# STATISTICAL ANALYSIS PLAN

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|---|---|
| Study protocol code | IEDAT-04-2022 |
| Biotrial code | 2ERYD1 |
| Study title | A Multi-center, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the **N**eurological Effects of **E**ryDex on subjects with **A**taxia **T**elangiectasia |
| Study investigational medicinal product | Dexamethasone sodium phosphate encapsulated in autologous erythrocytes (eDSP), formerly referred to as EryDex |
| Development phase | Phase 3 |
| Sponsor | Quince Therapeutics S.p.A.<br>Via Meucci, 3<br>20091 Bresso (MI), Italy<br>☎: +39 02 36504470<br>🖷: +39 02 36504474 |
| Version of the statistical analysis plan | V3.0 |
| Date of the statistical analysis plan | 14 October 2025 |

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| ABBREVIATION | DEFINITION |
|---|---|
| ADaM | Analysis Data Model |
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| ALT (SGPT) | Alanine Aminotransferase |
| ALP | Alkaline Phosphatase |
| AST (SGOT) | Aspartate Aminotransferase |
| A-T | Ataxia Telangiectasia |
| ATC | Anatomic Therapeutic Chemical |
| BDRM | Blind Data Review Meeting |
| BMD | Bone Mineral Density |
| BMI | Body Mass Index |
| CBC | Complete Blood Count |
| CDISC | Clinical Data Interchange Standards Consortium |
| CGI-C | Clinical Global Impression of Change |
| CGI-S | Clinical Global Impression of Severity |
| CI | Confidence Interval |
| CPK | Creatine Phosphokinase |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| DSP | Dexamethasone Sodium Phosphate |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| eDSP | encapsulated Dexamethasone Sodium Phosphate |
| EQ-5D-Y | EuroQOL 5D-Y |
| HDL | High Density Lipoprotein |
| i.e. | id est |
| ICARS | International Cooperative Ataxia Rating Scale |
| ICH | International Conference on Harmonisation |
| iDSMB | Independent Data Safety Monitoring Board |
| Ig | Immunoglobulin |
| IMP | Investigational Medicinal Product (Synonymous with “Study Drug”) |
| ITT | Intent-To-Treat |
| ITT (6-9) | Intent-To-Treat Population for Participants Aged 6-9 Years |
| ITT (10+) | Intent-To-Treat Population for Participants Aged 10 Years and above |

| ABBREVIATION | DEFINITION |
|---|---|
| IV | Intravenous |
| IWRS | Interactive Web Response System |
| LDH | Lactate Dehydrogenase |
| LDL | Low Density Lipoprotein |
| MAR | Missing At Random |
| MCH | Mean Corpuscular Hemoglobin |
| MCH | Mean Corpuscular Hemoglobin Concentration |
| MCV | Mean Corpuscular Volume |
| MEDDRA | Medical Dictionary for Regulatory Activities |
| MICARS | Modified International Cooperative Ataxia Rating Scale |
| MMRM | Mixed-Effect Model Repeated-Measure |
| MNAR | Missing Not at Random |
| PP | Per-Protocol Set |
| PT | Preferred Term |
| QOL | Quality-Of-Life |
| QT | Time Interval for Ventricular Depolarisation and Repolarisation |
| RBC | Red Blood Cell |
| RmICARS | Rescored Modified International Cooperative Ataxia Rating Scale |
| RDO | Retrieved Dropouts |
| RDW | Red Blood Cell Distribution Width |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAS® | Statistical Analysis System® |
| SD | Standard Deviation |
| SEM | Standard Error of The Mean |
| SOA | Schedule of Assessments |
| SOC | System Organ Class |
| SOP | Standard Operating Procedures |
| SP | Safety Population |
| TEAE | Treatment-Emergent Adverse Event |
| TFLS | Tables Listings and Figures |
| UK | United Kingdom |
| ULN | Upper Limit of Normal |
| US | United States |

| ABBREVIATION | DEFINITION |
|---|---|
| VAS | Visual Analogue Scale |
| WBC | White Blood Cell |

# 1 Introduction

The Statistical Analysis Plan (SAP) details the statistical methodology to be used for the analyses of study IEDAT-04-2022 and outlines the statistical programming specifications, tables, figures and listings. The SAP describes the demographics, efficacy and safety variables and population sets, anticipated data transformations and manipulations, and other details of the analyses not provided in the study protocol.

The analyses described are based upon the final clinical study protocols V5.0 EU specific dated 22 August 2025, v4.0 US specific dated 29 September 2025 and v4.0 UK specific dated 02 October and will be prepared in accordance with the International Conference for Harmonisation (ICH) E9.

Specifications of Tables, Figures and Listings (TFLs) are described in a separate document.

An independent Data Safety Monitoring Board (iDSMB) will review safety and tolerability data from the trial. The iDSMB will receive unblinded safety data for review at specified intervals and may recommend to modify or stop the trial if significant safety concerns are detected. All analyses/individual profiles that will be sent and that will be used by the iDSMB appointed for this study are not part of this document.

This SAP covers only the final analysis, at the end of the safety follow-up.

The SAP will be finalized and signed before the start of analysis and the lock of the database.

# *2 Study objectives*

## *2.1 Primary efficacy objective*

To evaluate the neurological effect of eDSP (encapsulated dexamethasone sodium phosphate), as measured by the change of the rescored modified International Cooperative Ataxia Rating Scale (RmICARS) from baseline to Visit 9 compared to placebo in ataxia telangiectasia (A-T) (6- to 9-year-old participants primary analysis population). *[The RmICARS is a re-scored version of the ICARS and consists of 9 items across 3 domains (kinetic domain and speech limited to one item each), totaling a maximum score of 29 points.]*

### *2.2 Key secondary efficacy objective*

To evaluate the effect of eDSP, compared to placebo, in A-T (6- to 9-year-old participants primary analysis population), based on:

- Change of Clinical Global Impression of Severity (CGI-S) from baseline to Visit 9.

### *2.3 Other secondary efficacy objective*

To evaluate the effect of eDSP, compared to placebo, in A-T (6- to 9-year-old participants primary analysis population), based on:

- Clinical Global Impression of Change (CGI-C) at Visit 9.

### *2.4 Exploratory objectives*

To evaluate the effect of eDSP, on Quality-of-Life (QoL), compared to placebo, in A-T (6- to 9-year-old participants primary analysis population), based on:

- Health-related QoL using the change from baseline to Visit 9 of the domains in the EuroQoL 5D-Y (EQ-5D-Y) Interviewer Administered Proxy version 1 for participants 6- to 9-year of age and self-reported for participants 10 years of age and older.
- Health-related QoL using the change from baseline to Visit 9 of the EQ-5D-Y total score and Visual Analogue Scale (VAS).

**Participants 10 Years and Older:**

These primary/secondary/exploratory efficacy objectives will also be evaluated for participants 10 years and older. These analyses will be performed as data summaries in this older age cohort.

Self-reported evaluations will be used for the health-related QoL of the domains in the EQ-5D-Y for these participants.

**All participants:**

An analysis of the primary endpoint only for all randomized participants (including both the 6-9 years-old and 10 years and older age groups) will be performed to evaluate efficacy across all ages.

### *2.5 Safety objectives*

To evaluate the safety and tolerability of eDSP compared to placebo in participants with A-T, based on the occurrence of Treatment-Emergent Adverse Events (TEAEs), including Serious Adverse Events (SAEs) and discontinuations due to Adverse Events (AEs), and changes in vital signs, laboratory parameters, electrocardiograms (ECGs), and physical/neurological examination findings.

Safety analyses will be performed on the total population, participants 6- to 9-years-old and participants ≥ 10-years-old.

# *3 Study methodology*

## *3.1 Protocol overview*

Study IEDAT-04-2022 is an international, multi-center, randomized, double-blind, placebo-controlled, Phase 3 clinical trial to assess the effect of EryDex treatment (dexamethasone sodium phosphate [DSP] encapsulated in autologous erythrocytes), administered by intravenous (IV) infusion once every 28 days (window -7 days, +2 days), on the neurological symptoms of participants with A-T.

Approximately 86 6- to 9-year-old participants meeting all of the inclusion/exclusion criteria will be randomized equally (1:1; approximately 43 per group) to one of two groups:

- **Group 1** – eDSP
- **Group 2** – Placebo

To ensure enrollment of the primary analysis population, the total number of participants 10 years of age and above will initially be limited to 1 per site without prior approval from the Sponsor (approximately 20 participants 10 years of age and above, 10 per treatment group, are expected to be enrolled).

Randomization will be stratified by age (6-9 and ≥10 years), gender (male; female), and by geographic region (US versus Rest of World countries).

Randomization will be performed through a centralized Interactive Web Response System (IWRS). Each participant will receive 6 infusions of eDSP or placebo, given at approximately monthly intervals (see flow chart for further details).

Study periods

The study will consist of a 30-day screening period followed by 6 treatments (each one to be administered every 28 days, with a window -7 days, +2 days). There is an additional safety follow-up period that ends with Visit 9, which is performed 30 days after the participant's last infusion of trial treatment, and prior to potential transition to the open-label extension study. Participants who complete the study's full treatment period and complete Visit 9 efficacy assessments will be required to perform the Safety Follow-up. All participants who discontinue prematurely (prior to Visit 9 [final visit]) will be asked to return for all final (Early Withdrawal/Visit 9) efficacy and safety evaluations.

Treatment arms

- Group 1 will receive eDSP by IV infusion of 17.4±5.4 mg (mean ± standard deviation [SD]). The infusion will be a total volume of approximately 70-80 mL (final volume of the bag minus the volume transferred into the satellite sample bag) and will be given over approximately 40 minutes.
- Group 2 will receive Placebo (sodium chloride 0.372% in water for injection encapsulated in autologous erythrocytes) by IV infusion. The infusion will be a total volume of approximately 70-80 mL (final volume of the bag minus the volume transferred into the satellite sample bag) given over approximately 40 minutes. The osmolality of the non-active principal in the Placebo (sodium chloride), is identical to that of the DSP solution used in the EryDex process for Group 1.

Study treatment will be administered by IV infusion approximately every 28 days calculated from the date of the first dose and re-adjusted based on the date of the previous treatment. There is an allowed window of -7 to + 2 days for each treatment visit. The window between an infusion and the subsequent one should be kept as regular as possible throughout the study, avoiding fluctuations in administration windows. Doses should not be given in any case less than 14 days apart.

### *3.2 Planned analyses*

Statistical analyses will be performed at the end of the safety follow-up.

## *4 Sample Size*

The sample size for this study is based on a comparison between treatment and control in the change from baseline to Visit 9 for the RmICARS. The null hypothesis will be no difference in the change from baseline RmICARS between treatment and control, with the alternative hypothesis of a difference of -2.4 between treatment and control [calculations based on the previous trial IEDAT-02-2015 (ATTeST) Clinical Study Report] A sample size of 86 participants 6 to 9 years old (43 per treatment group) is calculated to provide approximately 90% power with a two-sided test at 0.05 type I error, assuming a SD of 3.0 for the treatment group and 3.7 for the control group.

The number of participants enrolled 10 years and older is not based on the ability to detect a specific treatment effect. These participants will be described as an older age cohort with point estimates and confidence intervals for all efficacy endpoints.

## *5 Changes to the planned analysis from protocol*

There are no applicable changes to the planned analyses from the protocol, as the SAP is aligned with the statistical sections of the final protocol. The information below was previously included in Versions 1.0 and 2.0 of the SAP, and is retained here for ease of reference:

Following consultation with FDA, the primary population and primary Estimand defining the treatment effect of interest in the trial uses the hypothetical, composite and the treatment policy strategies.

The primary analysis will be conducted in all randomized participants aged 6-9-years-old, and by imputing datapoints after death to be the worst value for the endpoint at that visit the across the study.

Imputation of datapoints after treatment discontinuation due to AEs will occur under a missing not at random (MNAR) mechanism using a conservative approach which assumes that RmICARS scores after discontinuation due to AEs behave in the same way as the control group (hypothetical strategy).

Data collected regardless of the use of steroids or concomitant treatments will be used (treatment policy strategy), these intercurrent events are thus ignored (the occurrence of the intercurrent events is considered irrelevant in defining the treatment effect of interest). Data is assumed missing at random (MAR) in all other cases.

The analysis of CGI-S and CGI-C will impute missing values using the same approach as the primary analysis for the primary endpoint.

# *6 Statistical considerations*

Data will be analysed using SAS® software version 9.4 or higher (SAS institute Inc. Cary NC USA).

## *6.1 General specifications*

Descriptive statistics will be supplied according to the nature of the criteria:

- Quantitative variable: number of participants, number of participants with missing values, arithmetic mean, SD, 95% confidence interval, standard error of the mean (SEM), minimum, median and maximum, and quartiles if necessary
- Qualitative variable: number of participants, number of participants with missing values, absolute and relative frequencies per class. Percentages will be provided with one decimal place.

Unless otherwise specified, the calculation of percentages will be based on the sample size of the population of interest, as indicated in each table. Therefore, counts of missing values will be included in the denominator and displayed as a separate category if any.

No rounding will be applied in the data but rounding will be done for summary statistics.

Data will be organised by treatment group (Group 1 [eDSP], Group 2 [Placebo] and overall).

Unless otherwise indicated, all listings will be sorted by treatment group, participant and measurement time if applicable.

**Type I error rate**

Unless stated otherwise, statistical tests will focus on the 6 to 9-year-old age group, will be two-sided and will be carried out at the 5% level of significance. If applicable and unless otherwise specified, the calculated confidence intervals will be two-sided with a 95% confidence probability.

A hierarchical testing procedure will be used to control for multiplicity to maintain overall alpha at 5%. Specifically, CGI-S will be tested only if the test of RmICARS resulted in $p<0.05$, and the CGI-C would be tested only if CGI-S shows $p<0.05$.

The null (H0) and alternative (H1) hypotheses for the efficacy analysis of change from baseline in the RmICARS total score for the 6 to 9-year-old age group are:

- $H_0$: There is no difference between Group 1 (eDSP) and Group 2 (Placebo) with respect to RmICARS.
- $H_1$: There is a difference between Group 1 (eDSP) and Group 2 (Placebo) with respect to RmICARS.

**Baseline definition**

For all parameters other than efficacy, baseline will be defined as the last available measurement prior to the first IMP infusion. The selection of baseline value for each individual efficacy parameter will be specified in Section 9.

**Stratification factors**

As stratification is done at randomization by age (6- to 9-year-old and ≥ 10year-old), gender (male; female), and by geographic region, these stratum (as retrieved from the IWRS) will be used in all efficacy analyses. In case of inconsistencies between stratum at randomization (as planned by the IWRS) and stratum in the electronic case report form (eCRF) (or during the study), the stratum at randomization will be used.

### *6.2 Derivations*

**Study day**

All listings containing an evaluation date will display the study day defined as the day relative to the first infusion of study drug:

- Study day 1 will be defined as the day of the first infusion date.
- Study day -1 will be defined as the day prior to the first infusion date.
- There will be no study day 0.

**Duration**

- Duration (in days) will be calculated by the difference between the start and stop date + 1 (e.g. duration of a medication (days) = end of medication date - onset of medication date + 1).

### *6.3 Subgroups definition*

The following subgroups, to be evaluated in the 6 to 9-year-old age group, are defined as:

Gender:

- Female
- Male

Region:

- US
- Rest of the world

### *6.4 Handling of Dropouts*

Participants who discontinue treatment prematurely will be defined as dropouts. Those participants who discontinue treatment prematurely but return for scheduled efficacy assessments at Visit 6 and Visit 9 will comprise the retrieved dropouts (RDO).

### *6.5 Handling of missing values*

Missing Values When Computing Instrument Scores: if an item score is missing at baseline, the item score from screening will be carried forward. See Section 9.1.1 for additional instructions specific to the handling of missing RmICARS item scores at any visits.

### *6.6 Handling of retest values*

For all parameters and for participants with retest values, the last reliable value will be used for the measurement time before the first IMP infusion (provided it was measured before IMP infusion) and the first reliable value will be used for the measurement time after the first IMP infusion. A value will be considered as reliable if it is measured in appropriate conditions and without any technical problems.

### *6.7 Handling of incomplete/partial missing dates*

Unless otherwise specified (see hereafter), no imputation of incomplete dates will be performed. In all listings the documented date as given in the eCRF will be reported (e.g. 2023-03 if day is missing, but month and year available).

For Adverse Event:

A temporary imputation will be performed in order to derive the TEAE flag.

In case the AE start date is incomplete or missing, a worst-case allocation will be attributed according to the available parts of the AE start date:

(1) If day only is missing:

- If day is missing but year and month are the same as the first infusion date, the start date will be imputed with the minimum of the first infusion date and AE resolution date.
- In other cases, the missing day will be replaced by 1.

(2) If day and month only are missing:

- If day and month are missing but year is the same as the first infusion date, the start date will be imputed with the minimum of the first infusion date and AE resolution date.
- In other cases, the missing day will be replaced by 1 and the missing month will be replaced by January (01).

(3) If date is completely missing

- In case the start date is completely missing, the AE will be considered to have occurred during the treatment period and will be considered as emergent except if the stop date indicates differently.

AE end date may be also imputed if partial: missing day will be replaced by the last day of the month (if day is missing) or date of participant's death whatever comes first and the missing month will be replaced by December (12) (if month is missing) or date of participant's death whatever comes first.

For medications:

A temporary imputation for start date/end date will be performed to derive the classification of medication (prior or concomitant).

- Medication start date:
  - If the start day of medication is missing but year and month are the same as the first infusion date, the start date will be imputed with the first infusion date. Otherwise, it will be imputed to the first day of the month.
  - If both day and month are missing, the start date will be imputed as the first day of the year or as the first infusion date if year is the same as the year of the first infusion.
- Medication stop date:
  - if the stop day is missing, it will be imputed to the last day of the month or date of participant's death whatever comes first.
  - If both day and month are missing, the stop date will be imputed as the last day of the year or date of participant's death whatever comes first.

If the start or stop date is completely missing, no imputation will be performed and the determination of the classification (prior medication) will be based on non-missing stop or start date, respectively. Otherwise, the medication will be considered as concomitant.

# *7 Description of study participants*

## *7.1 Blind Data Review Meeting (BDRM)*

According to the ICH E9 guideline, the blind data review for the analysis will be carried out before the database lock. This pre-analysis review, blinded to treatment, should cover decisions concerning:

- The exclusion of participants or data from the analysis sets
- All other decision rules which could impact the analyses

Decisions made at this time will be described in the report, will be distinguished from those made after the statistician has had access to the treatment codes, as blind decisions will generally introduce less potential for bias. Statistician or other staff involved in unblinded interim analysis should not participate in the blind review or in making modifications to the statistical analysis plan. In case the blinding is compromised by the possibility that treatment induced effects may be apparent in the data, special care will be needed for the blind review.

## *7.2 Definition of analysis sets*

The following analysis sets will be defined:

- *Intent-to-treat (ITT) population*:
  The intent-to-treat (ITT) population is defined as all randomized participants.
- *ITT (6-9) population:*
  The ITT (6-9) population for the primary assessment of efficacy will be based on the ITT population of randomized participants 6 to 9 years old. The primary endpoint being the change of the RmICARS from baseline to Visit 9 compared to placebo.
- *ITT (10+) population:*
  The *ITT (10+)* population is defined as all participants 10 years and older who were randomized.
- *Per Protocol Population (PP)*: Subset of ITT (6-9) population composed of all participants aged 6 to 9 who qualify for the ITT (6-9) population, meet study drug adherence requirements, completed Visit 9, completed the treatment period of the study as planned and do not have disqualifying protocol deviations. Completing the treatment period of the study as planned will include participant completion of at least 5 doses of treatment within 200 days. Classification of participants in the PP Population will be performed in a blinded manner.
- *Safety Population (SP)*: any participant that receives at least one dose of the randomized treatment.

The ITT (6-9) population is the primary analysis population of interest and will be used to assess the RmICARS primary outcome.

Participants from the SP will be analysed according to the treatment actually received (and not according to the group allocated by the randomization). Participants from the ITT, ITT (6-9), ITT (10+) and the PP set will be analysed as randomized.

Final definitions of statistical sets will be agreed at the BDRM. The participants to be excluded from population sets and the reasons for their exclusion will be documented prior to database lock.

Analyses described in the present document will be performed on the population sets as summarized in the table below:

| | **All participants** | **ITT population** | **SP** | **ITT (6-9) population** | **PP population** | **ITT (10+) population** |
|---|---|---|---|---|---|---|
| Disposition | X | | | | | |
| Protocol deviations | | X | | | | |
| Demographic & baseline characteristics | | | X | X | | X |
| Exposure | | | X | X | | X |
| Safety | | | X | | | |
| Efficacy | | X[1] | | X | X[2] | X[3] |

[1]: supportive analysis, only performed for primary endpoint.
[2]: if there is more than 10% difference between ITT (6-9) population and PP population.
[3]: descriptive analyses only.

### *7.3 Participant disposition*

A summary table will be prepared by treatment group and overall and by geographic region for all participants with the description of:

- number of screened participants,
- number of screen failure (classified by main reason of failure),
- number of randomized participants,
- number of treated participants,
- number of randomized participants who completed the study,
- number of randomized participants who discontinued the study, classified by main reason of withdrawal.

Corresponding individual listings will be provided. Screen failures will be listed with the reasons for screen failure. Participants randomized but not treated will also be listed.

Frequency tables with the number (and percentage) of participants in each analysis set will be provided for the ITT population. Among participants excluded from the PP population, the number and percentage of participants meeting each specific exclusion category following determinations documented in the final BDRM will also be presented.

### *7.4 Protocol deviations*

Protocol deviations during the study will be listed in the “Protocol Deviations Specifications” and status of deviations (important=major/non-important=minor) will be determined and finalized during the BDRM.

A summary table by treatment group and overall with the number and percentage of participants presenting at least one deviation relating to inclusion/exclusion criteria, and for each individual inclusion or exclusion criterion with one or more deviations will be prepared for the ITT population.

A summary table by treatment group and overall with the number and percentage of participants presenting at least one important protocol deviation post inclusion will be prepared for the ITT population. Minor post-inclusions deviations will be only listed.

# *8 Demographic data and baseline characteristics*

The analyses of the demographic and baseline characteristics will be performed on the SP, ITT (6-9) and ITT (10+) populations, as will medical history, medications, and treatment exposure/compliance, while analyses of the EryDex process will be conducted in the SP only.

## *8.1 Demographic data*

Participants' demographic characteristics at baseline (age, gender, height, body weight, body mass index (BMI), region, country, race and ethnicity) will be summarised using frequency tables or summary statistics by treatment group and overall and listed:

- Age at randomization (years) as a continuous variable and as a categorical variable if applicable (6-9 years, ≥10 years): summary statistics,
- Gender: number (and %) of participants for Male, Female,
- Height, both measured (cm) and adjusted z-score: summary statistics,
- Body Weight, both measured (kg) and adjusted z-score: summary statistics,
- BMI, both measured (kg/m2) and adjusted z-score: summary statistics,
- Region: number (and %) of participants,
- Country: number (and %) of participants,
- Race: number (and %) of participants,
- Ethnicity: number (and %) of participants.

Adjusted z-scores for each of height, body weight, and BMI will be derived from CDC 2020 growth charts for children and adolescents aged 2 to 20 years, applying the LMS method as described on the CDC website: https://www.cdc.gov/growth-chart-training/hcp/computer-programs/sas.html?utm_source.

## *8.2 Baseline disease characteristics*

The following variables regarding disease characteristics at baseline will be summarized by treatment group and on overall and listed:

- RmICARS, mICARS and ICARS
- Genetic confirmation of A-T (Yes or No)
- Baseline laboratory parameters to assess disease severity (CD4+ lymphocytes count, α–fetoprotein, and CRP).

## *8.3 Medical History*

Information on significant medical history including history of disease, recorded at screening will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) using the latest version in effect at the time of the database lock.

Medical history will be summarized by treatment group and overall, ordered by system organ class (SOC) and preferred term (PT).

Medical history will be listed by treatment group and participant.

### *8.4 Medications*

All medications will be classified as prior or concomitant according to their start and stop dates compared to the date of the first infusion.

- **Concomitant** medications is a medication taken by the participant at any time during the study i;e. on or after the first infusion.
- **Prior** medications are medications that stop prior to the date and time of the first infusion.

In case the date values will not allow to allocate a medication to concomitant medication, the medication will be considered as concomitant medication.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary using the latest version in effect at the time of the database lock.

The following frequency tables will be provided by treatment group and overall, ordered by drug class [2nd level of Anatomical Therapeutic Chemical (ATC)] and medication drug name:

- Prior medications,
- Concomitant medications

A listing of prior medications and a listing of concomitant medications administered from the time of dosing of the study medication through completion of the final evaluation (Safety Follow-up) will be provided by treatment group.

### *8.5 Treatment exposure and compliance*

Duration of Treatment

Duration of treatment will be calculated in days as the date of the last infusion of study treatment – date of the first infusion of study treatment + 1.

Duration of treatment will be summarized using summary statistics for continuous variables.

Extent of Exposure

Total monthly treatment exposure is defined as the count of monthly treatments, including missed monthly treatments, from the first monthly treatment to the last monthly treatment.

Continuous Exposure is defined as monthly treatments with no missed treatments.

For each dosing condition (eDSP or placebo), separately, the number of participants with each total monthly treatment exposure will be summarized. For each total monthly treatment exposure, the number of participants in each of the following categories will be summarized:

- No missed monthly treatments (Continuous Exposure),
- One missed monthly treatment,
- Missing ≥ 2 non-consecutive monthly treatments,
- Missing ≥ 2 consecutive monthly treatments.

The number of participants in each of the following categories will be summarized by dosing condition (eDSP or placebo):

- One infusion out of window,
- Two infusions out of window,
- Three infusions out of window,
- Four infusions or more out of window.

A listing will be provided by treatment group.

Dosing Compliance

Percentage treatment compliance will be calculated for all treated participants using the following formula.

Compliance with study medication dosing (%) = $\frac{A}{P} \times 100$, where:

- A = Total number of infusions actually administered through Visit 9
- P = Total number of infusions scheduled to receive up to Visit 9

Dosing compliance will be summarized using summary statistics for continuous variables. The percentage of infusions received per participant which were within the protocol specified window of every 28 days (-7 days, +2 days) relative to each previous dose will also be summarized.

EryDex Process

The following items will be summarized using summary statistics for continuous variables by treatment group and overall, across all visits combined and by individual visit:

- Total volume of Final Collection Bag (mL) by center and overall
- eDSP cell count by CBC parameter (hematrocrit, hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin, mean corpuscular volume, erythrocytes, erythrocyte distribution width, leukocytes, and platelets)

The following items will be summarized using summary statistics for continuous variables by treatment group and overall, by center and overall, and across all visits combined and by individual visit:

- Time between “Time of Blood Collection” and “Start Time of EryDex Process”,
- Time between “Time of EryDex Process Completion” and “Actual Infusion Start Time”,
- Time between “Actual Infusion Start Time” and “Actual Infusion Stop Time”.

All information about EryDex process will be listed by treatment group.

DSP concentrations and DSP amount per bag

DSP amount per bag will be calculated given the following formula:
DSP mg/bag = DSP concentration (ug/mL) * 0.0787

DSP concentrations from sample bag as well as DSP amount per bag will be listed. DSP amount per bag will be also summarized by visit using summary statistics for continuous variables.

# *9 Efficacy data*

All primary and secondary efficacy analyses will be performed on both the ITT (6-9) (primary analysis) and the PP populations, while exploratory efficacy analyses will be performed on the ITT (6-9) population only. The primary endpoint will also be analysed in all participants (the ITT population). Only descriptive presentations by treatment group and by visit will be performed for the ITT (10+) population.

## *9.1 Primary endpoint*

### 9.1.1 Definition of Endpoint

**Rescored modified International Cooperative Ataxia Rating Scale (RmICARS)**

The ICARS is a 100-point, semi-quantitative scale offering a compartmentalized quantification of the following 4 sub- scores: Posture and Gait Disturbances (34 points), Kinetic Functions (52 points), Speech Disorders (8 points), and Oculomotor Disorders (6 points).

Rating of the ICARS will be performed at screening and at V1; the V1 assessment will be recorded and used for determining changes from baseline on treatment. In case of missing data at V1, the screening value will be used. The ICARS will also be assessed at Visit 6 and at Study Completion (Visit 9 - Day 168 or at early withdrawal).

The complete ICARS will be rated in the current study; however, for the primary efficacy endpoint, the "rescored 'Modified' ICARS" will be used.

The mICARS score ranges from 0 to 54, with higher scores indicative of more severely affected outcome. The mICARS excludes all Oculomotor Disorder items (items 17-19) and items 8-12 in the Kinetic Functions domain, as these items do not directly contribute to functioning.

The Rescored mICARS (RmICARS) is re-scored by collapsing categories within specific items resulting in a smaller total sum score across the ICARS domains. It consists of 9 items across 3 domains (kinetic domain and speech limited to one item each), totaling a maximum score of 29 points. See Appendix 2 for details.

Per the eCRF completion guidelines in place for answering all individual items in the ICARS assessment, the following rules are applied:

- **If an item was not performed because the participant can't complete the tasks** in the item as they should (due to the severity of their impairment due to AT), then the worst score should be assigned for the item
- **If an item was not performed (i.e. an item was not administered at all, because of safety concerns or other conditions, such as an IV line in place)**, no score should be assigned, and the appropriate reason should be documented
    - This means that neither the worst nor the best score should be assigned in such cases

In the event that one or more instances of unscored items are found at the completion of the trial, the following rule will be applied to provide a scaled RmICARS score:

> For any specific visit where one or more item scores are unavailable due to safety concerns or other conditions, but at least 5 of the 9 item level scores are available (i.e. >50%), a scaled total RmICARS score will be derived based on the sum of the observed scores divided by the sum of the maximum achievable scores among the available items: this proportion will be multiplied by the maximum RmICARS score of 29 points and then rounded to the nearest integer to provide a scale score on the appropriate range of 0 to 29 points. If 5 or more items are not scored, the RmICARS total score should be left missing, and handled as a missed visit and addressed using the imputation methods specified in the following sections.

### 9.1.2 Primary analysis

The objective of the primary efficacy analysis is to evaluate the neurological effect of eDSP, compared to placebo in ataxia telangiectasia (A-T) in 6- to 9-year-old participants. The

primary estimand defining the treatment effect of interest in the trial uses the hypothetical, composite and the treatment policy strategies specified in the draft ICH E9 (R1) Addendum and is defined by the following components:

- Treatment: eDSP vs placebo
- Target Population: 6- to 9-year-old
- Variable: Change from baseline to Visit 9 in RmICARS
- Intercurrent Events: AEs leading to treatment discontinuation, deaths, use of steroids or concomitant treatments
- Population-level summary: Mean difference

The analysis will be conducted by imputing datapoints after death to be the worst value for the endpoint at that visit across the study, and by imputing datapoints after treatment discontinuation due to AEs under a missing not at random (MNAR) mechanism to hypothesize what would have happened to the RmICARS score had behavior of withdrawing participants due to AEs been the same as in the control group (hypothetical strategy). Data collected regardless of the use of steroids or concomitant treatments will be used (treatment policy strategy), these intercurrent events are thus ignored (the occurrence of the intercurrent events is considered irrelevant in defining the treatment effect of interest).

The analysis of the primary efficacy data will be conducted after the multiple imputation of non-monotone and monotone missing data, resulting in the creation of a suitably large number of fully imputed datasets that will be individually analyzed and subsequently combined into one result. Initially, missing data that is non-monotone will be imputed in each of these datasets creating a monotone missing data pattern. Each monotone missing datapoint in each individual dataset is then imputed in one of three ways, depending on the reason for missingness and the missing data mechanism which is assumed:

- Missing data due to death will be imputed with the *worst* value for that endpoint at that visit across the study. This type of missing data will be assumed to be missing not at random (MNAR).
- Missing data due to treatment discontinuation due to AEs will be multiply imputed using a Jump to Reference (J2R) approach. This type of missing data will also be assumed to be missing not at random (MNAR).
- All other missing data that is not due to death or treatment discontinuation due to AEs will be multiply imputed using a Normal distribution within treatment group. This type of missing data will be assumed to be missing at random (MAR).

<u>Imputation of Non-Monotone Data</u>

Non-monotone missing data will be imputed under a MAR assumption using PROC MI. This will be done at least 50 times, resulting in the creation of at least 50 partially imputed datasets with a monotone missing data pattern.

Sample SAS code to impute non-monotone missing data to create 50 datasets with a monotone missing data pattern follows:

```
proc mi data = <input-dataset> nimpute = 50 seed = 123 out = data_mono;
      by trtn;
      var sexn region age baseRmICARS v6RmICARS v9RmICARS;
      mcmc impute = monotone chain = multiple prior = jeffreys;

run;
```

Where trtn is the treatment group, sexn is a variable for gender, region and age as continuous are variables for region and age respectively and baseRmICARS, v6RmICARS and v9RmICARS are RmICARS score at baseline, Visit 6 and Visit 9 respectively.

Imputation of Missing Data Due to Treatment Discontinuation Due to AEs

Data that is missing due to treatment discontinuation due to AEs is assumed to be MNAR, and in each monotone missing dataset will be imputed using PROC MI and a J2R approach. The J2R approach assumes missing data in the eDSP group has the same distribution as the placebo group after discontinuation. Once the eDSP participants cease the treatment, their mean response jumps to that of the placebo participants, essentially assuming that immediately upon withdrawal from the eDSP group, all benefit from the treatment is gone. Imputation is carried out first on missing Visit 6 data, and then on missing Visit 9 data resulting in the observations that have missing data due to treatment discontinuation due to AEs being fully imputed.

The output dataset from this step can be used as the input dataset for the imputation of missing Visit 9 values. Sample SAS code to impute missing Visit 9 values in each of the 50 datasets after subsetting the input dataset on all placebo participants and those eDSP participants with a missing Visit 9 value due to discontinuation due to AEs follows:

```
proc mi data = <input-dataset> seed = 123 nimpute = 1 out = <output-
dataset>;
      by _imputation_;
      var baseRmICARS v6RmICARS v9RmICARS;
      monotone reg (v9RmICARS);
run;
```

Baseline RmICARS and the RmICARS values at Visit 6 and Visit 9 will be included as model terms.

Imputation of Missing Data Due to Death

Missing data due to death is assumed to be MNAR and will be replaced with the worst-case RmICARS value at the visit of interest across the whole study. A multiple imputation approach is not used for this imputation step. This direct replacement results in the observations that have missing data due to death being fully imputed.

Imputation of All Other Missing Data

All remaining monotone missing data not due to treatment discontinuation due to AEs or death will be assumed to be MAR and will be imputed using PROC MI within treatment group, applying code similar to the sample SAS code above for imputing non-monotone missing data. Gender, region, age, baseline RmICARS and the RmICARS values at Visit 6 and Visit 9 will be included as model terms. This step results in the observations that have missing data not due to treatment discontinuation due to AEs or death being fully imputed.

Analysis and Combination of Fully Imputed Datasets

The imputed data from each step within each imputed dataset will be merged to create at least 50 fully imputed datasets. Change from baseline in RmICARS scores will be recalculated at each time point.

The change from baseline to Visit 9 in RmICARS 6-9 years old will be analyzed using a MMRM analysis. The analysis model will include the change from baseline to Visits 6 and 9 as the repeated measure, with treatment as the fixed effects and terms for region, gender, visit, and baseline RmICARS and age as continuous covariates, and the treatment-by-visit interaction. The treatment effect, together with the associated two-sided 95% confidence interval (CI) and p-value will be calculated. The covariance structure in the primary analysis will be estimated using robust estimation. If there are issues with model convergence, other covariance structures will be considered in the order autoregressive (AR(1)) and then compound symmetry (CS).

The SAS code for the PROC MIXED procedure to carry out the above MMRM analysis with an unstructured variance covariance structure is illustrated as follows:

```
proc mixed data = <input-dataset> empirical;
      by imputation;
      class subjid treatment region gender visit;
      model change=baseRmICARS treatment region sexn age visit
      treatment*visit /cl;
      repeated visit /type=un subject=subjid;
      lsmeans treatment*visit / diff cl;
      estimate "eDSP vs Placebo at Visit 9"
      treatment 1 -1 treatment*visit 0 1 0 -1 / cl;

run;
```

Model effect estimation will be based on restricted maximum likelihood.

Results will then be pooled across imputations using Rubin's rules to incorporate the between-imputation with the within-imputation variability and to obtain one single point and interval estimate using SAS PROC MIANALYZE.

```
proc mianalyze data = <input-dataset>;
      by treatment visit;
      modeleffects estim;
      stderr sem;
      ods output parameterestimates = parmest2(keep = parm estimate stderr
      lclmean uclmean probt);
run;
```

where *estim* and *sem* are the point estimate and SE from the MMRM analysis for each imputed dataset whereas *estimate, stderr, lclmean, uclmean*, and *probt* are the final pooled point estimate, SE, lower and upper confidence limits, and the p-value for the between group comparison.

The RmICARS score at baseline, Visit 6 and Visit 9 will be summarized using summary statistics appropriate for continuous data by treatment group. The change from baseline to both visits will also be summarized.

For the ITT (6-9) population only, a boxplot of the RmICARS score will be plotted by visit and treatment group. This box plot will be repeated for change from baseline in RmICARS score.

### 9.1.3 Sensitivity analyses

Retrieved Drop-Out (RDO) Imputation

For a sensitivity analysis of the J2R approach employed in the primary analysis, an RDO-based imputation method for MNAR data discontinuation due to AE data will be used. The RDO method is a trade-off between conservative missing not at random assumptions (Jump to Reference) and optimistic MAR assumptions. The RDO method will account for on- and off-treatment status. For participants with missing data at a specific visit due to AEs leading to treatment discontinuation, information is borrowed from participants in the same treatment arm who also discontinued treatment at or before that visit but with retrieved dropout data available. It assumes participants who discontinue the trial tend to have similar values on the endpoint, compared to those in the same treatment group who are already off treatment but remain in the study (RDO) after adjustment of age as continuous, gender and region covariates, baseline and last on-treatment visit RmICARS.

This sensitivity analysis will consist of the same analysis as the primary analysis but using RDO imputation instead of J2R imputation. The results will be compared to the primary analysis.

Tipping Point Analysis of MAR Imputation

To assess the impact of monotone missing data considered MAR (ie, due to reasons other than intercurrent events of death or discontinuation due to AEs), a sensitivity analysis will be applied to identify the “tipping point” where the treatment effect is no longer statistically significant. This imputation method will be employed for missing data in the primary efficacy analysis at Visit 9 not due to intercurrent events of death or discontinuation due to AEs, with the number of imputed datasets being at least 50 to make the results more reliable.

The following general approach will be applied using standard multiple imputation approaches:

1. For any missing data not due to death or discontinuation due to adverse events (which will continue to be imputed as described for the primary analysis), use the mean and SD of all non-missing values for that treatment group to generate the imputed values from a normal distribution.
2. Implement Step 1, at least 50 times so at least 50 complete datasets are produced. For each dataset, find the change from baseline to Visit 9 in RmICARS for each participant.
3. Analyze the complete datasets as stated for the primary analysis.
4. Combine the results from these datasets using Rubins methods.
5. Repeat Steps 1 to 4 but with a small shift (+δ) applied to the individual participant values for the change from baseline to Visit 9 in RmICARS in the eDSP treatment group (but not the control group). This shift is applied after Step 2, and the shift will be applied in order to reduce the treatment benefit of eDSP.
6. Display the estimated treatment effect and associated 2-sided CI and resultant p-value vs. degree of shift.

7. Repeat Steps 5 and 6, increasing the shift each time as +2δ, +3δ, . . ., +(treatment effect seen in primary analysis).
8. Identify the tipping point where the two-sided p>0.05.

A table presenting the primary efficacy analysis result in addition to each increasing value of δ and corresponding treatment effect, two-sided 95% CI, and p-value will be presented. Similarly, in order to visually support the resulting tipping point for the primary analysis imputation approach, a plot will be produced of the 95% confidence limits as a function of each value of δ from 0 (representing the calculated treatment effect from the primary efficacy analysis) to the estimated treatment effect (representing no difference between active and control arms), along with a vertical line denoting zero (signifying the threshold at which any 95% CIs overlapping with this line would fail to demonstrate statistical significance at the zero-sided level of 5%).

Overview of Primary and Sensitivity Analyses

The table below provides further details for the above estimand including analysis methods, imputation approaches and any planned sensitivity analyses:

| Study Objective | Study endpoint | Estimand | Analysis type | Analysis details |
|---|---|---|---|---|
| To evaluate the neurological effect of eDSP, compared to Placebo in ataxia telangiectasia (A-T) in 6- to 9-year-old participants | Change from baseline to Visit 9 in RmICARS | The mean difference between eDSP and Placebo in 6- to 9-year-old participants, assessing the change from baseline to Visit 9 in RmICARS regardless of whether participants used steroids or concomitant treatments, and if outcomes in participants after death are assumed to be as bad as the worst value at that visit across the study, and the RmICARS values of withdrawing participants due to AEs are the same as in the control group | Primary | MNAR imputation based on J2R for data-points after treatment discontinuation due to AEs or setting result to worst value at that visit across the study after deaths, and MAR for all other missing data + MMRM |
| | | | Sensitivity Analysis of MNAR Imputation for discontinuation due to AEs | MNAR imputation based on RDO for data-points after treatment discontinuation due to AEs or setting result to worst value at that visit across the study after deaths and MAR for all other missing data + MMRM |
| | | | Tipping Point Sensitivity Analysis of MAR Imputation | MNAR imputation based on J2R for data-points after treatment discontinuation due to AEs or setting result to worst value at that visit across the study after deaths, and tipping point analysis applied to MAR for all other missing data + MMRM |

### 9.1.4 Presentation of ICARS and mICARS scores

While the RmICARS will be used as the primary efficacy endpoint as discussed in Sections 9.1.1 through 9.1.3, analyses and summaries of the full ICARS and mICARS scores will also

be presented as requested by the European Medicines Agency (EMA). The change from baseline to Visit 9 in each of the ICARS and mICARS scores will be analyzed following the same approach as for the primary analysis for RmICARS, in the ITT (6-9) population. The total and sub-scores of the ICARS and the total mICARS score at baseline, Visit 6 and Visit 9 will be summarized using summary statistics appropriate for continuous data by treatment group in the ITT (6-9) and PP populations. The change from baseline to both visits will also be summarized. For the ITT (6-9) population only, boxplots of the ICARS and mICARS total scores will be plotted by visit and treatment group. These boxplots will be repeated for change from baseline in each total score.

### *9.2 Key Secondary efficacy endpoint*

The Clinical Global Impressions CGI (Guy, 1976) is the general name for two scales, the CGI-Severity scale (CGI-S) and CGI - Change scale (CGI-C). The CGI-S assesses the severity of the disease at a given point in time from 1 to 7.

In the current study, The CGI-S evaluation will be performed at Visit 1 (Baseline), Visit 6 and Visit 9. The CGI –S change from baseline will be classified as improved *versus* no change / worsened using the following classification rules:

- Visit n CGI-S – Baseline CGI-S > 0 is worsened
- Visit n CGI-S – Baseline CGI-S = 0 is no change
- Visit n CGI-S – Baseline CGI-S < 0 is improved

The proportion improved will be analyzed at Visit 9 with logistic regression, with covariates for age as continuous, baseline RmICARS, gender and region.

Odds ratio together with the associated 95% CI and p value will be calculated.

As a sensitivity analysis, the CGI-S with all categories will also be analyzed at Visit 9 using a proportional odds model with ordinal logistic regression with region, gender, baseline RmICARS, age as continuous and treatment. The estimate of the treatment effect odds ratio, together with the associated two-sided 95% CI and p value, will be calculated.

The analysis of CGI-S will impute missing values using the same approach as the primary analysis for the primary endpoint.

The CGI-S score at baseline, Visit 6 and Visit 9 will be summarized using summary statistics by treatment group. The change from baseline to both visits will also be summarized.

For the ITT (6-9) population only, a boxplot of the CGI-S score will be plotted by visit and treatment group. This boxplot will be repeated for change from baseline in CGI-S score.

### *9.3 Other Secondary efficacy endpoint*

The CGI-C scale assesses the change in the participant's overall clinical condition from baseline using a 7-point scale, ranging from 1 (very much improved) to 7 (very much worse), with a score of 4 indicating no change. The difference in the outcome on this ordinal scale at Visit 9 between treatment groups will be analyzed with a Proportional Odds logistic regression model. The resulting proportional odds ratio represents the likelihood of participants in the eDSP treatment group being in a better level of the CGI-C compared to the placebo participants. The proportional odds model will include covariates for baseline RmICARS, age as continuous, gender, and region. Summary statistics will be used to show the proportion of participants in each level. Should a level contain fewer than 5 participants across treatments, or only 1

participant in either treatment arm, the level will be collapsed to the next higher (worse) level. Within the range of responses, the proportion of participants who report any improvement 1-3, included *versus* those who report no change or worsening (levels 4-7, included) will be of primary interest. The estimate of the treatment effect odds ratio, with the associated two-sided 95% CI will be calculated.

If the proportional odds assumption is violated, then a logistic regression model with covariates for age as continuous, baseline RmICARS, gender, and region will be used to compare the two treatment arms. The response variable for this logistic regression will be the proportion of participants who report improvement (Levels 1-3) versus no change and worsened (Levels 4-7).

The analysis of CGI-C will impute missing values using the same approach as the primary analysis for the primary endpoint.

CGI-C scores at Visit 6 and Visit 9 will be summarized using summary statistics appropriate for the analysis by treatment group.

For the ITT (6-9) population only, a boxplot of the CGI-C score will be plotted by visit and treatment group.

### *9.4 Exploratory endpoints*

**EQ-5D-Y Interviewer Administered Proxy version 1 for participants 6- to 9-year of age and** EQ-5D-Y **self-reported for participants 10 years of age and older**

The EQ-5D-Y and the EQ-5D-5L descriptive systems comprise the same five dimensions however the EQ-5D-Y uses more appropriate, child-friendly wording.

The EQ-5D-Y consists of three pages: the title page, the EQ-5D-Y descriptive system (page 2), and the EQ VAS (page 3). The EQ VAS records the respondent's overall current health on a vertical VAS where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The EQ VAS provides a quantitative measure of the respondent's perception of their overall health. In the current study, for participants aged 6 to 9 years, the EQ-5D-Y Interviewer administered Proxy version 1 will be used (i.e., a version of the questionnaire that allows an interviewer to ask the caregiver (proxy) to rate the participant's health-related quality of life in their (the proxy's) opinion). In participants 10 years of age and older, the self-reported version of the EQ-5D-Y will be used.

The EQ-5D-Y is assessed at Screening, Visit 1, Visit 6, and Visit 9. The Visit 1 result will be considered the baseline score. Each of the 5 domains is evaluated on a 3-level scale (no problems, some problems, a lot of problems).

#### 9.4.1 EQ-5D-Y – each of 5 domains

Each of the 5 domains will be summarized separately. Each EQ-5D-Y domain score at baseline, at Visit 6 and Visit 9 will be summarized using summary statistics for categorical data (three specific categorical levels per domain) by treatment group. The change from baseline to both visits will also be summarized categorically (2 category improvement, 1 category improvement, no change, 1 category worsening, or 2 category worsening).

#### 9.4.2 EQ-5D-Y total score

The EQ-5D-Y total score will be the sum of categorical scores across all 5 domains, where 5 is the best total score and 15 is the worst total score. At each specific visit, the EQ-5D-Y total score will only be calculated if scores for all 5 domains are available; otherwise it will be

considered missing. The EQ-5D-Y total score will be summarized using summary statistics for continuous data at baseline, Visit 6, and Visit 9, along with the change from baseline to each follow-up visit.

The change from baseline to Visit 9 in EQ-5D-Y total score will be analyzed with Analysis of Covariance, with baseline score, region, gender, baseline RmICARS, and age as continuous as covariates.

As a supplemental analysis, the proportion of participants who do not worsen (i.e. no worsening in the total score from baseline to Visit 9) will be compared between the two treatment arms with logistic regression. The logistic regression model will include covariates for baseline score, region, gender, baseline RmICARS, and age as continuous.

For the ITT (6-9) population only, a boxplot of the EQ-5D-Y total score will be plotted by visit and treatment group. This boxplot will be repeated for change from baseline in EQ-5D-Y total score.

#### 9.4.3 EQ VAS

The change from baseline to Visit 9 of the EQ-VAS will be analyzed as described above for the EQ-5D-Y total score and summarized using summary statistics for continuous data by treatment group.

For the ITT (6-9) population only, a boxplot of the EQ-VAS will be plotted by visit and treatment group. This boxplot will be repeated for change from baseline in EQ-VAS.

### *9.5 10 years and older analyses*

Data on participants 10 years and older is supplementary to the primary analysis in 6- to 9-year-old participants.

These primary, secondary, and exploratory efficacy objectives will be summarized by treatment group and by visit for the ITT (10+) population. No formal statistical analysis will be performed.

### *9.6 Subgroup analysis*

Data on the primary and secondary endpoints will be summarized by treatment group and visit, including change from baseline to each visit, for the subgroups of gender and region. These summaries will be presented for the ITT (6-9) population.

## *10 Safety data*

The safety analyses will be performed on the Safety Population.

Safety analyses will be performed on the total population. Additional summaries of selected safety parameters will be performed on the subset of participants age 6- to 9-years-old and on participants aged ≥ 10-years-old.

### *10.1 Adverse events*

Adverse events will be coded according to MedDRA using the latest version in effect at the time of the database lock

Treatment-emergent adverse events (TEAEs) are defined as those AEs that started on or after the first drug infusion. Adverse events occurring >30 days after the last dose of study drug will not be considered treatment emergent.

General Rules for frequency tables

i. If an adverse event is reported for a participant more than once during the treatment emergent period, then the worst severity and the worst relationship will be counted.
ii. Adverse events considered drug-related will be those events with a relationship assessed as probable, possible or missing.
iii. If a participant has AEs with missing and non-missing grades, the maximum of non-missing grade will be taken into account in summary tables (this is applicable for AE with the same Preferred Term only).

AESI

The following treatment emergent adverse events are considered to be adverse events of special interest (AESI).

- **Adrenal insufficiency:** New onset of adrenal insufficiency (based on clinical symptoms and confirmed with either low cortisol and/or an abnormal ACTH stimulation test).
- **Infections of special interest:** New onset bacteremia, sepsis, pneumonia or opportunistic infections (e.g., candida sepsis, pneumocystis pneumonia, tuberculosis, toxoplasmosis, varicella zoster virus infection, herpes ophthalmicus, cytomegalovirus infection, aspergillosis, histoplasmosis).
- **Iron deficiency anemia:** New onset of iron deficiency anemia supported by laboratory testing (low hemoglobin and another measure suggesting low iron levels [e.g., low ferritin level, low serum iron, high total iron-binding capacity, low iron saturation]). Although iron deficiency anemia is typically mild and does not require rapid communication, this AE was selected as being of special interest since treatment with eDSP requires monthly blood draws in children who often have underlying iron deficiency.

The specific subset of MedDRA Preferred Terms which map to the above categories of AESI will be identified by the Sponsor based on a blinded review of all AEs and corresponding laboratory data as needed, in parallel with a targeted query process during data monitoring to confirm that all AEs mapped to the selected preferred terms meet the criteria for the above AESI criteria. This final set of identified Preferred Terms will be documented prior to database lock and unblinding.

Overview of AEs

An overall summary table of AEs occurring during the study will present the number of participants (and %) with at least one:

- AE.
- TEAE.
- TEAE by intensity (mild/moderate/severe).
- TEAE by relationship (related/not related).
- SAE.
- AEs leading to death.
- Related Serious TEAE.

- Related TEAE.
- TEAEs leading to study drug discontinuation.
- Adverse Event of Special Interest (AESI).

Overall summaries of adverse events will be presented in the overall safety population as well as in subgroups by age (6-9 years and ≥10 years), gender, and region.

Tables by System Organ Class (SOC) and Preferred Term (PT)

Summary of TEAEs will present the number of AEs, the number and percentage of participants by MedDRA SOC (ordered alphabetically) and PT (ordered alphabetically). Following summary tables will be provided by treatment group for:

- TEAEs.
- TEAEs by intensity (mild/moderate/severe).
- TEAE by relationship (related/not related).
- SAEs.
- TEAEs leading to death.
- Related Serious TEAEs.
- Related TEAEs.
- TEAEs leading to study drug discontinuation.
- Adverse Events of Special Interest (AESIs).

Additionally, a table of TEAEs ordered by decreasing incidence of PTs (based on the eDSP arm) will be provided.

Listings:

Listings of all AEs (TEAEs flagged) will be presented and sorted by treatment group, participant ID, start date, primary SOC, PT and verbatim text for all adverse events recorded during the study.

### *10.2 Listings of SAEs and AEs leading to death or discontinuation of the study drug as well as adverse events of special interest (AESIs) will be provided separately. Clinical laboratory data*

Clinical laboratory data will be measured according to the Schedule Of Assessments (SOA) (see section 14.1)

Standard Laboratory Evaluations: Hematology, biochemistry (including serum creatinine), and urinalysis:

- At screening,
- At baseline (only if abnormalities requiring follow-up were noted at the Screening evaluation),
- At Visit 6 and Visit 9.

**Table 1. Summary of standard laboratory analytes**

| **LABORATORY ANALYTES** | | | |
|---|---|---|---|
| **Hematology or CBC** | **Clinical Chemistry** | | **Urinalysis (automated)** |
| Hematocrit | Sodium | Alkaline phosphatase | Color |
| Hemoglobin | Potassium | LDH | pH |
| RBC count | Chloride | CPK | Specific gravity |
| WBC count | Calcium | Triglycerides | Protein |
| Differential WBC count | Phosphorus | Total cholesterol | Glucose |
| • Neutrophils | Serum iron[1] | HDL cholesterol | Ketones |
| • Lymphocytes | Bicarbonate | LDL cholesterol | RBC, WBC, casts * |
| • Monocytes | Glucose[1] | | Nitrites |
| • Eosinophils | BUN | | Bilirubin |
| • Basophils | Creatinine | | Hemoglobin |
| Platelets | Total bilirubin | | Urobilinogen |
| MCV | Albumin | | * Reflex microscopic analysis to be performed only if other analytes are abnormal on automated testing |
| MCH | Total protein | | |
| MCHC | AST (SGOT) | | |
| RDW | ALT (SGPT) | | |
| ***Special Diagnostic Tests:*** Female participants will have serum pregnancy test obtained at Screening. Females noted to be at Tanner Stage 2 or greater at Baseline will have a urine pregnancy test obtained and evaluated prior to infusion at Visits 1, 4, 5, 6, 7, 8 and a serum pregnancy test at Visit 9/Early Discontinuation, if noted to be at Tanner Stage 2 or greater at this Visit. | | | |

Special laboratory tests: CD4+ lymphocytes count, α–fetoprotein (not repeated at baseline), and CRP:

- At screening,
- At baseline (only if abnormalities requiring follow-up were noted at the Screening evaluation),
- At Visit 6 and Visit 9.

Cortisol:

- At screening,
- At treatment completion and when adrenal insufficiency is suspected.

The following panels will also be listed:

- Hemolysis Panel: free plasma hemoglobin, haptoglobin, bilirubin (total and conjugated), CBC, lactate dehydrogenase (LDH) and urinalysis,

- Red blood cell (RBC) antibodies (immunoglobulin [Ig]G, IgM, Qualitative Direct Coombs test),

- Free plasma hemoglobin (1 hour post infusion).

***General rules and definitions:***

A central laboratory will be used for analyzing samples for routine and special laboratory tests. In certain circumstances the Investigator may choose to utilize a local laboratory if there is an immediate need for the test results.

If a local value was used instead of a central value for an assessment planned in the protocol, the local value will be used.

As more than one laboratory will be then been implicated, a standardisation method will be required in order to take into account the multiple reference ranges [2]. The laboratory which has analysed the largest number of blood samples will be used as the reference laboratory.

Standardised values will be calculated using the following formula:

$$X_S = X_{LRef} + (X_{URef}-X_{LRef})*((X-X_L)/(X_U-X_L))$$

where

- X= measured value
- $X_S$= standardised value
- $X_L$ and $X_U$ = lower and upper limit values for the laboratory of the measured value
- $X_{LRef}$ and $X_{URef}$ = lower and upper limit values for the laboratory chosen as a reference

If a standardised value is negative, it will be set to zero. If a lower limit value ($X_L$ or $X_{LRef}$) is missing, it will be replaced by 0. If an upper limit value ($X_U$ or $X_{URef}$) is missing, values will not be standardised.

Standardised values will be used for the quantitative analyses, while initial values will be used for qualitative analyses. Initial values as well as standardised values will be presented in individual listings.

***Analysis:***

Data for each parameter of a continuous nature will be summarized by treatment at each visit using the summary statistics for continuous data. The change from baseline to each visit will be calculated and summarized. Data for each parameter of a categorical nature will be summarized descriptively using count and percentages for parameters with categorical results.

*Shift tables*

Shift tables will be provided for all values presenting the shift in abnormality post-baseline versus the baseline abnormality.

Moreover, participants with post-baseline aminotransferase elevations and total bilirubin by category will be summarized for worst post-baseline values and defined as:

- ALT >3x, >5x, >10x Upper Limit of Normal (ULN)
- AST >3x, >5x, >10x ULN
- ALT and AST >3x, >5x, and >10x ULN
- Total bilirubin >2x ULN
- ALT and AST >3x ULN and total bilirubin >2x ULN
- (ALT and/or AST >3x ULN) and ALP <2x ULN and total bilirubin >2x ULN

A participant with elevated laboratory parameters may belong to more than one category (e.g., if a participant has an ALT value = 6xULN, this participant will be presented under both >3xULN and >5xULN).

*Listings*

Values (raw data and changes from baseline) will be listed and data out of normal ranges will be flagged with clinical significance information.

Participants who meet potential Hy's Law laboratory criteria will be flagged in the listing. Hy's Law laboratory criteria are defined as any elevated ALT and/or AST of >3xULN that is associated with both an ALP <2xULN and an increase in bilirubin >2xULN.

## *10.3 Other safety parameters*

### 10.3.1 Physical/neurological examination findings

Physical and neurological examinations will be performed as specified on the SOA: at Screening, at Baseline, at Visits 4, 5, 6, 7, 8 and 9. The physical examination will include an examination of general appearance, skin, neck (including thyroid), eyes and ears, nose, mouth, throat, lungs, heart, abdomen, back, lymph nodes, extremities and nervous system. Genital, urinary tract and rectal examinations are not required. The findings will be entered on the Physical Examination section (or Adverse Event, as applicable) of the eCRF.

Physical and neurological examination data will be summarized by treatment and visit according to the treatment received.

### 10.3.2 Vital signs data

Vital signs will be measured as specified on the SOA: at Screening, at Baseline, at Visits 4, 5, 6, 7, 8 and 9. Vital signs will be measured within 15 minutes before and within 15 minutes after infusion at Baseline, Visits 4, 5, 6, 7 and 8. Weight and height will be measured just once per treatment visit - before the infusion at Baseline, Visits 4, 5, 6, 7 and 8.

The reported values of the vital signs data will be summarized by treatment at each visit using the summary statistics for continuous variables. Height, weight, and BMI will be summarized both as measured and by adjusted z-score, as described in Section 8.1.

Change from baseline to each post-baseline visit will be calculated for weight, height, and BMI, while change from pre-infusion to post-infusion at each treatment visit will be calculated for systolic and diastolic blood pressure, sitting pulse rate, respiration rate, and temperature. The change from baseline data will be summarized by treatment at each post-baseline visit using the summary statistics for continuous variables. The number and percentage of participants at each visit with the abnormalities in Table 2 (where increases or decreased correspond to changes from pre-infusion to post-infusion at each visit) will be summarized:

**Table 2. Vital Sign Abnormalities**

| Parameter | Unit | Category 1 | Category 2 |
|---|---|---|---|
| Systolic Blood Pressure | mmHg | Value ≤ 90 and ≥ 20 Decrease | Value ≥ 180 and ≥ 20 Increase |
| Diastolic Blood Pressure | mmHg | Value ≤ 50 and ≥ 15 Decrease | Value ≥ 105 and ≥ 15 Increase |
| Sitting Pulse Rate | bpm | Value ≤ 50 and ≥ 15 Decrease | Value ≥ 120 and ≥ 15 Increase |
| Respiration Rate | breaths/ minute | < 12 | > 25 |
| Temperature | C | NA | Value ≥ 38.3 and ≥ 1.1 Increase |

### 10.3.3 Electrocardiogram data

All participants will have a standard 12-lead ECG performed as specified on the SOA: at Screening, at Baseline (only if abnormalities requiring follow-up were noted at the Screening evaluation), at Visit 9. If clinically significant abnormal findings are noted at Screening and do not normalize on the repeat ECG evaluation at Baseline (done in triplicate), the participant will not be enrolled. If clinically significant abnormalities are found, the participant's ECG should be repeated at regular intervals until it returns to normal.

All ECG parameters for all visits will be summarized by treatment. Additionally, categorical analysis of QTcF outliers based on baseline and highest post baseline results meeting the following criteria will be presented by treatment:

- Maximum Post Baseline QTcF:
  - > 450 msec to ≤ 480 msec
  - > 480 msec to ≤ 500 msec
  - > 500 msec
- Maximum Change from Baseline to Post Baseline QTcF:
  - > 30 msec to ≤ 60 msec
  - > 60 msec
- Maximum Post Baseline QTcF and Change from Baseline (CFB):
  - > 480 msec to ≤ 500 and CFB > 30 msec to ≤ 60 msec
  - > 480 msec to ≤ 500 and CFB > 60 msec
  - > 500 msec and CFB > 30 msec to ≤ 60 msec
  - > 500 msec and CFB > 60 msec

### 10.3.4 Sterility Testing of EryDex

All participants will have culture-based sterility tests of infusions (encapsulated DSP or placebo) conducted at dosing visits 1, 4, 5, 6, 7, and 8. Sterility results for samples from all infusions will be summarized by treatment and visit, as well as overall across all visits combined. For each specified time point (overall or individual visit), the proportion of samples testing positive/contaminated, negative/not contaminated, or missing will be presented for each of the categories of pre-processing blood culture, eDSP sterility culture, eDSP retention sample culture (if applicable), and post-infusion blood culture from the participant (if applicable) will be summarized, along with the specific species of any positive or contaminant organism identified. The proportion of infusions with final determination of contamination by result status (true positive, false positive, or indeterminate) as assessed by the investigator will also be presented.

### 10.3.5 Columbia Suicide Severity Rating Scale (C-SSRS)

C-SSRS surveys will be performed as specified on the SOA: at Screening, at Baseline, at Visits 4, 5, 6, 7, 8 and 9. Suicide ideation score results (measured on a scale of 0 to 5) will be presented as a frequency distribution and summarized by treatment at each visit, including change from baseline to each visit. All other C-SSRS survey results will be listed.

For the ITT (6-9) population only, a boxplot of the ideation severity score will be plotted by visits and treatment groups. This boxplot will be repeated for change from baseline in ideation severity.

### 10.3.6 Bone Mineral Density (BMD)

Bone mineral density z-scores will be summarized and analyzed in a manner similar to the standard laboratory evaluations, with descriptive statistics by visit and treatment, including change from baseline, for each applicable combination of parameter (area, bone mineral content, bone mineral density raw and z-score, fat mass, lean mass, and spine width) and scan location (L1, L2, L3, L4, and L1-L4 vertebra, and total body less head).

### 10.3.7 Tanner Staging

The number and percentage of safety population participants at each Tanner stage will be summarized separately for males and females by treatment and by visit. The Tanner Staging score will be derived from the genitalia score and will be used in data summaries. The genitalia score and pubic hair score will be listed.

### 10.3.8 Adrenal Insufficiency Signs and Symptoms

Signs and symptoms related to adrenal insufficiency will be listed.

## *11 Procedures and data formats*

Standard operating procedures (SOPs) will be followed, including for the programming of the statistical analyses, results editing and quality control.

Derived data produced for the generation of TFLs will follow CDISC ADaM standard (ADaM Model v. 2.1 / ADaM IG v. 1.1 or later version).

## *12 Reporting conventions*

All tables, figures and listings are detailed in section 14.2 and will be prepared using SAS® software as rtf files and the rtf files will be compiled as PDF files (one PDF file by main section).

Footers will be presented as follows: --- STUDY IEDAT-04-2022/ <name of the program>.SAS / <name of the output>.RTF / DDMMMYY HH:MM ---.

Table and Listing Page Set Up Requirements:

- Font Type = Courier New
- Font Size = 8 pt (at a minimum)
- Page Margins: Top=2 cm; Bottom=2 cm; Left=2 cm; Right=2 cm
- Paper Size = A4 (21 cm x 29.7 cm)
- Page Orientation: Landscape
- Graphs: Portable Network Graphics (PNG) format

Summary statistics will be presented as follows.

| Parameter (unit) | Statistics / Category | Group X (N=xx) | Group Y (N=xx) |
|---|---|---|---|
| Quantitative variable (unit)* | N (missing) | xx (xx) | xx (xx) |
| | Mean ± SD | xx.xx ± xx.xx | xx.xx ± xx.xx |
| | SEM | xx.xx | xx.xx |
| | Median | xx.xx | xx.xx |
| | Min ; Max | xx.x ; xx.x | xx.x ; xx.x |
| Qualitative variable | Class 1 n (%) | xx (xx.x) | xx (xx.x) |
| | Class 2 n (%) | xx (xx.x) | xx (xx.x) |
| | Missing (if applicable) | xx (xx.x) | xx (xx.x) |

Decimals:

- All statistics, except the minimum and the maximum, will be provided with an additional decimal place compared to the variable itself.
- Percentages will be displayed with one decimal.
- P-values will be rounded to four decimals. P-values less than 0.0001 will be displayed as "<0.0001".

Other reporting conventions

As a general rules, data and times will be displayed in tables or listings as follows

- Dates: YYYY-MM-DD
- Date/time: YYYY-MM-DDThh:mm
- Time: hh:mm.

## *13 References*

1. Guy W. Clinical Global Impressions. 1976. National Institute of Mental Health. ECDEU Assessment Manual for Psychotherapy.
2. Karvanen J. The statistical basis of laboratory data normalization. Drug Information Journal. 2003;37(1):101-107.

# *14 Appendices*

## *14.1 Appendix 1 - Flow chart/Schedule of assessments of the study*

| **Visit** | **Screening** | **V1** | **V2 (d)** | **V3(d)** | **V4** | **V5** | **V6** | **V7** | **V8** | **V9 (b) c)** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Dose** | | **Dose 1(a) Baseline** | | | **Dose 2** | **Dose 3** | **Dose 4** | **Dose 5** | **Dose 6** | **Trial Completion /Early Withdrawal** |
| **Visit Window** | **Up to 30 days before Dose 1** | | **24 hours after V1** | **Day 14 (±3 days)** | Each treatment must be scheduled every 28 days (window -7 days, +2 days) calculated from the previous visit | | | | | 28 days (window -7 days, +2 days), calculated from the previous visit |
| Informed Consent | X | | | | | | | | | |
| Medical History/Demographics | X | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | X | | | | | | | | |
| EryDex Infusion | | 1 | | | 2 | 3 | 4 | 5 | 6 | |
| Neurological Examination | X | X | | | | | X | | | X |
| Physical Examination | X | X | | | X | X | X | X | X | X |
| Tanner Scale (p) | | X | | | | | | | | X |
| Vital Signs, Height, Weight | X | X (l) | | | X(l) | X(l) | X(l) | X(l) | X(l) | X |
| Early morning plasma cortisol test (h) | X | As needed | | | | | | | | X |
| ECG | X | X(e) | | | | | | | | X |
| Routine Laboratory Tests (f) | X | X(e) | | | | | X | | | X |
| BMD, where countries allow | | X | | | | | | | | X |
| ICARS | X | X | | | | | X | | | X |
| C-SSRS (j) | X | X | | | X | X | X | X | X | X |
| Special Laboratory Tests (g) | X | X | | | | | X | | | X |
| Pregnancy testing (n) | X | X | | | X | X | X | X | X | X |
| Quality of Life EQ-5D-Y (q) | | X | | | | | X | | | X |
| CGI-C | | | | | | | X | | | X |
| CGI-S (videotaped at V1) | | X | | | | | X | | | X |
| Hemolysis Panel (k) | As needed | | | | | | | | | |
| RBC antibodies (k) | As needed | | | | | | | | | |
| Free plasma hemoglobin (k) | As needed | | | | | | | | | |
| Blood sample for biomarker development (o) | | X | | | | | X | | | X |
| Pre-dose aerobic blood culture (m) | | X | | | X | X | X | X | X | |
| Culture-based sterility test on | | X | | | X | X | X | X | X | |

| **Visit** | **Screening** | **V1** | **V2 (d)** | **V3(d)** | **V4** | **V5** | **V6** | **V7** | **V8** | **V9 (b) c)** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Dose** | | **Dose 1(a) Baseline** | | | **Dose 2** | **Dose 3** | **Dose 4** | **Dose 5** | **Dose 6** | **Trial Completion /Early Withdrawal** |
| **Visit Window** | **Up to 30 days before Dose 1** | | **24 hours after V1** | **Day 14 (±3 days)** | Each treatment must be scheduled every 28 days (window -7 days, +2 days) calculated from the previous visit | | | | | 28 days (window -7 days, +2 days), calculated from the previous visit |
| EryDex (m) | | | | | | | | | | |
| EryDex sample for CBC, DSP content (i) | | X | | | X | X | X | X | X | |
| Prior/Concomitant Medications | Throughout the duration of the trial | | | | | | | | | |
| Adverse Events | Throughout the duration of the trial | | | | | | | | | |

*Abbreviations:* ACTH = adrenocorticotropic hormone; AE = adverse event; BMD = bone mineral density; CBC = complete blood count; CGI-C = Clinical Global Impression of Change; CGI-S = Clinical Global Impression of Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; D = Day; DSP = dexamethasone sodium phosphate; ECG = electrocardiogram; EQ-5D-Y = EuroQol 5D-Y; ICARS = International Cooperative Ataxia Rating Scale; SAE = serious adverse event; V = visit.

***Notes:***

Each treatment must be scheduled every 28 days (window -7/+2 days), calculated from the previous infusion. The window between an infusion and the subsequent one should be kept as regular as possible throughout the trial, avoiding fluctuations in administration windows. In any case, infusions should not be given fewer than 14 days apart.

Any instances where it is not possible to administer the infusion within the designated window should be documented as a protocol deviation and the Investigators should immediately contact the Medical Monitor to discuss if the participant may continue in the trial, and if so, to agree on the path forward that will best ensure the participant's safety and meet the protocol goals.

Unless specifically described, the trial visits must be performed on site. Under exceptional/specific circumstances (such as public health reasons, participant's illness), remote visits can be allowed on a case-by-case basis, if onsite visits are not allowed. In such instances, the Investigators should immediately contact the Medical Monitor to discuss the visit's conduct. Any missed procedure that cannot be done remotely will be identified as a protocol deviation.

At each applicable Visit, the ICARS should be the first scale administered, followed by the CGI-S/CGI-C, and then by the EQ-5D-Y Interviewer Administered Proxy version 1 for participants 6 to 9 years of age and the self-reported version for participants ≥10 years of age. Neurological assessments must be performed before any phlebotomy or intravenous insertion so that the upper extremity neurological exam is not impeded by an intravenous line, except at screening and Visit 9.

*Footnotes:*

a) Baseline visit is designed as a single-day visit but, in case of logistical issues for a particular participant, the visit can be performed over a 2-day period. In this case, the day of the first dose will be considered as Baseline, and subsequent treatments will be calculated from the previous dose.
b) Efficacy evaluations (Visit 9) will be used as the Endpoint assessments for all efficacy measures.
c) Participants who discontinue prematurely will still be asked to perform this visit. Participants who complete the trial's full treatment period and complete the trial assessments may elect to receive treatment with eDSP in an OLE trial.
d) Visits 2 and 3 should be performed remotely, by phone, unless there are specific safety/medical concerns that would prompt an onsite visit.
e) These evaluations will be repeated only if abnormalities requiring follow-up were noted at the Screening evaluation; results from the repeat assessments must be available at baseline to confirm eligibility before the participant can be randomized to treatment. If the Screening ECG is found to have abnormalities requiring follow-up, it will be repeated (in triplicate) at Baseline and evaluated to determine eligibility prior to randomization.
f) Routine laboratory assessments to include complete hematology, biochemistry (including serum creatinine), and urinalysis.

g) Special laboratory tests include CD4+ lymphocytes count, α–fetoprotein (not repeated at baseline), and C-reactive protein.
h) A sample will be collected before 8:00 AM for measurement of plasma cortisol during the screening period, prior to randomization at baseline. If the basal cortisol level is within the reference normal range, the participant can be enrolled in the trial. If the 8:00 AM cortisol level is below 3-5 µg/dL (depending on assay) regardless of symptoms, or the participant exhibits signs or symptoms of adrenal insufficiency (see Appendix 7) and has a cortisol <10 µg/dL, the participant will receive a high-dose ACTH stimulation test as soon as possible. If the ACTH stimulation test is normal, the participant can be enrolled after the effects of the ACTH have dissipated (e.g., 30 days after ACTH administered, resulting in a prolongation of the screening period). If the participant fails the ACTH stimulation test, they will be excluded from the trial treatment and from continuing further participation in the trial (this is not applicable at V9 testing) and referred to an endocrinologist (a pediatric endocrinologist, depending on participant's age) with a recommendation to prescribe stress dose steroids. In addition to the testing during the screening period (prior to randomization), a blood sample to be collected before 8:00 AM for measurement of plasma cortisol in the following instances: (1) when participants are symptomatic, and (2) when participants are at most risk for adrenal insufficiency and adrenal crisis, such as following discontinuation or interruptions of dexamethasone dosing (i.e., loading failures and following discontinuation of the trial treatment).
i) Upon completion of the EryDex System process, the remaining sample in the satellite sample bag or, if this is not available, a sample collected from another EryDex sampling point, will be used for determination of DSP content and CBC.
j) C-SSRS: to be administered at all the visits. "Baseline-Screening" version at Screening and "Since Last Visit" version at all subsequent visits.
k) Participants in whom there is a clinical suspicion of hemolysis during the trial may have the following testing performed depending on the clinical circumstances and as determined by the Investigators: hemolysis panel [free plasma hemoglobin, haptoglobin, bilirubin (total and conjugated), complete blood count, lactate dehydrogenase, and urinalysis], red blood cell antibodies (immunoglobulin G, immunoglobulin M), Qualitative Direct Coombs test, and Free Plasma Hemoglobin (1 hour after infusion).
l) Vital signs are to be measured within 15 minutes before and within 15 minutes after infusion at Visits 1, 4, 5, 6, 7, and 8. Weight and height to be measured just once per treatment visit and before the infusion.
m) One mL of blood to be collected after blood diversion for aerobic culture, before EryDex process. Upon completion of the EryDex System process, a sample of EryDex (approximately 1 mL per inoculum for a total of 2 mL) will be collected from the satellite sample bag to perform a culture-based sterility test. A 1-mL sterile sample of EryDex will be stored under refrigeration as a "Retention Sample."
n) Female participants will have a serum pregnancy test obtained at Screening. Females noted to be at Tanner Stage 2 or greater at Baseline will have a urine pregnancy test obtained and evaluated before each infusion at Visits 1, 4, 5, 6, 7, 8 and a serum pregnancy test at Visit 9/Early Discontinuation, if noted to be at Tanner Stage 2 or greater at this Visit.
o) For participants who have provided specific consent.
p) Should the Principal Investigator/delegated Investigator note evidence, or should the parent report any evidence of female trial participants approaching puberty (e.g., breast development, pubic hair, or onset of menses) after the Baseline and during the trial, an ad hoc full Tanner staging will be performed to ensure female participants will start pre-treatment pregnancy testing, as needed.
q) EQ-5D-Y Interviewer Administered Proxy version 1 for participants 6 to 9 years of age and self-reported for participants 10 years of age and older

## *14.2 Appendix 2 - RmICARS*

The table below reflects the calculation the RmICARS, re-scored by collapsing categories within specific items as recommended by the US FDA.

| ICARS Items | | Score | Original mICARS Scoring | Rescored mICARS Method 2 (FDA) |
|---|---|---|---|---|
| I. Posture/Gait Disturbance | 1 – Walking Capacities: Observed during a 10-meter test including a half-turn near a wall, about 1.5 m (Score 0-8) | Normal | 0 | 0 |
| | | Almost normal naturally, but unable to walk with feet in tandem position | 1 | 0 |
| | | Walking without support, but clearly abnormal and irregular | 2 | 1 |
| | | Walking without support but with considerable staggering; difficulties in half turn | 3 | 2 |
| | | Walking with autonomous support no longer possible; the patient uses the episodic support of the wall for a 10 meter test | 4 | 3 |
| | | Walking only possible with one stick | 5 | 3 |
| | | Walking only possible with two special sticks or with a stroller | 6 | 3 |
| | | Walking only with accompanying person | 7 | 3 |
| | | Walking impossible, even with accompanying person (wheelchair) | 8 | 4 |
| | 2 – Gait Speed: Observed in patients with preceding scores 1-3; preceding score >=4 | Normal | 0 | 0 |
| | | Slightly reduced | 1 | 0 |
| | | Markedly reduced | 2 | 1 |
| | | Extremely slow | 3 | 2 |
| | gives automatically score 4 in this test (Score 0-4) | Walking with autonomous support no longer possible | 4 | 3 |
| | 3 – Spread of Feet in Natural Position Without Support, Eyes Open: The patient is asked to find a comfortable position, then the distance between medial malleoli is measured (Score 0-4) | Normal (<10 cm) | 0 | 0 |
| | | Slightly enlarged (>10 cm) | 1 | 0 |
| | | Clearly enlarged (25 cm < spread < 35 cm) | 2 | 1 |
| | | Severly enlarged (>35 cm) | 3 | 2 |
| | | Standing in natural position impossible | 4 | 3 |
| | 4 – Standing Capacities, eyes open: The patient is asked first to stand on one foot, if impossible, to stand with feet in tandem position; if impossible, to stand with feet together; for the natural position, the patient is asked to find a comfortable standing position (Score 0-6) | Normal: able to stand on one foot more than 10 seconds | 0 | 0 |
| | | Able to stand with feet in tandem, but no longer able to stand on one foot more than 10 seonds | 1 | 0 |
| | | Able to stand with feet together, but no longer able to stand with feet in tandem position | 2 | 1 |
| | | No longer able to stand with feet together, but able to stand in natural position without support, with no or moderate sway | 3 | 2 |
| | | Standing in natural position without support, with considerable sway and considerable corretions | 4 | 2 |
| | | Unable to stand in natural position without strong support of the arms | 5 | 3 |
| | | Unable to stand at all, even with strong support of the arms | 6 | 4 |
| | 5 – Body Sway with Feet Together, Eyes Open (Score 0-4) | Normal | 0 | 0 |
| | | Slight osillations | 1 | 0 |
| | | Moderate oscillations (<10 cm at the level of head) | 2 | 1 |

| | | | | |
|---|---|---|---|---|
| | | Severe oscillations (>10 cm at the level of head), threatening the upright position | 3 | 2 |
| | | Immediate falling | 4 | 3 |
| | 6 – Body Sway With Feet Together, Eyes Closed (Score 0-4) | Normal | 0 | 0 |
| | | Slight osillations | 1 | 0 |
| | | Moderate oscillations (<10 cm at the level of head) | 2 | 1 |
| | | Severe oscillations (>10 cm at the level of head), threatening the upright position | 3 | 2 |
| | | Immediate falling | 4 | 3 |
| | 7 – Quality of Sitting Position: Thighs together, on a hard surface, arms folded (Score 0-4) | Normal | 0 | 0 |
| | | With slight oscillations of the trunk | 1 | 0 |
| | | With moderate osillations of the trunk and legs | 2 | 1 |
| | | With severe disequilibrium | 3 | 2 |
| | | Impossible | 4 | 3 |
| II. Kinetic Disorders | 13R – Pronation-Supination alternating movements: The subject, comfortably sitting on a chair, is asked to raise his/her forearm vertically and to make alternative | Normal | 0 | Excluded |
| | | Slightly irregular and slowed | 1 | |
| | | Clearly irregular and slowed, but without sway of the elbow | 2 | |
| | | Extremely irregular and slowed movement, with sway of the elbow | 3 | |
| | movements of the hand. Each hand is moved and assessed separately (right – left; Score 0-4) | Movement completely disorganized or impossible | 4 | |
| | 13L – Pronation-Supination alternating movements: The subject, comfortably sitting on a chair, is asked to raise his/her forearm vertically and to make alternative movements of the hand. Each hand is moved and assessed separately (right – left; Score 0-4) | Normal | 0 | Excluded |
| | | Slightly irregular and slowed | 1 | |
| | | Clearly irregular and slowed, but without sway of the elbow | 2 | |
| | | Extremely irregular and slowed movement, with sway of the elbow | 3 | |
| | | Movement completely disorganized or impossible | 4 | |
| | 14 – Drawing the Archimedes' spiral on a pre-drawn pattern | Normal | 0 | 0 |
| | | Impairment and decomposition, the line quitting the pattern slightly but without hypermetric swerve | 1 | 0 |
| | | Line completely out of the pattern without re-crossings and/or hypermetric swerves | 2 | 1 |
| | | Major disturbance due to hypermetria and decomposition | 3 | 1 |
| | | Drawing completely disorganized or impossible | 4 | 2 |
| III. Speech Disorders | 15 – Dysarthria: fluency of speech: the patient is asked to repeat several times a standard sentence, always the same (Score 0-4) | Normal | 0 | Excluded |
| | | Mild modification of fluency | 1 | |
| | | Moderate modification of fluency | 2 | |
| | | Considerably slow and dysarthric speech | 3 | |
| | | No speech | 4 | |
| | 16 – Dysarthria: clarity of speech (Score 0-4) | Normal | 0 | 0 |
| | | Suggestion of slurring | 1 | 1 |
| | | Definite slurring, most words understandable | 2 | 2 |
| | | Severe slurring, speech not understandable | 3 | 3 |
| | | No speech | 4 | 4 |

### *14.3 Appendix 3 - List of tables, figures and listings included in the clinical study report*

A separate TFLs shells document will detail all programming specifications.

| NUMBER | TITLE |
|---|---|
| **14** | **TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT** |
| **14.1** | **Demographic data** |
| **14.1.1** | **Description of study participants** |
| 14.1.1.1 | Overall Participants Disposition – All Participants |
| 14.1.1.2 | Participants Disposition by Region – All Participants |
| 14.1.1.3 | Analysis Sets – Intent-to-Treat Population |
| **14.1.2** | **Protocol deviations** |
| 14.1.2.1 | Deviations Relating to Inclusion/Exclusion Criteria – Intent-to-Treat Population |
| 14.1.2.2 | Important Protocol Deviations – Intent-to-Treat Population |
| **14.1.3** | **Demographic data and baseline characteristics** |
| 14.1.3.1.1 | Demographic data – Safety Population |
| 14.1.3.1.2 | Demographic data – ITT (6-9) Population |
| 14.1.3.1.3 | Demographic data – ITT (10+) Population |
| 14.1.3.2.1 | Study Disease Characteristics – Safety Population |
| 14.1.3.2.2 | Study Disease Characteristics – ITT (6-9) Population |
| 14.1.3.2.3 | Study Disease Characteristics – ITT (10+) Population |
| **14.1.4** | **Medical history** |
| 14.1.4.1 | Medical history – Safety Population |
| 14.1.4.2 | Medical history – ITT (6-9) Population |
| 14.1.4.3 | Medical history – ITT (10+) Population |
| **14.1.5** | **Prior and Concomitant Medications** |
| 14.1.5.1.1 | Prior Medications – Safety Population |
| 14.1.5.1.2 | Prior Medications – ITT (6-9) Population |
| 14.1.5.1.3 | Prior Medications – ITT (10+) Population |
| 14.1.5.2.1 | Concomitant Medications – Safety Population |
| 14.1.5.2.2 | Concomitant Medications – ITT (6-9) Population |
| 14.1.5.2.3 | Concomitant Medications – ITT (10+) Population |
| **14.1.6** | **Exposure and Compliance** |
| 14.1.6.1.1 | Duration of Treatment (Days) – Safety Population |
| 14.1.6.1.2 | Duration of Treatment (Days) – ITT (6-9) Population |
| 14.1.6.1.3 | Duration of Treatment (Days) – ITT (10+) Population |
| 14.1.6.2.1 | Extent of Exposure – Safety Population |

| | |
|---|---|
| 14.2.1.15 | mICARS Score – Summary Statistics – Per Protocol Population |
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