18 years), race, ethnicity, body height, body weight, BMI and BMI group (underweight ≤18.5, 18.5 < normal weight≤ 24.9, 25 < overweight ≤ 29.9, obesity = BMI of 30 or greater) will be summarized with descriptive statistics or frequency counts for all patients in the safety populations.

4.2 MEDICAL HISTORY

Medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) Terminology. Events will be coded to System Organ Class (SOC) and preferred term (PT) using MedDRA Version 22.0 or higher. The number and percent of subjects with clinically significant medical history at screening will be summarized by SOC and PT for the safety populations.

4.3 PRIOR AND CONCOMITANT MEDICATION

Prior medications are defined as medications that started prior to the first dose of study drug. Concomitant medications are defined as medications (other than the study drug) taken on or after the first dose of the study drug during the entire study. Medications started before the first dose of study drug and continuing at the time of the first dose of study drug are considered both prior medication and concomitant medication. As for the medications that stopped with end date prior to study drug start date will be considered as prior medications. Partial dates for prior/concomitant medication will be classified based on rules in Section 2.3.4.

All investigator terms for medications recorded on the CRF will be coded using the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) drug dictionary (WHODrug, March 2019 B3). Summaries of prior and concomitant medications will be provided by level 3 ATC classification and preferred term using frequency and percentages for the safety population. If ATC level 3 is not applicable, then the level 2 ATC will be used.

5. STUDY DRUG

5.1 TREATMENT COMPLIANCE

As for each subject, the individual compliance rate will be summarized by descriptive statistics for the safety population.

FCM Compliance = (total dose of iron administered/target dose) ×100

5.2 EXTENT OF EXPOSURE

The total calculated FCM dose to be given (mg), the total dose of elemental iron administered (mg), the number of infusions and treatment duration (days) will be summarized descriptively.

6. EFFICACY ANALYSES

All primary and secondary efficacy analyses will be based on the safety population unless otherwise specified. Missing data will be imputed per Section 2.3.4 for primary and secondary efficacy endpoints (no imputation for descriptive statistical summaries). P-values to determine the mean difference between baseline and Day 35 will be reported. The mean difference and corresponding 95% confidence interval will be tabulated where appropriate.

6.1 PRIMARY EFFICACY ANALYSIS

6.1.1 Change in Hgb from baseline to Day 35

The primary efficacy endpoint is the change in Hgb from baseline to day 35. The actual value of Hgb on baseline, Day 35, and change from baseline to Day 35 will be summarized via descriptive statistics.

The change in Hgb from baseline to Day 35 will be assessed using paired t-tests (two-sided test, α=0.05). Baseline Hgb will be defined as the last Hgb obtained before the first dose. Missing value will be imputed using LOCF as specified in Section 2.3.4.

6.2 SECONDARY EFFICACY ANALYSES

6.2.1 Change in ferritin from baseline to Day 35

The actual value of ferritin on baseline, Day 35, and change from baseline to Day 35 will be summarized via descriptive statistics.

The change in ferritin from baseline to day 35 will be assessed using paired t-tests (two-sided test, α=0.05). Baseline ferritin will be defined as the last ferritin obtained before the first dose. Missing value will be imputed using LOCF as specified in Section 2.3.4.

6.2.2 Change in TSAT from baseline to Day 35

The actual value of TSAT on baseline, Day 35, and change from baseline to Day 35 will be summarized via descriptive statistics.

The change in TSAT from baseline to day 35 will be assessed using paired t-tests (two-sided test, α=0.05). Baseline TSAT will be defined as the last TSAT obtained before the first dose. Missing value will be imputed using LOCF as specified in Section 2.3.4.

6.2.3 Change in Hgb, ferritin, TSAT and Reticulocyte Hemoglobin Content from baseline throughout the Study

The actual value of Hgb, ferritin, TSAT and reticulocyte hemoglobin content (CHr) on baseline, each post-baseline visit (Day 7, 14, 28 and 35), and change from baseline to each post-baseline visit will be summarized via descriptive statistics.

7. SAFETY ANALYSES

All safety analyses will be performed on the safety population. Safety assessments include:

- Extent of exposure
- Adverse events
- Laboratory assessments (hematology, iron indices, chemistry, and other)
- Vital signs

Baseline of clinical laboratory findings will be defined as the last value obtained before the first dose of study drug.

7.1 ADVERSE EVENTS

Adverse events (AEs) will be coded by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Adverse event

summaries will exclude preferred terms that describe asymptomatic serum ferritin, TSAT, and reticulocyte values (or changes). This approach is justified by the reporting of these values in efficacy summaries and is consistent with the protocol-defined reporting standards for hemoglobin/hematocrit and low iron indices. For the purposes of this study, non-serious anemia (hemoglobin or hematocrit below the normal range or worsened from baseline) or iron deficiency (iron indices below the normal range or worsened from baseline) will not be considered adverse events. Anemia or iron deficiency will be considered end points if an intervention is required.

A treatment-emergent adverse event (TEAE) is defined as an event with onset date on or after the study drug start date. Partial date TEAE classification rules refer to Section 2.3.4. Only TEAEs will be included in summary tables.

The incidence of TEAEs will be summarized as the number (percentage) of subjects with TEAEs within SOC and PT. Subjects who report the same PT on multiple occasions will be counted once for the PT: under the highest severity (severe > moderate > mild) CTCAE when summarized by severity and under the closest relationship (probably related > possibly related > unlikely related > none) to study drug when summarized by relationship. If a subject reports multiple PT for a SOC, the subject will be counted only once for that SOC. Events with unknown severity or relationship will be counted as unknown.

TEAEs will be summarized as below.

- An overview table, including number of subjects with
    - TEAEs
    - serious TEAEs
    - study drug related TEAEs
    - study drug related Serious TEAEs
    - TEAEs by severity
    - TEAEs leading to study drug discontinuation or withdrawal from study
    - TEAEs leading to death
- TEAE by SOC
- TEAE by PT
- TEAE by SOC and PT
- TEAE by SOC, PT, and Severity (CTCAE)
- Study drug related TEAEs by SOC, PT
- Serious TEAEs by SOC and PT
- Study drug related serious TEAEs by SOC and PT

- TEAEs leading to study drug discontinuation or withdrawal from study by SOC and PT
- TEAEs leading to death by SOP and PT

Unless otherwise stated, all TEAE tables will be sorted by SOC and PT in decreasing frequency of the number and percentage of subjects.

7.1.1 Adverse Events of Special Interest

Adverse events of special interest include hypophosphatemia, hypersensitivity/anaphylactoid reactions, injection/infusion site reactions, and cardiovascular events. The search strategy will be identified as follows:

- TEAEs of hypophosphatemia:
  - MedDRA PT Blood phosphorus decrease
  - MedDRA PT Blood phosphorus abnormal
  - MedDRA PT Hypophosphataemia
  - MedDRA PT Hypophosphataemic rickets
  - MedDRA PT Rickets familial hypophosphataemic

- TEAEs indicative of hypersensitivity/anaphylactoid reactions:
  - SMQ Anaphylactic reaction
  - SMQ Angioedema
  - PT Hypersensitivity

- TEAEs of injection/infusion site reactions:
  - MedDRA HLT Infusion site reactions
  - MedDRA HLT Injection site reactions
  - MedDRA HLT Administration site reactions NEC
  - MedDRA PT Infusion related reaction

- Cardiovascular TEAEs:
  - Cardiovascular disorders SOC
  - Vascular disorders SOC

The AEs of special interest will be summarized as below:

- Treatment-emergent AESI by SOC and PT
- Serious treatment-emergent AESI by SOC, PT
- Serious or severe treatment-emergent AESI by SOC and PT

7.2 CLINICAL LABORATORY PARAMETERS

Laboratory assessments include hematology, clinical chemistry, and iron indices:

- Hematology: Hgb, Hct, RBC, WBC, MCV, MCH, MCHC, RDW, platelets, differential

count, reticulocyte count and CHr

- Clinical chemistry: sodium, potassium, chloride, BUN, creatinine, albumin, alkaline phosphatase, total bilirubin, GGT, AST, ALT, LDH, calcium, phosphorus, glucose, bicarbonate and magnesium.

- Iron indices: serum iron, serum ferritin, and total iron binding capacity (TIBC), and percentage serum transferrin saturation (TSAT).

- Other: Serum pregnancy test

All laboratory parameters will be presented in conventional units. The actual value and mean change from baseline to each scheduled visit will be summarized using descriptive statistics for each laboratory test group above.

Time course table for serum phosphate will be constructed for subjects in safety population. Descriptive statistics of days to first value of specified CTC grade and days to return to normal will be summarized. Only the subjects with a normal serum phosphate baseline value will be included in this table.

The number and percent of subjects with treatment-emergent potentially clinically significant (PCS) laboratory values after baseline will be summarized by visit. The denominator is all subjects with normal baseline and at least one post baseline assessment in the safety population and the numerator is the number of subjects with PCS (i.e., meets Grade 3 or Grade 4 AE scale defined in Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 from March 2017 (Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, US Department of Health and Human Services)) at any post-baseline visit.

Shift from baseline AE grade to maximum post-baseline AE grade, and shift from baseline to the last visit in terms of AE grade will be summarized, separately.

The AE grade for Chemistries and Hematology are defined in Appendix 1.1. BUN, hematocrit, bands and iron indices do not have adverse event scales available and are not evaluated separately as possible AEs.

7.3 VITAL SIGNS AND PHYSICAL EXAMINATION FINDINGS

7.3.1 Vital Signs

Vital signs will be collected including sitting body temperature, blood pressure (BP) and heart rate. On study drug dosing days BP and heart rate will be collected pre-dosing, immediately (within 5 minutes) post, and 30 minutes post dosing, and body temperature will be collected on each dosing day. The actual value and the change in vital signs (including sitting heart rate and blood pressure) from pre-infusion to each post-infusion time point will be summarized descriptively on each dosing day. Markedly abnormal values should be determined by PALS

Guidelines, 2015 in Appendix 1.2. Children >15 years of age will use the criteria for 15 years old children.

7.3.2 Physical Examination

Physical examination (PE) results were collected at Day 0 and Day 35 including six body systems, i.e. skin, cardiovascular, pulmonary/respiration, abdominal, central nervous system and musculoskeletal/extremities. Each component of the baseline physical examination will be recorded as normal or abnormal. Each component of the post baseline physical examinations will be recorded as No Change from Baseline PE or Change from Baseline PE. The number and percent of subjects who have normal, abnormal and significant changes at each visit will be summarized in table.

8. INTERIM ANALYSES AND DATA AND SAFETY MONITORING BOARD (DSMB)

8.1 INTERIM ANALYSES

No formal interim analysis is planned for this study.

8.2 DATA AND SAFETY MONITORING BOARD (DSMB)

No Data Safety Monitoring Board for this study.

9. SUMMARY OF MAJOR CHANGES IN THE PLANNED ANALYSES

Compared with the study protocol (03 December 2019 Administrative Change 1), below items are the major changes made in this SAP:

1. The LOCF imputation method was proposed for paired t-test for primary and secondary efficacy endpoints in SAP.

2. The scale defined in Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 from March 2017 (Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, US Department of Health and Human Services) will be used to identify abnormal clinical laboratory values instead of toxicity criteria from the National Cancer Institute Common Terminology Criteria version 5 for Adverse Events specified in the protocol.

10. APPENDICES

APPENDIX 1.1 ADVERSE EVENT SCALE

CHEMISTRIES Adverse Event Scale				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Calcium, High (mg/dL; *mmol/L*) *≥ 7 days of age*	10.6 to < 11.5 *2.65 to < 2.88*	11.5 to < 12.5 *2.88 to < 3.13*	12.5 to < 13.5 *3.13 to < 3.38*	≥ 13.5 *≥ 3.38*
Calcium, Low (mg/dL; *mmol/L*) *≥ 7 days of age*	7.8 to < 8.4 *1.95 to < 2.10*	7.0 to < 7.8 *1.75 to < 1.95*	6.1 to < 7.0 *1.53 to < 1.75*	< 6.1 *< 1.53*
Creatinine, High *Report only one*	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 130*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*

ULN and LLN required for the chemistries AE Scale
(based on the high and low range from Covance Central Laboratory Services Manual, American Regent, Inc)

Sex	Age	Alkaline Phosphatase LLN (U/L)	ALT ULN (U/L)	AST ULN (U/L)	Age	Creatinine ULN (mg/dL)	Age	Albumin LLN (g/dL)
Female	1-4 yr	<108	>34	>56	1-4 yr	>0.4	2 m–4 yr	<2.8
	4-7 yr	<96	>34	>48	4-7 yr	>0.5	4-16 yr	<2.9
	7-10 yr	<69	>34	>40	7-10 yr	>0.6	16-18 yr	<3.3
	10-15 yr	<51	>34	>40	10-13 yr	>0.7	18 yr	<3.3
	15-18 yr	<31	>34	>40	13-16 yr	>0.8		
	18 yr	<31	>34	>34	16-18 yr	>0.9		
					18 yr	>1.1		
Male	1-4 yr	<104	>34	>69	1-4 yr	>0.4	2 m–4 yr	<2.8

	4-7 yr	<93	>34	>59	4-7 yr	>0.5	4-16 yr	<2.9
	7-10 yr	<86	>34	>40	7-10 yr	>0.6	16-18 yr	<3.3
	10-15 yr	<95	>43	>40	10-13 yr	>0.7	18 yr	<3.3
	15-18 yr	<50	>43	>40	13-16 yr	>0.9		
	18 yr	<31	>43	>36	16-18 yr	>1.1		
					18 yr	>1.2		

HEMATOLOGY Adverse Event Scale				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Absolute Neutrophil Count (ANC), Low (cells/mm3; *cells/L*) *> 7 days of age*	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*
Hemoglobin, Low (g/dL; *mmol/L*) *≥ 13 years of age (male only)*	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
Platelets, Decreased (cells/mm3; *cells/L*)	100,000 to < 125,000 *100.000 x 10^9 to < 125.000 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
WBC, Decreased (cells/mm3; *cells/L*) *> 7 days of age*	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*

APPENDIX 1.2 PEDIATRIC VITAL SIGNS REFERENCE CHART

Heart Rate		
Normal Heart Rate by Age (beats/minute) **Reference: PALS Guidelines, 2015**		
Age	**Awake Rate**	**Sleeping Rate**
Neonate (<28 d)	100-205	90-160
Infant (1 mo-1 y)	100-190	90-160
Toddler (1-2 y)	98-140	80-120
Preschool (3-5 y)	80-120	65-100
School-age (6-11 y)	75-118	58-90
Adolescent (12-15 y)	60-100	50-90

Blood Pressure			
Normal Blood Pressure by Age (mm Hg) **Reference: PALS Guidelines, 2015**			
Age	**Systolic Pressure**	**Diastolic Pressure**	**Systolic Hypotension**
Birth (12 h, <1000 g)	39-59	16-36	<40-50
Birth (12 h, 3 kg)	60-76	31-45	<50
Neonate (96 h)	67-84	35-53	<60
Infant (1-12 mo)	72-104	37-56	<70
Toddler (1-2 y)	86-106	42-63	<70 + (age in years x 2)
Preschooler (3-5 y)	89-112	46-72	<70 + (age in years x 2)
School-age (6-9 y)	97-115	57-76	<70 + (age in years x 2)
Preadolescent (10-11 y)	102-120	61-80	<90
Adolescent (12-15 y)	110-131	64-83	<90

Temperature	
Normal Temperature Range by Method **Reference: CPS Position Statement on Temperature Measurement in Pediatrics, 2015**	
Method	Normal Range (oC)
Rectal	36.6-38
Ear	35.8-38
Oral	35.5-37.5
Axillary	36.5-37.5