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Official Title

A Phase 3 Open-Label Study of Safety, Pharmacokinetics, and Activity of Weekly Subcutaneous Pegzilarginase in Subjects <24 Months Old With Arginase 1 Deficiency

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Revision History

Version	Author	Date	Reason for Revision
1.0	DH	07Aug2024	Final version 1.0
2.0	DH	14Jan2025	Final version 2.0 - Arginine results from Charles River Laboratories will be used for analysis and not from eCRF - Clarification of calculation of GMFM-66 score
3.0	DW	07Aug2025	- Minor adaptions in layout or clarifications to analysis. - The combined Visit 13/ET will only be displayed if at least one subject has an early termination visit. - Laboratory: handling of values below/above the lower/upper limit of quantification [e.g. < 0.5] - Use both CDC and WHO growth charts for derivation of growth percentiles, depending on age, in line with the protocol.

Table of Contents

List of Abbreviations

In the following abbreviations are listed as used within this statistical analysis plan or which might occur within the table, listing and graph outputs:

ADA	Anti-drug antibodies
AE	Adverse event
ARG1	Arginase 1
ARG1-D	Arginase 1 deficiency
ATC	Anatomical therapeutic chemical
BMI	Body mass index
CDC	Centers for disease control and prevention
(e)CRF	(electronic) Case report form
CS	Clinically significant
ECG	Electrocardiogram
EU	European Union
FAS	Full analysis set
GMFM	Gross motor function measure
HSR	Hypersensitivity reaction
ICH	International council for harmonization of technical requirements for pharmaceuticals for human use
IMP	Investigational medicinal product
ISR	Injection site reaction
KSA	Kingdom of Saudia Arabia
MedDRA	Medical dictionary for regulatory activities
N	Number of subjects
NCS	Not clinically significant
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred term
QW	Once weekly
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SFU	Safety follow-up
SOC	System organ class
TEAE	Treatment-emergent adverse event
TLG	Tables, listings, graphs
UK	United Kingdom
WHO	World health organization

1 Introduction

This Statistical Analysis Plan (SAP) was defined by the Sponsor and CRO FGKs responsible Statistician. It is based upon the Study Protocol (version 2.0 of 31May2024) and electronic Case Report Form (eCRF) Specification 1.0 of 29Jul2024 and contains detailed description of the statistical methods.

The SAP was finalized prior to enrolment of first study subject.

1.1 Study Objectives

Primary Objective

- To evaluate the effect of pegzilarginase on plasma arginine concentrations in subjects <24 months of age with arginase 1 deficiency (ARG1-D)

Secondary Objectives

- To evaluate the safety of pegzilarginase
- To characterize the pharmacokinetic (PK) profile of pegzilarginase
- To evaluate the pharmacodynamic (PD) response of pegzilarginase
- To describe changes in physical function

1.2 Study Design

This is a phase 3 open-label, single-arm, non-controlled, repeat dosing, multicentre study to evaluate the safety, PK, and PD of weekly subcutaneous (SC) administration of pegzilarginase in subjects with ARG1-D who are < 24 months of age. The study consists of a screening period of up to 4 weeks, a subsequent 12-week treatment period, and a safety follow-up period of 8 weeks.

After inclusion in the study, all subjects will receive a once weekly (QW) SC pegzilarginase dose starting at 0.1 mg/kg for 12 weeks with the ability to adjust the dose in 0.05 mg/kg increments between 0.05 mg/kg and 0.2 mg/kg to maintain pre-dose arginine level in the predefined range of 50 - 150 µM.

This study is conducted at 3 sites in the European Union (EU) and United Kingdom (UK).

1.3 Sample Size Justification

The sample size of 3 subjects is solely based on clinical considerations and the EU Paediatric Investigational Plan.

2 Statistical Analysis Sets

Set	Definition
Enrolled set (ENR)	All subjects for whom the informed consent form was signed.
Full analysis set (FAS)	All subjects who are enrolled and received at least 1 dose of study drug.

The FAS will be the primary analysis set and will be used for all analyses except disposition of subjects and analysis sets, end of treatment and study termination and SAE listings which will be displayed for all enrolled subjects.

3 Subgroup Analysis

No subgroup analyses are planned.

4 Efficacy and Safety Variables

4.1 Primary Endpoint

- Change from Baseline in plasma arginine after 12 weeks of pegzilarginase treatment

4.2 Secondary Endpoints

- Adverse events (AEs), including hypersensitivity reactions (HSRs), injection site reactions (ISRs) and hyperammonaemic events
- Clinical laboratory tests (chemistry, hematology, coagulation), plasma ammonia and occurrence of prolonged hypoargininaemia
- Vital signs, physical examinations, growth assessments, and electrocardiograms (ECGs)
- PK parameters evaluation
- PD response evaluation: Anti-drug antibodies (ADA), levels of plasma arginine and plasma ornithine
- Changes in physical function after 12 weeks of pegzilarginase treatment as measured by Gross Motor Function Measure (GMFM)-66 Parts A through E.

4.3 Other Endpoints

- Diet records

5 Statistical Evaluation

5.1 General Analysis Considerations

All data obtained in this study and documented in the eCRF will be listed stratified by subject and statistically summarized as appropriate.

For qualitative variables the number and percentage in each category will be calculated. Percentages will be presented to one decimal place. The calculation of percentages will be based on the number of non-missing values, if not stated otherwise. Missing values (including user-defined missing values as "not done", "unknown", "not applicable", "not documented") will not be presented and not included in the calculation of percentages.

For quantitative variables, unless otherwise stated, the mean, standard deviation, minimum, median, and maximum will be provided. In the description of the tables this will be denoted by „basic statistics". Preliminary rounding of CRF entries will not be performed, derived or standardized values will be rounded to a reasonable number of digits. Mean, median and standard deviation will be presented with one decimal place more than the precision of the data. Minimum and maximum will be presented with the same precision as the raw data. In basic statistics tables, the overall number of missing values will not be given.

If different units are used for one laboratory value, the values will all be converted to one unit (unit that occurs most frequently if available) and only converted values will be used in tables. In listing both original and converted values will be displayed. Original and converted values will be rounded to the same number of significant digits.

The following conversion factors will be used:

Parameter	Observed unit according to eCRF	Unit used for analysis	Factor for conversion from observed to analysis unit
Alanine aminotransferase	IU/L	U/L	1
Alkaline phosphatase	IU/L	U/L	1
Aspartate aminotransferase	IU/L	U/L	1
Creatinine	mg/L	mg/dL	0.1
	Umol/L	mg/dL	0.0113
Hematocrit	ratio	%	100
	L/L	%	100
Hemoglobin	g/L	g/dL	0.1
Lactate dehydrogenase	IU/L	U/L	1
Total bilirubin	umol/L	mg/dL	0.0585

5.2 Specifications and Definitions

Specifications or definitions of the following items might be given:

- Baseline is defined as the last non-missing pre-dose value. For arginine the Screening value

is used as Baseline

- Change from Baseline is calculated as follows: post-Baseline value – Baseline value
- Percentage change from Baseline is calculated as follows: 100 * [(post-Baseline value – Baseline value) / Baseline value]
- For subjects that were re-screened, only data from the last screening will be listed and analyzed unless noted otherwise.
- Unscheduled visits will only be listed and not included in any tables except table "Subjects per visit".
- Early Termination visits will be displayed combined with Visit 13 as Visit 13/ET. The combined Visit 13/ET will only be displayed if at least one subject has an early termination visit.
- Visit terminology:

Notation used in the protocol	**Notation used for tables, listings and graphs**
Screening	Screening*
Visit 1	Visit 1
Visit 2	Visit 2
Visit 3	Visit 3
Visit 4	Visit 4
Visit 5	Visit 5
Visit 6	Visit 6
Visit 7	Visit 7
Visit 8	Visit 8
Visit 9	Visit 9
Visit 10	Visit 10
Visit 11	Visit 11
Visit 12	Visit 12
Visit 13	Visit 13~
Visit 13/Early Termination Visit	Visit 13/ET~
Visit 14 safety follow-up (SFU)	SFU
Unscheduled Visit	Unscheduled Visit

ET = Early termination

** If the screening was repeated, only data from the last screening will be used in tables and listings.*

~ Visit 13 efficacy and safety follow-up is a combined visit of either the regular Visit 13 (168-hours after last dose) or an early termination Visit. In TLGs, two presentations of this visit will be shown:

-"Visit 13": only regular Visit 13 will be included.

-"Visit 13/ET": both regular Visit 13 visits and early termination visits will be included.

5.3 Disposition of Subjects and Analysis Sets

The disposition of subjects and analysis sets, subjects per center and per country, inclusion and exclusion criteria, and the status at end of study and end of treatment will be listed for all subjects of the Enrolled Set.

No inferential assessments will be performed on disposition data.

5.4 Demographics and Other Covariates

No inferential assessments will be performed on demographics and other covariates. All variables will be analyzed for the FAS, unless otherwise specified.

5.4.1 Demographic Data

Demographic data (age at time of consent [Months], year of birth, sex, ethnicity and race) will be summarized descriptively.

5.4.2 Medical History

Medical coding of medical history will be performed with Medical dictionary for regulatory activities (MedDRA). MedDRA version 27.0 will be used for the duration of the study.

The number and percentage of subjects with a medical history will be summarized by System Organ Class (SOC) and Preferred Term (PT) number and percentage of subjects with a medical history term/diagnosis will be displayed by body system.

5.4.3 Prior and Concomitant Medication

Medications will be coded by WHODrug Global version of 01Mar2024.

Previous medication administered within 30 days prior to first dose are documented in the eCRF with the exception of botulinum toxin, which is collected for 16 weeks prior to dosing. All prior and concomitant medication reported in the eCRF will be summarized descriptively by anatomical therapeutic chemical (ATC) level 2, ATC level 3, and preferred name.

If no preferred name can be found in the WHODrug Global for a documented medication, an umbrella term from the WHODrug Global will be used instead. A corresponding footnote will be added to the tables and listings concerned.

In listings, the generic name and all coding levels used for tabulation will be displayed. Non-drug therapy will be listed only.

5.4.4 Concomitant Diagnostic and Medical Procedures and Surgeries

Concomitant diagnostic and medical procedures and surgeries will be listed only.

5.5 Other Variables as Measured at Baseline

5.5.1 Disease Characteristics

Disease characteristics will be listed only.

5.5.2 ARG1 Gene Mutation

ARG1 Gene Mutation details will be listed only.

5.5.3 ARG1-D Symptoms

ARG1-D symptoms will be listed only.

5.5.4 Motor Function

Motor function will be listed only.

5.6 Exposure

Exposure to IMP will be listed only. Administered dose at each visit will be calculated as administered dose [mg/kg] = total volume administered [mL] * 5 / weight [kg]. For the calculation of the administered dose the weight at the current visit will be used. If the weight is not available the baseline weight will be used. Total volume administered and total administered dose in mg and mg/kg will be calculated as the sum of administered volume, and administered dose in mg and mg/kg respectively from all individual visits, i.e 12 weeks treatment.

5.7 Efficacy Analysis

All endpoints will be analyzed descriptively. This is a study with no confirmatory inferential testing planned. All analyses will be done for the FAS.

5.7.1 Analysis of Primary Endpoint

Arginine can be assessed up to 3 times during the screening period. The highest value will be used for Baseline. For the analysis of the primary endpoint only the plasma arginine measurement at Baseline and Visit 13 will be evaluated. In listings, all screening values may be displayed marked as Measurement 1, Measurement 2, Measurement 3 and a flag for the highest value.

Absolute values, changes from Baseline and the percentage change from Baseline will be summarized as reported by Charles River Laboratories. Arginine measurements for the primary endpoint will be listed together with the secondary endpoint plasma arginine. Details of the listings are described in section 5.7.2.

5.7.2 Analysis of Secondary Endpoints

For all secondary endpoints, all available visits including both Visit 13/ET and Visit 13 will be included in tables and listing. Visit 13 includes all assessments from Visit 13/ET from subjects that did not terminate study treatment early (Did the subject complete the study treatment = No in end of treatment-form in eCRF).

<u>Adverse Events (AEs)</u>

AEs will be coded by using the medical dictionary for regulatory activities (MedDRA) version 27.0.

An AE is considered related, if the relationship is assessed as 'related' in eCRF question "Was this adverse event related to study treatment?". An AE with missing relationship is considered 'related'.

AEs leading to dose interruption are defined as AEs with 'Action Taken with Study Treatment = Drug interrupted' and AEs leading to discontinuation of treatment are defined as AEs with 'Action Taken with Study Treatment = Drug withdrawn'.

If an AE is treatment-emergent will be decided based on questions "Did the adverse event start after first administration of study treatment" and "Did the adverse event worsen on or after first administration of study treatment?" on the AE-form in eCRF. A TEAE is defined as an AE that begins or worsens (increases in severity) on or after the date (and time if known) of the first dose

of the study drug. If the answer to at least one of the question "Did the adverse event start or worsen after first administration of study treatment" or "Did the adverse event worsen on or after first administration of study treatment?" is missing, the AE will be considered a TEAE unless AE end date indicates otherwise. The reporting period for serious AEs (SAEs) is the period from the signing of informed consent continuing through the last study SFU visit, and for non-serious AEs from first dose of study medication through the last SFU visit.

(S)AEs of subjects not in FAS will be listed only.

TEAEs will be provided by system organ class (SOC) and preferred term (PT) (MedDRA). The number of events, as well as the number and percentage of affected subjects will be reported.

Additionally, related TEAEs, serious TEAEs (SAEs), related serious TEAEs, TEAEs leading to dose interruptions, TEAEs leading to discontinuation of treatment and TEAEs leading to death will be tabulated.

Furthermore, TEAEs will be presented by severity and by SOC and PT.

Hypersensitivity Reaction

Hypersensitivity Reactions will be tabulated by SOC and PT.

Injection Site Reaction

Injection Site Reactions will be tabulated by SOC and PT

Hyperammonaemic Events

Hyperammonaemic Events will be tabulated by SOC and PT.

Prolonged Hypoargininaemia

Prolonged Hypoargininaemia will be tabulated by SOC and PT

Clinical Laboratory

Clinical laboratory blood samples (chemistry, haematology, coagulation) will be obtained and processed locally.

All parameters are quantitative.

Chemistry and Haematology are assessed at Screening or Visit 1, Visit 4, Visit 8, Visit 13/ET and SFU. Coagulation is assessed at Screening or Visit 1, Visit 13/ET and SFU.

For all laboratory values, absolute values, changes from Baseline and the assessment of the result will be summarized by visit.

If the value of a laboratory parameter is below/above the lower/upper limit of quantification [e.g. < 0.5], the value of the limit of quantification itself [e.g. 0.5] will be used for statistical evaluations and summary tables.

The following parameters are assessed:

Chemistry: total bilirubin, alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH), sodium, potassium, chloride, creatinine, blood urea nitrogen (BUN)

Haematology: red blood cell count (RBC), hemoglobin, hematocrit, white blood cell count (WBC), neutrophils (absolute), neutrophils (relative), lymphocytes (absolute), lymphocytes (relative),

monocytes (absolute), monocytes (relative), eosinophils (absolute), eosinophils (relative), basophils (absolute), basophils (relative), platelets

Coagulation: partial thromboplastin time (PTT), prothrombin time, prothrombin international normalized ratio (INR).

Plasma Ammonia:

Plasma ammonia is assessed at Screening or Visit 1, Visit 4, Visit 8, Visit 13/ET and SFU.

Absolute values and changes from Baseline will be summarized by visit.

Vital Signs

Vital signs are assessed at all visits. The parameters pulse rate [beats/min], systolic blood pressure [mmHg], diastolic blood pressure [mmHg], respiration rate [breaths/min] and body temperature [C°] will be assessed once at each visit.

For all parameters, absolute values, changes from Baseline and the assessment of the result will be summarized by visit.

Physical Examination

Physical examination is done at Screening, Visit 1, Visit 4, Visit 8, Visit 10, Visit 13/ET and SFU.

The following systems are assessed:

- Head, eyes, ears, nose, and throat
- Cardiovascular
- Dermatological
- Musculoskeletal
- Respiratory
- Gastrointestinal
- Neurological.

Frequency tables for physical examination assessment (Normal / Abnormal - not clinically significant / Abnormal - clinically significant / Not done) will be provided by visit.

Growth Assessments

Height [cm], weight [kg], and head circumference [cm] will be collected at Visit 1, Visit 4, Visit 8, Visit 13/ET and SFU.

The percentiles height-for-age, weight-for-age, weight-for-height, and head circumference-for-age are obtained from the WHO (for subjects with age below 24 months) or CDC Growth Charts (for subjects who age above 24 months during the course of the study).

For the calculations, the age at growth assessments in days will be obtained by multiplying age in months given at time of consent by (365.25/12), and add 15 days and add the number of days between growth assessment and time of consent. Age in months is age in days divided by (365.25/12).

The SAS-programs and datasets used are available under:

CDC Growth Charts:https://www.cdc.gov/growth-chart-training/hcp/computer-programs/sas.html

WHO Growth Charts:https://www.cdc.gov/growth-chart-training/hcp/computer-programs/sas-who.html

For all parameters including parameters calculated with the Growth Charts, absolute values and changes from Baseline will be summarized by visit.

Electrocardiograms

An ECG will be obtained at Screening, Visit 13/ET and SFU.

The following parameters are assessed: Heart Rate [beats/min], PR Interval [msec], QRS Duration [msec], QT interval [msec], QTcB interval [msec] and QTcF interval [msec].

For all parameters, absolute values, changes from Baseline and the assessment of the result will be summarized by visit.

PK parameters

The analysis of PK parameters will be described in a separate analysis plan. Collection of samples (date and time) for PK analysis will be listed.

Anti-drug Antibodies (ADA)

ADA analyses results will be delivered by BioAgilytix and details of the data structure are given in a separate data transfer specification.

ADA is assessed at Screening or Visit 1, Visit 2, Visit 4, Visit 8, Visit 13/ET and SFU.

ADA results are assessed as qualitative data and number and percentage will be displayed for each visit. The results of the ADA titres will be tabulated for visits where ADA detected.

Plasma Arginine

Plasma arginine will be delivered by Charles River Laboratories and details of the data structure are given in a separate data transfer specification. Data will be reconciled with eCRF data as specified in the data transfer specification. Both Arginine results provided by Charles River Laboratories and CRF results will be included in listings. Only Arginine results provided by Charles River Laboratories will be used for analysis. Arginine is measured at Screening, Visit 1, Visit 2, Visit 3, Visit 4, Visit 6, Visit 8, Visit 10, Visit 13/ET and SFU. Arginine can be assessed up to 3 times during the screening period. The highest value will be used as Baseline value. In listings, all screening values may be displayed marked as Measurement 1, Measurement 2, Measurement 3 and additionally the Baseline value will be displayed. One additional arginine sample per subject will be collected between 24- and 48-hours post-dose at each of the Visits 2, 4, and 10 for PD analyses. The additional measurement will be included in listings with timepoint ='Postdose'.

Absolute values, changes from Baseline and the percentage change from Baseline will be summarized by visit and timepoint. Furthermore, number and proportion of measurements within the normal range (40-115 µM) and within the guideline level (< 200 µM) will be presented by visit and timepoint.

Plasma Ornithine

Plasma ornithine will be delivered by Charles River Laboratories and details of the data structure are given in a separate data transfer specification. Ornithine is measured at Screening, Visit 1 and Visit 13/ET. Absolute values, and changes from Baseline will be summarized by visit.

Gross Motor Function Measure (GMFM-66)

Neuromotor assessment is done at Screening and Visit 13/ET.

The GMFM is a clinical measure designed to evaluate gross motor function in children with cerebral palsy by observing the subject's ability to initiate and complete certain movements.

GMFM-66 consists of 66 items. For this study, the dimensions of the GMFM-66 will be used as age appropriate and feasible at the Investigator's discretion for each subject for Screening and Visit 13/ET.

GMFM-66 covers dimension A through to E, using a four-point scale:

- Dimension A assesses lying and rolling
- Dimension B assesses sitting
- Dimension C assesses crawling and kneeling
- Dimension D assesses standing
- Dimension E assesses walking, running, and jumping.

If any individual dimension A through E of the GMFM-66 assessment is not feasible for the individual subject (missing individual items is acceptable) at Screening, that entire Part of the GMFM-66 will not be completed at Visit 13/ET.

A four-point scale is used for the scoring of Items:

- 0 = does not initiate
- 1 = initiates
- 2 = partially completes
- 3 = completes.

The total dimensions reported as Total dimension A, Total dimension B, etc. in eCRF and the total score calculated as the sum of all total dimensions will be summarized by study visit. For the total dimensions and the total score change from Baseline and percentage change from Baseline will also be tabulated.

Assistive devices for GMFM-66 will also be listed.

5.8 Analysis of Other Variables

Diet Records

A diet diary will be kept for three consecutive days between Screening and Visit 1 and for 3 consecutive days between Visit 12 and Visit 13/ET. Results are listed only.

5.9 Protocol Deviations

Protocol deviations as collected in the eCRF (subject related PDs) and PD tracker (subject unrelated PDs) will be listed. Details of PD collection including the PD tracker are given in the PD handling plan. All protocol deviations assessments classified as major or minor will be reviewed at the data review meeting. Note: The protocol deviations were not completely reviewed during the data review meeting but shortly thereafter via email correspondance. The reviewed protocol deviations have been documented and attached to the data review meeting minutes.

5.10 Medication Error, Overdose, Misuse, Abuse

Medication error, overdose, misuse and abuse will be listed only.

5.11 Interim Analysis

No interim analysis will be performed.

5.12 Missing Values

No missing value imputation methods will be applied except for the weight for the exposure calculation (see section 5.6 for details)

All analysis will be done on a valid case basis, i.e., for missing observations no imputation techniques will be applied. Missing values will remain missing.

Incomplete (only partially missing) start and end dates will be imputed for adverse events (see section 5.7.2). In listings, dates will be presented as recorded.

5.13 Data Base Closure and Data Review Meeting

The data base will be locked before the analysis. All parameters will be checked, as specified in the data validation plan and all queries resolved before data base closure and analysis.

FGK will provide the Sponsor with all planned subject listings (as defined in Appendix A) prior to a data review meeting. A data review meeting will be conducted based on all data after review of the provided listings by the Sponsor and prior to data base lock.

5.14 Miscellaneous

A detailed description of the planned tables, listings and graphs is given in Appendix A.

The design of the outputs will be determined by the technical possibilities within SAS and may not look identical to the description. However, all information as mentioned will be included.

The variables for the specific listings are explicitly given in the description of listings. All listings will be presented for the FAS, if not stated differently. Dates and times will be displayed in data listings using the format YYYY-MM-DD and hh:mm:ss or hh.mm, respectively.

Enrolled but not treated subjects (e.g., withdrawal before treatment) will be considered in listings describing disposition of subjects (including treatment and study termination), analysis sets, in-/exclusion criteria (including date informed consent signed), as well as subject demographics and serious adverse events.

The following title will be used for all generated tables, listings, and graphs:

CAEB1102-301A <Table/Listing/Graph x.x> Page # of #
Final Analysis < Description of contents>
<Analysis Set >

The numbering NNN of the tables/listings/graphs will be stated in the detailed description (Appendix A).

Following footnote will be used for all generated tables, listings, and graphs:

Program: <Name of program> Run Date/Time: <Actual date(yyyy-mm-ddThh.mm)>

All tables, listings, and graphs will be generated in DIN A4 paper format.

The statistical evaluation will be performed using SAS version 9.4 or higher.

6 Changes to the Analyses Planned in the Protocol

In the following, any changes on statistical aspects as described in the protocol are given:

- Disposition of subjects and some Baseline characteristics are only listed and not tabulated.

Statistical Analysis Plan
Appendix A

List of generated summary tables, listings, and graphs

Version 3.0

Tables, listings and graphs might differ from the ones described in the following in terms of their layout (eg, labels and order of variables or footnotes).

Overview of TLGs
• Listing 1.1.1: Disposition of Subjects and Analysis Sets
• Listing 1.1.2: Subjects Excluded from Analysis Sets
• Listing 1.1.3: Study Visits
• Listing 1.2.1: End of Treatment/End of Study
• Table 2.1: Subject Demographics
• Table 2.2: Medical History
• Table 2.3: Prior and Concomitant Medication
• Listing 2.1: Subject Demographics
• Listing 2.2: Medical History
• Listing 2.3: Prior and Concomitant Medication
• Listing 2.4: Concomitant Diagnostic and Medical Procedures and Surgeries
• Listing 2.5: Disease Characteristics
• Listing 2.6: ARG1 Gene Mutation
• Listing 2.7: ARG1-D Symptoms
• Listing 2.8: Baseline Motor Function
• Listing 3.1: IMP Administration
• Listing 3.2: IMP Exposure
• Table 4.1: Plasma Arginine after 12 weeks of treatment – Primary Endpoint
• Table 5.1.1: TEAEs by System Organ Class and Preferred Term
• Table 5.1.2: TEAEs by System Organ Class, Preferred Term, and Severity
• Table 5.1.3: Related TEAEs by System Organ Class and Preferred Term
• Table 5.1.4: Serious TEAEs by System Organ Class and Preferred Term
• Table 5.1.5: Related and Serious TEAEs by System Organ Class and Preferred Term
• Table 5.1.6: TEAEs Leading to Dose Interruptions by System Organ Class and Preferred Term
• Table 5.1.7: TEAEs Leading to Discontinuation of Treatment by System Organ Class and Preferred Term
• Table 5.1.8: TEAEs Leading to Death by System Organ Class and Preferred Term
• Listing 5.1.1: Adverse Events
• Listing 5.1.2: Serious Adverse Events
• Table 5.2.1: Hypersensitivity Reactions by System Organ Class and Preferred Term
• Table 5.3.1: Injection Site Reactions by System Organ Class and Preferred Term
• Table 5.4.1: Hyperammonaemic Events by System Organ Class and Preferred Term
• Table 5.5.1: Prolonged Hypoargininaemia by System Organ Class and Preferred Term
• Table 5.6.1: Clinical Laboratory - Chemistry -Assessments and Basic Statistics
• Table 5.6.2: Clinical Laboratory - Hematology – Assessments and Basic Statistics
• Table 5.6.3: Clinical Laboratory - Coagulation – Assessments and Basic Statistics
• Listing 5.6.1: Clinical Laboratory - Chemistry
• Listing 5.6.2: Clinical Laboratory - Hematology
• Listing 5.6.3: Clinical Laboratory - Coagulation
• Table 5.7.1: Clinical Laboratory – Plasma Ammonia – Assessments and Basic Statistics
• Listing 5.7.1: Clinical Laboratory – Plasma Ammonia
• Table 5.8.1: Vital Signs - Assessments and Basic Statistics
• Listing 5.8.1: Vital Signs
• Table 5.9.1: Physical Examination
• Listing 5.9.1: Physical Examination
• Table 5.10.1: Growth Assessments - Basic Statistics
• Listing 5.10.1: Growth Assessments

1 Disposition of Subjects

1.1 Disposition of Subjects and Analysis Sets

Listing 1.1.1: Disposition of Subjects and Analysis Sets
Enrolled Set
Variables: Date of Screening Visit, ICF Signed (Yes/ No), Date ICF Signed, Protocol Version, All IC Met (Yes/No), Violated IC^, Any EC Violated (Yes/No), Violated EC^, All IC and No EC Met (Yes/ No), Subject Eligible (Yes/ No), FAS (Yes/ No)
stratified by Subject and Visit
Footnote 1: IC = Inclusion criteria, EC = Exclusion criteria..
Footnote 2: ^ Numbers (CRF) of violated IC or EC.

Listing 1.1.2: Subjects Excluded from Analysis Sets
Enrolled Set
Variables: Subject, Country, Center, Full Analysis Set (FAS) (Yes/ No), Reason for not in FAS
stratified by Subject

Listing 1.1.3: Study Visits
Full Analysis Set
Variables: Visit (Screening / Visit 1, …), Visit Performed (Yes/ No), Reason not Done, Date of Visit, Type (Follow-up/ Early Termination), Drop-Out (Yes/ No), Location Visit (Site/ Subject's Home/ Other)/ Specification, Reason Unscheduled Visit, Assessments done at Unscheduled Visit, Other Medical History
stratified by Subject

1.2 Discontinuation

Listing 1.2.1: End of Treatment/End of Study
Enrolled Set
Variables: Treatment Completion (Yes/ No), Treatment End Date, Reason Discontinuation (Adverse event/ Death/ Lack of Efficacy/ Lost to Follow-up/ Physician Decision/ Progressive

Disease/ Protocol Deviation/ Screen Failure/ Study Terminated by Sponsor/ Withdrawal of Consent/ Other) / AE No./ PD No/ Death Date/ Specification,
Study Completion (Yes/ No), Study End Date, Reason for Discontinuation (Adverse Event/ Death/ Lack of Efficacy/ Lost to Follow-up/ Physician Decision/ Progressive Disease/ Protocol Deviation/ Screen Failure/ Study Terminated by Sponsor/ Withdrawal of Consent/ Other)/ AE No./ PD No/ Specification Adverse Events Present (Yes/ No), Medication Errors Present (Yes/ No), Concomitant Medications Present (Yes/ No), Procedures Present (Yes/ No), Protocol Deviations Present (Yes/ No)
stratified by Subject

2 Demographics and Other Covariates

Table 2.1: Subject Demographics
Full Analysis Set
Variables: Year of Birth, Sex (Male/ Female), Ethnicity (Hispanic or Latino/ Not Hispanic or Latino/ Not reported/ Unknown), Race (American Indian or Alaska Native/ Asian/ Black or African American/ Native Hawaiian or Other Pacific Islander/ Not reported/ Unknown/ Other)
*Basic statistics for Age [Months]^*
Footnote 1: ^ Age at time of consent.

Table 2.2: Medical History
Full Analysis Set
Variables: Body System/ Preferred Name (n_{MHs}, n(%))

Table 2.3: Prior and Concomitant Medication
Full Analysis Set
Variables: ATC Level 2/ ATC Level 3/ Preferred Name (n_{CMs}, n (%))
Footnote 1: All previous medication administered within 30 days prior to first dose (with the exception of botulinum toxin, which should be collected for 16 weeks prior to dosing) and concomitant medications as reported in eCRF.
Footnote 2: The number of subjects at an ATC level is not necessarily the sum of those at the lower levels since a subject may report multiple CMs within a level. CMs coded by WHODrug Global 01Mar2024.
Footnote 3: If no preferred name can be found in the WHODrug Global for a documented medication, an umbrella term from the WHODrug Global is used instead.
Footnote 4: Only drug therapy is tabulated. Non-drug therapy is listed only.
Note: Table will be sorted by alphabetical ATC class.

Listing 2.1: Subject Demographics
Full Analysis Set
Variables: Year of Birth, Age [Months]^, Sex (Male/ Female), Ethnicity (Hispanic or Latino/ Not Hispanic or Latino/ Not reported/ Unknown), Race (American Indian or Alaska Native/ Asian/ Black or African American/ Native Hawaiian or Other Pacific Islander/ Not reported/ Unknown/ Other)
stratified by Subject
Footnote 1: ^ Age at time of consent.

Listing 2.2: Medical History
Full Analysis Set
Variables: No., Medical History Term/Diagnosis, Preferred Term, System Organ Class, Start Date, End Date, Ongoing
stratified by Subject

Listing 2.3: Prior and Concomitant Medication
Full Analysis Set
Variables: No., Type of Medication (Procedure Agent/ Ammonia Scavenger/ Metabolic Formula/ Amino Acids Supplementation/ Antihistamines/Corticosteroids as IMP Premedication/ Anti-Seizure Medication/ Other), Subtype (Arginine free AA/ Low arginine AA), Medication Name, Indication (Adverse Event/ Medical History/ Prophylaxis/ Nutritional Supplementation/

ARG1-D Symptoms/ Other), Specification, AEs, MHs, Preferred Name, ATC Level 2, ATC Level 3, ARG1-D Symptoms (Spasticity/ Seizures/ Cognitive/Language Delays, Muscle cramps/ Liver Injury and/or Dysfunction), Start Date, End Date/Ongoing, Prior Medication (Yes/No), Dose/Unit/Form/Frequency/Route,
stratified by Subject
Note: Only subjects with medication(s) are presented
Footnote 1: CMs coded by WHODrug Global 01Mar2024.
Footnote 2: If no preferred name can be found in the WHO-DD for a documented medication, an umbrella term from the WHO-DD is used instead.
Footnote 3: Non-drug therapy is not coded and is not included in Table 2.3.

Listing 2.4: Concomitant Diagnostic and Medical Procedures and Surgeries
Full Analysis Set
Variables: No., Procedure, Start Date, End Date/Ongoing (Yes/ No), Indication (Adverse Event/ Medical History/ Prophylaxis/ Nutritional Supplementation/ ARG1-D Symptoms/ Other), AEs, MHs, Specification, ARG1-D Symptoms (Spasticity/ Seizures/ Cognitive/Language Delays, Muscle cramps/ Liver Injury and/or Dysfunction), Frequency (Once/ As Needed/ Daily/ Twice per Day/ 3 Times per Day/ Every other Day/ Every Week/ 2 Times per Week/ 3 Times per Week/ Every 2 Weeks/ Every Month/ Twice per Month/ Every two Months/ Every 3 Months/ Intermittent/ Occasional/ Continuous/ Unknown/ Other)/Specification
stratified by Subject
Note: Only subjects with concomitant diagnostic and medical procedures and surgeries are presented

Listing 2.5: Disease Characteristics
Full Analysis Set
Variables: Subject, Method of Diagnosis (Arginine Levels/ RBC Enzyme Activity/ DNA Testing/ Newborn Screening/ Other)/ Specification, Genetic Mutation Date DNA Collection, Arginase 1 Activity in RBC, Date Sample Collection, Result, Unit (U/mL/ umol/ h/g/ Other), Date Newborn Screening

Listing 2.6: ARG1 Gene Mutation
Full Analysis Set
Variables: No., Coding Sequence Change, Amino Acid Change, Gene Variant (Homozygous/ Heterozygous), Method
stratified by Subject

Listing 2.7: ARG1-D Symptoms
Full Analysis Set
Variables: Subject, Spasticity (Yes/ No), Start Date, Level (Mild/ Moderate/ Severe), Location (Right Upper Limb/ Left Upper Limb/ Right Lower Limb/ Left Lower Limb), Seizures (Yes/ No), Start Date, Last Date, Number in in Last Month, Number in Last Year, Cognitive Delays (Yes/ No), Start Date, Description, Language Delays (Yes/ No), Start Date, Description, Muscle Cramps (Yes/ No), Start Date, Description, Location, Frequency, Liver Abnormalities(Yes/ No), Start Date, Abnormality (ALT/AST elevation/ PT/INR elevation/ Abnormal Fibrogen GGT Elevation/ Other), , Other Symptoms
Footnote 1: Other Symptoms can be found in Listing 2.2, Medical History.

Listing 2.8: Baseline Motor Function

Full Analysis Set

Variables: Subject, Assessed (Yes/ No), Reason not Performed, Date, Walking Ability Short*(Normal/ Minimal/Moderate Impairment/ Severe Impairment/ Not able), Moderate**(Normal/ Minimal/Moderate Impairment/ Severe impairment/ Not able), Long***(Normal/ Minimal/Moderate Impairment/ Severe impairment/ Not able), Ability to Climb Stairs (Normal/ Minimal/Moderate Impairment/ Severe impairment/ Not able), Assisted Devices Used (Yes/ No), Distances(Short Distances (e.g. at Home - 5 Meters)/ Moderate Distances (e.g. at School - 50 Meters)/Longer Sustained Distances (e.g. Shopping at a Store - 500 Meters)), Device(Ankle-Foot Orthosis (AFO)/ Single tip Cane/ Quad Cane/ Forearm Crutches/ Standard Walker/ Rolling 2-wheeled Walker/ Four-Wheeled Walker/ Wheelchair/ Other)/Specification

Footnote 1: * Short distances (e.g. at home - 5 meters)

Footnote 2: ** Moderate distances (e.g. at school - 50 meters)

Footnote 3: ** Longer sustained distances (e.g. shopping at a store - 500 meters)

3 Exposure

Listing 3.1: IMP Administration

Full Analysis Set

Variables: Visit, Any Treatment (Yes/ No). Reason not Done, Lot Number, Start Date, Start Time, Dose Level [mg/kg], Total Volume Administered [mL], Administered Dose [mg], Administered Dose [mg/kg], Weight Assessed, Time of Weight, Weight [kg], , Dose Adjusted(Yes/ No), Reason for Adjustment (Dose Decrease: 2 Consecutive Arginine Results < 50 µM /Dose Increase: 2 Consecutive Arginine Results > 150 µM/ Dose Interruption due to AE/ Other), Medication Error (Yes/ No)

stratified by Subject

Footnote 1*: Administered Dose [mg/kg] = Total Volume Administered [mL] * 5 / Weight [kg]*

Footnote 2*: For the calculation of the administered dose, the weight documented on the IMP injection log for the current visit is used. If the weight is not available, the weight from the Assessment of Growth log (marked with *) is used and if no weight is documented for a visit, the baseline weight is used (marked with +).*

Listing 3.2: IMP Exposure

Full Analysis Set

Variables: Total Volume Administered [mL], Total Administered Dose [mg], Total Administered Dose [mg/kg]

stratified by Subject

Footnote 1: The total volume administered, and total administered dose is summed up from respective single values at individual visits (12 weeks treatment).

4 Primary Endpoint

Table 4.1: Plasma Arginine after 12 weeks of treatment – Primary Endpoint
Full Analysis Set
Basic statistics for absolute values and absolute and percentage change from Baseline

5 Secondary Endpoints

5.1 Adverse Events

Table 5.1.1: TEAEs by System Organ Class and Preferred Term
Full Analysis Set
Variables: System Organ Class / Preferred Term (n_{AEs}, n (%))
Footnote 1: The number of subjects at a SOC level is not necessarily the sum of those at the PT levels since a subject may report multiple AEs within a SOC level. AEs coded by MedDRA V27.0.
Note: Table will be sorted by alphabetical system organ class.

Table 5.1.2: TEAEs by System Organ Class, Preferred Term, and Severity
Full Analysis Set
Variables: System Organ Class / Preferred Term / Severity (Mild/ Moderate/ Severe) (n_{AEs}, n (%))
Footnote 1: The number of subjects at a SOC level is not necessarily the sum of those at the PT levels since a subject may report multiple AEs within a SOC level. AEs coded by MedDRA V27.0.
Note: Table will be sorted by alphabetical system organ class.

Table 5.1.3: Related TEAEs by System Organ Class and Preferred Term
Full Analysis Set
Variables: System Organ Class / Preferred Term (n_{AEs}, n (%))
Footnote 1: TEAEs assessed as related to study treatment or with relationship missing are considered as related TEAEs.
Footnote 2: The number of subjects at a SOC level is not necessarily the sum of those at the PT levels since a subject may report multiple AEs within a SOC level. AEs coded by MedDRA V27.0.
Note: Table will be sorted by alphabetical system organ class.

Table 5.1.4: Serious TEAEs by System Organ Class and Preferred Term
Full Analysis Set
Variables: System Organ Class / Preferred Term (n_{AEs}, n (%))
Footnote 1: TEAEs documented as serious on the AE form are tabulated.
Footnote 2: The number of subjects at a SOC level is not necessarily the sum of those at the PT levels since a subject may report multiple AEs within a SOC level. AEs coded by MedDRA V27.0.
Note: Table will be sorted by alphabetical system organ class.

Table 5.1.5: Related and Serious TEAEs by System Organ Class and Preferred Term
Full Analysis Set
Variables: System Organ Class / Preferred Term (n_{AEs}, n (%))
Footnote 1: TEAEs documented as serious on the AE form are tabulated.
Footnote 2: The number of subjects at a SOC level is not necessarily the sum of those at the PT levels since a subject may report multiple AEs within a SOC level. AEs coded by MedDRA V27.0.
Note: Table will be sorted by alphabetical system organ class.

Table 5.1.6: TEAEs Leading to Dose Interruptions by System Organ Class and Preferred Term
Full Analysis Set
Variables: System Organ Class / Preferred Term (n_{AEs}, n (%))
Footnote 1: TEAEs leading to dose interruption defined as TEAEs with 'Action Taken with Study Treatment = Drug interrupted'.
Footnote 2: The number of subjects at a SOC level is not necessarily the sum of those at the PT levels since a subject may report multiple AEs within a SOC level. AEs coded by MedDRA V27.0.
Note: Table will be sorted by alphabetical system organ class.

Table 5.1.7: TEAEs Leading to Discontinuation of Treatment by System Organ Class and Preferred Term
Full Analysis Set
Variables: System Organ Class / Preferred Term (n_{AEs}, n (%))
Footnote 1: TEAEs leading to discontinuation of Treatment are defined as TEAEs with 'Action Taken with Study Treatment = Drug withdrawn'.
Footnote 2: The number of subjects at a SOC level is not necessarily the sum of those at the PT levels since a subject may report multiple AEs within a SOC level. AEs coded by MedDRA V27.0.
Note: Table will be sorted by alphabetical system organ class.

Table 5.1.8: TEAEs Leading to Death by System Organ Class and Preferred Term
Full Analysis Set
Variables: System Organ Class / Preferred Term (n_{AEs}, n (%))
Footnote 1: The number of subjects at a SOC level is not necessarily the sum of those at the PT levels since a subject may report multiple AEs within a SOC level. AEs coded by MedDRA V27.0.
Note: Table will be sorted by alphabetical system organ class.

Listing 5.1.1: Adverse Events
Enrolled Set
Variables: No., Reported Term, System Organ Class, Preferred Term, Start Date, Start Time/Unknown, End Date/Ongoing, End Time/Unknown, Duration [days], TEAE (Yes/ No), Start After First Administration (Yes/ No), Worsen After First Administration (Yes/ No), SAE (Yes/ No), Severity (Mild/ Moderate/ Severe),Relationship to IMP (Not related/ Related), Relationship to Non-Study-Treatment (Yes/ No) /Specification, Action with IMP (Dose increased/ Dose not changed/ Dose reduced/ Drug interrupted/ Drug withdrawn/ Not applicable/ Unknown), Other Action Taken/ Specification of Other, Outcome (Fatal/ Not recovered/not resolved/ Recovered/resolved/ Recovered/resolved with sequelae/ Recovering or resolving/ Unknown), AE Hypersensitivity Reaction (Yes/ No), Injection Site Reaction (Yes/ No), Hyperammonaemic Event (Yes/ No), Prolonged Hypoargininaemia (Yes/ No)
stratified by Subject
Footnote 1: If an AE is treatment-emergent is decided based on question "Did the adverse event start after first administration of study treatment?" and "Did the adverse event worsen on or after first administration of study treatment?". If the questions were not completely answered, the AE will be considered as TEAE unless the AE end date indicates otherwise.

Footnote 3: AEs coded by MedDRA V27.0.

Listing 5.1.2: Serious Adverse Events
Enrolled Set
Variables: No., Reported Term, Preferred Term, System Organ Class, Start Date, Start Time, Stop Date/Continuing, TEAE, + all other variables on SAE-form
stratified by Subject
Footnote 1: If an AE is treatment emergent is decided based on question "Did the adverse event start after first administration of study treatment?" and "Did the adverse event worsen on or after first administration of study treatment?". If the questions were not completely answered, the AE will be considered as TEAE unless the AE end date indicates otherwise.
Note: All variables from SAE-form will be listed except information entered by medical monitor, information about signatures or personal information of investigator.

5.2 Hypersensitivity Reaction (HSR)

Table 5.2.1: Hypersensitivity Reactions by System Organ Class and Preferred Term
Full Analysis Set
Variables: System Organ Class / Preferred Term (n_{AEs}, n (%))
Footnote 1: The number of subjects at a SOC level is not necessarily the sum of those at the PT levels since a subject may report multiple AEs within a SOC level. AEs coded by MedDRA V27.0.
Note: Table will be sorted by alphabetical system organ class.

5.3 Injection Site Reaction

Table 5.3.1: Injection Site Reactions by System Organ Class and Preferred Term
Full Analysis Set
Variables: System Organ Class / Preferred Term (n_{AEs}, n (%))
Footnote 1: The number of subjects at a SOC level is not necessarily the sum of those at the PT levels since a subject may report multiple AEs within a SOC level. AEs coded by MedDRA V27.0.
Note: Table will be sorted by alphabetical system organ class.

5.4 Hyperammonaemic Events

Table 5.4.1: Hyperammonaemic Events by System Organ Class and Preferred Term
Full Analysis Set
Variables: System Organ Class / Preferred Term (n_{AEs}, n (%))
Footnote 1: The number of subjects at a SOC level is not necessarily the sum of those at the PT levels since a subject may report multiple AEs within a SOC level. AEs coded by MedDRA V27.0.
Note: Table will be sorted by alphabetical system organ class.

5.5 Prolonged Hypoargininaemia

Table 5.5.1: Prolonged Hypoargininaemia by System Organ Class and Preferred Term
Full Analysis Set
Variables: System Organ Class / Preferred Term (n_{AEs}, n (%))

Footnote 1: The number of subjects at a SOC level is not necessarily the sum of those at the PT levels since a subject may report multiple AEs within a SOC level. AEs coded by MedDRA V27.0.
Note: Table will be sorted by alphabetical system organ class.

5.6 Clinical Laboratory

Table 5.6.1: Clinical Laboratory - Chemistry -Assessments and Basic Statistics
Full Analysis Set
Basic statistics for absolute values and absolute change from Baseline
Variables: Assessment (Normal/ Abnormal — not Clinically Significant/ Abnormal - Clinically Significant)
stratified by Visit and Laboratory Parameter

Table 5.6.2: Clinical Laboratory - Hematology – Assessments and Basic Statistics
Full Analysis Set
Basic statistics for absolute values and absolute change from Baseline
Variables: Assessment (Normal/ Abnormal — not Clinically Significant/ Abnormal – Clinically Significant)
stratified by Visit and Laboratory Parameter

Table 5.6.3: Clinical Laboratory - Coagulation – Assessments and Basic Statistics
Full Analysis Set
Basic statistics for absolute values and absolute change from Baseline
Variables: Assessment (Normal/ abnormal — not Clinically Significant/ Abnormal – Clinically Significant)
stratified by Visit and Laboratory Parameter

Listing 5.6.1: Clinical Laboratory - Chemistry
Full Analysis Set
Variables: Visit, Sample Collected (Yes/ No)/Reason not Collected, Date, Time, Parameter, Lab Performed (Not done)/ Reason, Result [Unit], Change from Baseline , Assessment (Normal/ Abnormal — not Clinically Significant/ Abnormal – Clinically Significant), Original Result [Unit] Linked (Adverse event/ Medical history/ ARG1-D symptoms/ Other)/Specification Other/
stratified by Subject
Note 1*: If a result was converted to a different unit both original and converted result will be displayed.*
Footnote 2: The last value prior to IMP administration is used as Baseline.

Listing 5.6.2: Clinical Laboratory - Hematology
Full Analysis Set
Variables: Visit, Sample Collected (Yes/ No) / Reason not Collected, Date, Time Parameter, Lab Performed (Not done)/ Reason, Result [Unit], Change from Baseline, Assessment (Normal/ abnormal — not Clinically Significant/ Abnormal – Clinically Significant), Original Result [Unit] Linked (Adverse event/ Medical history/ ARG1-D Symptoms/ Other)/Specification Other
stratified by Subject
Note 1*: If a result was converted to a different unit both original and converted result will be displayed.*
Footnote 2: The last value prior to IMP administration is used as Baseline.

Listing 5.6.3: Clinical Laboratory - Coagulation
Full Analysis Set
Variables: Visit, Sample Collected (Yes/ No)/ Reason not Collected, Date, Time, Parameter, Lab Performed (Not Done)/ Reason, Result [Unit], Change from Baseline, Assessment (Normal/ Abnormal — not Clinically Significant/ Abnormal – Clinically Significant), Original Result [Unit] , Linked (Adverse event/ Medical history/ ARG1-D symptoms/ Other)/Specification Other/ Specification ARG1-D symptoms
stratified by Subject
Note 1*: If a result was converted to a different unit both original and converted result will be displayed.*

5.7 Footnote 2: The last value prior to IMP administration is used as Baseline.Plasma Ammonia

Table 5.7.1: Clinical Laboratory – Plasma Ammonia – Assessments and Basic Statistics
Full Analysis Set
Basic statistics for absolute values and absolute change from Baseline for Plasma Ammonia
stratified by Visit

Listing 5.7.1: Clinical Laboratory – Plasma Ammonia
Full Analysis Set
Variables: Visit, Sample Collected (Yes/ No), Reason not Collected, Date, Time, Result, Unit, Change from Baseline, Assessment (Normal/ Abnormal — not Clinically Significant/ Abnormal – clinically Significant), Linked (Adverse event/ Medical history/ ARG1-D symptoms/ Other)/Specification Other/ Specification ARG1-D symptoms
stratified by Subject
Footnote 1: The last value prior to IMP administration is used as Baseline.

5.8 Vital Signs

Table 5.8.1: Vital Signs - Assessments and Basic Statistics
Full Analysis Set
Basic statistics for absolute values and absolute change from Baseline
Variables: Assessment (Normal/ Abnormal — not Clinically Significant/ Abnormal - Clinically Significant)
stratified by Visit and Parameter

Listing 5.8.1: Vital Signs
Full Analysis Set
Variables: Visit, Vital Signs Performed (Yes/ No), Reason not Performed, Date, Time, Parameter, Completion Status (Not Done), Position* (Sitting/ Supine), Result, Change from Baseline, Assessment (Normal/ Abnormal — not Clinically Significant/ Abnormal – clinically Significant), Linked (Adverse event/ Medical history/ ARG1-D symptoms/ Other)/Specification Other/ Specification ARG1-D symptoms
stratified by Subject
Footnote 1: ** Only for blood pressure assessment.*
Footnote 2: The last value prior to IMP administration is used as Baseline.

5.9 Physical Examinations

Table 5.9.1: Physical Examination
Full Analysis Set
Variables: Visit / Assessment (Normal/ Abnormal - not clinically significant/ Abnormal - clinically significant/ not Done)
stratified by Physical Examination System

Listing 5.9.1: Physical Examination
Full Analysis Set
Variables: Visit, Physical Examinations Performed (Yes/ No), Reason not Performed, Date, Time, System, Result (Normal/ Abnormal, not clinically significant/ Abnormal, clinically significant/Not done~~),~~ Abnormal Finding, Linked (Adverse event/ Medical History/ ARG1-D symptoms/ Specification Other)
stratified by Subject

5.10 Growth Assessments

Table 5.10.1: Growth Assessments - Basic Statistics
Full Analysis Set
Basic statistics for absolute values and absolute change from Baseline
stratified by Visit and Parameter

Listing 5.10.1: Growth Assessments
Full Analysis Set
Variables: Visit, Growth Assessments Performed (Yes/ No), Reason not Performed, Date, Time, Growth Chart Used, Age at Assessments * [days/ months], Parameter, Status (Not Done), Result, Change from Baseline
stratified by Subject
Footnote 1: Percentiles are obtained from WHO growth charts for age below 24 months and from CDC growth charts for age of 24 months or above.
Footnote 2: * Age at growth assessments in days was obtained by multiplying age in months given at time of consent by (365.25/12), and add 15 days and add the number of days between growth assessment and time of consent. Age in months is age in days divided by (365.25/12).
Footnote 3: The last value prior to IMP administration is used as Baseline.

5.11 Electrocardiograms

Table 5.11.1: ECG - Assessments and Basic Statistics
Full Analysis Set
Basic statistics for absolute values and absolute change from Baseline
Variables: Assessment (Normal/ Abnormal — not Clinically Significant/ Abnormal - Clinically Significant)
stratified by Visit and Parameter

Listing 5.11.1: ECG
Full Analysis Set
Variables: Visit, ECG Performed (Yes/ No), Reason not Performed, Date, Position (Sitting/ Standing/ Supine), Parameter (Heart Rate [beats/min], PR Interval [msec], QRS Duration [msec], QT interval [msec], QTcB interval [msec], QTcF interval [msec], ECG Assessment), Result, Change from Baseline, Assessment (Normal/ Abnormal, not clinically significant/

Abnormal, clinically significant), Linked to (Adverse event/ Medical history, ARG1-D symptoms / Specification Other),
stratified by Subject
Footnote 1: The last value prior to IMP administration is used as Baseline.

5.12 Pharmacokinetics

Listing 5.12.1: Pharmacokinetics – Sample Collection
Full Analysis Set
Variables: Visit, *Timepoint,* Sample Collected (Yes/ No), Reason not Done, Date, Time
stratified by Subject

5.13 Anti-drug Antibodies

Table 5.13.1: Anti-drug Antibodies
Full Analysis Set
Basic statistics for titre
Variables: *Screening* (Detected/ Not Detected), *Confirmatory* (Detected/ Not Detected),
Stratified by Visit
Note: Titre is only included if ADA detected in confirmatory testing.

Listing 5.13.1: Anti-drug Antibodies
Full Analysis Set
Variables: Visit, Sample Collected (Yes/ No), Reason not Collected, Date, Time, Result, Unit
stratified by Subject

5.14 Plasma Arginine

Table 5.14.1: Plasma Arginine – Within Normal Range, Within Guidance Level and Basic Statistics
Full Analysis Set
Basic statistics for absolute values and absolute and percentage change from Baseline
Variables: Normal Range (Yes/ No), Within Guideline level (Yes/ No)
stratified by Visit (Baseline/ Visit 1/ Visit 2/ Visit 3/ Visit 4/ Visit 6/ Visit 8/ Visit 10/ Visit 13/ Visit 13/ET/ SFU) and Timepoint (Pre-Dose/ Post-Dose)
Footnote 1: Normal Range is defined as 40-115 µM and guideline level means plasma arginine <200 µM.

Listing 5.14.1: Plasma Arginine
Full Analysis Set
Variables: Visit, Timepoint, Sample collected (Yes/ No), Reason not Collected, Date, Time, Arginine [umol/L]*, Arginine [uM]^, Change from baseline [umol/L], Percentage change from baseline [%], Assessment (Normal/ Abnormal — not Clinically Significant/ Abnormal – clinically Significant), Linked (Adverse event/ Medical history/ ARG1-D symptoms/ Other)/Specification Other/ Specification ARG1-D symptoms
stratified by Subject
Footnote 1: *as reported in eCRF
Footnote 2: ^as reported by central laboratory and used for analysis.

5.15 Plasma Ornithine

Table 5.15.1: Plasma Ornithine - Basic Statistics
Full Analysis Set
Basic statistics for absolute values and absolute change from Baseline
stratified by Visit

Listing 5.15.1: Plasma Ornithine
Full Analysis Set
Variables: Visit, Sample collected (Yes/ No), Reason not Collected, Date, Time, Central Laboratory Information: Ornithine [uM], Change from baseline [uM]
stratified by Subject
Footnote 1: The last value prior to IMP administration is used as Baseline.

5.16 Gross Motor Function Measure (GMFM-66)

Table 5.16.1: GMFM-66 – Basic Statistics – Absolute and Percentage Change
Full Analysis Set
Basic statistics for absolute values and absolute and percentage change from Baseline in the Total Dimensions and the Total Score
stratified by GMFM-66 Dimension/ Total Score and Visit

Listing 5.16.1: GMFM-66
Full Analysis Set
Variables: Visit, GMFM-66 Performed (Yes/ No), Reason not Collected, Date, GMFCS Level (I/ II/ III/ IV/ V), Indicative Regular Performance (Yes/ No), Comment, Assistive Device (Yes/ No)/Specification/ No/ Aid/Orthosis(Rollator/ Pusher/ …)/ Specification/ Dimension assistive device (A. lying and rolling/ B. sitting/ C. crawling and kneeling/ D. standing/ E. walking, running and jumping), Total Dimension/Overall (Total Score/ A . lying and rolling/ B. sitting/ C. crawling and kneeling/ D. standing/ E. walking, running and jumping), Dimension Performed (Yes/ No/ Not Applicable), Score, Absolute Change from Baseline, Percentage Change from Baseline, Item (2.Sup: Brings Hands to Midline, Fingers One With the Other/ …), Item Score
stratified by Subject

6 Other Relevant Variables

6.1 Diet Records

Listing 6.1: Diet Records

Full Analysis Set

Variables: Visit (Screening, Visit13/ET), Diary Reviewed (Yes/ No), Reason not Reviewed, Total Calories [kcal/day], Calories [kcal/kg], Total Protein [g/day], Natural Protein [g/day], Essential Amino Acids (EAA) Protein [g/day]

stratified by Subject

Footnote 1*: Prescribed values are added in parentheses after consumed values.*

7 Protocol Deviations and Medication Error, Overdose, Misuse and Abuse

Listing 7.1: Protocol Deviations
Full Analysis Set
Variables: Subject, No. + all variables on eCRF/PD-tracker
Footnote 1: Protocol deviations as collected and classified in the eCRF and PD-tracker (if there are any additional PDs in the PD-tracker).

Listing 7.2: Medication Error, Overdose, Misuse, Abuse
Full Analysis Set
Variables: No., Type (Medication Error/ Accidental Overdose/ Intentional Overdose/ Misuse/ Abuse), Resulted in AE/SAE, AE, Start Date, Start Time, End Date, End Time, Action Study Treatment (Dose Increased, Dose not Changed, Dose Reduced, Drug Interrupted, Drug Withdrawn, Not Applicable: e.g., if Subject Died or Treatment had been Completed Prior to Reaction/Event/ Unknown), Last Dose Date, Dose Change Start Date, Restart Date, Dose Change End Date, Adjusted/Increased/Reduced Dose per administration [mg/kg], Other Actions/Specification, Narrative
stratified by Subject