STATISTICAL ANALYSIS PLAN

An Open-Label, Multicenter Study to Evaluate the Long-Term Safety, Tolerability, and Efficacy of AEB1102 in Patients with Arginase I Deficiency

Protocol: CAEB1102-102A

Protocol Number: CAEB1102-102A

Protocol Version and Date:
Original Protocol, Version 1, 09 MAR 2017
Protocol Amendment 1, 17 APR 2018
Protocol Amendment 1.1, 14 MAY 2018 (Withdrawn)
Protocol Amendment 1.2, 30 NOV 2018 UK country-specific
Protocol Amendment 2, 28 MAR 2019
Protocol Amendment 2.1, 08 MAY 2019 UK country-specific
Protocol Amendment 3.0, 17 OCT 2019
Protocol Amendment 4.0, 05 May 2020
Protocol Amendment 5.0, 09 OCT 2020

Name of Test Drug: AEB1102 (pegzilarginase)

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Analysis Plan Date: 21JUL2021

Analysis Plan Version: 3.0

Version Number	Summary of Changes	Version Date
0.1	Initial version to client.	28JUN2019
0.2	Updated based on client comments	12JUL2019
1.0	Final version to client for review and approval.	13JUL2020
2.0	Updates for final analysis	24JUN2021
3.0	Changes from team to align with Phase III	21JUL2021

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APPROVAL SIGNATURE PAGE

Protocol Title:	**An Open-label, Multicenter Study to Evaluate the Long-Term Safety, Tolerability, and Efficacy of AEB1102 in Patients with Arginase I Deficiency**
Protocol Number:	CAEB1102-102A
SAP Date / Version:	Version 3.0/ 21JUL2021

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol and the clinical development plan.

[redacted]

Date

[redacted]

Date

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LIST OF ABBREVIATIONS

Abbreviation	Definition
6MWT	Six-minute walk test
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
ARG1-D	Arginase 1 deficiency
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BBS	Berg Balance Scale
BUN	Blood urea nitrogen
CI	Confidence interval
CRU	Clinical research unit
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Coefficient of variation
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EOT	End of Therapy
FAS	Full Analysis Set
GCs	Guanidino Compounds
GMFCS	Gross Motor Function Classification System
GMFM	Gross Motor Function Measure
IV	Intravenous
KABC-II	Kaufman Assessment Battery for Children II
MAS	Modified Ashworth Scale
max	Maximum
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
min	Minimum
PCS	Potentially clinically significant
PD	Pharmacodynamic(s)
PDAS	Pharmacodynamic Analysis Set
PedsQL	PedsQL Measurement Model for the Pediatric Quality of Life Inventory

Abbreviation	Definition
PEG	Polyethylene glycol
PK	Pharmacokinetic(s)
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	Preferred Term
QoL	Quality of life
QW	Once weekly
RAVLT	Rey Auditory Verbal Learning Test
RBC(s)	Red blood cell(s)
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TOVA	Test of Variables of Attention
ULN	Upper Limit of Normal
VABS-II	Vineland Adaptive Behavior Scales II
WAIS-IV	Wechsler Adult Intelligence Scale IV
WHODrug	World Health Organization Drug Dictionary
WISC-V	Wechsler Intelligence Scale for Children V
WPPSI-IV	Wechsler Preschool and Primary Scale of Intelligence IV
ZBI-12	Short Form Zarit Burden Interview

1. PURPOSE

This document is the statistical analysis plan (SAP) that is used for analysis and reporting, including tables, listings, and figures, for Study 102A, a Phase 2 open-label study in subjects with Arginase 1 deficiency (ARG1-D) and hyperargininemia investigating the long-term safety, tolerability, and efficacy of intravenous (IV) or subcutaneous (SC) pegzilarginase administration. The analyses specified in this SAP will be used to support the clinical study report (CSR), publications, and regulatory submissions.

This SAP is based on Protocol Amendment 5.0, which was approved on 09 October 2020.

2. STUDY POPULATION

This study of pegzilarginase was planned in a population of at least 10 pediatric and adult subjects who completed Study CAEB1102-101A (hereafter referred to as "Study 101A") and who are eligible for continued treatment with pegzilarginase.

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of the study is:

- To evaluate the long-term safety and tolerability of IV or SC pegzilarginase administered for up to 4 years in subjects with ARG1-D and hyperargininemia

3.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate the long-term effects of pegzilarginase in subjects with ARG1-D and hyperargininemia on sustained reduction of arginine levels
- To evaluate the long-term effects of pegzilarginase on plasma guanidino compounds (GCs)
- To characterize repeat-dose pharmacokinetics (PK) of pegzilarginase administered IV or SC
- To evaluate the long-term effects of pegzilarginase on stabilization or improvement of neurological/neuromotor manifestations, using objective measures:
    - Six-Minute Walk Test (6MWT)
    - Berg Balance Scale (BBS)
    - Gross Motor Function Measure (GMFM)
    - Modified Ashworth Scale (MAS) Score

    - Purdue Pegboard Test
  - To evaluate the long-term effects of pegzilarginase on select manifestations of ARG1-D:
    - Frequency of seizures
    - Frequency of hyperammonemic episodes

3.2.1 Exploratory Objectives

The exploratory objectives of the study are:

- To compare the PK and pharmacodynamics (PD) of different routes (IV and SC) of pegzilarginase administration
- To examine the long-term changes in exploratory biomarkers including additional amino acids (ornithine, glutamine, leucine, isoleucine, and valine) and blood urea nitrogen (BUN) after administration of pegzilarginase
- To evaluate the long-term effects of pegzilarginase on stabilization or improvement of neurocognitive, developmental, and quality of life (QoL) measures, selected based on subject age
  - Intelligence:
    - Wechsler Adult Intelligence Scale IV (WAIS-IV)
    - Wechsler Intelligence Scale for Children V (WISC-V)
    - Wechsler Preschool and Primary Scale of Intelligence IV (WPPSI-IV)
  - Memory:
    - Rey Auditory Verbal Learning Test (RAVLT)
    - Atlantis Subtest on the Kaufman Assessment Battery for Children II (KABC-II)
  - Attention:
    - c) version 9
  - Adaptive Behavior:
    - Vineland Adaptive Behavior Scales II (VABS-II)
  - Development
    - Growth parameters (length/stature, weight, head circumference, height, and weight centiles)
  - QoL:
    - Patient-Reported Outcomes Measurement Information System (PROMIS) Parent Proxy Profile, PROMIS Pediatric Profile, PROMIS 29, or the PedsQL Measurement Model for the Pediatric Quality of Life (PedsQL) Inventory
    - Short Form Zarit Burden Interview (ZBI-12)

4. STUDY METHODS

This section of the SAP (Section 4) provides background for the reader and is intended to summarize methodology from the protocol. No new methodology or additional detail is introduced. Any discrepancies between the protocol language and the text in this section are inadvertent and should not be interpreted as a change to the protocol language. This section will not be updated for changes to the protocol based on subsequent protocol amendments.

4.1 Overview of Study Design

Study 102A is a long-term, open-label extension study of pegzilarginase for up to 4 years in approximately 10 pediatric and adult subjects with ARG1-D and hyperargininemia who participated in Study 101A.

Dosing in an individual subject will commence approximately 4 weeks (but no sooner than 3 weeks) after the last dose of study drug in Study 101A. The pegzilarginase dose level and frequency will initially match the dose and regimen the subject was receiving at the end of Study 101A but may be adjusted if clinically indicated in the opinion of the Investigator in consultation with the Sponsor. The first 24 doses in this study will be administered using the IV route weekly. The first 12 IV doses will be administered in the clinical research unit (CRU). After the initial 12 IV doses, subjects may be dosed outside of the CRU (ie, by home health care professionals) if considered safe and appropriate in the opinion of the Investigator in consultation with the Sponsor.

Safety, tolerability, immunogenicity, PK, PD, neuromotor, and neurocognitive assessments as evaluated in Study 101A will continue for the duration of this long-term extension study, although with different frequency.

A follow-up visit will be scheduled approximately 4 weeks after the completion of the final dose of pegzilarginase.

4.2 Number of Subjects

All qualified pediatric and adult subjects who participated in Study 101A will be allowed to participate in this study.

4.3 Dosing

The recommended dosing schedule is as follows:

- IV administration once weekly (QW) for Weeks 1 to 24
- SC administration QW for Weeks 25 to 48
- As clinically indicated thereafter for Years 2, 3, and 4

4.4 Discontinuation of Subjects from Treatment or Assessment

Subjects (or their legal guardians) have the right to withdraw from the study at any time for any reason. The Investigator may discontinue a subject from the study for any of the following reasons:

- Occurrence of an adverse event (AE), development of an intercurrent illness/condition, or change in subject's condition that leads the Investigator to be concerned about the subject's welfare
- Intolerable toxicity in the judgment of the Investigator
- Subject is uncooperative or noncompliant with study procedures/responsibilities
- Pregnancy in a female subject during the study
- Withdrawal of consent
- Subject is lost to follow up
- Death

The reason for a subject's withdrawal from the study will be recorded in the electronic case report form (eCRF). Subjects who withdraw from study participation for any reason may not re-enter the study at any time.

Subjects who are discontinued from the study will be asked to complete follow-up visit procedures.

4.5 Replacement of Subjects

Subjects who withdraw from the study prematurely will not be replaced.

4.5.1 Drug Safety Criteria

Dosing will be interrupted, or subsequent doses postponed as clinically indicated for any subject who:

- Experiences a serious adverse event (SAE) during dosing that the Investigator believes to be possibly related to pegzilarginase, including any moderate or severe hypersensitivity reaction or hyperammonemia requiring hospitalization.
- Has any clinically significant signs or symptoms that could be attributed to low arginine levels and are temporally related to objective measures of low plasma arginine

Events requiring interruption of study drug administration will be reviewed by the Sponsor (who may also consult the Data Safety Monitoring Board [DSMB]). Following this review, treatment may be continued at the discretion of the Investigator following consultation with the Sponsor.

5. STUDY ENDPOINTS

5.1.1 Primary Outcome Measures

Primary safety and tolerability outcome measures will include:

- AEs/SAEs
- Physical examinations
- Vital signs
- Electrocardiograms (ECGs)
- Clinical laboratory studies (serum chemistries, hematology, coagulation, urinalysis)
- Low plasma arginine levels associated with clinically significant symptoms
- Clinically significant hyperammonemia
- Immunogenicity safety measures (levels of anti-pegzilarginase and anti-polyethylene glycol [PEG] antibodies)

5.1.2 Secondary Outcome Measures

Secondary outcome measures will include:

- Changes in plasma arginine levels
- Changes in plasma guanidino compound levels
- PK parameters
- Neurological/neuromotor manifestations, using functional and spasticity measurements:
    - 6MWT
    - BBS
    - GMFM
    - MAS Score
    - Purdue Pegboard Test
- Other manifestations of ARG1-D:
    - Frequency of seizures
    - Frequency of hyperammonemic episodes, as measured from laboratory evaluations of ammonia levels and relevant AEs
    - Incidence of transaminase elevations, as measured from laboratory evaluations of liver function tests and relevant AEs

Note that collection of assessments is inconsistent from subject to subject because of protocol amendments.

5.1.3 Exploratory Outcome Measures

Exploratory outcome measures include:

- Comparison of the PK and PD of pegzilarginase between different routes of administration (IV and SC)
- Changes in exploratory biomarkers after long-term administration of pegzilarginase:
    - Additional amino acids (eg, ornithine, glutamine, leucine, isoleucine, and valine)
    - BUN
- The long-term effects of pegzilarginase on neurocognitive, developmental, and QoL, will be measured for the following categories:
    - Intelligence (WAIS-IV, WISC-V, WPPSI-IV)
    - Memory (RAVLT, Atlantis Subtest on the KABC-II)
    - Attention (TOVA version 9)
    - Adaptive Behavior (VABS-II)
    - Development (growth parameters of length/stature, weight, head circumference)
    - QoL (PROMIS or PedsQL, ZBI-12)

6. DATA CAPTURE AND PROCESSING

Data will be captured on the eCRF and maintained in a Medidata Rave clinical database. All data will undergo a rigorous review process including electronic and manual data checks. Periodic data quality reviews will also be conducted to minimize errors and omissions.

7. ANALYSIS AND REPORTING

7.1 Interim Analyses

Interim outputs may be generated for purposes of data review, publication at scientific meetings, or regulatory filings.

7.2 Final Analysis

Statistical tests may be performed as part of the descriptive analyses, as a measure of observed effects of pegzilarginase relative to observed variability. Such tests will be performed at 2-sided α=0.05 unless otherwise stated and will not be adjusted for multiplicity. The term “statistically significant” may be used to describe results where the

p-value is no greater than 0.05; this phrase will be considered to mean "nominally statistically significant" and will not imply a prespecified hypothesis test.

This study is an extension of Study 101A. Results from Study 101A for demographics and baseline characteristics are included in analyses from this study. Additionally, baseline information from Study 101A will be included in analyses of arginine, GCs, 6MWT, GMFM, BBS, MAS Score, and Purdue Pegboard.

Final data summaries, figures, and listings will be prepared as identified in this SAP after subjects complete the study and following database lock. Any changes to the analyses described in the SAP will be documented in the CSR.

8. SAMPLE SIZE DETERMINATION

The sample size of approximately 10 pediatric and adult subjects was determined using clinical, rather than statistical, considerations. This sample size may lack power to distinguish a statistically significant result.

9. DATA PREPARATION

9.1 Input Data

Study data will be collected by independent vendors and sent to eCS who will be managing the data for this study. E-Clinical Solutions will be responsible for providing coded values for medical history, AEs, and prior and concomitant procedures using MedDRA Version 24.0, or later. Prior and concomitant medications will be coded by using the WHODrug version Global B3 2021 03, or later.

Data transfer will be based on study deliverable timelines determined by all parties involved.

9.2 Output Data

Data from eDC will be transferred and incorporated into standard formats following the Study Data Tabulation Model (SDTM). Data will then be mapped to analysis datasets using the Analysis Data Model (ADaM). Both SDTM- and ADaM-formatted data will be used to create the tables, figures, and listings (TFLs).

SDTM will follow the SDTM version 1.4 model and will be implemented using the SDTM Implementation Guide version 3.2 and the SDTM Controlled Terminology version 2016-06-24. ADaM data will follow the ADaM version 2.1 model and will be implemented using the ADaM Implementation Guide version 1.3. Both SDTM and ADaM will be validated using Pinnacle 21 version 2.2. Any discrepancies in the validation will be noted in reviewer's guides accompanying the final data transfers.

Define.xml will be created for SDTM and ADaM using the Define-XML version 2.0 model.

Note: if during the course of this study there are any updates in versioning to the above criteria, the most recent version may be utilized.

10. ANALYSIS SETS

Data for all enrolled (consented) subjects will be listed regardless of whether they received study medication or not (eg, any subject enrolled [consented] but never treated will be included in data listings and listed under "never treated"), unless otherwise noted. Analysis sets for tabulations and figures are defined below for the following analysis sets: All Consented Subjects Set and the FAS.

10.1 All Consented Subjects Set

The All Consented Subjects set includes all subjects who signed informed consent.

10.2 Full Analysis Set (FAS)

The FAS includes all subjects who received any study medication. The FAS is used for evaluating subject characteristics, treatment administration, efficacy, and safety endpoints. This analysis set will include Study 101A baseline data and all Study 102A data for the subjects who have received at least 1 dose of pegzilarginase in the current study.

10.3 Pharmacodynamic Analysis Set (PDAS)

The PDAS includes all subjects in the FAS who were enrolled (consented) in the study and had any valid arginine concentration-time data. If all subjects in the FAS were also in the PDAS, separate analyses will not be performed for the PDAS.

11. GENERAL STATISTICAL CONSIDERATIONS

11.1 General Statistical Methodology

Subject data collected on the eCRF will be listed and summarized. Note that summaries will be produced for an assessment only if there are at least 4 subjects who have data for the given assessment at baseline and at least one post-baseline time point. All data (from both planned and unplanned visits) for all enrolled (consented) subjects will be listed.

For the descriptive statistics of data by visit, summaries will include data collected at planned, protocol-specified study visits only. Summaries of abnormal values will include data from all visits including early termination visits and unscheduled visits.

For continuous variables, number of non-missing observations (n), mean, standard deviation (SD), median, minimum (min) and maximum (max) will be presented. Where noted, change from baseline and/or percent change from baseline will be reported. The number of subjects (n), mean, SD, median, min, max, coefficient of variation (CV%), geometric mean, and geometric CV% will be presented for PK parameters, as appropriate. Analysis of PK parameters will be provided in a separate report.

Discrete variables will be summarized as the number (n) and percentage (%) of observations within each category by visit and timepoint. As needed, a category of "Not Reported" will be included in summaries of categorical variables to capture observations that are unavailable. The number of subjects with non-missing data will be used as the denominator for percentage calculations unless otherwise noted.

For safety data presented by age group, the age groups are:

- 2 to 11 years
- 12 to 17 years
- ≥18 years

Hypothesis testing may be performed as part of the descriptive analyses, as a measure of observed effects of pegzilarginase. These analyses will be performed using paired *t*-tests and may be conducted on observed data, change from baseline, and/or percent change from baseline, as relevant.

11.1.1 Definitions of Baseline

11.1.1.1 Vital Signs, ECGs, Laboratory Data, and Amino Acids

For vital signs, ECGs, and laboratory data, baseline is defined as the latest non-missing assessment attained prior to the date/time of first dose of study treatment in Study 102A.

11.1.1.2 Arginine, Ornithine, and GCs

For arginine, ornithine, and GCs, the Study 101A or 102A baseline is defined as the average of all non-missing assessments attained prior to the date/time of first dose of study treatment in the respective study, if there are multiple assessments. If there is only a single assessment attained prior to the date/time of first dose of study treatment for arginine, ornithine, and GCs, then those single assessments are defined as baseline.

11.1.1.3 Neuromotor, Neurocognitive, Developmental, and QoL Variables

Study 101A Baseline is defined as the assessment taken prior to the first dose of study treatment in Study 101A for all neuromotor, neurocognitive, developmental, and QoL variables. For Study 102A, baseline values will be taken from 1) the baseline visit that should occur approximately 4 weeks (but no sooner than 3 weeks) after the last dose of study medication on Study 101A or 2). From the 101A study follow-up assessment if the Study 101A follow-up assessments were collected within 4 weeks of the baseline visit of Study 102A. Per protocol, the 102A Screening visit could occur at any time between the last dose on Study 101A and the baseline visit on Study 102A. The Screening and baseline visits may occur on the same day as long as that day is at least 3 weeks after the last dose on Study 101A.

11.1.2 Changes from Baseline

Change from baseline for a given assessment will only be reported if the given assessment is collected at both baseline and post-baseline assessments.

11.1.3 Handling of Missing Data

All data will be analyzed as collected in the database. In general, missing data, unless noted otherwise will not be imputed.

11.1.4 Unscheduled Visits

Data collected outside of a scheduled visit will be summarized at the next scheduled visit. If multiple assessments or unscheduled visits occur near the same time point, the visit closest to the planned visit will be tabulated.

Missing Date Components of AEs, Concomitant Medications, and Medical History

Every attempt will be made to obtain complete dates for AEs, concomitant medications, and medical history; however, in the case of incomplete dates, the missing Day, Month, or Year will be represented in listings as "UN," "UNK," or "UNKN," respectively. Missing Hour or Minute in dates will be represented as "UN."

Partial/missing start and end dates for AEs and concomitant medications will be imputed as follows so that a complete date can be used to flag data as treatment emergent or concomitant with treatment:

Partial/missing start date:

- Dates with missing day only will be imputed as the 1st of the month unless the month and year are same as the month and year of first dose of study medication, in which case missing day will be imputed as the first dose day of study medication.

- Dates with both day and month missing will be imputed as 1 Jan unless the year is same as the year of first dose of study medication, in which case missing day and month will be imputed as the first dose day and month of study medication.

- Completely missing dates will be imputed as the first dose date of study medication unless the end date is on or before the first dose date of study medication, in which case missing date will be imputed as 1 Jan of the same year as the end date.

Partial/missing end date:

- Dates with missing day only will be imputed as the last day of the month unless the month and year are the same as the month and year of the last dose of study medication, in which case missing day will be imputed as the last dose day of study medication.

- Dates with both day and month missing will be imputed as 31 Dec unless the year is same as the year of the last dose of study medication, in which case missing day and month will be imputed as the last dose day and month of study medication.

- If the ongoing flag is missing or "Yes," then the date will not be imputed unless death date is available, in which case the missing date will be imputed as the death date. If ongoing is "No" then the missing end date will be imputed as the last dose date.

- If the imputed date is after the date of death, then the end date will be set equal to the date of death.

The original dates will be displayed in data listings and the imputed dates will be used in derivations only (study day, treatment-emergence status, etc.).

For the "time since", the following equation will be used:

- Time (months) = (Date of the first dose - date of initial symptom[s] +1)/ 30.42.

If the month and year of the initial symptom(s) are provided but the day is missing, the missing day is imputed as 01. If only the year is provided, then the missing month and day are imputed as Jan 1 for the calculation. If the year is missing, the subject will be excluded from the analysis. If the imputed initial symptom(s) date is after the first dose date, the time will be imputed as 1 day. The same imputation method as described above will be applied to dates used to calculate "age at" values.

AEs with Missing Severity and/or Relationship

Every attempt will be made to obtain complete information for AEs regarding severity and relationship(s); however, in the case of missing data, the AE severity and/or relationship will be classified as "Severe" and/or "Related", respectively.

AEs leading to Dose Interruption

For the CSR summaries of AEs leading to dose interruption, the following action taken categories from the eCRF are mapped to "Dose Interrupted" per SDTM terminology: "dose held", "dose interrupted", and "missed dose".

Laboratory Values with < or > Inequality Symbols

Some continuous laboratory data include "<" or ">" symbols. Data will be presented in listings with their inequality symbol; however, for tabulation of summary statistics of safety laboratory results, the number associated with the inequality sign will be used for statistical calculations.

11.1.5 Derived and Computed Variables

The following derived and computed variables have been identified as important for pre-specified and exploratory analyses. Additional computed variables may be required to aid in analysis. The SAP will not be amended to describe additional computed variables. Computed variables added after approval of the SAP will be described in the CSR.

Modified Ashworth Scale (MAS) Score

Muscle group scores of 1+ will be converted to 1.5 for computational purposes. Data points collected while subjects who were taking a concomitant medication for spasticity (eg, botox) will be excluded.

To examine lower body spasticity, the sum of the MAS scores for the lower body muscle groups (right hamstrings, left hamstrings, left quadriceps, right quadriceps) will be calculated. A sum score per muscle group will be calculated as the sum of MAS score for lower body muscle groups divided by the number of impacted lower body muscle groups at baseline. These scores and changes from Baseline will be presented by visit for both Study 101A and 102A Baseline values.

Improvement in spasticity corresponds to a reduction in the MAS score per muscle group from Baseline based on the 4 lower body muscle groups at the respective week. Worsening in spasticity corresponds to an increase in the MAS score per muscle group from Baseline scores based on the 4 lower body muscle groups at the respective week. Analyses will be conducted for both Study 101A and 102A Baseline values.

Study Days Relative to First Administration of Study Medication

Study Day 1 is the day of the first administration of study medication (in Study 102A); negative Study Days occur prior to first administration of study medication, and positive Study Days are those after the first administration of study medication – eg, Study Day 1 is the day of the first administration of study medication (in Study 102A), Study Day 2 is

the day immediately following the first administration of study medication. Study day will be presented in the data listings.

Extent of Exposure

The following formulas will be used to calculate the duration of exposure (weeks) of time on treatment in Study 102A on IV, SC, and IV combined with SC :

Duration of Exposure $_{(IV)}$ = [Minimum (Last IV Dose Date, Death Date) – First IV Dose Date (102A) + 1] +7 / 7.

Duration of Exposure $_{(SC)}$ = [Minimum (Last SC Dose Date, Death Date) – First SC Dose Date (102A) + 1] +7 / 7.

Duration of Exposure $_{(IV + SC)}$ = [Minimum (Last Dose Date, Death Date) – First Dose Date (102A) + 1] +7 / 7.

12. SUBJECT CHARACTERISTICS AND DEMOGRAPHICS

12.1 Enrollment and Disposition of Subjects

The number of subjects will be presented for the following in the All Consented Subjects Set:

- Number of subjects in the All Consented Subjects Set
- Number of subjects in the FAS
- Number of subjects in the PDAS

Summary statistics including numbers and percentages will be presented for the following in the FAS:

- Number of subjects who completed the study
- Subjects who discontinued the study along with the reasons for discontinuation as follows:
    - Occurrence of an AE, development of an intercurrent illness/condition, or change in subject's condition that leads the Investigator to be concerned about the subject's welfare
    - Intolerable toxicity in the judgment of the Investigator
    - Subject is uncooperative or non-compliant with study procedures/responsibilities
    - Pregnancy in a female subject during the study
    - Withdrawal of consent
    - Subject is lost to follow up
    - Death
    - Other

Subjects are considered to have completed the study if the answer to "Did the subject complete the study as per protocol?" on the Subject Disposition CRF page is "Yes."

A subject disposition flowchart, with information similar to that contained in a CONSORT diagram, will be created for this study.

12.2 Protocol Deviations

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of study data or that may significantly affect a subject's rights, safety, or well-being. All deviations related to COVID-19 are considered as important deviations. A summary of all important protocol deviations overall and by category will be presented; additionally, the COVID-19 related deviations will also be presented separately overall and by category.

Specific categories may include:

- Informed Consent
- Key Inclusion and Exclusion Criteria
- Use of Prohibited Medications
- IRB Reporting Criteria
- Investigational Product Compliance
- SAE Safety Reporting Criteria
- Study Procedures Criteria
- Visit Schedule Criteria

All protocol deviations will be listed for subjects in the FAS for whom deviations were reported.

12.3 Demographics and Baseline Characteristics

Demographics – age, age group (2 to 11 years, 12 to 17 years, or ≥18 years), sex, child-bearing potential (female subjects only [listing only]), race, and ethnicity – and baseline subject characteristics – height (cm), height centiles, height z-scores, weight (kg), weight centiles, and weight z-scores- will be tabulated using all subjects in the FAS. Note that subjects who select more than 1 race will be grouped into the category "Multiple Races" for purposes of summarization.

The following baseline characteristics were collected in Study 101A and will be summarized as continuous or categorical variables, where appropriate:

- Subject disease characteristics include:
  - Age at initial symptom(s) (years)
  - Age at Diagnosis (years)

- Age at Genetic Diagnosis (years)
- Age at Last IQ Test (years)
- Presence or absence of ARG1-D-related mutation
- Percent arginase activity in red blood cells (RBCs)
- Whether or not the subject suffers from seizures
- Number of seizure episodes in the last month and last year
- Whether or not the subject has documented developmental delay
  - Development appropriate age
- IQ test result
- Level (and location – upper and lower limbs) of spasticity
- Whether or not the subject is ambulatory
- Whether or not the subject has any documented liver function abnormalities (and what those abnormalities are)
- Whether or not the subject has consistent episodes of nausea and/or vomiting
- The number of hyperammonemic episodes last month and last year
- Family and sibling history of ARG1-D
- Subject hospitalized in the last 2 years
- Other Disease Manifestations
- GMFCS Level
- Region (US, Outside US)

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA®) Version 24.0. Medical history will be listed for all enrolled (consented) subjects (system organ class [SOC], preferred term [PT], and verbatim term) and summarized by SOC and PT in the FAS.

12.4 Prior/Concomitant Medications and Procedures

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) version Global B3 2021 03. Prior medications include medications that were taken prior to the first dose of any study treatment in the current study. Concomitant medications during the treatment period include medications that started at any time and were taken at any time after the start of study treatment in the current study until 30 days after the end of study treatment. Prior procedures include procedures done prior to the first dose of any study treatment in Study 102A.

The number and percentage of subjects taking concomitant medications during the treatment period will be summarized by Anatomical Therapeutic Chemical (ATC) classification and PT for the FAS. Although a subject may have taken the same medication multiple times, the subject is counted only once within an ATC classification. Any individual subject may contribute to two or more prior or concomitant medication

PTs in the same classification. A similar summary of subjects taking prior medications will be presented.

A listing of all prior and concomitant medications will be provided. In this data listing, medications will be flagged as either prior, concomitant or both prior and concomitant.

Concomitant procedures include any procedures done after the first dose of any study treatment in Study 102A until 30 days after the end of study treatment.

A listing of prior and concomitant procedures will be provided.

Historical data for hospitalizations in the prior 2 years as collected on the hospitalization log will be listed.

12.5 Drug Exposure

Study drug administration data will be summarized by dose for the FAS using the formula defined in Section 11.1.5. All study drug administration data will be listed. In addition, a listing for infusion interruptions will be produced.

12.6 Efficacy

12.6.1 Arginine

Arginine concentration data will be summarized with descriptive statistics (n, mean, SD, median, min, max). Descriptive statistics will be used to summarize these data based on the actual value and the change from (Study 101A and 102A) baseline value at each timepoint of assessment by dose, day, and nominal timepoint. The proportions of subjects whose arginine value is below the target guidance level of 200 µM will be included in this summary, as will the proportions of subjects whose arginine value is within normal range (defined as 40 to 115 µM). In addition, the average of the last 4 non-missing arginine values will be calculated for each 12-week interval in the study, eg, the arginine values from Weeks 9, 10, 11, and 12 will be averaged and denoted as the Week 12 arginine result. A boxplot figure will also be produced that displays the 168-hour post-dose plasma arginine levels at each timepoint of assessment.

If a particular assessment of an arginine concentration is below the limit of quantitation, the result will be included in summaries by imputing half the value of the quantitation limit.

12.6.2 Clinical Outcomes Assessments

Details of the clinical outcomes assessments are described in the protocol in Sections 11.4 (Neurological/Neuromotor Function Testing) and 11.5 (Neurocognitive, Developmental, and Quality of Life (QoL) Assessments).

The clinical outcomes assessments (COAs), changes from baseline, and percent changes from baseline will be summarized with descriptive statistics at each timepoint of assessment for the following measures (Note: as defined in Section 11.1, only assessments with 4 or more subjects with an assessment at baseline and post-baseline values will be summarized):

- Neurocognitive, developmental, and QoL measures, selected based on subject age and cognitive ability:
  - Neurological manifestations, utilizing functional and spasticity measures:
    - 6MWT (observed distance in meters, change from [Study101A and 102A] baseline, and percent change from [Study 101 and 102A] baseline over time)
    - BBS (for 14 tasks and total score over time and change from [Study 101A and 102A] baseline)
    - GMFM (by GMFCS [I vs II/III] and overall, over time for each dimension and change from [Study 101 and 102A] baseline)
    - MAS Score (over time and change from [Study 101A] baseline for lower body muscle groups)
    - Purdue Pegboard (over time and change from [Study 101 and102A] baseline) Z scores
  - Intelligence:
    - WAIS-IV (over time and change from [Study 102A] baseline for each score and total score)
    - WISC-V (over time and change from [Study 102A] baseline for each score and total score)
    - WPPSI-IV (over time for each subtest and total score and change from [Study 102A] baseline)
    - Full Scale IQ (FSIQ) scores for all Wechsler Instruments (over time and change from [Study 102A] baseline)
  - Memory:
    - RAVLT (over time for each trial and overall score and change from [Study 102A] baseline)
    - Atlantis subtest on the KABC-II (over time for each trial and overall score and change from [Study 102A] baseline)
  - Attention:
    - TOVA (version 9) (for each measure [speed, accuracy, and consistency] and overall score and change from [Study 102A] baseline)

- Adaptive Behavior:
  - Adaptive Behavior Assessment System (ABAS) (over time for each item and change from [Study 102A] baseline [raw and scaled score, sums, and standard score])
  - VABS-II (over time for each parameter and change from [Study 102A] baseline)
- Development
  - Growth parameters (length/stature, weight, head circumference, height and weight centiles, calculated z-scores) (by age group and overall, over time, and change from [Study 101A and 102A] baseline)
- Quality of Life:
  - PROMIS Parent Proxy Profile, PROMIS Pediatric Profile, PROMIS 29 or the PedsQL Measurement Model for the Pediatric Quality of Life Inventory (over time and change from [Study 102A] baseline for each domain and pain intensity score [pediatric/adult/proxy])
  - ZBI-12 (over time for each question and change from [Study 102A] baseline)
- Frequency of seizures
- Occurrence and frequency of hyperammonemic episodes

Separate listings of the above measures will be provided. In addition to these separate listings, a by-subject listing will be appended to the tables for 6MWT, GMFM-D, GMFM-E, BBS, MAS, and Purdue Pegboard.

Figures will be produced for the 6MWT, GMFM-D, GMFM-E, BBS Total, and Purdue Pegboard. Note that baseline from both Study 101A and Study 102A will be included in the figures.

12.6.3 Analyses Using Minimal Clinically Important Differences (MCIDs)

Additional exploratory analyses using minimal clinically important differences (MCIDs) will be conducted. While there are no established MCIDs in ARG1-D patients, the MCIDs elected for use have been defined in other disease states with similar manifestations to ARG1-D patients.

Analyses will be conducted using the following MCIDs:

1. 6MWT – ≥9% change from (Study 101A and 102A) baseline (Schrover 2017)

2. GMFM-D – ≥2.4, ≥3.3, and ≥1.5 improvement from (Study 101A and 102A) baseline for Gross Motor Function Category Levels I, II, and III, respectively (Oeffinger 2008)
3. GMFM-E – ≥4.0, ≥2.8, and ≥1.8 improvement from (Study 101A and 102A) baseline for Gross Motor Function Category Levels I, II, and III, respectively (Oeffinger 2008)

Results of these analyses will be summarized and listed using the calculated MCID values. Additionally, the percentage of subjects who are considered "clinical responders" will also be included in this summary. Clinical Response will be defined in 2 ways, both of which will be included in the summary: 1) a subject who improved by at least 1 MCID on either the 6MWT, GMFM-D, or GMFM-E and 2) a subject who improved by at least 1 MCID on either the 6MWT, GMFM-D, or GMFM-E, but did not have clinically meaningful worsening on either of the other 2.

Results of these analyses will be summarized and listed using the calculated MCID values. The percentage of subjects who are considered "clinical responders" will also be included in this summary.

12.6.4 Patient Profiles

To help describe subject journey through the 101A and 102A studies, by-subject figures will be produced showing the subject's arginine values and dosing information, GC values, and the efficacy assessments of the 6MWT, GMFM-E, GMFM-D, MAS Lower Body, Berg Balance, and Purdue Pegboard tests.

12.7 Pharmacodynamic Analyses

The full amino amino acid profile and GCs concentration data will be summarized with descriptive statistics (n, mean, SD, median, min, max). Descriptive statistics will be used to summarize these data based on the actual value and the change from (Study 101A and 102A) baseline value at each timepoint of assessment by dose, day, and nominal timepoint. For GCs, the average of the last 4 non-missing GC values will be calculated for each 12-week interval in the study, eg, the GC values from Weeks 9, 10, 11, and 12 will be averaged and denoted as the Week 12 GC result. Figures will be produced for mean guanidino compound levels versus arginine and for ornithine.

Amino acids levels and levels of GCs will be listed. Values outside the normal range will be flagged.

If an assessment of a PD concentration is below the limit of quantitation, the result will be included in summaries by imputing half the value of the quantitation limit.

12.8 Safety

12.8.1 Study Drug Administration and Exposure

Study drug administration details and treatment exposure data will be listed.

12.8.1.1 Study Drug Administration

Study drug administration details will be summarized by route of administration [intravenous (IV), subcutaneous (SC), and IV combined with SC]. Also included in the summary are IV dose interruptions, action taken for IV interruption, and the reason why the IV dose was not fully administered.

12.8.1.2 Duration of Treatment Exposure

The duration of exposure in weeks will be tabulated with descriptive statistics by route of administration (IV, SC, and IV combined with SC).

Duration of exposure will also be summarized by the following categories:

- ≤4 weeks
- >4 to ≤24 weeks
- >24 weeks to ≤48 weeks
- >48 weeks to ≤96 weeks
- >96 weeks to ≤144 weeks
- >144 weeks

The mean dose of pegzilarginase for each subject will be tabulated with descriptive statistics by route of administration (IV, SC, and IV combined with SC).

12.8.2 Adverse Events

All subjects will be assessed regularly for the potential occurrence of treatment-emergent AEs (TEAEs) from the first dose of study drug in this study continuing through the last study follow-up visit. TEAEs will be defined as those events which are newly occurring or worsening from baseline (ie, on or after the first dose of study drug in Study 102A). The reporting period for nonserious and serious AEs is the period from the first dose of study drug in Study 102A continuing through the last study follow-up visit. If an AE occurs for a continuous time period from pre-study to on-study and becomes more severe after the start of dosing, it will be considered treatment-emergent. Events that are related to study drug will also be considered treatment emergent.

All TEAEs will be coded using MedDRA Version 24.0 terminology. The incidence of Aes will be summarized and tabulated by MedDRA SOC and PT.

The Investigator will determine the severity of each AE and will record it on the source documents and AE eCRF, using the categories defined below:

- Mild: No limitation of usual activities
- Moderate: Some limitation of usual activities
- Severe: Inability to carry out usual activities

Any AE that is classified as definitely related, probably related or possibly related to study drug will be considered related. In the case of multiple occurrences of the same AE reported by the same subject, each subject will be counted only once for each PT. In tables where the severity or relationship of the event to study drug is tabulated, the AE with the greatest severity or strongest relationship to the study drug will be the event counted. An AE with a missing severity and/or relationship to the medication will be classified as "Severe" and/or "Related," respectively, for the purpose of analysis and summarization.

Any subject from Study 102A who has received 1 or more doses of study medication in Study 102A is included in the analysis.

A summary overview of the incidence of TEAEs will be provided, including the number of events and the numbers and percentages of subjects with any TEAE, by severity of the TEAE, with any study drug-related TEAE, with any TEAE requiring dose reduction, with any TEAE leading to discontinuation of study drug, with any SAE, with any study drug-related SAE, and any TEAE with a fatal outcome.

TEAEs will be summarized with subject incidence in descending frequency as follows:

- Summary of All TEAEs by System Organ Class (SOC) and Preferred Term (PT) Including Counts of Events and Frequency of Occurrence
- TEAEs by System Organ Class (SOC) and Preferred Term (PT)
- TEAEs by System Organ Class (SOC) and Preferred Term (PT) by Age Group
- TEAEs Occurring in ≥15% Subjects by PT
- TEAEs by SOC, PT, and Maximum Severity
- Drug-Related TEAEs by SOC, PT, and Maximum Severity
- Drug-Related TEAEs Occurring in ≥15% Subjects by PT
- TEAEs Occurring in ≥15% Subjects by Route of Administration, Dose, Age Group, Sex, and Region and PT
- Summary of All Treatment-Emergent SAEs by SOC and PT Including Counts of Events and Frequency of Occurrence
- Treatment-Emergent SAEs by SOC and PT
- Treatment-Emergent SAEs by SOC, PT, and Maximum Severity
- Treatment-Emergent SAEs by Age Group and PT
- Treatment-Emergent Drug-Related SAEs by SOC and PT

- TEAEs Leading to Discontinuation of Study Drug by SOC and PT
- TEAEs Leading to Dose Interruption of Study Drug by SOC and PT
- SAEs Leading to Death by SOC and PT

Summaries will be provided for the FAS. A listing will be presented for all AEs with details including, but not limited to, dates of onset, severity, drug relationship, action taken, outcome, and route of administration of pegzilarginase at the time of AE onset.

12.8.3 Other Significant Adverse Events

Three separate summaries of "Other Significant AEs" will be presented by PTs described in the following sections below that include the following information: total number of events reported, seriousness, relationship, severity, and subject numbers and counts of events per subject for each included PT.

12.8.3.1 Hypersensitivity Events

Although hypersensitivity was not listed as an AESI in Study 101A and Study 102A, it is being included as an "Other Significant AE". Hypersensitivity is a known AE associated with biological therapy and monitoring of the frequency/severity of these episodes was conducted.

Hypersensitivity AEs will be defined using the narrow MedDRA Standardized MedDRA Query (SMQ) for "Hypersensitivity Reactions".

The number of subjects reporting at least 1 hypersensitivity AE along with the incidence of hypersensitivity AEs will be summarized by SOC and PT. A by-subject listing of hypersensitivity AEs will be presented.

12.8.3.2 Injection Site Reaction Events

Injection site reactions are common effects of biologic treatments given via an injection. They include various reactions at the site of the injection. The adverse events of injection site reaction will be defined using the MedDRA Higher Level Term (HLT) "Injection Site Reactions".

The number of subjects reporting at least 1 adverse event of injection site reaction along with the incidence of AEs of injection site reaction will be summarized by SOC and PT. A by-subject listing of AEs of injection site reactions will be presented.

12.8.3.3 Hyperammonemia Events

Significant, symptomatic hyperammonemia, often called a hyperammonemic episode or crisis, will be defined as an AE in a subject with a confirmed ammonia level ≥100 μM and one or more symptoms related to hyperammonemia requiring hospitalization or emergency room management. A summary of hyperammonemic episodes will be provided as part of the clinical outcomes assessments.

Although hyperammonemia was not listed as an AESI in Study 101A and Study 102A, it is being included as an "Other Significant AE" because of the potential impact of hyperammonemic episodes on subject safety and the validity of clinical assessments. Monitoring of contributing factors and the frequency/severity of these episodes was conducted.

Hyperammonemia TEAEs will be summarized using the Aeglea-defined Query MedDRA PTs of:

- Hyperammonaemia;
- Hyperammonaemic crisis;
- Hyperammonaemic encephalopathy; and
- Ammonia increased.

The number of subjects reporting at least 1 event of hyperammonemia along with the incidence of AEs of hyperammonemia will be summarized by SOC and PT. A by-subject listing of AEs related to hyperammonemia will be presented.

12.8.3.4 Liver Function Test AEs

Liver function test AEs are known disease manifestations of ARG1-D. Although not listed as an AESI in Study 101A and Study 102A, these AEs are being included as "Other Significant AEs" because of the potential impact of on subject safety. Frequent monitoring of ALT and AST values was conducted.

The liver function test AEs will be defined using the MedDRA Higher Level Term (HLT) "Liver function analyses". The preferred terms "Ammonia increased" and "Hyperammonaemia" will not be included in these summaries as both terms are already included in the analysis of Hyperammonemia AEs.

The number of subjects reporting at least 1 Liver Function Test AE along with the incidence of these AEs will be summarized by SOC and PT. A by-subject listing of these AEs will be presented.

12.8.4 Laboratory Results

Laboratory tests will include hematology, chemistry, urinalysis, coagulation, plasma ammonia, and pregnancy test results. These data will be listed with values outside the normal range flagged.

For quantitative chemistry (including plasma ammonia), hematology, coagulation, and urinalysis parameters, descriptive statistics will be used to summarize laboratory measurements based on the actual value and the change from (Study 102A) baseline value at each timepoint of assessment. In addition, the max, min, and last observed value

during the treatment period will be presented. A listing of serum tryptase and complement C3 will be produced for subjects who experienced a hypersensitivity reaction.

12.8.4.1 Liver Function Test Abnormalities

The incidence of the following liver function abnormality categories will be summarized for the liver function parameters of alanine aminotransferase (ALT), aspartate aminotransferase (AST), Alkaline Phosphatase (ALP), and Total Bilirubin:

For ALT, AST and either ALT or AST
• > 3 × ULN
• > 5 × ULN
• > 10 × ULN
• > 20 × ULN
Alkaline phosphatase,
• >1.5 × ULN
• >2 × ULN
Total bilirubin
• >1.5 × ULN
• >2 × ULN
ALT or AST >3 × ULN and total bilirubin >1.5 × ULN*
ALT or AST >3 × ULN and total bilirubin >2 × ULN*
• ALT or AST >3 × ULN, total bilirubin >2 × ULN and no ALP > 2 × ULN*
• ALT or AST >3 × ULN, total bilirubin >2 × ULN and ALP < 2 × ULN*

*ALT, AST, bilirubin, and alkaline phosphatase values are grouped within 3 days of each other.

A listing of subjects who meet these LFT abnormality categories will be presented.

Shift tables will be presented to summarize the incidence rates of the liver function abnormality categories from (Study 102A) baseline.

For the assessment of liver function test abnormalities, all scheduled and unscheduled visits will be considered.

Figures of liver function test parameters by time of assessment point will be produced including pegzilarginase dosing information. Additionally, plots of maximum ALT vs maximum total bilirubin and maximum AST vs maximum total bilirubin will be produced for all subjects.

12.8.4.2 Ammonia Increases

The methods for measuring plasma ammonia levels vary among individual local laboratories and values obtained using different assay methods may not be interchangeable because the normal ranges and therapeutic target levels are dependent on the assay method used by the individual local laboratory. Therefore, normalized ammonia (µM) will be calculated using the formula:

Normalized ammonia (µM) = ammonia in µM x (35/ULN of the specified laboratory reference range for each assay)

Summaries of the event count and frequency of increases in normalized ammonia levels will be produced for subjects with ammonia values of ULN to ≤100 µM, >100 µM to <250 µM, ≥250 µM to <500 µM, and ≥500 µM. Additionally, a box plot of normalized ammonia values at each timepoint of assessment will be presented.

12.8.5 Vital Signs and Weight

Vital signs including temperature (ºC), pulse rate (beats/min), respiratory rate (breaths/min), systolic blood pressure (mmHg), and diastolic blood pressure (mmHg) will be listed and summarized across time. The summaries will include changes from Study 102A baseline.

The primary means of assessing vital sign and weight changes is through assessing AEs related to vital signs and weight. Summaries of vital signs will also be created by visit, showing the maximum deviation (increase and decrease) from the pre-infusion vital sign assessment for that visit.

Descriptive statistics will be used to summarize weight based on the actual value and the change from (Study 102A) baseline value at each timepoint of assessment.

12.8.6 Electrocardiograms

The primary means of assessing ECG results is through assessing AEs related to ECGs.

ECG parameters [heart rate, PR, QRS, QT, QTc (Bazett and Fridericia)] will be summarized using descriptive statistics (e.g. N, mean, SD, median and range) and will be presented for Baseline (Study 102A) and actual values and change from Baseline values by visit. The number and percentage of subjects with QTc prolongation at any post-baseline visit will also be summarized:

- QTc>450
- QTc>480
- QTc>500

The number and percentage of subjects with a change from Baseline in QTc of ≥30msec and ≥60msec will also be summarized.

A listing of ECG results as well as a listing including descriptions of ECG abnormalities will be produced. Investigator assessment of clinical significance will also be provided in the listing.

12.8.7 Physical Examination

The primary means of assessing physical examination results is through assessing Aes related to the physical examination.

No summaries of physical examination are planned, but a listing of abnormal changes in physical examination will be produced.

12.9 Other Assessments

12.9.1 Diet Record

Descriptive statistics will be reported on a subject's 3-day diet record as captured on the CRF. Change from Baseline and percent change from Baseline for the following 6 parameters will be summarized by visit:

- Total prescribed natural protein/day (grams)
- Total consumed natural protein/day (grams)
- Total prescribed EAA (protein)/day (grams)
- Total consumed EAA (protein)/day (grams)
- Total prescribed protein/ day (EAA plus natural) (grams)
- Total consumed protein/ day (EAA plus natural) (grams)

A consistent diet is defined as one in which the prescribed and consumed natural protein, medical food EAA, and calories are within ±15% from Baseline. The number and percentages with an increase or decrease of more than 15% from Baseline for each parameter will be summarized by visit. Summaries will be produced for both the 101A and 102A Baseline values. A listing of subjects with increases or decreases more than 15% of respective Baseline value will be presented.

The dietary record will be listed in conjunction with body weights. Exploratory analyses of protein consumption versus arginine levels may be performed.

12.9.2 Summary of COVID-19 Information During the Study

The number and percentage of subjects who tested positive for COVID-19 during the study will be summarized. The date and result of testing will be listed.

The number and percentage of subjects who received a COVID-19 vaccination during the study will also be summarized. Vaccination details (number of doses, vaccine manufacturer, side effects reported) will be presented in a data listing.

12.10 Pharmacokinetic, Pharmacodynamic and Immunogenicity Analyses

PK and PD analyses as well as the immunogenicity assessment for this study will be executed by independent vendors. The analysis plan(s) will be described in separate documents. A summary of the results will be presented in the main study CSR while additional details will be available in separate reports.

A listing of sampling times and antibody results will be presented.

12.11 Additional Exploratory Analyses

Additional exploratory analyses may be performed as deemed appropriate; such analyses are considered hypothesis-generating rather than confirmatory and are not considered violations of the SAP.

13. APPENDICES

13.1 Schedule of Assessments for Weeks 1 – 12 (IV) (Protocol Table 1)

			Weekly (QW) IV Dosing											
	Scr	**BL[a]**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**Wk 9**	**Wk 10**	**Wk 11**	**Wk 12**
Informed consent	X													
Inclusion/exclusion	X													
Medical history		X												
Height, weight[b]		X				X				X				X
Physical examination		X												X
ECG		X												X
Clinical laboratory tests[c]		X	X							X				
Complement C3 and tryptase[c]		X												
Pregnancy test[d]		X	X			X				X				X
3-day diet record[e]			X			X				X				X
Pegzilarginase dosing[f]			X	X	X	X	X	X	X	X	X	X	X	X
Arginine/ornithine[g]			X	X	X	X	X	X	X	X	X	X	X	X
Guanidino compounds[g]			X	X	X	X	X	X	X	X	X	X	X	X
PK profile[h]			X							X				
ALT/AST profiles, ammonia[i]		X	X			X				X				X
ADA[j]			X			X				X				X
Other amino acids (glu, val, leu, ile)			X											X
Neurological/neuromotor, adaptive behavior, and QoL assessments[k]		X												X
Neurocognitive and developmental assessments[l]		X												
Clinical growth assessments[m]		X												
Clinic/CRU visit[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[o]		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X
Seizure frequency		X	X	X	X	X	X	X	X	X	X	X	X	X

ADA = anti-drug antibodies (anti-pegzilarginase antibodies); ALT = alanine aminotransferase; AST = aspartate aminotransferase; BL = baseline; CRU = clinical research unit; ECG = electrocardiogram; EOI = end of infusion; glu = glutamine; ile = isoleucine; IV= intravenous; leu = leucine; PEG = polyethylene glycol; PK = pharmacokinetic; Scr = screening; QOL = quality of life; QW = once weekly; val = valine; Wk = week.
NOTE: Efforts should be made to collect all blood samples where clinically practical. Samples collected after the end of infusion (IV dosing) should be collected within approximately 30 minutes. Deviations from blood sampling time points are allowable to accommodate patient or site scheduling. If a sample is unable to be collected, this should be noted in the patient's records but will not constitute a protocol deviation. The actual date and time of collection of all samples obtained must be recorded on the specimen sent to the laboratory and in the patient's source document and in the case report forms (CRFs).

NOTE: The protocol allows flexibility in dosing regimen after the first 12 weeks. The protocol allows that patients may stay on a regimen for more or less than 12 weeks and may switch between regimens as clinically indicated. The procedures and evaluations conducted at any visit will coincide with the above table based on the regimen the patient is assigned to at the time of the visit (with the exception of dosing at the site after the first twelve weeks and after the fourth SC dose).

Gray shading = predose, EOI, and postdose at 4 hours, 8 hours, 24 hours, 48 hours, 120 hours, and 168 hours (also occurs 8 weeks after any dose [mg/kg], regimen, or route-of-administration change).
Diagonal shading = predose and 4 hours postdose.

[a] The Baseline visit should occur approximately 4 weeks (but no sooner than 3 weeks) after the last dose of study medication on the 101A study. The 101A study follow-up assessments may substitute for Study CAEB1102-102A Baseline assessments if the 101A follow up assessments were collected within 4 weeks of the Baseline visit of the 102A study. The Screening visit can occur at any time between the last dose on the 101A study and the Baseline visit on this study. The Screening and Baseline visits may occur on the same day as long as that day is at least 3 weeks after the last dose on the 101A study.

[b] Height will be collected at baseline for all patients and every 12 weeks thereafter for pediatric patients only. Weight will be obtained during the baseline period and approximately every 4 weeks during dosing. The baseline weight can be used to calculate each total dose, unless a subsequent weight obtained indicates a >10% change from the baseline weight.

[c] Clinical safety laboratory tests should be repeated at Week 1 if Week 1 is performed greater than 14 days from the baseline visit. Serum tryptase and serum complement C3 will also be obtained in the event of a hypersensitivity reaction. Samples should be obtained no later than 3 hours after the start of the reaction and at 24 hours after the start of the reaction.

[d] Pregnancy test can either be a serum or a urine test.

[e] Patients will complete a 3-day diet record using a diary to collect the information prior to dosing visit every 4 weeks beginning prior to the first dose at Week 1.

[f] See Protocol Section 9.6.1 for details regarding dosing, including frequency and route.

[g] Samples for arginine, ornithine, and guanidino compounds will be collected prior to dosing for every dose during the first 24 weeks or as clinically indicated. A predose sample must also be obtained before any dose or route-of-administration change and prior to the 3 subsequent doses at the new dose level. In addition, at Week 1, Week 8, Week 24, and 8 weeks after any dose change, sampling times will be predose, within 30 minutes after infusion (IV only), and postdose at approximately 4, 8, 24, 48, 120, and 168 hours. An approximate 2-hour fast should be observed prior to all sampling for amino acids and within 1 hour prior to dose, except where operationally and/or clinically not possible.

[h] PK samples for pegzilarginase will be collected at Week 1, Week 8, Week 24, and 8 weeks after any dose change. Sampling times will be predose, within 30 minutes after infusion (IV only), and postdose at approximately 4, 8, 24, 48, 120, and 168 hours. A predose sample will also be obtained before any dose or route-of-administration change and prior to the 3 subsequent doses at the new dose level.

[i] Samples for ALT/AST and ammonia will be collected at baseline, pre-dose and 4 hours post-dose every 4th dose for the first 24 weeks. In addition, at Week 1, Week 8, Week 24, and 8 weeks after any dose change, sampling times will be predose, within 30 minutes after infusion (IV only), and postdose at approximately 4, 8, 24, 48, 120, and 168 hours.

[j] Anti-drug antibodies (ADA) will be collected prior to dosing (within 1 hour of dose) at Week 1 then at every 4 weeks for the first 12 weeks, then every 8 weeks. ADA testing will include assessment of antibodies against pegzilarginase and against polyethylene glycol (PEG). An unscheduled sample for ADA assessment will be obtained in the event of a moderate or severe hypersensitivity reaction. Patients who test positive for ADA will be followed and re-tested approximately every 2 to 3 months after the end of the study until ADA levels return to baseline.

[k] Neurological/neuromotor, adaptive behavior, and QOL assessments will be collected at baseline, 12 weeks, and 24 weeks: 6-Minute Walk Test, Modified Ashworth Scale, Gross Motor Function Measure, Berg Balance Scale, Purdue Pegboard Test; Vineland Adaptive Behavior Scales II; PROMIS (for patients that began the 101A study utilizing a PROMIS test) or PedsQL Measurement Model for the Pediatric Quality of Life Inventory (for patients that did not begin the 101A study utilizing a PROMIS tool); 36 Item Short Form Health Survey (SF 36); Short Form Zarit Burden Interview (ZBI-12). On days when a timed walk test is scheduled, it should be performed before any other neurological/neuromotor, developmental, or neurocognitive tests scheduled for that day. These assessments may be delayed up to 2 weeks to accommodate scheduling.

[l] Neurocognitive and developmental, assessments will be collected at baseline and 24 weeks using age appropriate assessments: Wechsler Adult Intelligence Scale IV; Wechsler Intelligence Scale for Children V; Wechsler Preschool and Primary Scale of Intelligence IV; Bayley Scales of Infant Development III; Rey Auditory Verbal Learning Test; Atlantis subtest on the Kaufman Assessment Battery for Children II; Test of Variables of Attention version 9. These assessments may be delayed up to 2 weeks to accommodate scheduling.

[m] Growth assessments will be performed for pediatric patients (ages 2 to 18): age-appropriate length/height, weight, head circumference measures.

[n] Admission to CRU and observation time in CRU post infusion will be the clinical decision of the Investigator. After Week 12, if appropriate in the opinion of the Investigator, home health care visits may be utilized. Patients will be required to return to the CRU at Week 24 or as clinically indicated in the opinion of the Investigator.

[o] Vital signs will be obtained within 60 min prior to dosing and within 10 min after the end of dosing.

13.2 Schedule of Assessments for Weeks 13 – 24 (IV) (Protocol Table 2)

	Weekly (QW) IV Dosing											
	Wk 13	**Wk 14**	**Wk 15**	**Wk 16**	**Wk 17**	**Wk 18**	**Wk 19**	**Wk 20**	**Wk 21**	**Wk 22**	**Wk 23**	**Wk 24**
Height, weight[a]				X				X				X
Physical examination												X
ECG												X
Clinical laboratory tests				X								X
Complement C3 and tryptase												
Pregnancy test[b]				X				X				X
3-day diet record[c]				X				X				X
Pegzilarginase dosing[d]	X	X	X	X	X	X	X	X	X	X	X	X
Arginine/ornithine[e]	X	X	X	X	X	X	X	X	X	X	X	X
Guanidino compounds[e]	X	X	X	X	X	X	X	X	X	X	X	X
PK profile[f]												X
ALT/AST profiles, ammonia[g]				X				X				X
ADA[h]								X				
Other amino acids (glu, val, leu, ile)												X
Neurological/neuromotor, adaptive behavior, and QoL assessments[i]												X
Neurocognitive and developmental assessments[j]												X
Clinical growth assessments[k]												X
Clinic/CRU visit[l]												X
Vital signs[m]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Seizure frequency	X	X	X	X	X	X	X	X	X	X	X	X

ADA = anti-drug antibodies (anti-pegzilarginase antibodies); ALT = alanine aminotransferase; AST = aspartate aminotransferase; BL = baseline; CRU = clinical research unit; ECG = electrocardiogram; EOI = end of infusion; glu = glutamine; ile = isoleucine; IV= intravenous; leu = leucine; PEG = polyethylene glycol; PK = pharmacokinetic; Scr = screening; QOL = quality of life; QW = once weekly; val = valine; Wk = week.
NOTE: The protocol allows flexibility in dosing regimen after the first 12 weeks. The protocol allows that patients may stay on a regimen for more or less than 12 weeks and may switch between regimens as clinically indicated. The procedures and evaluations conducted at any visit will coincide with the above table based on the regimen the patient is assigned to at the time of the visit (with the exception of dosing at the site after the first twelve weeks and after the fourth SC dose).

Gray shading = predose, EOI, and postdose at 4 hours, 8 hours, 24 hours, 48 hours, 120 hours, and 168 hours (also occurs 8 weeks after any dose [mg/kg], regimen, or route-of-administration change route change).
Diagonal shading = predose and 4 hours postdose.

[a] Height will be collected at baseline for all patients and every 12 weeks thereafter for pediatric patients only. Weight will be obtained during the baseline period and approximately every 4 weeks during dosing. The baseline weight can be used to calculate each total dose, unless a subsequent weight obtained indicates a >10% change from the baseline weight.

[b] Pregnancy test can either be a serum or a urine test.

[c] Patients will complete a 3-day diet record using a diary to collect the information prior to dosing visit every 4 weeks beginning prior to the first dose at Week 1.

[d] See Protocol Section 9.6.1 for details regarding dosing, including frequency and route.

[e] Samples for arginine, ornithine, and guanidino compounds will be collected prior to dosing for every dose during the first 24 weeks or as clinically indicated. A predose sample must also be obtained before any dose or route-of-administration change and prior to the 3 subsequent doses at the new dose level. In addition, at Week 1, Week 8, Week 24, and 8 weeks after any dose change, sampling times will be predose, within 30 minutes after infusion (IV only), and postdose at approximately 4, 8, 24, 48, 120, and 168 hours. An approximate 2-hour fast should be observed prior to all sampling for amino acids and within 1 hour prior to dose, except where operationally and /or clinically not possible.

[f] PK samples for pegzilarginase will be collected at Week 1, Week 8, Week 24, and 8 weeks after any dose change. Sampling times will be predose, within 30 minutes after infusion (IV only), and postdose at approximately 4, 8, 24, 48, 120, and 168 hours. A predose sample will also be obtained before any dose or route-of-administration change and prior to the 3 subsequent doses at the new dose level.

[g] Samples for ALT/AST and ammonia will be collected at baseline, pre-dose and 4 hours post-dose every 4th dose for the first 24 weeks. In addition, at Week 1, Week 8, Week 24, and 8 weeks after any dose change, sampling times will be predose, within 30 minutes after infusion (IV only), and postdose at approximately 4, 8, 24, 48, 120, and 168 hours.

[h] Anti-drug antibodies (ADA) will be collected prior to dosing (within 1 hour of dose) at Week 1 then at every 4 weeks for the first 12 weeks, then every 8 weeks. ADA testing will include assessment of antibodies against pegzilarginase and against polyethylene glycol (PEG). An unscheduled sample for ADA assessment will be obtained in the event of a moderate or severe hypersensitivity reaction. Patients who test positive for ADA will be followed and re-tested approximately every 2 to 3 months after the end of the study until ADA levels return to baseline.

[i] Neurological/neuromotor, adaptive behavior, and QOL assessments will be collected at baseline, 12 weeks, and 24 weeks: 6-Minute Walk Test, Modified Ashworth Scale, Gross Motor Function Measure, Berg Balance Scale, Purdue Pegboard Test; Vineland Adaptive Behavior Scales II; PROMIS (for patients that began the 101A study utilizing a PROMIS test) or PedsQL Measurement Model for the Pediatric Quality of Life Inventory (for patients that did not begin the 101A study utilizing a PROMIS tool); 36 Item Short Form Health Survey (SF 36); Short Form Zarit Burden Interview (ZBI-12). On days when a timed walk test is scheduled, it should be performed before any other neurological/neuromotor, developmental, or neurocognitive tests scheduled for that day. These assessments may be delayed up to 2 weeks to accommodate scheduling.

[j] Neurocognitive and developmental, assessments will be collected at baseline and 24 weeks using age appropriate assessments: Wechsler Adult Intelligence Scale IV; Wechsler Intelligence Scale for Children V; Wechsler Preschool and Primary Scale of Intelligence IV; Bayley Scales of Infant Development III; Rey Auditory Verbal Learning Test; Atlantis subtest on the Kaufman Assessment Battery for Children II; Test of Variables of Attention version 9. These assessments may be delayed up to 2 weeks to accommodate scheduling.

[k] Growth assessments will be performed for pediatric patients (ages 2 to 18): age-appropriate length/height, weight, head circumference measures.

[l] Admission to CRU and observation time in CRU post infusion will be the clinical decision of the Investigator. After Week 12, if appropriate in the opinion of the Investigator, home health care visits may be utilized. Patients will be required to return to the CRU at Week 24 or as clinically indicated in the opinion of the Investigator.

[m] Vital signs will be obtained within 60 min prior to dosing and within 10 min after the end of dosing.

13.3 Schedule of Assessments for Weeks 25 – 37 (SC) (Protocol Table 3)

	Weekly (QW) SC Dosing												
	Wk 25	**Wk 26**	**Wk 27**	**Wk 28**	**Wk 29**	**Wk 30**	**Wk 31**	**Wk 32**	**Wk 33**	**Wk 34**	**Wk 35**	**Wk 36**	**Wk 37**
Height, weight[a]				X				X				X	
ECG												X	
Clinical laboratory tests								X					
Complement C3 and tryptase[b]													
Pregnancy test[c]				X				X				X	
3-day diet record[d]				X				X				X	
Pegzilarginase dosing[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Arginine/ornithine[f]	X	X	X	X		X		X				X	
Guanidino compounds[f]	X	X	X	X		X		X				X	
PK profile[g]	X	X	X	X				X				X	
Additional PK[h]													
ALT/AST profiles, ammonia[i]								X				X	
ADA[j]												X	
Other amino acids (glu, val, leu, ile)												X	
Neurological/neuromotor, adaptive behavior, and QoL assessments[k]												X	
Neurocognitive and developmental assessments[l]													
Clinical growth assessments[m]													
Clinic/CRU visit[n]	X	X	X	X								X	
Vital signs[o]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Seizure frequency		X	X	X	X	X	X	X	X	X	X	X	X

ADA = anti-drug antibodies (anti-pegzilarginase antibodies); ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRU = clinical research unit; ECG = electrocardiogram; glu = glutamine; ile = isoleucine; IV = intravenous; leu = leucine; PEG = polyethylene glycol; PK = pharmacokinetic; SC = subcutaneous; QOL = quality of life; QW = once weekly; val = valine; Wk = week.
NOTE: Efforts should be made to collect all blood samples where clinically practical. Samples collected after the end of infusion (IV dosing) should be collected within approximately 30 minutes. Deviations from blood sampling time points are allowable to accommodate patient or site scheduling. If a sample is unable to be collected, this should

be noted in the patient's records but will not constitute a protocol deviation. The actual date and time of collection of all samples obtained must be recorded on the specimen sent to the laboratory and in the patient's source document and in the case report forms (CRFs).

NOTE: The protocol allows flexibility in dosing regimen after the first 12 weeks. The protocol allows that patients may stay on a regimen for more or less than 12 weeks and may switch between regimens as clinically indicated. The procedures and evaluations conducted at any visit will coincide with the above table based on the regimen the patient is assigned to at the time of the visit (with the exception of dosing at the site after the first twelve weeks and after the fourth SC dose).

Gray shading = predose, and postdose at 4 hours, 8 hours, 24 hours, 48 hours, 120 hours, and 168 hours (also occurs 8 weeks after any dose [mg/kg], regimen, or route-of-administration change).
Diagonal shading = predose and 4 hours postdose.

[a] Height will be collected every 12 weeks for pediatric patients only. Weight will be obtained during the baseline period and approximately every 4 weeks during dosing. The baseline weight can be used to calculate each total dose, unless a subsequent weight obtained indicates a > 10% change from the baseline weight.

[b] Serum tryptase and serum complement C3 will be obtained in the event of a hypersensitivity reaction. Samples should be obtained no later than 3 hours after the start of the reaction and at 24 hours after the start of the reaction.

[c] Pregnancy test can either be a serum or a urine test.

[d] Patients will complete a 3-day diet record using a diary to collect the information prior to dosing visit every 4 weeks beginning prior to the first dose at Week 1.

[e] See Protocol Section 9.6.1 for details regarding dosing, including frequency and route.

[f] Samples for arginine, ornithine, and guanidino compounds will be collected prior to dosing every second dose or as clinically indicated. A predose sample must also be obtained before any dose or route-of-administration change and prior to the 3 subsequent doses at the new level. In addition, at 8 weeks after any dose or route-of-administration change, sampling times will be predose, within 30 minutes after infusion (IV only), and postdose at approximately 4, 8, 24, 48, 120, and 168 hours. An approximate 2-hour fast should be observed prior to all sampling for amino acids and within 1 hour prior to dose, except where operationally and/or clinically not possible.

[g] PK samples for pegzilarginase will be collected at the start of SC dosing (Wk 25) and 8 weeks after any dose or route-of-administration change. Sampling times will be predose, within 30 minutes after infusion (IV only), and postdose at approximately 4, 8, 24, 48, 120, and 168 hours. A predose sample will also be obtained before any dose or route-of-administration change and prior to the 3 subsequent doses at the new dose level.

[h] Additional PK samples for pegzilarginase will be collected during SC dosing after the patient has received a minimum of 4 consecutive doses of pegzilarginase with no missed doses or changes in dose levels. This PK sampling will occur at the subject's next regularly scheduled visit in which neuromotor and/or neurocognitive assessments are conducted, based on the subject's availability for repeat samples. If it is not feasible to obtain this additional PK profile at the next neurocognitive or neuromotor assessment visit, additional PK samples may be taken during the course of any other visit. Sampling times will be predose, postdose at approximately 4, 8, 24, 48, 72, 96, 120, 144, and 168 hours. This PK sampling may be repeated 8 weeks later if a subject misses any sampling timepoint. An additional ADA sample will be taken at the 168-hour timepoint of this additional PK sampling.

[i] Samples for ALT/AST and ammonia will be collected pre-dose and 4 hours post-dose every 12 weeks. In addition, at 8 weeks after any dose or route-of-administration change, sampling times will be predose, within 30 minutes after infusion (IV only), and postdose at approximately 4, 8, 24, 48, 120, and 168 hours.

[j] Anti-drug antibodies (ADA) will be collected prior to dosing (within 1 hour of dose) every 8 weeks until Week 36, then approximately every 12 weeks during the dosing period, and at follow-up. ADA testing will include assessment of antibodies against pegzilarginase and against polyethylene glycol (PEG). An unscheduled sample for ADA assessment will be obtained in the event of a moderate or severe hypersensitivity reaction. Patients who test positive for ADA will be followed and re-tested approximately every 2 to 3 months after the end of the study until ADA levels return to baseline. An additional ADA sample will be taken at the 168-hour timepoint of the additional PK sampling.

[k] Neurological/neuromotor, adaptive behavior, and QOL assessments will be collected at 36 and 48 weeks: 6-Minute Walk Test, Modified Ashworth Scale, Gross Motor Function Measure, Berg Balance Scale, Purdue Pegboard Test; Vineland Adaptive Behavior Scales II; PROMIS (for patients that began the 101A study utilizing a PROMIS test) or PedsQL Measurement Model for the Pediatric Quality of Life Inventory (for patients that did not begin the 101A study utilizing a PROMIS tool); 36 Item Short Form Health Survey (SF 36); Short Form Zarit Burden Interview (ZBI-12). On days when a timed walk test is scheduled, it should be performed before any other neurological/neuromotor, developmental, or neurocognitive tests scheduled for that day. These assessments may be delayed up to 2 weeks to accommodate scheduling.

[l] Neurocognitive and developmental, assessments will be collected at 48 weeks using age appropriate assessments: Wechsler Adult Intelligence Scale IV; Wechsler Intelligence Scale for Children V; Wechsler Preschool and Primary Scale of Intelligence IV; Bayley Scales of Infant Development III; Rey Auditory Verbal Learning Test; Atlantis subtest on the Kaufman Assessment Battery for Children II; Test of Variables of Attention version 9. These assessments may be delayed up to 2 weeks to accommodate scheduling.
[m] Growth assessments will be performed for pediatric patients (ages 2 to 18): age-appropriate length/height, weight, head circumference measures.
[n] Admission to CRU and observation time in CRU post infusion will be the clinical decision of the Investigator. It is recommended that if patients are switched to SC dosing, at least the first 4 SC doses be administered in the clinic (Weeks 25, 26, 27, and 28). After Week 28, if appropriate in the opinion of the Investigator, home health care visits may be utilized. Patients will be required to return to the CRU at Week 36 and Week 48 or as clinically indicated in the opinion of the Investigator.
[o] Vital signs will be obtained within 60 min prior to dosing and within 10 min after the end of dosing.

13.4 Schedule of Assessments for Weeks 38 – 48 (SC) (Protocol Table 4)

	Weekly (QW) SC Dosing										
	Wk 38	**Wk 39**	**Wk 40**	**Wk 41**	**Wk 42**	**Wk 43**	**Wk 44**	**Wk 45**	**Wk 46**	**Wk 47**	**Wk 48**
Height, weight[a]			X				X				X
Physical examination											X
ECG											X
Clinical laboratory tests			X								X
Complement C3 and tryptase[b]											
Pregnancy test[c]			X				X				X
3-day diet record[d]			X				X				X
Pegzilarginase dosing[e]	X	X	X	X	X	X	X	X	X	X	X
Arginine/ornithine[f]	X		X		X		X		X		X
Guanidino compounds[f]	X		X		X		X		X		X
PK profile[g]											
Additional PK[h]											
ALT/AST profiles, ammonia[i]											X
ADA[j]											X
Other amino acids (glu, val, leu, ile)											X
Neurological/neuromotor, adaptive behavior, and QoL assessments[k]											X
Neurocognitive and developmental assessments[l]											X
Clinical growth assessments[m]											X
Clinic/CRU visit[n]											X
Vital signs[o]	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Seizure frequency	X	X	X	X	X	X	X	X	X	X	X

ADA = anti-drug antibodies (anti-pegzilarginase antibodies); ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRU = clinical research unit; ECG = electrocardiogram; glu = glutamine; ile = isoleucine; IV = intravenous; leu = leucine; PEG = polyethylene glycol; PK = pharmacokinetic; SC = subcutaneous; QOL = quality of life; QW = once weekly; val = valine; Wk = week.

NOTE: Efforts should be made to collect all blood samples where clinically practical. Samples collected after the end of infusion (IV dosing) should be collected within approximately 30 minutes. Deviations from blood sampling time points are allowable to accommodate patient or site scheduling. If a sample is unable to be collected, this should

be noted in the patient's records but will not constitute a protocol deviation. The actual date and time of collection of all samples obtained must be recorded on the specimen sent to the laboratory and in the patient's source document and in the case report forms (CRFs).

NOTE: The protocol allows flexibility in dosing regimen after the first 12 weeks. The protocol allows that patients may stay on a regimen for more or less than 12 weeks and may switch between regimens as clinically indicated. The procedures and evaluations conducted at any visit will coincide with the above table based on the regimen the patient is assigned to at the time of the visit (with the exception of dosing at the site after the first twelve weeks and after the fourth SC dose).

Gray shading = predose, and postdose at 4 hours, 8 hours, 24 hours, 48 hours, 120 hours, and 168 hours (also occurs 8 weeks after any dose [mg/kg], regimen, or route change)
Diagonal shading = predose and 4 hours postdose

[a] Height will be collected every 12 weeks for pediatric patients only. Weight will be obtained during the baseline period and approximately every 4 weeks during dosing. The baseline weight can be used to calculate each total dose, unless a subsequent weight obtained indicates a > 10% change from the baseline weight.

[b] Serum tryptase and serum complement C3 will be obtained in the event of a hypersensitivity reaction. Samples should be obtained no later than 3 hours after the start of the reaction and at 24 hours after the start of the reaction.

[c] Pregnancy test can either be a serum or a urine test.

[d] Patients will complete a 3-day diet record using a diary to collect the information prior to dosing visit every 4 weeks beginning prior to the first dose at Week 1.

[e] See Protocol Section 9.6.1 for details regarding dosing, including frequency and route.

[f] Samples for arginine, ornithine, and guanidino compounds will be collected prior to dosing every second dose or as clinically indicated. A predose sample must also be obtained before any dose or route-of-administration change and prior to the 3 subsequent doses at the new level. In addition, at 8 weeks after any dose or route-of-administration change, sampling times will be predose, within 30 minutes after infusion (IV only), and postdose at approximately 4, 8, 24, 48, 120, and 168 hours. An approximate 2-hour fast should be observed prior to all sampling for amino acids and within 1 hour prior to dose, except where operationally and/or clinically not possible.

[g] PK samples for pegzilarginase will be collected at the start of SC dosing (Wk 25) and 8 weeks after any dose change. Sampling times will be predose, within 30 minutes after infusion (IV only), and postdose at approximately 4, 8, 24, 48, 120, and 168 hours. A predose sample will also be obtained before any dose or route-of-administration change and prior to the 3 subsequent doses at the new dose level.

[h] Additional PK samples for pegzilarginase will be collected during SC dosing after the patient has received a minimum of 4 consecutive doses of pegzilarginase with no missed doses or changes in dose levels. This PK sampling will occur at the subject's next regularly scheduled visit in which neuromotor and/or neurocognitive assessments are conducted, based on the subject's availability for repeat samples. Sampling times will be predose, postdose at approximately 4, 8, 24, 48, 72, 96, 120, 144, and 168 hours. This PK sampling may be repeated 8 weeks later if a subject misses any sampling timepoint. An additional ADA sample will be taken at the 168 hour timepoint

[i] Samples for ALT/AST and ammonia will be collected pre-dose and 4 hours post-dose every 12 weeks. In addition, at 8 weeks after any dose or route-of-administration change, sampling times will be predose, within 30 minutes after infusion (IV only), and postdose at approximately 4, 8, 24, 48, 120, and 168 hours.

[j] Anti-drug antibodies (ADA) will be collected prior to dosing (within 1 hour of dose) every 8 weeks until Week 36, then approximately every 12 weeks during the dosing period, and at follow-up. ADA testing will include assessment of antibodies against pegzilarginase and against polyethylene glycol (PEG). An unscheduled sample for ADA assessment will be obtained in the event of a moderate or severe hypersensitivity reaction. Patients who test positive for ADA will be followed and re-tested approximately every 2 to 3 months after the end of the study until ADA levels return to baseline. An additional ADA sample will be taken at the 168-hour timepoint of the additional PK sampling.

[k] Neurological/neuromotor, adaptive behavior, and QOL assessments will be collected at 36 and 48 weeks: 6-Minute Walk Test, Modified Ashworth Scale, Gross Motor Function Measure, Berg Balance Scale, Purdue Pegboard Test; Vineland Adaptive Behavior Scales II; PROMIS (for patients that began the 101A study utilizing a PROMIS test) or PedsQL Measurement Model for the Pediatric Quality of Life Inventory (for patients that did not begin the 101A study utilizing a PROMIS tool); 36 Item Short Form Health Survey (SF 36); Short Form Zarit Burden Interview (ZBI-12). On days when a timed walk test is scheduled, it should be performed before any other neurological/neuromotor, developmental, or neurocognitive tests scheduled for that day. These assessments may be delayed up to 2 weeks to accommodate scheduling.

[l] Neurocognitive and developmental, assessments will be collected at 48 weeks using age appropriate assessments: Wechsler Adult Intelligence Scale IV; Wechsler Intelligence Scale for Children V; Wechsler Preschool and Primary Scale of Intelligence IV; Bayley Scales of Infant Development III; Rey Auditory Verbal Learning Test; Atlantis subtest on the Kaufman Assessment Battery for Children II; Test of Variables of Attention version 9. These assessments may be delayed up to 2 weeks to accommodate scheduling.

[m] Growth assessments will be performed for pediatric patients (ages 2 to 18): age-appropriate length/height, weight, head circumference measures.
[n] Admission to CRU and observation time in CRU post infusion will be the clinical decision of the Investigator. It is recommended that if patients are switched to SC dosing, at least the first 4 SC doses be administered in the clinic (Weeks 25, 26, 27, and 28). After Week 28, if appropriate in the opinion of the Investigator, home health care visits may be utilized. Patients will be required to return to the CRU at Week 36 and Week 48 or as clinically indicated in the opinion of the Investigator.
[o] Vital signs will be obtained within 60 min prior to dosing and within 10 min after the end of dosing (for either IV or SC dosing).

13.5 Schedule of Assessments for Year 2 (Weeks 52 – 104) (Protocol Table 5)

	Weekly (QW) Dosing													
	Wk 52	**Wk 56**	**Wk 60**	**Wk 64**	**Wk 68**	**Wk 72**	**Wk 76**	**Wk 80**	**Wk 84**	**Wk 88**	**Wk 92**	**Wk 96**	**Wk 100**	**Wk 104**
Height, weight[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination						X						X		
ECG												X		
Clinical laboratory tests		X		X		X		X		X		X		X
Complement C3 and tryptase[b]														
Pregnancy test[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
3-day diet record[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pegzilarginase dosing[e]	Weekly													
Arginine/ornithine[f]	Collect prior to dosing every second dose													
Guanidino compounds[f]	Collect prior to dosing every second dose													
PK profile[g]														
Additional PK[h]														
ALT/AST profiles, ammonia[i]			X			X			X			X		
ADA[j]			X			X			X			X		
Other amino acids (glu, val, leu, ile)			X			X			X			X		
Neurological/neuromotor, adaptive behavior, and QoL assessments[k]						X						X		
Neurocognitive and developmental assessments[l]						X						X		
Clinical growth assessments[m]						X						X		
Clinic/CRU visit[n]			X			X			X			X		
Vital signs[o]	Weekly													
Concomitant medications	Weekly													
Adverse events	Weekly													
Seizure frequency	Weekly													

ADA = anti-drug antibodies (anti-pegzilarginase antibodies); ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRU = clinical research unit; ECG = electrocardiogram; glu = glutamine; ile = isoleucine; IV = intravenous; leu = leucine; PEG = polyethylene glycol; PK = pharmacokinetic; SC = subcutaneous; QOL = quality of life; QW = once weekly; val = valine; Wk = week.

NOTE: Efforts should be made to collect all blood samples where clinically practical. Samples collected after the end of infusion (IV dosing) should be collected within approximately 30 minutes. Deviations from blood sampling time points are allowable to accommodate patient or site scheduling. If a sample is unable to be collected, this should

be noted in the patient's records but will not constitute a protocol deviation. The actual date and time of collection of all samples obtained must be recorded on the specimen sent to the laboratory and in the patient's source document and in the case report forms (CRFs).

NOTE: The protocol allows flexibility in dosing regimen after the first 12 weeks. The protocol allows that patients may stay on a regimen for more or less than 12 weeks and may switch between regimens as clinically indicated. The procedures and evaluations conducted at any visit will coincide with the above table based on the regimen the patient is assigned to at the time of the visit (with the exception of dosing at the site after the first twelve weeks and after the fourth SC dose).

Gray shading = predose, and postdose at 4 hours, 8 hours, 24 hours, 48 hours, 120 hours, and 168 hours (also occurs 8 weeks after any dose [mg/kg], regimen, or route-of-administration change)
Diagonal shading = predose and 4 hours postdose

[a] Height will be collected every 12 weeks for pediatric patients only. Weight will be obtained during the baseline period and approximately every 4 weeks during dosing. The baseline weight can be used to calculate each total dose, unless a subsequent weight obtained indicates a > 10% change from the baseline weight.

[b] Serum tryptase and serum complement C3 will be obtained in the event of a hypersensitivity reaction. Samples should be obtained no later than 3 hours after the start of the reaction and at 24 hours after the start of the reaction.

[c] Pregnancy test can either be a serum or a urine test.

[d] Patients will complete a 3-day diet record using a diary to collect the information prior to dosing visit every 4 weeks beginning prior to the first dose at Week 1.

[e] See Protocol Section 9.6.1 for details regarding dosing, including frequency and route.

[f] Samples for arginine, ornithine, and guanidino compounds will be collected prior to dosing every second dose or as clinically indicated. A predose sample must also be obtained before any dose or route change and prior to the 3 subsequent doses at the new level. In addition, at 8 weeks after any dose or route-of-administration change, sampling times will be predose, within 30 minutes after infusion (IV only), and postdose at approximately 4, 8, 24, 48, 120, and 168 hours. An approximate 2-hour fast should be observed prior to all sampling for amino acids and within 1 hour prior to dose, except where operationally and/or clinically not possible.

[g] PK samples for pegzilarginase will be collected at the start of SC dosing (Wk 25) and 8 weeks after any dose change. Sampling times will be predose, within 30 minutes after infusion (IV only), and postdose at approximately 4, 8, 24, 48, 120, and 168 hours. A predose sample will also be obtained before any dose or route-of-administration change and prior to the 3 subsequent doses at the new dose level.

[h] Additional PK samples for pegzilarginase will be collected during SC dosing after the subject has received a minimum of 4 consecutive doses of pegzilarginase with no missed doses or changes in dose levels. This PK sampling will occur at the subject's next regularly scheduled visit in which neuromotor and/or neurocognitive assessments are conducted, based on the subject's availability for repeat samples. Sampling times will be predose, postdose at approximately 4, 8, 24, 48, 72, 96, 120, 144, and 168 hours. This PK sampling may be repeated 8 weeks later if a subject misses any sampling timepoint. An additional ADA sample will be taken at the 168-hour timepoint.

[i] Samples for ALT/AST and ammonia will be collected pre-dose and 4 hours post-dose every 12 weeks. In addition, at 8 weeks after any dose or route-of-administration change, sampling times will be predose, within 30 minutes after infusion (IV only), and postdose at approximately 4, 8, 24, 48, 120, and 168 hours.

[j] Anti-drug antibodies (ADA) will be collected prior to dosing (within 1 hour of dose) every 8 weeks until Week 36, then approximately every 12 weeks during the dosing period, and at follow-up. ADA testing will include assessment of antibodies against pegzilarginase and against polyethylene glycol (PEG). An unscheduled sample for ADA assessment will be obtained in the event of a moderate or severe hypersensitivity reaction. Patients who test positive for ADA will be followed and re-tested approximately every 2 to 3 months after the end of the study until ADA levels return to baseline. An additional ADA sample will be taken at the 168-hour timepoint of the additional PK sampling.

[k] Neurological/neuromotor, adaptive behavior, and QOL assessments will be collected at 36 and 48 weeks: 6-Minute Walk Test, Modified Ashworth Scale, Gross Motor Function Measure, Berg Balance Scale, Purdue Pegboard Test; Vineland Adaptive Behavior Scales II; PROMIS (for patients that began the 101A study utilizing a PROMIS test) or PedsQL Measurement Model for the Pediatric Quality of Life Inventory (for patients that did not begin the 101A study utilizing a PROMIS tool); 36 Item Short Form Health Survey (SF 36); Short Form Zarit Burden Interview (ZBI-12). On days when a timed walk test is scheduled, it should be performed before any other neurological/neuromotor, developmental, or neurocognitive tests scheduled for that day. These assessments may be delayed up to 2 weeks to accommodate scheduling.

[k] Neurocognitive and developmental, assessments will be collected at 48 weeks using age appropriate assessments: Wechsler Adult Intelligence Scale IV; Wechsler Intelligence Scale for Children V; Wechsler Preschool and Primary Scale of Intelligence IV; Bayley Scales of Infant Development III; Rey Auditory Verbal Learning Test; Atlantis subtest on the Kaufman Assessment Battery for Children II; Test of Variables of Attention version 9. These assessments may be delayed up to 2 weeks to accommodate scheduling.
[m] Growth assessments will be performed for pediatric patients (ages 2 to 18): age-appropriate length/height, weight, head circumference measures.
[n] Admission to CRU and observation time in CRU post infusion will be the clinical decision of the Investigator. After Week 28, if appropriate in the opinion of the Investigator, home health care visits may be utilized. Patients will be required to return to the CRU as clinically indicated in the opinion of the Investigator.
[o] Vital signs will be obtained within 60 min prior to dosing and within 10 min after the end of dosing (for either IV or SC dosing).

13.6 Schedule of Assessments for Year 3 (Weeks 108 – 144) (Protocol Table 6)

	Weekly (QW) Dosing										
	Wk 108	**Wk 112**	**Wk 116**	**Wk 120**	**Wk 124**	**Wk 128**	**Wk 132**	**Wk 136**	**Wk 140**	**Wk 144**	**EOT/ SFU**
Height, weight[a]	X	X	X	X	X	X	X	X	X	X	X
Physical examination				X						X	X
ECG										X	X
Clinical laboratory tests		X		X		X		X		X	X
Complement C3 and tryptase[b]											
Pregnancy test[c]	X	X	X	X	X	X	X	X	X	X	X
3-day diet record[d]	X	X	X	X	X	X	X	X	X	X	
Pegzilarginase dosing[e]	Weekly										
Arginine/ornithine[f]	Collect prior to dosing every second dose									X	X
Guanidino compounds[f]	Collect prior to dosing every second dose									X	X
PK profile[g]											
Additional PK[h]											
ALT/AST profiles, ammonia[i]	X			X			X			X	X
ADA[j]	X			X			X			X	X
Other amino acids (glu, val, leu, ile)	X			X			X			X	X
Neurological/neuromotor, adaptive behavior, and QoL assessments[k]				X						X	X
Neurocognitive and developmental assessments[l]				X						X	X
Clinical growth assessments[m]				X						X	X
Clinic/CRU visit[n]	X			X			X			X	X
Vital signs[o]	Weekly										
Concomitant medications	Weekly										
Adverse events	Weekly										
Seizure frequency	Weekly										

ADA = anti-drug antibodies (anti-pegzilarginase antibodies); ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRU = clinical research unit; ECG = electrocardiogram; glu = glutamine; ile = isoleucine; IV = intravenous; leu = leucine; PEG = polyethylene glycol; PK = pharmacokinetic; SC = subcutaneous; QOL = quality of life; QW = once weekly; val = valine; Wk = week.

NOTE: Efforts should be made to collect all blood samples where clinically practical. Samples collected after the end of infusion (IV dosing) should be collected within approximately 30 minutes. Deviations from blood sampling time points are allowable to accommodate patient or site scheduling. If a sample is unable to be collected, this should

be noted in the patient's records but will not constitute a protocol deviation. The actual date and time of collection of all samples obtained must be recorded on the specimen sent to the laboratory and in the patient's source document and in the case report forms (CRFs).

NOTE: The protocol allows flexibility in dosing regimen after the first 12 weeks. The protocol allows that patients may stay on a regimen for more or less than 12 weeks and may switch between regimens as clinically indicated. The procedures and evaluations conducted at any visit will coincide with the above table based on the regimen the patient is assigned to at the time of the visit (with the exception of dosing at the site after the first twelve weeks and after the fourth SC dose).

Gray shading = predose, and postdose at 4 hours, 8 hours, 24 hours, 48 hours, 120 hours, and 168 hours (also occurs 8 weeks after any dose [mg/kg], regimen, or route-of-administration change).
Diagonal shading = predose and 4 hours postdose.

[a] Height will be collected every 12 weeks for pediatric patients only. Weight will be obtained during the baseline period and approximately every 4 weeks during dosing. The baseline weight can be used to calculate each total dose, unless a subsequent weight obtained indicates a > 10% change from the baseline weight.

[b] Serum tryptase and serum complement C3 will be obtained in the event of a hypersensitivity reaction. Samples should be obtained no later than 3 hours after the start of the reaction and at 24 hours after the start of the reaction.

[c] Pregnancy test can either be a serum or a urine test.

[d] Patients will complete a 3-day diet record using a diary to collect the information prior to dosing visit every 4 weeks beginning prior to the first dose at Week 1.

[e] See Protocol Section 9.6.1 for details regarding dosing, including frequency and route.

[f] Samples for arginine, ornithine, and guanidino compounds will be collected prior to dosing every second dose or as clinically indicated. A predose sample must also be obtained before any dose or route change and prior to the 3 subsequent doses at the new level. In addition, at 8 weeks after any dose or route-of-administration change, sampling times will be predose, within 30 minutes after infusion (IV only), and postdose at approximately 4, 8, 24, 48, 120, and 168 hours. An approximate 2-hour fast should be observed prior to all sampling for amino acids and within 1 hour prior to dose, except where operationally and/or clinically not possible.

[g] PK samples for pegzilarginase will be collected at the start of SC dosing (Wk 25) and 8 weeks after any dose change. Sampling times will be predose, within 30 minutes after infusion (IV only), and postdose at approximately 4, 8, 24, 48, 120, and 168 hours. A predose sample will also be obtained before any dose or route-of-administration change and prior to the 3 subsequent doses at the new dose level.

[h] Additional PK samples for pegzilarginase will be collected during SC dosing after the patient has received a minimum of 4 consecutive doses of pegzilarginase with no missed doses or changes in dose levels. This PK sampling will occur at the subject's next regularly scheduled visit in which neuromotor and/or neurocognitive assessments are conducted, based on the subject's availability for repeat samples. Sampling times will be predose, postdose at approximately 4, 8, 24, 48, 72, 96, 120, 144, and 168 hours. This PK sampling may be repeated 8 weeks later if a subject misses any sampling timepoint. An additional ADA sample will be taken at the 168-hour timepoint

[i] Samples for ALT/AST and ammonia will be collected pre-dose and 4 hours post-dose every 12 weeks. In addition, at 8 weeks after any dose or route-of-administration change, sampling times will be predose, within 30 minutes after infusion (IV only), and postdose at approximately 4, 8, 24, 48, 120, and 168 hours.

[j] Anti-drug antibodies (ADA) will be collected prior to dosing (within 1 hour of dose) every 8 weeks until Week 36, then approximately every 12 weeks during the dosing period, and at follow-up. ADA testing will include assessment of antibodies against pegzilarginase and against polyethylene glycol (PEG). An unscheduled sample for ADA assessment will be obtained in the event of a moderate or severe hypersensitivity reaction. Patients who test positive for ADA will be followed and re-tested approximately every 2 to 3 months after the end of the study until ADA levels return to baseline. An additional ADA sample will be taken at the 168-hour timepoint of the additional PK sampling.

[k] Neurological/neuromotor, adaptive behavior, and QOL assessments will be collected at 36 and 48 weeks: 6-Minute Walk Test, Modified Ashworth Scale, Gross Motor Function Measure, Berg Balance Scale, Purdue Pegboard Test; Vineland Adaptive Behavior Scales II; PROMIS (for patients that began the 101A study utilizing a PROMIS test) or PedsQL Measurement Model for the Pediatric Quality of Life Inventory (for patients that did not begin the 101A study utilizing a PROMIS tool); 36-Item Short-Form Health Survey (SF-36); Short Form Zarit Burden Interview (ZBI-12). On days when a timed walk test is scheduled, it should be performed before any other neurological/neuromotor, developmental, or neurocognitive tests scheduled for that day. These assessments may be delayed up to 2 weeks to accommodate scheduling.

[l] Neurocognitive and developmental, assessments will be collected at 48 weeks using age appropriate assessments: Wechsler Adult Intelligence Scale IV; Wechsler Intelligence Scale for Children V; Wechsler Preschool and Primary Scale of Intelligence IV; Bayley Scales of Infant Development III; Rey Auditory Verbal Learning Test; Atlantis subtest on the Kaufman Assessment Battery for Children II; Test of Variables of Attention version 9. These assessments may be delayed up to 2 weeks to accommodate scheduling.
[m] Growth assessments will be performed for pediatric patients (ages 2 to 18): age-appropriate length/height, weight, head circumference measures.
[n] Admission to CRU and observation time in CRU post infusion will be the clinical decision of the Investigator. After Week 28, if appropriate in the opinion of the Investigator, home health care visits may be utilized. Patients will be required to return to the CRU at Week 36 and Week 48 or as clinically indicated in the opinion of the Investigator.
[o] Vital signs will be obtained within 60 min prior to dosing and within 10 min after the end of dosing (for either IV or SC dosing).

13.7 Schedule of Assessments for Year 4 (Weeks 145 to 192 or EOT/SFU) (Protocol Table 7)

	Weekly (QW) Dosing												
	Wk 148	**Wk 152**	**Wk 156**	**Wk 160**	**Wk 164**	**Wk 168**	**Wk 172**	**Wk 176**	**Wk 180**	**Wk 184**	**Wk 188**	**Wk 192**	**EOT/SFU**
Height[a]												X	X
Weight[b]			X			X			X			X	X
Physical examination													X
ECG													X
Clinical laboratory tests						X						X	X
Pregnancy test[c]	X	X	X	X	X	X	X	X	X	X	X	X	X
3-day diet record[d]													X
Pegzilarginase dosing[e]	Weekly												
Arginine/ornithine[f]						X						X	X
Guanidino compounds[f]						X						X	X
ADA[g]													X
Other amino acids (glu, val, leu, ile)													X
Neurological/neuromotor, adaptive behavior, and QoL assessments[h]													X
Neurocognitive and developmental assessments[i]													X
Clinical growth assessments[j]												X	X
Clinic/CRU visit[k]						X						X	X
Vital signs[l]	Weekly												
Concomitant medications	Weekly												
Adverse events	Weekly												
Seizure frequency	Weekly												

ADA = anti-drug antibodies (anti-pegzilarginase antibodies); ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRU = clinical research unit; ECG = electrocardiogram; EOT/SFU = end of treatment/study follow-up visit; glu = glutamine; ile = isoleucine; IV = intravenous; leu = leucine; PEG = polyethylene glycol; PK = pharmacokinetic; SC = subcutaneous; QOL = quality of life; QW = once weekly; val = valine; Wk = week.

[a] Height will be collected every 48 weeks for pediatric patients only starting at Week ~~96~~145.

[b] Weight will be obtained during the baseline period and approximately every 12 weeks during dosing starting at Week 96. The baseline weight can be used to calculate each total dose, unless a subsequent weight obtained indicates a > 10% change from the baseline weight.
[c] Pregnancy test can either be a serum or a urine test.
[d] The 3-day diet record will not be required in Year 4 (after Week 144) other than at the EOT/SFU visit.
[e] See Section **Error! Reference source not found.** for details regarding dosing, including frequency and route.
[f] An approximate 2-hour fast should be observed prior to all sampling for amino acids and within 1 hour prior to dose, except where operationally and/or clinically not possible.
[g] ADAs will not be collected in Year 4 of the study other than at the EOT/SFU visit.
[h] Neurological/neuromotor, adaptive behavior, and QoL assessments will not be collected in Year 4 of the study other than at the EOT/SFU visit.
[I] Neurocognitive and developmental assessments will not be collected in Year 4 of the study other than at the EOT/SFU visit.
[j] Growth assessments (age-appropriate length/height, weight, head circumference measures) will be performed for pediatric patients (ages 2 to 18) at Week 192 in Year 4 and at the EOT/SFU visit:
[k] Admission to CRU and observation time in CRU post infusion will be the clinical decision of the Investigator. After Week 28, if appropriate in the opinion of the Investigator, home health care visits may be utilized. Patients will be required to return to the CRU every 24 weeks starting at Week 96, or as clinically indicated in the opinion of the Investigator.
[l] Vital signs will be obtained within 60 min prior to dosing (for either IV or SC dosing) starting at Week 97.

14. REFERENCES

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15. TABLES, LISTINGS, AND FIGURES

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15.2 Listings

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