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STUDY TITLE:

PHASE I/IIA GENE TRANSFER CLINICAL TRIAL FOR VARIANT LATE INFANTILE NEURONAL CEROID LIPOFUSCINOSIS, DELIVERING THE *CLN6* GENE BY SELF-COMPLEMENTARY AAV9

PROTOCOL NUMBER: AT-GTX-501-01

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LIST OF ABBREVIATIONS

Abbreviation	Term
ADaM	analysis data model
AE	adverse event
ATC	anatomical therapeutic chemical
BMI	body mass index
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
cm	centimeter
CSR	clinical study report
DOB	date of birth
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
EEG	electroencephalograms
eCRF	electronic case report form
FAS	full analysis set
IA	interim analysis
ICH	International Conference on Harmonisation
ITT	intent-to-treat
kg	kilogram
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
PCS	potentially clinically significant
PedsQL	Pediatric Quality of Life
PT	preferred term
SAE	serious adverse event
SAF	safety analysis set
SAS	statistical analysis system
SAP	statistical analysis plan
SD	standard deviation
SDTM	study data tabulation model
SE	standard error
SMQ	Standardized MedDRA Queries

Abbreviation	Term
SOC	system organ class
TEAE	treatment-emergent adverse event
UBDRS	Unified Batten Disease Rating Scale
WHO	World Health Organization
vLINCL6	variant late infantile neuronal ceroid lipofuscinosis 6

1. INTRODUCTION

This statistical analysis plan (SAP) describes the planned data analyses and statistical methods to be utilized for Study AT-GTX-501-01, based on the global protocol version 17. This document was developed per Amicus standard operating procedure SOP-ATCRA-008-v3.0 and is consistent with the International Conference on Harmonisation (ICH) E9 Guideline. The purpose of this document is to provide details on study populations, derivation of the variables, handling of missing data, and details on the statistical methods to be used to analyze the efficacy and safety data for the study.

The final SAP will be approved and filed before database is locked. The analyses and statistical methods specified in the final SAP will supersede those described in the study protocol or amendments. A clinical study report (CSR) will be prepared after the database lock and completion of statistical analyses.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

The primary objective of this study is:

- To evaluate the safety of AT-GTX-501 in the treatment of variant late infantile neuronal ceroid lipofuscinosis 6 (vLINCL6) Batten disease. Evaluations are based on adverse events (AEs), clinical laboratory test results, and other safety measures.

2.1.2. Secondary Objectives

The secondary objective of this study is:

- To evaluate the potential for prolonged survival or maintenance of motor, language, visual, and cognitive function. The outcome measures include the Hamburg (scale), the Unified Batten Disease Rating Scale (UBDRS), brain magnetic resonance imaging (MRI), cognitive and language evaluations, the Pediatric Quality of Life™ (PedsQL) inventory, ophthalmologic examinations, and long-term monitoring electroencephalograms (EEGs). The primary efficacy outcome will be the Hamburg Motor and Language scores.

2.2. Study Endpoints

2.2.1. Safety Endpoints

Safety endpoints include:

- Incidence rate and severity of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Incidence rate and severity of treatment-related TEAEs
- Change from baseline over time in physical and neurological exam findings, vital sign measurements, electrocardiogram (ECG), and clinical laboratory test results

2.2.2. Efficacy Endpoints

2.2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is:

- The rate of decline from baseline to Month 24 in the Hamburg Motor and Language scores.

2.2.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are changes from baseline over time on the following assessments:

- the Unified Batten Disease Rating Scale (UBDRS)

- cognitive and language evaluations by:
  - Development Profile™-3
  - Mullen Scale of Early Learning
  - Preschool Language Scales-5th Edition (PLS-5)

3. STUDY DESIGN

3.1. Summary of Study Design

This is an open-label study in subjects with vLINCL6 disease who receive a single intrathecal administration of AT-GTX-501.

Safety and efficacy are evaluated over a 2-year period. The efficacy assessments in this study are to evaluate motor, language, visual, and cognitive function, as well as survival and other outcome measures. In Year 1, subjects are tested at baseline, receive AT-GTX-501 on Day 0, and return for visits on Days 7, 14, 21, and 30 (Visits 3 to 6), and then every 3 months for Visits 7 (Month 3) to 10 (Month 12). In Year 2, data are collected every 3 months.

Following completion of this study, subjects are asked to transfer to a long-term follow-up study (Study AT-GTX-501-02) where follow-up data is planned to be collected for 13 years.

3.2. Definition of Study Drugs

AT-GTX-501 is a self-complementary adeno-associated viral vector, serotype 9 (scAAV9) containing the human CLN6 gene under the control of a hybrid promoter (a cytomegalovirus enhancer fused to the chicken-β actin promoter). Each subject received via a 10 mL BD syringe (Luer-Lok™ Tip), a single dose of 1.5×10^{13} vector genomes AT-GTX-501. The AT-GTX-501 (pre-mixed with Omnipaque™) is delivered through a single intrathecal injection into the subarachnoid space via lumbar puncture, into the subject's cerebrospinal fluid (CSF). Following injection, subjects are placed in the Trendelenburg position, with their body tilted head-down and feet elevated for approximately 15 minutes.

3.3. Sample Size Considerations

Thirteen subjects were enrolled into this study.

3.4. Randomization

Not applicable as all subjects receive the same treatment.

3.5. Clinical Assessments

The schedule of study assessments and procedures is presented in Table 3 of the protocol AT-GTX-501-01.

4. INTERIM ANALYSES

No formal interim analysis was planned as the current trial is an open-label and single arm trial.

5. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

5.1. General Summary Table and Individual Subject Data Listing Considerations

Summary tables and listings will have text (eg, headers or footers) providing short explanatory notes that cover, as appropriate: date of data extraction, date of output generation, Statistical Analysis System (SAS) program name, and any other output-specific details that require further elaboration. For tables, the last line of the title will provide the analysis group being summarized.

Descriptive statistics will be prepared for baseline, each visit, and change from baseline to each visit (if appropriate).

Row entries in post text tables are made only if data exist for at least one subject (eg, a row with all zeroes will not appear). The only exception to this rule applies to tables that summarize the study termination status of subjects (eg, reasons for not completing the study). In this case, zeroes will appear for study termination reasons that no subject satisfied. The summary tables will clearly indicate the number of subjects to which the data apply and data that is unknown or not performed will be distinguished from missing data. All data collected will be reported in data listings.

5.2. General Post-text Summary Table and Individual Subject Data Listing Format Considerations

The convention will be to number tables and listings using a decimal system to reflect main levels of unique tables and listings and sub-levels of replicate tables and listings. The first level number will be consistent with the corresponding CSR appendix in which the tables or listings will appear. Thus, all post text tables and figures will have a main number level 14 and listings will have a main number level 16.

Subject accounting and final disposition, analysis populations, protocol deviations and/or violations, demographics and baseline profile will appear as the second level number (Table 14.1 series). Efficacy tables will be 14.2 series, while safety tables will come next (14.3 series). Similar conventions will be applied to the subject data listings and figures/graphs.

Whether in the title or body of a table or listing, units will always be specified for all appropriate data. Metric system units will be used (eg, degrees Celsius (°C) for temperature, kilograms (kg) for body weight, and centimeters (cm) for height).

In general, the listings will be sorted and presented by subject number. From left to right, the columns will include the subject number, visit number, visit name, visit date, and days relative to the date of administration of the AT-GTX-501.

5.3. Data Management

Datasets will be created according to Clinical Data Interchange Standards Consortium (CDISC) standards. The most current or latest version of the Study Data Tabulation Model (SDTM) datasets will be used. All statistical and data analyses, SDTMs and Analysis Data Model

(ADaM) datasets will be created using (SAS®) software version 9.4 or later. The data specifications and reviewer's guide will also be developed.

5.4. Data Presentation Conventions

5.4.1. Descriptive Statistics

Data will be summarized overall, with descriptive statistics and/or response frequencies.

For numerical data, descriptive statistics will include number of subjects with non-missing data (n), mean, standard deviation, median, minimum, and maximum. For categorical data, descriptive statistics will be category frequency counts and proportions (or percentages) of the number of subjects used in the analysis. The counts for the categories for 'Missing,' 'Unknown,' or 'Not applicable' will be provided as appropriate, but the percentages will not be provided.

5.4.2. Rounding

In general, the minimum and maximum will be reported to the same number of decimal places as the data. The mean, median, and confidence intervals will be rounded to one more decimal place than the data. The standard deviation will be rounded to two more decimal places than the data. Proportions will be reported as percentages rounded to one decimal place.

Each subject's age will be truncated to a whole number (rather than rounded).

5.4.3. p-values

P-values resulting from statistical tests will be presented to three decimal places. If a p-value is < 0.001, it will be presented as "< 0.001."

5.4.4. Dictionaries

The Medical Dictionary for Regulatory Activities (MedDRA, version 23.0 or later version) will be used to code adverse events and medical history into system organ class (SOC) and preferred term (PT) within SOC. The enhanced version of the World Health Organization Drug Dictionary (WHO DDE, Sep 2014 or later version) will be used to code all medications (prior and concomitant) to anatomical therapeutic chemical (ATC) class and preferred drug names.

5.5. Analysis Populations

5.5.1. Enrolled Population

The Enrolled Population consists of all subjects who provide written informed consent. This population will be used for the summary of disposition and analysis of populations.

5.5.2. Safety Population

This population consists of all subjects who were treated with AT-GTX-501. This population will be used for the summary of demographics, baseline characteristics, assessment and reporting of all safety data for the study.

5.5.3. Full Analysis Set

This full analysis set (FAS) consists of subjects who were treated with AT-GTX-501 and had an analyzable primary efficacy outcome (Hamburg Motor + Language aggregate score) at baseline. This analysis set will be used for the summary of efficacy data for the study.

5.5.4. Natural History Cohort

To provide additional context to current AT-GTX-501-01 efficacy data, a natural history cohort consisting of subjects from the following source will be used:

- 23 subjects from an ongoing CLN6 natural history study at Nationwide Children's Hospital (NCH; NCT03285425).

Among the 23 subjects in the CLN6 natural history study:

- 5 subjects had juvenile onset instead of late-infantile onset, as evidenced by an age of first motor or language symptom onset greater than 4 years.
- 1 subject did not fully develop language ability (not able to speak two-word sentences), and thus could not be scored for the Language domain of the Hamburg scale.

As a result, these 6 subjects are excluded and thus there are a total of 17 subjects in the natural history cohort.

Two sample comparisons will analyze Hamburg scores between treated subject data from Study AT-GTX-501-01 and the natural history data. Descriptive subject level analyses with respect to the subject age and baseline Hamburg scores of treated subjects may be considered.

5.6. Baseline Definition

Study AT-GTX-501-01

For all efficacy and safety data, the baseline value is defined as the last non-missing measurement obtained on or before the administration of the AT-GTX-501.

Natural History Cohort

For the unmatched analyses of Hamburg scores, the baseline derivation is described in Section 7.1.2.

For the comparisons of Hamburg scores using many to one matching, the baseline derivation is described in Section 7.1.6.

5.7. Derived and Transformed Data

5.7.1. Calculations Using Dates

5.7.1.1. Baseline Age and Age at Each Visit

Baseline age for enrolled subjects will be calculated as the truncated difference (ie, fractional part ignored) between the date of the informed consent and the subject's birth date (DOB)

adjusted for years, ie, Baseline Age = int[(Date of Informed Consent – DOB)/365.25)] where int() returns the integer portion of a calculated value.

Efficacy data will be listed by study visit and the age (months) at each visit, which will be derived as

Age (months) at a visit = int[(date of visit – date of birth + 1)/30.4]

where int() returns the integer portion of a calculated value.

For natural history control in the primary endpoint comparison, age (months) for an assessment or event will be used. See Section 7.1.2 for more details.

5.7.1.2. Study Day

For Study AT-GTX-501-01, study day for an assessment or event will be calculated relative to the date of administration of AT-GTX-501 as

Study day = date of assessment or event – date of administration of AT-GTX-501

Study day will be used in the listings for adverse event related data.

5.7.2. Change from Baseline

The change from baseline will be calculated as the post-baseline visit value minus the baseline value (ie, the value prior to or on the date of administration of AT-GTX-501).

5.7.3. Visit Windows

Below is the visit window for the analysis visit definition. If more than one visit occurs with an analysis visit, then the visit closest to the target date will be used for analysis.

Table 1: Visit Window for Analyses

Visit	Target Day	Day Range
Baseline		Screening, 0
Day 1	1	1, 1
Day 2	2	2, 3
Week 1 (Day 7)	7	4, 10
Week 2 (Day 14)	14	11, 17
Week 3 (Day 21)	21	18, 24
Month 1 (Day 30)	30	25, 59
Month 3	90	60, 136
Month 6	183	137, 227
Month 9	273	228, 318
Month 12	365	319, 410
Month 15	456	411, 501

Table 1: Visit Window for Analyses (Continued)

Visit	Target Day	Day Range
Month 18	548	502, 593
Month 21	639	594, 684
Month 24	730	685, last visit date

Unscheduled and scheduled visits will be mapped according to the range, so that by-visit analysis will include data from all the visits (both scheduled and unscheduled).

5.7.4. Multiple Assessments

If multiple assessments including assessments at unscheduled visit, are associated with a nominal visit post-baseline, only the assessment performed at the schedule visit will be used in the by-visit summary.

5.8. Handling of Missing Data

For the FAS in Study AT-GTX-501-01, analyses will be performed using observed data. Missing data will not be imputed.

As the data in the natural history cohort were collected retrospectively, only milestone ages corresponding to Hamburg scores were available. Therefore, scores at any given age will be derived using a step function as follows:

- Scores between two milestone ages will be imputed as the score at the younger age (ie, scores at the previous milestone age will be carried forward).
- Scores at any age older than the milestone age for the score of 0 will be 0.
- Scores at any age older than the final milestone age with a non-zero score or the age of death will be missing.

5.8.1. Missing Start and Stop Dates for Adverse Events

For AEs, partially missing start dates will be imputed for the purpose of determining treatment-emergence only.

Partially missing start dates will be imputed as follows:

For missing day:

- If the month and year are equal to the month and year of the date of gene transfer, then the date of gene transfer will be used.
- Otherwise, the first day of the month will be used.

For missing day and month:

- If the year is equal to the year of gene transfer, then the date of gene transfer will be used.
- Otherwise, the first day of the month and the first month of the year will be used.

If the stop date is not missing and the imputed start date is after the stop date, then the stop date will be used.

If the start date is completely missing and the stop date is on or after the date of gene transfer, the AE will be considered a treatment-emergent adverse event (TEAE).

If both start date and stop date are missing, the AE will be considered a TEAE.

Missing stop dates for adverse events will not be imputed.

5.8.2. Missing Adverse Event Intensity and Relationship

If an AE is missing the intensity or relationship to study drug, the AE will be classified under the maximum intensity grade that is not death (ie, Grade 4) or the maximum relationship (ie, definite), respectively.

5.8.3. Missing Start and Stop Dates for Prior and Concomitant Medications

Partially missing medication start dates will be imputed in a similar manner as described in Section 5.8.1 for imputing missing AE start dates. Missing stop dates for medications will not be imputed. If when using these rules, the imputed start date is after the stop date, then the start date will be left as missing and the medication will be considered a concomitant medication for the purpose of the analysis.

5.8.4. Handling of Missing Efficacy Data

For Study AT-GTX-501-01, efficacy analyses are performed using observed data. Missing data will not be imputed.

As the data in the natural history cohort were collected retrospectively, only milestone ages corresponding to Hamburg score declines were available. Therefore, scores at any given age will be derived using a step function as follows:

- Scores between two milestone ages will be imputed as the score at the younger age (ie, scores at the previous milestone age will be carried forward).
- Scores at any age older than the milestone age for the score of 0 will be 0.
- Scores at any age older than the final milestone age with a non-zero score or the age of death will be missing.

Missing dates will not be imputed in the analysis.

6. STUDY SUBJECT ACCOUNTING AND DISPOSITION

6.1. Disposition

A complete accounting of subject participation in the study will be created. A summary table will track subjects from written informed consent through their exit from the study and account for subject evaluation in the analysis population/sets.

The number and percentage of subjects who were screened, enrolled, treated (ie, Safety Population), completed, and discontinued the study will be summarized. The primary reason for study discontinuation as recorded on the electronic case report form (eCRF) will be included.

A listing of subject disposition will also be provided.

6.2. Protocol Deviations

Major protocol deviations will be summarized by category. A listing of all the protocol deviations will also be provided.

6.3. Demographic and Baseline Characteristics

Study AT-GTX-501-01

Demographic variables include baseline age, sex, race, ethnicity, height, body weight, and body mass index (BMI). Summaries of the demographic variables will be produced for the Safety Population.

Age at baseline will be summarized in both years and months using age at the administration of AT-GTX-501, which will be derived as follows:

Age at baseline (months) = int[(date of administration of AT-GTX-501 – date of birth + 1)/30.4]

Age at baseline (years) = int[Age at baseline (months)/12]

where int() returns the integer portion of a calculated value.

Age at symptom onset will be derived using the natural history portion of the UBDRS scale, as the earliest age of any symptoms.

BMI (kg/m^2) will be calculated using height (cm) and weight (kg) as follows:

BMI (kg/m^2) = weight (kg)/(height (cm)/100)^2

Baseline Hamburg Motor, Language, and Motor + Language aggregate scores will also be summarized for the FAS.

By-subject listings will be provided that include the demographic and baseline data, as well as CLN6 gene mutations 1 and 2.

Natural History Cohort

Demographic and baseline characteristics will be summarized. The variables include sex, age of first clinical sign (months), age of decline in motor function (months), and age of decline in language ability (months).

A by-subject listing of the above demographic and baseline characteristics, as well as the first and second CLN6 alleles, will also be provided.

6.4. Listing of Subject Inclusion and Exclusion Criteria

This data, although not summarized in table format, will be listed on an individual subject basis.

6.5. Medical History and Medical Conditions Present at Entry

A summary table of the number and percentage of subjects with medical history by system organ class (SOC) and preferred term (PT) will be generated. Medical history will be sorted alphabetically by SOC and PT within the same SOC. For this summary table, a subject may appear more than once if he/she has more than one medical history coded under different SOC or PT categories. However, the subject will be counted only once in the overall category.

A by-subject listing of medical history with SOC and PT along with verbatim term will also be provided.

6.6. Prior Medications and Medications Present at Entry

Prior medications are those started prior to the date of administration of AT-GTX-501.

A summary table of the number and percentage of subjects with prior medication by the second anatomical therapeutic chemical (ATC) class (denoted as ATC level 2 hereafter) and preferred drug name will be produced. Prior medications will be sorted alphabetically by ATC level 2 and preferred drug name within the same ATC level 2. For this summary table, a subject may appear more than once if he/she has more than one prior medication coded under different ATC or preferred drug name categories. However, the subject will be counted only once in the overall category.

A by-subject listing of all medications will be provided, with indicators for the type of medications (prior or concomitant).

6.7. Other Baseline Data

Other data at baseline (eg, clinical laboratory results, physical and neurological examination results, and vital signs data) will be included in the by-visit summary tables for these parameters and will not be summarized separately.

Supportive data listings including all information collected in the eCRFs for these parameters will also be provided.

6.8. Duration in Study

For Study AT-GTX-501-01, descriptive statistics for duration since administration of AT-GTX-501 will be provided. Duration since administration of AT-GTX-501 will be derived in months as follows:

Duration (months) = (date of last visit– date of administration of AT-GTX-501 + 1)/30.4

Duration will be rounded to the first decimal place in the analysis.

6.9. Concomitant Medications

Medications taken on or after the date of administration of AT-GTX-501 will be considered as concomitant medications.

A summary table of the number and percentage of subjects with concomitant medication will be produced by ATC level 2 and preferred drug name. Concomitant medications will be sorted alphabetically by ATC level 2 and preferred drug name within the same ATC level 2. For this summary table, a subject may appear more than once if he/she has more than one concomitant medication coded under different ATC or preferred drug name categories. However, the subject will be counted only once in the overall category.

A by-subject listing of all medications will be generated and include ATC level 2, preferred drug name along with reported drug name. Prior and concomitant medications will be indicated in this listing.

A separate listing of medication of interest (eg, anti-seizure medications) will be generated.

7. EFFICACY ANALYSES

Observed values and changes from baseline for each efficacy endpoint will be summarized with descriptive statistics at each analysis visit, based on the FAS, unless otherwise stated. Mean plots including standard error bars at each visit for the observed values and changes from baseline will be provided, as appropriate.

7.1. Analysis of the Primary Efficacy Endpoint

7.1.1. Description of Primary Efficacy Outcomes

Hamburg scale scores to be analyzed include the following:

- Motor and Language domain scores, which range from 0 to 3
- The Motor + Language aggregate score, which is the sum of Motor and Language domain scores and ranges from 0 to 6

Each domain is scored on a 0 to 3 scale, where 3 is considered normal and 0 indicates complete loss of function. As a result, for the Motor + Language aggregate score, 6 is considered normal and 0 indicates complete loss of function.

If either Motor or Language domain score is missing at a visit, the Motor + Language aggregate score will be set to missing for the visit.

7.1.2. Rate of Decline in Hamburg Scores

Study AT-GTX-501-01

For each subject in the FAS of Study AT-GTX-501-01, rates of decline in Hamburg scores are derived as follows:

1. Determine the slope as

   Slope = (Score at last assessment – Score at baseline)/(Age at last assessment – Age at baseline)

2. Calculate the rate of decline as the negative of the slope, scaled to 24 months:

   Rate of decline = (-1) * 24 * Slope

Natural History Cohort

For each subject in the natural history cohort, rates of decline in Hamburg scores are derived as follows, using Hamburg Motor + Language aggregate score as illustration:

1. Identify the starting point and the ending point.
   a. The starting point is the combination of the starting score and starting age, determined as follows:
      i. The starting score is the earliest score < 6.
      ii. If there are multiple assessments with the starting score, the starting age is the mid-point between the ages at the first and last of these assessments; otherwise, the starting age is the age at the assessment.

b. The ending point is the combination of the ending score and ending age, determined as follows:

i. The ending score is the latest score > 0.
ii. The ending age is the age at the last assessment with the ending score.

2. Determine the slope as

Slope = (Ending score – Starting score)/(Ending age – Starting age)

3. Calculate the rate of decline as the negative of the slope, scaled to 24 months:

Rate of decline = (-1) * 24 * Slope

Descriptive statistics of rates of decline in Hamburg Motor + Language aggregate, Motor, and Language scores will be provided. Differences between the FAS of Study AT-GTX-501-01 and the natural history cohort will be summarized with mean, standard error, and 95% confidence interval (CI), and tested using a two-sample t-test. Subjects in the natural history cohort who had Ending age – Starting age < 24 months will be excluded from this analysis.

As a sensitivity analysis, the above analysis will be repeated for the Hamburg Motor + Language aggregate score, excluding subjects in the FAS of Study AT-GTX-501-01 who had a baseline score of 6.

In addition, change from baseline in Hamburg scores will be derived and summarized.

Study AT-GTX-501-01

For Study AT-GTX-501-01, change from baseline at a post-baseline visit will be calculated as

Change from baseline at a visit = value at the visit – value at baseline

Natural History Cohort

For the natural history cohort, the starting age and starting score derived above will be used as the baseline. Starting from the baseline, scores at subsequent visits in 3-month intervals will be derived using the step function as described in Section 5.8.4. Change from baseline at the subsequent visits will then be derived in the same way as for Study AT-GTX-501-01.

Descriptive statistics of the Hamburg Motor + Language aggregate, Motor, and Language scores at 3-month intervals until Month 24, and their changes from baseline will be provided. A plot of mean (± SE) change from baseline comparing the FAS of Study AT-GTX-501-01 with the natural history cohort will also be provided.

Lastly, overlay plots of mean Hamburg Motor + Language aggregate, Motor, and Language scores by age (months) of all subjects in Study AT-GTX-501-01 and all natural history subjects will be produced to compare their scores over time graphically.

7.1.3. Proportion of Subjects with Decline in Hamburg Scores

Changes from baseline in Hamburg scores at Month 24 will be categorized as +1, 0, -1 and ≤ -2, and summarized for both the FAS of Study AT-GTX-501-01 and the natural history cohort.

A proportion of subjects who had unreversed 2-point decline (ie, change from baseline ≤ -2 that was not reverted back later) in Hamburg Motor + Language aggregate score will be summarized, with risk difference and its exact 95% CI provided together with the Fisher's exact test p-value

for the difference between the FAS of Study AT-GTX-501-01 and the natural history cohort. For the natural history subjects, once the score was declined, it is assumed that it did not revert back so a simple decline is treated as an unreversed decline in the analysis.

This analysis will be repeated for the proportions of subjects with 2-point decline and 1-point decline in Hamburg Motor and Language scores.

Natural history subjects who had the last milestone age < 24 months from the baseline age will be excluded from the analyses.

7.1.4. Time to Unreversed Decline in Hamburg Scores

An unreversed decline of 2 points is defined as any decline of 2 points or more that had not reverted back to a 1-point decline (or better) as of the last recorded observation. For the natural history subjects, once the score was declined, it is assumed that it did not revert back so a simple decline is treated as an unreversed decline in the analysis.

Study AT-GTX-501-01

For each subject in the FAS of Study AT-GTX-501-01, derive the time to unreversed 2-point decline as follows:

- Identify the first assessment with a score ≤ baseline score – 2 and none of the subsequent assessments have scores > baseline score – 2. If such a sustained decline exists, then the subject has an event and the time (months) is

  Time = (date of the first assessment – baseline date + 1)/30.4.

- If no such assessment exists (including the case when the last assessment is the only one with a score ≤ baseline score – 2), then the subject is censored and the time (months) is

  Time = (date of last assessment – baseline date + 1)/30.4.

Natural History Cohort

For each natural history subject, derive the time to unreversed 2-point decline as follows:

- Identify the starting point and the ending point as in Section 7.1.2.
- Exclude the subject from analysis if Ending age – Starting age is < 24 months.
- Identify the first assessment when the score is ≤ Starting score – 2.
  - If no such assessment exists, then the subject is censored and the time (months) is

    Time = (Ending age – Starting age)

  - If an assessment exists such that the score = Starting score – 2, then the subject has an event and the time (months) is

    Time = (Age of the first assessment – Starting age)

  - If the subject has no score = Starting score – 2 but has scores < Starting score – 2, then the subject has an event and the missing time point (when 2-point decline

started) is imputed with a linear interpolation using age at the last assessment with score > Starting score – 2 and the first assessment with score < Starting score – 2.

The time to unreversed 2-point decline will be analyzed using the Kaplan-Meier method. The proportion of subjects experiencing such a decline and those censored by Month 24, will be provided. Log-rank test p-value comparing the two Kaplan-Meier curves will be provided. Hazard ratio and 95% CI using Cox proportional hazard model with only the treatment group factor will also be provided.

The above analyses will be performed for Hamburg Motor + Language aggregate, Motor, and Language scores. For the analyses of Hamburg Motor and Language domain scores, 1-point decline will be used instead.

7.1.5. Subject Profile Plots

Study AT-GTX-501-01

For each subject in Study AT-GTX-501-01, profile plots of Hamburg scale (Motor + Language aggregate, Motor, Language, Visual, Seizure scores) will be generated by age at each assessment in months. A by-subject listing of the Hamburg scales at each visit will include raw score, and their changes from baseline, and the age (in months) corresponding to each visit.

Natural History Cohort

For each subject in the natural history cohort, profile plots of Hamburg Motor + Language aggregate, Motor, and Language scores will be generated by age in months. As the natural history data were collected retrospectively, only milestone ages corresponding to Hamburg score declines were available. Therefore, the plots of Hamburg scores were step functions with declines at milestone ages only. A by-subject listing of the Hamburg Motor + Language aggregate, Motor, and Language scores at the milestone ages will also be provided.

7.1.6. Comparisons with Natural History Cohort Using Many to One Matching

For each subject in the efficacy analysis subset of Study AT-GTX-501-01 (denoted as a treated subject), many to one matching will be used to compare one treated subject with multiple natural history subjects in the natural history cohort. The matching between the treated subject and the natural history subjects will be performed using the starting score (ie, score at baseline) of the treated subject and/or the starting and ending ages (eg, age at baseline and age at the last visit, respectively of the treated subject).

Since the age for subjects in Study AT-GTX-501-01 and the natural history subjects are not aligned, the step function described in Section 5.8.4 will be used to derive the scores of each natural history subject at specific ages in the analyses.

7.1.6.1. Primary Matching Method: Exact Matching at Baseline Score and Age

For each treated subject, natural history subjects who had the same score (as the baseline score of the treated subject) at the same age (as the baseline age of the treated subject) are selected using this matching method. The baseline score and baseline age of the treated subject will be the starting score and starting age for the matching natural history subjects. The scores at Month 24 visit after baseline for the natural history subjects will be derived using the step function as

described in Section 5.8.4. Natural history subjects who had missing scores at Month 24 visit will be excluded from the matching analysis. Details are given in Appendix A.

Once the matching natural history subjects have been selected for each treated subject, the following analyses will be performed:

1. A bubble plot will be created to show for each treated subject the matching natural history subjects and their respective changes from baseline at Month 24 in the Hamburg Motor + Language aggregate score, where the bubbles are proportional to the number of matched subjects at the respective changes from baseline.
2. For each treated subject, change from baseline at Month 24 in the Hamburg Motor + Language aggregate score will be listed, together with the mean score change and the number of the matching natural history subjects.
3. For each treated subject, whether the subject had unreversed 2-point decline at Month 24 in the Hamburg Motor + Language aggregate score (Yes/No) will be listed, together with the proportion and the number of subjects with 2-point decline among the matching natural history subjects.

The above analyses of changes from baseline and proportion of decline will be repeated for the Hamburg Motor and Language scores, respectively. In each individual Hamburg score, proportion of subjects with 1-point decline will be considered.

7.1.6.2. Additional Matching Methods

Two additional matching methods are used for supportive analyses.

1. Matching by baseline score: For each treated subject, natural history subjects who had the same score as the baseline score of the treated subject are selected. The milestone age corresponding to the baseline score will be used as the starting age for the matching natural history subjects, except when the baseline score is at the maximum score (eg, 6 for the Hamburg Motor + Language aggregate score). When the baseline score is at the maximum score, the midpoint between birth (ie, 0 month) and the next milestone age will be used as the starting age for the matching natural history subjects. Details are given in Appendix B.
2. Matching by baseline score and age within ± 6 months: For each treated subject, natural history subjects who had the same baseline score as the treated subject at a milestone age that is within ± 6 months of the baseline age for the treated subject are selected. The milestone age corresponding to the baseline score will be used as the starting age for the matching natural history subjects. Details are given in Appendix C.
3. Sibling plots: Subjects that have siblings within the study and across study cohorts. Four siblings were treated in the current study, and three other treated subjects have siblings in the natural history cohort. Sibling plots of Hamburg Motor and Language scores over age at assessment in month will be generated to investigate whether treatment effects are the same for siblings and whether treated subjects' responses are different from those of untreated siblings. Sibling plots of other subscores (visual, seizures) of four treated siblings in the current study will be generated as the natural history dataset does not contain those scores.

7.2. Analyses of the Secondary Efficacy Endpoints

For secondary efficacy endpoints, descriptive analyses will be performed on the FAS of Study AT-GTX-501-01. Descriptive statistics of observed values and changes from baseline at each analysis visit will be provided.

7.2.1. Analyses of Unified Batten Disease Rating Scale

To assess progression in children with CLN6 Batten disease, each treated subject in Study AT-GTX-501-01, the rate of decline from baseline to Month 24 in the UBDRS subscale score (Behavioral Assessment, Capability Assessment - Actual Vision, Physical Assessment, Seizure Assessment) is calculated as follows:

1. change from baseline (CFBL) in the UBDRS subscale score at Month 24 is derived as:

   CFBL at Month 24 = (Score at last assessment – Score at baseline)

2. Change in UBDRS subscale score every 2 years is calculated as CFBL at Month 24 divided by the study month of the last assessment (study day of the last assessment divided by 30.4), ie:

   Change every 2 years = [CFBL at Month 24/(Study day of last assessment/30.4)] * 24

Details of UBDRS score and handling a missing response are given in Appendix D.

Descriptive statistics of the UBDRS subscale scores at visits for Day -30 to Day -2 (baseline/screening), Day 30, and for Months 3, 6, 9, 12, 15, 18, 21, and 24, and their changes from baseline will be provided for Study AT-GTX-501-01 treated subjects.

7.2.2. Analyses of Mullen Scale of Early Learning

Age-equivalent and raw scores of cognitive and motor ability in each area (visual reception, fine motor, expressive language, receptive language, and early learning composite) will be summarized by visit with descriptive statistics.

7.2.3. Analyses of Development Profile™-3

Development Profile is a patient-reported outcome tool (or caregiver checklist) used to screen children (birth through < 13 years of age) for developmental delays in 5 areas (physical, adaptive behavior, social-emotional, cognitive, communication, and general development).

Standard scores in each area will be summarized by visit with descriptive statistics. Scores reported as "< 50" or "N/A" will not be included in the summary.

7.2.4. Analyses of Preschool Language Scales-5th Edition (PLS-5) (Birth to 7 Years, 11 Months of Age)

The PLS-5 is a comprehensive developmental language assessment with items that range from pre-verbal, interaction-based skills to emerging language to early literacy.

Age-equivalent scores in each area (Auditory Comprehension, Expressive Communication, Total language score) will be summarized by visit with descriptive statistics.

Standard scores in each area will also be summarized by visit with descriptive statistics. Scores reported as "< 50" or "N/A" will not be included in the summary.

8. SAFETY ANALYSES

Safety will be evaluated by adverse events, clinical safety laboratory data, vital signs, ECGs, physical and neurological examinations, and concomitant medications as described in detail below. All analyses of the safety data will be performed on the Safety Population.

8.1. Adverse Events

An AE will be classified as a TEAE if

- the AE started on or after the date of administration of AT-GTX-501, or
- the AE started before the date of administration of AT-GTX-501 but worsened after the date of administration of AT-GTX-501

An overall summary of adverse events will be provided for the following:

- TEAEs
- Treatment-related TEAEs
- Grade 3 or 4 TEAEs
- Serious AEs (SAEs)
- Treatment Emergent Serious Adverse Events (TESAEs)
- Treatment-related TESAEs
- TEAEs leading to study drug discontinuation
- TEAEs leading to death

AE assessed by the investigator as definitely, probably, or possibly related to AT-GTX-501 will be considered "related" to AT-GTX-501; AEs assessed as unlikely or unrelated will be considered "not related" to AT-GTX-501.

In the overall summary, the number and percentage of subjects with each type of events will be provided, along with the number of events.

A by-subject listing of all AEs will also be provided in which TEAEs will be flagged. Included in the listing will be the subject ID, start and end dates and study days of the AE, SOC, PT and verbatim for the AE, AE seriousness (Yes/No), intensity (1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening, 5 = death), relationship to study treatment (definitely, probably, possible, unlikely, unrelated), action taken (none, dose interrupted, drug withdrawn), and outcome (recovered, recovered with sequelae, not recovered, fatal).

8.1.1. Summaries of TEAEs

The number and percentage of subjects with TEAEs will be summarized by SOC and PT within each SOC, as well as by PT only. A similar display will present TEAEs related to study treatment. Moreover, the number of TEAEs (as opposed to the number and percentage of subjects) will be presented in the summaries.

A by-subject listing of grade 3 or 4 TEAEs, will also be provided.

8.1.2. Summaries of Incidence Rates for Treatment Emergent Serious Adverse Events, Discontinuations Due to Treatment Emergent Adverse Events, and Death

The number and percentage of subjects who experienced treatment emergent serious adverse events (SAEs) will be presented by SOC and by preferred term within each SOC. TEAEs leading to study discontinuation, and deaths will be similarly presented.

By-subject listings of SAEs, TEAEs leading to study discontinuation, and deaths will be provided. The SAE listing will indicate if an SAE is a TEAE.

8.2. Clinical Safety Laboratory Data

Descriptive statistics for clinical safety laboratory test data will be presented at each visit, starting at baseline, by laboratory test category (clinical chemistry, hematology, and urinalysis). Change from baseline to post-baseline visit will also be presented.

Baseline for laboratory test results is defined as the last assessment prior to the date of gene transfer regardless of whether it was scheduled, repeated, or unscheduled. All subjects in the Safety Population with a baseline laboratory assessment will be included.

Tables displaying shifts from baseline to abnormal post-baseline laboratory test result at any time before or at the end of study visit, will be provided by laboratory test category and laboratory test parameter using the laboratory test normal ranges with categories of below, within, or above the normal range. Data listings for all laboratory results will be generated.

8.3. Vital Signs

Descriptive statistics for vital signs (systolic blood pressure, diastolic blood pressure, body temperature, pulse rate, and respiration rate) will be presented at each visit, starting at baseline. Change from baseline to post-baseline visit will also be presented.

8.4. Electrocardiograms

The number and percentage of subjects with the following overall Electrocardiogram (ECG) evaluation will be presented from baseline to post-treatment at each visit:

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

Clinically significant abnormal ECG results as assessed by the investigator will be summarized to present the number and percentage of subjects with reported adverse events.

8.5. Physical and Neurological Examinations

Physical examination results will be presented for each body organ system examined, at each visit. The number and percentage of subjects judged to be normal, abnormal (specify body organ system, clinically significant or not), or not performed will be summarized.

Neurological examination results will be similarly summarized.

By-subject listings will be generated and include the information collected on the eCRF (eg, body organ system for physical examination and neurological examination investigator observation [ie, normal or abnormal] or not performed, and any investigator comments) at each visit.

8.6. Immunogenicity Assessments

Blood sample collection for immunogenicity assessments were performed at baseline and at each site visit from Day 7 through Month 24. Assessments include measurements of anti-AAV9 and anti-CLN6 antibodies and measurement of T-cell responses (eg, separate IFN-γ ELISpot assays to detect T-cell responses to CLN6 peptides or AAV9). Antibody Titers and Elispot assay results will be summarized by Subcategory for Immunogenicity Test (AAV9, CLN6) at each visit.

8.7. Electroencephalograms

A long-term (up to 24 hours) monitoring electroencephalogram (EEG) is performed at site visits on Day -30 to Day -2 (baseline/screening), Month 12, and Month 24.

The number and percentage of subjects with abnormality in EEG test results will be presented:

EEG exam and state:

- When subjects' states were awake and asleep - abnormal and normal, and
- Seizures during EEG - absent or present

EEG with epileptiform discharge – present (specify anatomic location) clinically significant or not.

Tables will be utilized to summarize seizures, and any epileptiform activity at each visit.

8.8. Other Study Data

Other study data, including ophthalmologic examinations, MRI, Pediatric Quality of Life Inventory, Interviews and data Collection on Subject Status and Function will be listed in by-subject listings.

9. IMPORTANT POTENTIAL RISK ANALYSIS

The following important potential risks have been identified for AT-GTX-501 based on the general risks that are common to all AAV vectors:

- Elevated aminotransferases
- Transient thrombocytopenia
- Dorsal root ganglion inflammation due to AAV9 vector

In addition, post-treatment thrombotic microangiopathy will be investigated to address whether it is associated with AAV vector.

9.1. Elevated Aminotransferases Including Post-Treatment Hepatotoxicity

Immune-mediated acute, subacute and chronic liver injury or failure from baseline (Day 0) to post-treatment visit Day 30, from Day 0 to Month 3 (Day 136), and from Day 0 to Month 24 will be evaluated as follows.

- A number and percentage of subjects with post-treatment asymptomatic elevation of aminotransferases (in alanine aminotransferease [ALT], aspartate transaminase [AST], total bilirubin, prothrombin time [PT], prothrombin international normalized ratio [INR], alkaline phosphatase [ALP])
  - ALT or AST > 3 x ULN and Total bilirubin > 2 x ULN
  - Prothrombin time prolonged by > 4 seconds or INR is > 1.5
  - ALP > 3 x ULN
- A number and percentage of subjects with post-treatment symptomatic hepatotoxicity and liver enzyme elevation (assessed by investigator) from Day 0 to 30, from Day 31 to Month 3, and from Day 0 to Month 24 (CRF: Adverse events - (1) Preferred Term (PT) for symptomatic hepatotoxicity: nausea, vomiting, decreased appetite, fatigue, jaundice, abdominal pain upper) (2) Preferred Term (PT) for liver enzyme elevation: hepatic function abnormal, hypertransaminasemia, transaminases increased, transaminases abnormal, alanine aminotransferase increased, and aspartate aminotransferase increased)

To understand causality in liver enzymes increase (ALT and AST 3 x ULN) and symptomatic (Standardized MedDRA Queries (SMQ) - Liver related investigations, signs and symptoms) manifestation of hepatoxicity as adverse events, listing will be generated with concomitant glucocorticoid treatment from the following source.

[CRF-Concomitant Medication:
Glucocorticoids: prednisone, prednisolone, dexamethasone
Indication: prophylaxis or immunosuppression
Route: oral or systemic (IV)]

9.2. Transient Thrombocytopenia

Transient thrombocytopenia will be evaluated by frequency table analysis on post-treatment decreased platelet count (below 140 x 10^3 mcL) from baseline (Day 0) to Day 30.

9.3. Post-treatment Dorsal Root Ganglion (DRG) Neurotoxicity

Post-treatment DRG neurotoxicity will be evaluated by

A number and percentage of subjects with abnormal neurological exam sensory evaluations from baseline (Day 0) to Month 24 including all visits. [CRF: neurological exam, sensory] and adverse events (serious and nonserious) of peripheral neuropathy origin: [CRF-Adverse Events, PT of tingling, burning, weakness and numbness in extremities, neuropathic pain and MedDRA HLT of Spinal Cord and Nerve root disorders NEC, Thoracic spinal cord and nerve root disorders, Cervical spinal cord and nerve root disorders].

9.4. Post-treatment Thrombotic Microangiopathy (TMA)

Post-treatment TMA will be evaluated by a frequency table with number and percentage of subjects from Day 0 to month 24 including all visits with abnormal clinical laboratory test results and adverse events:

- Low platelet count (below 140 x 10^3 mcL) and hemoglobin < 10 g/dL [CRF: Hematology labs]
- PT: acute kidney injury or PT: thrombotic microangiopathy or PT: thrombotic thrombocytopenic purpura (TTP) or PT: haemolytic uremic syndrome (HUS) [CRF: Adverse Events]. Note: seizures (AE) will be excluded as disease-related adverse event.

9.5. Adverse Events of Special Interest Analysis

For AT-GTX-501 below have been identified as Adverse events of special interest (AESI) as per the Investigator's Brochure.

- Liver enzyme elevations and liver function abnormalities (see PTs in Appendix E)
- New incidence or exacerbation of malignancies or pre-existing/prior rheumatologic, autoimmune, or hematologic disorders in the following source [CRF-Adverse Events
  (a) SOC='Immune system disorders'
  (b) SMQ Level 2: Blood premalignant disorders, Narrow (see PTs in Appendix F)
  (c) SMQ Level 2: Haematopoietic cytopenias affecting more than one type of blood cell, Broad and Narrow (see PTs in Appendix G)
  (d) PT: Neoplasm (see PTs in Appendix H)]

9.6. Immuno-mediated Response Management with Glucocorticoids

Per protocol AT-GTX 501-01, section 9.1.1, all subjects were to receive a 30-day immunosuppressive treatment with prednisone/prednisolone 1 mg/kg/day (a maximum dose of 60 mg/day) and taper it over 4-7 weeks depending on blood level of liver enzymes.

The following frequency table analyses will be conducted to understand the therapeutic role of concomitant glucocorticoid regimen in management of the immune-mediated response to AAV9 gene therapy descriptive analyses of glucocorticoids dose adjustment, prolonged treatment including redosing and taper duration will be performed.

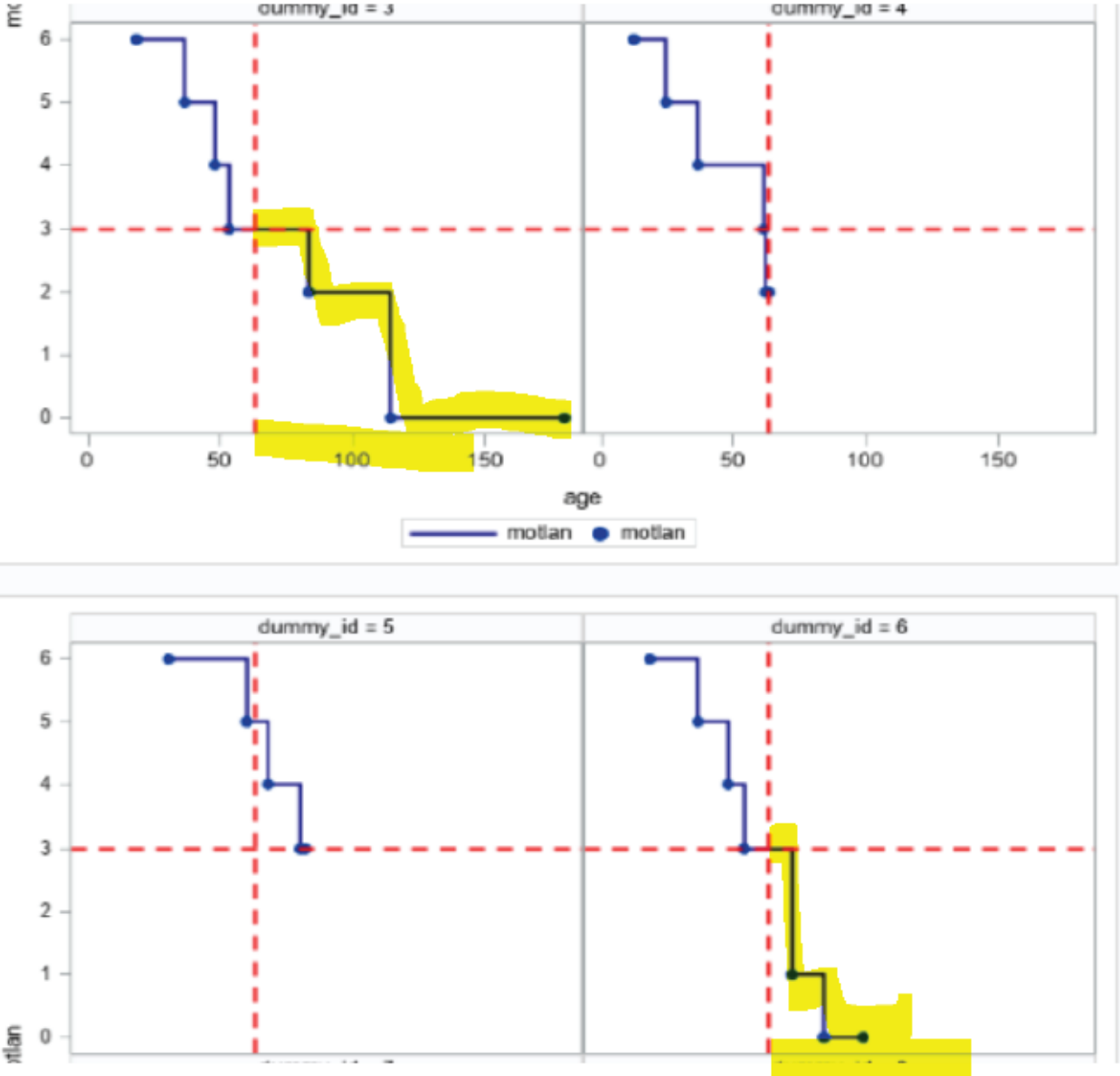
- A number and percent of subjects with increased dose (> 1 to 2 mg/kg/day) of glucocorticoids anytime from Day -1 to Month 3

  [CRF-Concomitant Medications
  Glucocorticoids: prednisone, prednisolone, dexamethasone
  Indication: prophylaxis or immunosuppression
  Route: oral or systemic (IV)]

- A number and percentage of subjects with prolonged (≥ 7 weeks) glucocorticoid taper (ie, dose decrease over 7 weeks and longer)
- A number and percentage of subjects with > 30-day to 120 days glucocorticoid treatment regimen including additional dosing
- A number and percentage of subjects with manifested symptomatic infection(s) from baseline (Day 0) to Month 3. [CRF: Adverse events; SOC=Infections and Infestation]

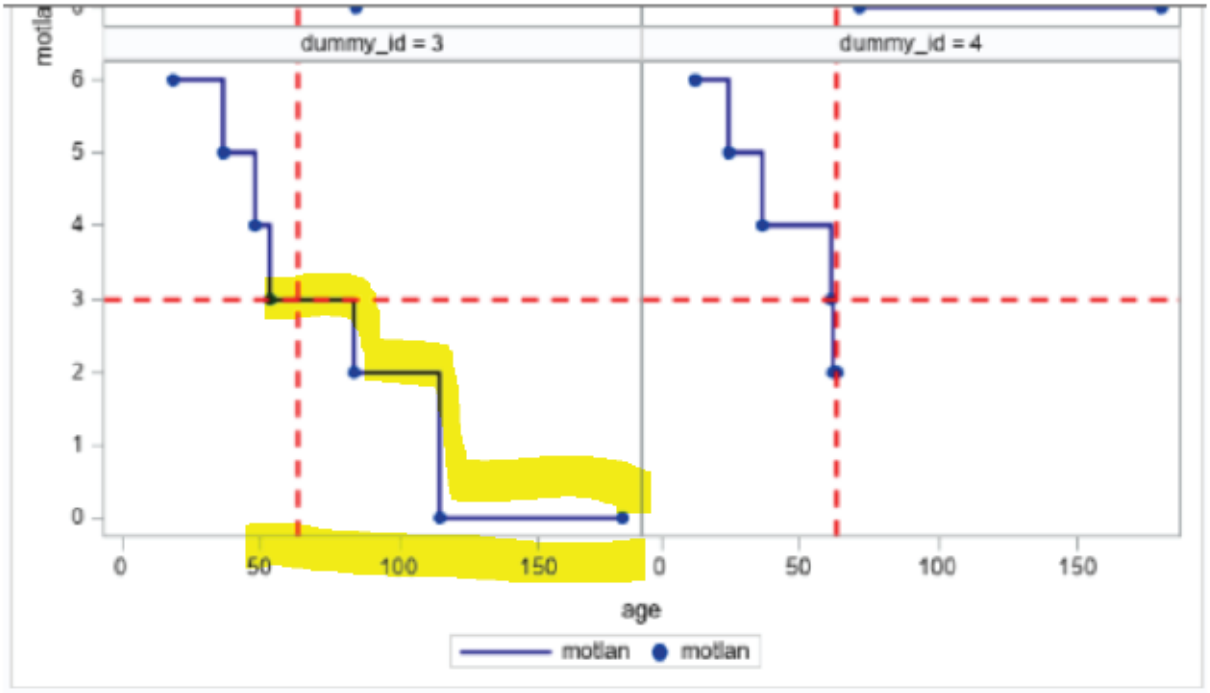
APPENDIX A. MATCHING BY BASELINE SCORE AND AGE (IN MONTH)

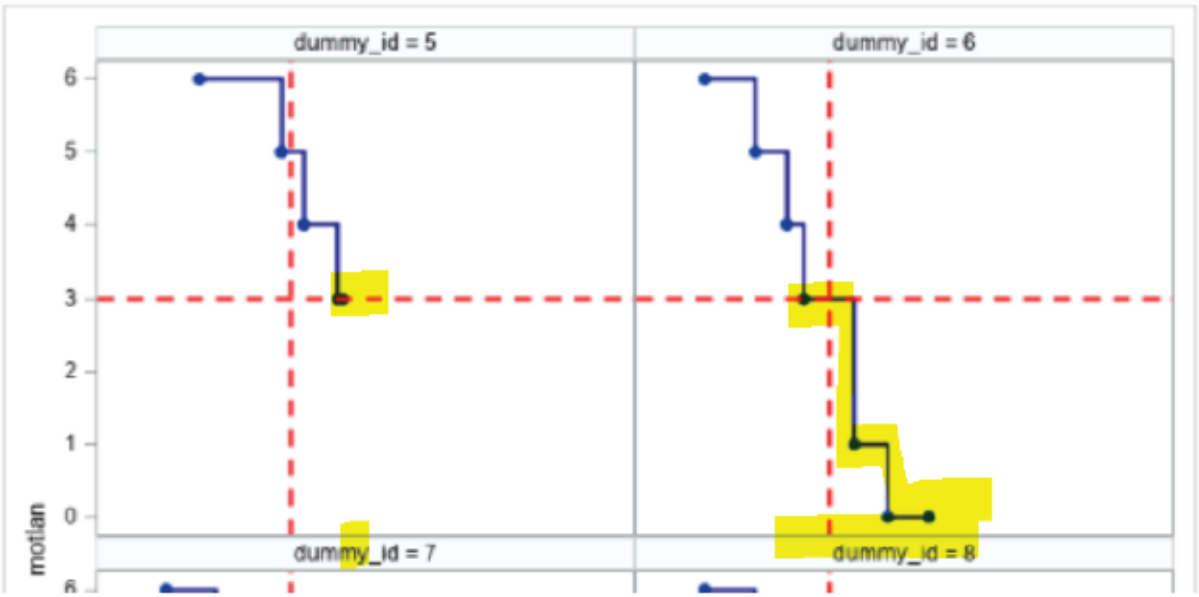
1. Suppose that a CLN6 treated subject has baseline score S at age A month.
2. For each subject in the natural history cohort:
   a. Determine whether subject has score S.
   b. Search interval of age (A_1, A_2), where A_1 = month with score S and A_2 = month with score S_2 (less than S) is defined.
   c. If the interval (A_1, A_2) contains A, then construct data; record (S, A) as a baseline record, (S_2, A_2) and forward as post-baseline records for the analyses.
3. Example with baseline score S = 3 at baseline age A = 63 months



APPENDIX B. MATCHING BY BASELINE SCORE

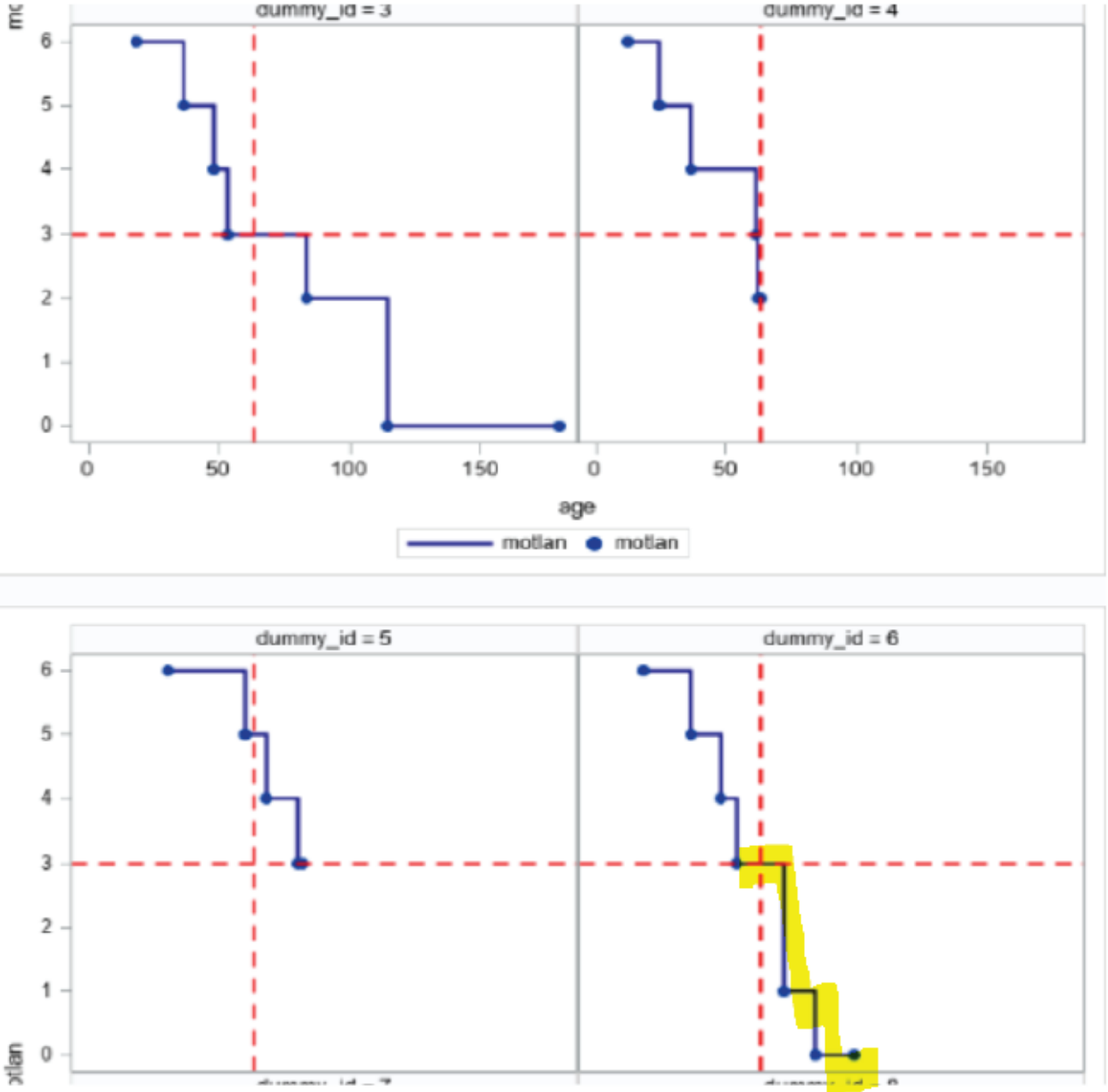
1. Suppose that a CLN6 treated subject has baseline score S at age A month.
2. For each subject in the natural history cohort:
   a. Determine whether subject has score S.
   b. Search interval of age (A_1, A_2), where A_1 = month with score S and A_2 = month with score S_2 (less than S).
   c. Construct data; record (S, A_1) as a baseline record, (S_2, A_2) and forward as post-baseline records for the analyses.
3. Example with baseline score S = 3 at baseline age A = 63 months





APPENDIX C. MATCHING BY BASELINE SCORE AND AGE (IN MONTH) ± 6 MONTH

1. Suppose that a CLN6 treated subject has baseline score S = 3 age A = 63 month.
2. For each subject in the natural history cohort:
   a. Determine whether subject has score S.
   b. Search interval of age (A_1, A_2), where A_1 = month with score S and A_2 = month with score S_2 (less than S).
   c. If there is a interval (A_1, A_2) where A_2 is defined and ($0 \leq A - A_1 \leq 6$), then construct data; record (S, A_1) as a baseline record, (S_2, A_2) and forward as post-baseline records.
3. Example with baseline score S = 3 at baseline age A = 63 months



APPENDIX D. UBDRS DERIVATION

1. UBDRS - PHYSICAL ASSESSMENT:
    a. UBDRS1+ UBDRS1A+ UBDRS2+…+UBDRS19+UBDRS20
    b. Include all UBDRSxA (for Right) and UBDRSxB (for left)
    c. For missing data, refer to section 6 below.
2. UBDRS - SEIZURE ASSESSMENT:
    a. UBDRS23+ …+UBDRS33+(UBDRS34-1)
    b. UBDRS34 - 1 (subtraction of 1) adjusts to have No = 1 and Yes = 0 for the question 34. ANTICONVULSANT ADJUSTMENT REQUIRED TO CONTROL SEIZURES IN PAST MONTH
    c. For missing data, refer to section 6 below.
3. UBDRS - BEHAVIORAL ASSESSMENT:
    a. UBDRS36A+UBDRS36B+ …+UBDRS44A+UBDRS44B+(UBDRS45-1)
    b. UBDRS45 - 1 (subtraction of 1) adjusts to have No = 1 and Yes = 0 for the question 45. MEDICATION REQUIRED FOR BEHAVIOR
    c. For missing data, refer to section 6 below.
4. UBDRS - CAPABILITY ASSESSMENT ASSUMING NORMAL VISION:
    a. UBDRS47+ …+UBDRS51.
    b. For missing data, refer to section 6 below.
5. UBDRS - CAPABILITY ASSESSMENT ASSUMING ACTUAL VISION:
    a. UBDRS52+ …+UBDRS56.
    b. For missing data, refer to section 6.
6. Missing Data
    a. If missing scores of QSSTRESN in this calculation (QSORRES in ('Not Applicable' 'Information Unavailable') are due to remote visit, then total score is missing.
    b. If missing score of QSSTRESN comes from QSORRES in ('Not Applicable' 'Information Unavailable'))but other scores are available at site visit, then
        i. If rate of questions with missing response is > 20%, then total score is missing.
        ii. If rate of questions with missing response is ≤ 20%, then do the following imputation:
            1. Replace QSSTRESN with integer value X and DTYPE = 'Imputed'
            2. A = total score of the completed items/maximum total score of the completed items
            3. X = ceil(A*Maximum score of the specific Q that was not answered).
    c. Example; Suppose that a subject has missing response in one question

qstestcd	qstest	qscat	Qsscat	qsorres	qsstresc	qsstresn
UBDRS47	SCHOOL	UBDRS	Capability Assessment - Normal Vision	Information Unavailable	Information Unavailable	.
UBDRS48	CHORES	UBDRS	Capability Assessment - Normal Vision	able to do simple chores independently	able to do simple chores independently	2
UBDRS49	PLAY	UBDRS	Capability Assessment - Normal Vision	able to play simple games with help	able to play simple games with help	1
UBDRS50	ADL	UBDRS	Capability Assessment - Normal Vision	gross tasks only	gross tasks only	1
UBDRS51	CARE LEVEL	UBDRS	Capability Assessment - Normal Vision	home	home	2

A = 6/(3+3+3+2) = 6/11
X = ceil((6/11)*3) = ceil(1.63) = 2
DTYPE = 'imputed'

APPENDIX E. SELECTED PTS OF LIVER RELATED INVESTIGATIONS, SIGNS AND SYMPTOMS (SMQ)

Preferred Terms	Scope
Alanine aminotransferase abnormal	Narrow
Alanine aminotransferase increased	Narrow
Aspartate aminotransferase abnormal	Narrow
Aspartate aminotransferase increased	Narrow
AST/ALT ratio abnormal	Narrow
Bilirubin conjugated abnormal	Narrow
Bilirubin conjugated increased	Narrow
Bilirubin urine present	Narrow
Blood bilirubin abnormal	Narrow
Blood bilirubin increased	Narrow
Blood bilirubin unconjugated increased	Narrow
Gamma-glutamyltransferase abnormal	Narrow
Gamma-glutamyltransferase increased	Narrow
Hepatic enzyme abnormal	Narrow
Hepatic enzyme increased	Narrow
Hepatic function abnormal	Narrow
Hyperbilirubinaemia	Narrow
Hypertransaminasaemia	Narrow
Liver function test abnormal	Narrow
Liver function test increased	Narrow
Mitochondrial aspartate aminotransferase increased	Narrow
Transaminases abnormal	Narrow
Transaminases increased	Narrow
Urine bilirubin increased	Narrow
Blood alkaline phosphatase abnormal	Broad
Blood alkaline phosphatase increased	Broad
Hypoalbuminaemia	Broad

APPENDIX F. SELECTED PTS OF BLOOD PREMALIGNANT DISORDERS (SMQ)

Preferred Terms	Scope
5q minus syndrome	Narrow
Blast cell count increased	Narrow
Blast cell proliferation	Narrow
Blast cells present	Narrow
Bone marrow infiltration	Narrow
Essential thrombocythaemia	Narrow
Hypergammaglobulinaemia benign monoclonal	Narrow
Megaloblasts increased	Narrow
Myelodysplastic syndrome	Narrow
Myelodysplastic syndrome transformation	Narrow
Myelodysplastic syndrome unclassifiable	Narrow
Myelofibrosis	Narrow
Myeloid metaplasia	Narrow
Myeloproliferative neoplasm	Narrow
Polycythaemia vera	Narrow
Primary myelofibrosis	Narrow
Refractory anaemia with an excess of blasts	Narrow
Refractory anaemia with ringed sideroblasts	Narrow
Refractory cytopenia with multilineage dysplasia	Narrow
Refractory cytopenia with unilineage dysplasia	Narrow

APPENDIX G. SELECTED PTS OF HAEMATOPOIETIC CYTOPENIAS AFFECTING MORE THAN ONE TYPE OF BLOOD CELL (SMQ)

Preferred Terms	Scope
Aplastic anaemia	Narrow
Autoimmune aplastic anaemia	Narrow
Bicytopenia	Narrow
Bone marrow failure	Narrow
Cytopenia	Narrow
Febrile bone marrow aplasia	Narrow
Full blood count decreased	Narrow
Gelatinous transformation of the bone marrow	Narrow
Immune-mediated pancytopenia	Narrow
Pancytopenia	Narrow
Panmyelopathy	Narrow
Aspiration bone marrow abnormal	Broad
Biopsy bone marrow abnormal	Broad
Blood count abnormal	Broad
Blood disorder	Broad
Bone marrow disorder	Broad
Bone marrow infiltration	Broad
Bone marrow myelogram abnormal	Broad
Bone marrow necrosis	Broad
Bone marrow toxicity	Broad
Congenital aplastic anaemia	Broad
Haematotoxicity	Broad
Myelodysplastic syndrome	Broad
Myelodysplastic syndrome transformation	Broad
Myelofibrosis	Broad
Myeloid metaplasia	Broad
Plasmablast count decreased	Broad
Primary myelofibrosis	Broad
Scan bone marrow abnormal	Broad

APPENDIX H. SELECTED HLGTS OF NEOPLASM

High Level Group Terms
Breast neoplasms malignant and unspecified (incl nipple)
Endocrine neoplasms malignant and unspecified
Gastrointestinal neoplasms malignant and unspecified
Haematopoietic neoplasms (excl leukaemias and lymphomas)
Hepatobiliary neoplasms malignant and unspecified
Leukaemias
Lymphomas Hodgkin's disease
Lymphomas NEC
Lymphomas non-Hodgkin's B-cell
Lymphomas non-Hodgkin's T-cell
Lymphomas non-Hodgkin's unspecified histology
Mesotheliomas
Metastases
Miscellaneous and site unspecified neoplasms malignant and unspecified
Nervous system neoplasms malignant and unspecified NEC
Ocular neoplasms
Plasma cell neoplasms
Renal and urinary tract neoplasms malignant and unspecified
Reproductive and genitourinary neoplasms gender unspecified NEC
Reproductive neoplasms female malignant and unspecified
Reproductive neoplasms male malignant and unspecified
Respiratory and mediastinal neoplasms malignant and unspecified
Skeletal neoplasms malignant and unspecified
Skin neoplasms malignant and unspecified
Soft tissue neoplasms malignant and unspecified