STATISTICAL ANALYSIS PLAN

EryDel S.p.A

Via Meucci 3, Bresso (MI), (Italy)

A Multi-center, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Effects of *I*ntra-*E*rythrocyte *D*examethasone Sodium Phosphate on Neurological Symptoms in Patients with Ataxia Telangiectasia

Clinical Study Protocol No.: IEDAT-02-2015

IND Number: 115929

Prepared by

PPD

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LIST OF ABBREVIATIONS

AE	Adverse Events
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
AST	Aspartate Transaminase
AT	Ataxia Telangiectasia
A-T NEST	Ataxia-Telangiectasia Neurological Examination Scale Toolkit
BDRM	Blinded Data Review Meeting
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CGI-C	Clinical Global Impression of Change from Baseline
CGI-S	Clinical Global Impression of Severity (structured)
CPK	Creatine Phospho Kinase
CNS	Central Nervous System
COVID-19	Disease caused by SARS-CoV-2
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CRO	Contract Research Organization
DOB	Date of Birth
ECG	Electrocardiogram
EQ-5D-5L	EuroQol 5D Five-level version
FAS	Full Analysis Set
FWER	Family-wise error rate
HBsAg	Hepatitis B Surface Antigen
HBc	Hepatitis B Core
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HTLV	Human T-Lymphocyte Virus
ICARS	International Cooperative Ataxia Rating Scale
ICH	International Conference on Harmonization

IMP	Investigational Medicinal Product
ITT	Intention To Treat
IVRS	Interactive Voice Response System
Kg	Kilogram
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LOCF	Last Observation Carried Forward
MMRM	Mixed Model Repeated Measure
MCV	Mean Corpuscular Volume (MCV)
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MITT	Modified Intention to Treat
OC	Observed Cases
pBAR	Probabilistic Baseline Randomization
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per Protocol
QOL	Quality of Life
RBC	Red Blood Cell
RDO	Retrieved Dropout
RDW	Red Cell Distribution Width
SAP	Statistical Analysis Plan
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SP	Safety Population
TEAE	Treatment Emergent Adverse Event
VABS	Vineland Adaptive Behaviors Scale
WBC	White Blood Cell

1. INTRODUCTION

The purpose of Study IEDAT-02-2015, A Multi-center, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Effects of *I*ntra-*E*rythrocyte *D*examethasone Sodium Phosphate on Neurological Symptoms in Patients with Ataxia Telangiectasia, is to demonstrate the safety and efficacy of the EryDex System end product (EDS-EP) in subjects with ataxia telangiectasia (AT). The EDS is a combination product that is used to load dexamethasone sodium phosphate (DSP) into autologous erythrocytes, creating the EDS-EP, which is infused into the patient.

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for protocol IEDAT-02-2015 Version 11.0, Final, 24 June 2020.

The purpose of this SAP is to outline the planned analyses to support the completion of the Clinical Study Report (CSR) for study IEDAT-02-2015. The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any *post hoc* or unplanned analyses not identified in this SAP will be clearly identified as such in the CSR.

This document includes the analysis of the initial treatment period (Period 1) and the extension treatment period, which consists of Period 2 [Visit 9 (Month 6) to Visit 12 (Month 9)] and Period 3 which consists of [Visit 12 (Month 9) toV15 to Month 12)].

Low dose is defined as an approximate dose range between 5-10 mg EDS-EP and high dose is defined as an approximate dose range between 14-22 mg EDS-EP. This document is referencing placebo, low dose, and high dose.

All subjects who complete 12 months of treatment in the trial, complete the study assessments (and Retrieved Dropouts who return for the final Visit 15 ["Month 12"] efficacy assessment), and provide informed consent will be eligible to continue treatment with EDS-EP in an open-label, extension study (IEDAT-03-2016).

1.1 Study Objectives

The proposed study was designed to assess the efficacy and safety of administration of two dose levels of EDS-EP, when compared with placebo, in subjects with AT.

Initial Treatment Period

Primary Efficacy Objective:

- To evaluate the effect of two dose ranges (~5-10 and ~14-22 mg DSP/infusion) of EryDex System end product (EDS-EP), compared to placebo, on central nervous system (CNS) symptoms measured by the Modified International Cooperative Ataxia Rating Scale (mICARS) in subjects with AT. The Full ICARS will also be evaluated.

Key Secondary Efficacy Objective:

  - To evaluate the effect of EDS-EP, compared to placebo, in this population on the Clinical Global Impression of Change from baseline (CGI-C).

Safety Objective:

- To evaluate the safety and tolerability of EDS-EP, compared to placebo, in AT subjects, based on the occurrence of Treatment-Emergent Adverse Events (TEAEs), including

Serious Adverse Events and discontinuations due to adverse events, and changes in vital signs, laboratory parameters, ECGs and physical/neurological examination findings.

Other Secondary Efficacy Objectives:

- To evaluate the effect of EDS-EP, compared to placebo, in this population on the Clinical Global Impression of Severity (CGI-S; structured)
- To evaluate the effect of EDS-EP, compared to placebo, in this population, on adaptive behavior measured by the Vineland Adaptive Behavior Scales (VABS).

Tertiary Objectives:

- To evaluate the effect of EDS-EP on health-related Quality of Life (QoL) using the EQ-5D-5L scale;
- To assess the pharmacokinetic and pharmacodynamic relationships between dexamethasone administered through EDS-EP and safety, tolerability, and demographic variables;
- To evaluate the pharmacokinetic (PK) profile of dexamethasone administered through EDS-EP at two dose levels based on pooled data from all subjects in each treatment group. A determination of individual PK parameters will be performed for subjects with an adequate number of PK blood samples after the initial infusion.

Exploratory Objective:

- To collect data on the use of the Ataxia-Telangiectasia Neurological Examination Scale Toolkit (A-T NEST) concurrent with the ICARS, CGI-S (structured) and CGI-C, as well as its use in languages other than English, and to compare it with the data from the scales referenced to assess the psychometric properties of the A-T NEST.

All data collected on the A-T NEST from selected study centers on Day 2 and subsequent visits will be delivered to John Hopkins Statistical group for evaluation of the data, and performance of any analyses needed to determine/confirm the psychometric properties of the scale, and such analysis will be described in documentation apart from this statistical analysis plan.

Extension Treatment Period

Primary Objective:

- To evaluate the efficacy of two dose ranges (~5-10 and ~14-22 mg DSP/infusion) of EDS-EP, compared to placebo, in treating CNS symptoms in AT subjects during long-term treatment, as measured by the Modified ICARS. The Full ICARS will also be evaluated.

Secondary Objectives:

- To evaluate the long-term safety and tolerability of EDS-EP in AT subjects;
- To compare the effects of the two dose ranges of EDS-EP on the clinician's global impression (CGI-C and CGI-S [structured]), adaptive behavior (VABS), and QoL (EQ-5D-5L scale).

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1.2 Study Design

This is an international (North America, Europe, Africa, Asia, and Australia), multi-center, one year, randomized, double-blind, placebo-controlled, Phase III study, designed to assess the effect of two non-overlapping dose ranges of EDS-EP, administered by IV infusion once per month, on neurological symptoms of subjects with AT. All subjects who complete the assessments as designed over the initial treatment period of the trial will be eligible to continue in an additional double-blind, placebo-controlled extension designed to collect information on the long-term safety and efficacy of the trial treatments.

The protocol planned for 180 subjects to be enrolled, and those meeting all of the inclusion/exclusion criteria were randomized to receive one of the two dose ranges of EDS-EP or placebo (1:1:1 with the intent of randomizing 60 subjects per group) as follows:

- **Group 1, Low Dose, EDS-EP low dose range of ~5-10 mg DSP/infusion:** CCI [redacted]
- **Group 2, High Dose, EDS-EP high dose range of ~14-22 mg DSP/infusion:** CCI [redacted]
- **Group 3, Placebo EDS infusion:** CCI [redacted]

Due to the impact of COVID-19, the company decided to complete enrollment with 175 patients.

A minimization procedure was employed to ensure that the proportions of male and female, and younger (6 to <10 years) and older (≥10 years) subjects are comparable across the three treatment groups. Every attempt was made to ensure the same balance was achieved across different regions. In the Initial Treatment Period, each subject will receive 6 infusions of EDS-EP (low or high dose) or placebo, given at monthly intervals. Similarly, subjects entering the Extension Treatment Period will continue on the randomized treatment and will receive 6 monthly infusions of EDS-EP or placebo.

Randomization/placebo switching will take place at 3 time points, as described in Section 5.1.7.

1.3 Study Timepoints

Study visits, associated target days, and associated target visit windows are presented in Tables 1 and 2 for the initial treatment period and the extension treatment period, respectively. Per database specifications, most data are collected on visit specific CRFs and therefore the scheduled visit number is inherently assigned in such cases.

For all analysis populations (see Section 2 of this statistical analysis plan) except the Per Protocol Population, if data are recorded on a CRF with a scheduled visit, the data will be associated with the scheduled visit for analysis and listing purposes.

For the Per Protocol Population, data records will be associated with a visit for analysis and listing according to the target visit windows in Tables 1 and 2; note that each visit assignment will be made relative to the day of the immediately preceding dose. Subject exclusion from the Per

Protocol Population will depend upon the elapsed time between first dose and the "Month 6" visit, and also upon the number of doses missed prior to the "Month 6" visit (see Section 2).

Table 1. Study Timing: Initial Treatment Period

Visit	Target Day	Target Visit Window
Screening	-30 to -1	
Visit 1	Day 0/1	
Visit 2	2	
Visit 3	15	15±7 days
Visit 4	30	Not before 21 days after the prior infusion (Infusion 1), +10 days
Visit 5	60	Not before 21 days after the prior infusion (Infusion 2), +10 days
Visit 6	90	Not before 21 days after the prior infusion (Infusion 3), +10 days
Visit 7	120	Not before 21 days after the prior infusion (Infusion 4), +10 days
Visit 8	150	Not before 21 days after the prior infusion (Infusion 5), +10 days
Visit 9	180	Not before 21 days after the prior infusion (Infusion 6), +10 days

Note: As a result of the defined target visit window intervals in protocol Version 10, the maximum possible number of days per protocol in the initial treatment period is 228 days.

Table 2. Study Timing: Extension Treatment Period

Visit	Target Day	Target Visit Window
Visit 9a	180	Not before 21 days after the prior infusion (Infusion 6), +10 days
Visit 10	210	Not before 21 days after the prior infusion (Infusion 7), +10 days
Visit 11	240	Not before 21 days after the prior infusion (Infusion 8), +10 days
Visit 12	270	Not before 21 days after the prior infusion (Infusion 9), +10 days
Visit 13	300	Not before 21 days after the prior infusion (Infusion 10), +10 days

Table 2. Study Timing: Extension Treatment Period

Visit	Target Day	Target Visit Window
Visit 14	330	Not before 21 days after the prior infusion (Infusion 11), +10 days
Visit 15	360	Not before 21 days after the prior infusion (Infusion 12), +10 days
Visit 16	390	30 days after subject final assessment or at least 60 days after their last infusion, whichever is longer

The schedule of assessments for the initial treatment period and extension treatment period is in Appendix I.

2. STUDY POPULATIONS

The following analysis sets will be used:

- Safety Population (SP): all subjects who received any amount of randomized treatment.
- Full Analysis Set (FAS) (also referred to as MITT – Modified Intent-to-Treat): All randomized subjects who received at least one dose of study medication and had at least one post-baseline efficacy assessment of the primary efficacy variable.
- Per Protocol Population (PP): all subjects enrolled into the study who fulfilled all Inclusion/Exclusion criteria, did not have any major protocol violations, and completed the Initial Treatment Period of the study as planned. Completing the initial treatment period of the study as planned will include subject completion of at least 5 doses of treatment (allowing ≤1 missed dose, see Section 5.2.4), including the Visit 8 dose and the ICARS and CGI-C assessments performed at Visit 9 ("Month 6") within 228 days. Subjects who discontinue the investigational product prematurely due to AEs, without protocol violations, and return for their final evaluation, will still be part of the PP population. Additional per protocol populations, including patients who complete the initial treatment period within a duration greater than 228 days, may be identified and used for sensitivity analyses.

3. STUDY ENDPOINTS

The study endpoints will be evaluated after the initial treatment period and after the extension period. The results of the initial treatment period will be the basis of the primary evaluation of efficacy.

The primary efficacy endpoint in Section 3.1 will be based on the Modified International Cooperative Ataxia Rating Scale (mICARS) score. This modified ICARS excludes items 17-19 related to oculomotor function, and Items 8-12 related to kinetic functions from the full 100 point ICARS (see Section 4). The full ICARS, which is the validated scale and the preference of European Regulators, will also be presented as a sensitivity analysis.

3.1 Efficacy Endpoints

Initial 6-Month Treatment Period

Primary Efficacy Endpoint

- The change of the Modified International Cooperative Ataxia Rating Scale (mICARS) scores from baseline to Visit 9. The change in the full ICARS from baseline to Visit 9 will be presented as a sensitivity analysis.

Key Secondary Efficacy Endpoint

- CGI-C at Visit 9

Other Secondary Efficacy Endpoints

- The change of CGI-S (structured) score from baseline to Visit 9.
- The change of VABS score from baseline to follow-up based on repeated measures at Visit 6 and Visit 9

Tertiary Efficacy Endpoints

- The change of QOL scores (EQ-5D-5L scale) from baseline to follow-up based on repeated measures at Visit 6 ("Month 3") and Visit 9 ("Month 6")

Supplemental Analysis

The modified ICARS will be rescored, using two separate methods, collapsing categories within specific items. Each method will result in a smaller total sum score across the ICARS domains. These will be referred to as Rescored mICARS Method 1 (key opinion leader [KOL] suggested) and Rescored mICARS Method 2 (CCI definition), to prevent confusion with modified ICARS. Details of the mapping to each of these abbreviated scales are presented in Appendix II and Appendix III, respectively, of this document.

Extension Treatment Period (Months 6 to Month 12 of the study)

For the Extension Treatment Period, comparisons will be made for the 'Modified' ICARS, CGI-C, CGI-S (structured), VABS, and QoL [EQ-5D-5L] using the same methods as for the initial treatment period with missing values imputed in the same way. In addition, the full ICARS, Rescored mICARS Method 1, and Rescored mICARS Method 2 will be evaluated using the same methods as the modified ICARS.

3.2 Safety Endpoints

Safety will be evaluated by analysis of the following parameters:

- Adverse events and related AEs;
- Serious AEs and related SAEs;
- Discontinuation due to AE;
- Laboratory results (clinical chemistry, hematology, and urinalysis);
- Special laboratory parameters (HbA1c, CD4+ lymphocytes count, α-fetoprotein, CRP, and RBC antibodies [IgG, IgM and Qualitative Direct Coombs test]);

- Sterility testing of EDS-EP;
- Vital signs;
- Physical and neurological examination findings;
- 12-lead standard ECG;
- Bone mineral density;
- Tanner staging;
- C-SSRS.

3.3 Pharmacokinetic Endpoints

Pharmacokinetic analysis will be done on the following endpoints, and full details will be provided in a separate PK Analysis Plan.

- Population PK analysis for dexamethasone administered via EDS, based on pooled data for dexamethasone plasma concentrations from all samples obtained from subjects in each of the EDS treatment groups.
- PK parameters calculated for each subject, based on plasma levels of dexamethasone: C_{max}, t_{max}, AUC, and apparent half-life.

3.4 Pharmacodynamic Endpoints

Exploratory analyses will be performed to assess the relationship of mini-ATM levels to efficacy and safety outcomes.

4. DEFINITIONS AND DERIVED VARIABLES

Study Day

Study Day 1 will be defined as the date of the start of the first infusion of study drug. Per CDISC guidelines, Study Day -1 will be day immediately preceding Study Day 1, and negative study days will be measured backwards from Study Day -1 (that is, Study Days -2, -3, -4, etc). There will be no Study Day 0 per CDISC guidelines, thus Study Day -1 will correspond to "Study Day 0" as mentioned in the protocol.

Age

Age will be calculated using the date of birth (DOB) and the date of randomization and will be presented in data displays as an integer using the integer ("int") function in SAS. In the database, age will be given with two decimals.

Age = (DOB – Date of Randomization) / 365.25

Body Mass Index (BMI)

BMI will be calculated using weight in kg and height in m.

BMI = Weight (Kg)/Height $(m)^2$

The International Cooperative Ataxia Rating Scale (ICARS)

The International Cooperative Ataxia Rating Scale (Trouillas, 1997), the most frequently used clinician (neurologist) rated measure in patients with ataxias, was developed by a Committee of the

World Federation of Neurology to help standardize common manifestations of syndromes that lead to cerebellar dysfunction. 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).

To maximize the consistency of the data obtained from the ICARS, the same neurologist, well trained in the use of the ICARS and with expertise in the field of AT disorders, will evaluate the same subject at approximately the same time throughout the study. At each site, qualified raters will be trained to criteria at the Investigator's meeting and will receive ongoing training during the trial. The ICARS rater will perform the rating on each subject without consulting the results from the previous visit. In addition, video recording will be performed during each ICARS administration (though not required at Screening), according to a standardized procedure. The video recordings from each subject will be sent to an independent remote rater, where they will be blindly evaluated in random order. The speech domain items (Items 15 and 16) will be rated only by local raters who are familiar with the local language. The ICARS ratings from the independent remote rater, making use of the speech domain items which come only from the local raters, will be used for the primary efficacy endpoint analysis which is the mICARS.

Rating of the ICARS will be performed 24 hr before Baseline (Day -1) and at Baseline (Day 0); the Day 0 assessment will be recorded and used for determining changes from baseline on treatment. The ICARS will also be assessed at Visit 6 ("Month 3") and at Endpoint (Visit 9 ["Month 6"] or at early discontinuation) during the Initial Treatment Period, and at Visit 12 ("Month 9") and Visit 15 ("Month 12") (or at early discontinuation) during the Extension Treatment Period.

The ICARS score is the total sum of the sub scores and ranges from 0 to 100, with 100 being indicative of the most severely affected outcome. The 'Modified' ICARS (mICARS) score is the total sum of the sub scores excluding Items 17-19 related to oculomotor function and Items 8-12 related to kinetic function; these sub scores have been removed per CCI request. The 'Modified' ICARS score ranges from 0 to 54, with higher scores indicative of more severely affected outcome.

The baseline score by the central rater for the ICARS will be assessed at Visit 1, and the score closest to dosing will be accepted; therefore, the Day 1 value will be used where present, otherwise the Day 0 value will be used. If both the Day 1 and Day 0 assessments are missing, the Screening value by the local rater will be used.

Initial 6-Month Treatment Period

Change from baseline will be calculated by using the following formula =

(mICARS Score at Visit 6 ("Month 3") - Baseline mICARS Score)

(mICARS Score at Visit 9 ("Month 6") - Baseline mICARS Score)

Extension Treatment Period

For subjects randomized to EDS-EP and placebo subjects who are not switched to EDS-EP (original treatment assignment), the change from baseline will be calculated by using the the last assessment prior to first dose as baseline. For the placebo subjects who are switched to EDS-EP at either Visit 9 ("Month 6") or Visit 12 ("Month 9"), the last mICARS Score prior to the switch will be used as baseline. Change will be calclulated as follows:

(mICARS Score at Visit 12 ("Month 9") - Baseline mICARS Score)

(mICARS Score at Visit 15 ("Month 12") - Baseline mICARS Score)

The Clinical Global Impression (CGI-C and CGI-S [structured])

The Clinical Global Impression (CGI) consists of two 7-point, clinician-rated, Likert-type scales assessing change from baseline (CGI-C) and severity of neurological symptoms (CGI-S [structured]) (Guy, 1976).

In the current study, an overall assessment of the change in the subject's neurological symptoms of AT, compared to the status at baseline, will be made using the CGI-C. CGI-C scores range from 1 (very much improved) through 7 (very much worse). CGI-C is assessed at Visit 6 ("Month 3") and Visit 9 ("Month 6") during the initial treatment period, and at Visit 12 ("Month 9") and Visit 15 ("Month 12") of the extension treatment period.

In addition, the severity of neurological symptoms at baseline and at each subsequent time point will be assessed using the CGI-S (structured). No version of the CGI-S exists which has been specifically adapted for use in AT patients; therefore, a structured 5-point version was developed which takes into account the severity of the following symptoms of AT: ataxia (walking), dysarthria, dysmetria, extrapyramidal symptoms (chorea, myoclonus, dystonia, and tremor), and eye movements (Nissenkorn, 2015). Ratings of none, mild, moderate, severe, and very severe are selected based on the level of symptomatology. CGI-S (structured) is assessed at Visit 6 ("Month 3") and Visit 9 ("Month 6") during the initial treatment period, and at Visit 12 ("Month 9") and Visit 15 ("Month 12") of the extension treatment period.

Vineland Adaptive Behaviors Scale (VABS)

Functional intelligence generally is defined as one's ability to behave adaptively in daily life. Specifically, it includes the person's ability to express and comprehend language, behave appropriately in interpersonal situations, understand and use social behaviors, protect himself/herself, and care for himself/herself, in terms of personal hygiene and domestic independence. Although several scales and observation systems for measuring adaptive behavior have been developed since the 1940s when the construct of adaptive behavior was formally introduced, one of the most widely accepted scales is the Vineland Adaptive Behavior Rating Scales (VABS) (Sparrow, 2005).

The VABS is used primarily with children and adolescents from birth to age 18 years but may be used for adults suspected of having a mental handicap based on obtained IQ. The scale measures adaptive behavior in four major domains, Communication, Daily Living Skills, Socialization, and Motor Skills. These domains include several subdomains, as follows:

- **Communication:** Receptive, Expressive, Written
- **Daily Living Skills:** Domestic, Personal, Community
- **Socialization:** Interpersonal Relationships, Play & Leisure, Coping Skills
- **Motor Skills:** Gross, Fine.

VABS is assessed at Visit 1 (Day 0), Visit 6 ("Month 3"), and Visit 9 ("Month 6") during the initial treatment period, and at Visit 12 ("Month 9") and Visit 15 ("Month 12") of the extension treatment period. The Visit 1 result will be used as the baseline score. For the placebo subjects that switched to EDS-EP at or after Visit 9 ("Month 6"), the last assessment prior to treatment with EDS-EP will be used as baseline for the comparisons to Visit 12 ("Month 9") and Visit 15 ("Month 12").

EQ-5D-5L Quality of Life (QOL) scale

The EQ-5D-5L is assessed at Screening, Visit 1 (Day 0), Visit 6 ("Month 3"), and Visit 9 ("Month 6") during the initial treatment period, and at Visit 12 ("Month 9") and Visit 15 ("Month 12") of the extension treatment period. The Visit 1 result will be considered the baseline score. For the placebo subjects that switched to EDS-EP at or after Visit 9 ("Month 6"), the last assessment prior to treatment with EDS-EP will be used as baseline for the comparisons to Visit 12 ("Month 9") and Visit 15 ("Month 12").

C-SSRS

The C-SSRS is assessed at Visit 1 (Day 0), Visit 4 ("Month 1"), Visit 5 ("Month 2"), Visit 6 ("Month 3), Visit 7 ("Month 4"), Visit 8 ("Month 5"), and Visit 9 ("Month 6") during the initial treatment period, and at Visit 10 ("Month 7"), Visit 11 ("Month 8"), Visit 12 ("Month 9"), Visit 13 ("Month 10"), Visit 14 ("Month 11"), and Visit 15 ("Month 12") of the extension treatment period. The result at Visit 1 is the baseline score for the calculation of the change from baseline. For the placebo subjects that switched to EDS-EP at or after Visit 9 ("Month 6"), the last assessment prior to treatment with EDS-EP will be used as baseline for the comparisons to Visit 12 ("Month 9") and Visit 15 ("Month 12").

Prior/Concomitant Medications

Concomitant medications are any medication with use meeting at least one of the following four criteria. All other medication uses will be classified as "prior".

- Non-study medications with a start or stop date on or after the date of the first infusion of study treatment;
- Non-study medications that started prior to the first infusion of study treatment and are ongoing during the treatment period;
- Non-study medications with partial start dates that indicate that the medication could be concomitant in relation to the date of the first infusion of study treatment;
- Non-study medications with completely missing start dates, unless their stop dates confirm otherwise (i.e. the stop date is before the first infusion of study treatment).

5. STATISTICAL METHODOLOGY

5.1 Statistical and Analytical Issues

5.1.1 Statistical Methods

All eCRF data collected will be presented within data listings. The data listings will be sorted by treatment group, subject screening number, and visit. Any data collected on subjects that were screened but subsequently not randomized, will be presented within a non-randomized group.

The date format for all presentations will be 'ddmmmyyyy'.

The treatment labels for all tables, figures, and listings will be:

- **Group 1, Low Dose:** EDS-EP ~5-10 mg
- **Group 2, High Dose:** EDS-EP ~14-22 mg

- **Group 3:** Placebo

All statistical methods will be based on the International Conference on Harmonization (ICH)-E9 Guidance for Industry "Statistical Principles for Clinical Trials".

Any changes concerning the statistical analysis will be documented in an amendment to the statistical analysis plan, and/or will be described in the CSR.

If any of the assumptions underlying the formal statistical methods proposed are violated during the analysis on the final data, an alternative, more appropriate, statistical method will be used and any changes will be documented in the statistical methods section of the clinical study report (CSR), including the rationale for use.

All data will be summarized by treatment group. In addition, where appropriate, a total column will be included to summarize all subjects. Where appropriate, data will be summarized by visit in addition to treatment group.

The three treatment groups will be compared for baseline/screening demographic data (i.e., age, gender, ethnicity, and race), region, and medical history data. Demographic and historical data will be assessed for potential differences between treatment groups by means of descriptive statistics. Demographic and baseline data will be presented using the FAS and Safety Population.

P-values will be rounded to four decimal places. P-values less than 0.0001 will be reported as "<0.0001" in tables. All statistical analyses will be performed using SAS® software version 9.4 or higher (Copyright, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute, Inc., Cary, North Carolina, USA).

Categorical variables will be summarized using frequencies and percentages. Percentages will be presented to 1 decimal place. In cases where the percentage calculated is > 0% and < 0.1%, "<0.1%" will be presented against the count. In cases where the percentage calculated is 100.0%, "100%" will be presented without the decimal.

Continuous variables will be summarized using descriptive statistics (number of subjects with an observation [n], mean, standard deviation [SD], median, minimum [min], and maximum [max]) where n ≥2. Unless otherwise specified, the mean and median for a continuous variable will be presented to 1 more decimal place than the original (raw) values and the SD will be presented to 2 more decimal places than the original values. The min and max will be presented to the same number of decimal places as the original values.

5.1.2 Handling of Dropouts

Subjects who discontinue treatment prematurely will be defined as dropouts. Those subjects who discontinue treatment prematurely but return for scheduled efficacy assessments at Visit 6 ("Month 3"), Visit 9 ("Month 6"), Visit 12 ("Month 9"), and Visit 15 ("Month 12") will comprise the retrieved dropouts (RDO). Missing data will be handled as described below.

5.1.3 Handling Missing Data

Baseline Values

If values are missing at the baseline visit (Day 0/1), and the data are also recorded at screening, then the screening value will be used in the summaries and calculations of change from baseline. Otherwise, the baseline value will be missing for safety and efficacy endpoints.

Missing Efficacy Assessments

The missing data methods are an integral part of the data analysis for efficacy and are described in full in Section 5.3. For the primary analyses of mICARS, the use of a mixed-effect model repeated measure (MMRM) model allows for missing data and assumes the data are missing completely at random (MCAR), so no imputations will be performed.

For sensitivity analysis, several multiple imputation methods will be used:

1. Impute all missing data within the original treatment group.
2. Impute all data missing due to COVID-19 related restrictions to the original treatment group and impute from the control group (Jump to Reference) for all other missing data. The COVID-19 disruption is across the entire study and can be considered as random across subject characteristics and factors that may be related to treatment or outcome, so imputation assuming Missing at Random should be appropriate. Additional factors, such as the number of treatments received, can be added to the imputation model. Details to show that these subjects continued their visits up to the point of restrictions being imposed by the pandemic and did not discontinue treatment due factors related to the study protocol or outcome will be provided.
3. Impute all missing data from the control group (Jump to Reference).

In addition, last observation carried forward [LOCF] and observed cases [OC] will be used. The LOCF method will employ the last observation carried forward; this may be the baseline value if the subject has no follow-up values. The OC method will employ only observed cases for the time points of interest (i.e., for repeated measures analysis of Visit 6 ["Month 3"] and Visit 9 ["Month 6"] both mICARS must be observed/collected to be included in the analysis). A specific analysis using retrieved dropouts will not be performed (see Section 5.10).

Missing data for all other efficacy analyses not using MMRM will use Multiple Imputation #1 as described above), with the other imputation methods, LOCF and OC, for sensitivity.

Missing Values When Computing Instrument Scores

In the computation of scores for the instruments in use (for example, ICARS), missing values will be handled according to published guidelines/instructions related to the instrument.

In the case of ICARS, the published guideline/instructions will take precedence, but the following rules will be applied if not addressed in the published guideline/instructions.

- If an individual item is missing from the Day 1 ICARS, it will be taken from the Day 0 ICARS.
- If an individual item is missing from a follow-up visit assessment, the same item will be used from the local rater ICARS data.

5.1.4 Handling Data Collected Out of Window

Efficacy scales (e.g., ICARS, QoL, etc.) collected outside of the per-protocol windows (for example, per Appendix I, ICARS is scheduled for collection only at Visit 6, 9, 12, and 15) will be included in the analyses based on the nominal visit label. During the initial 6-month treatment period, Visit 9 (Month 6) must occur within 228 day window for the per protocol analysis. All data will be presented in the listings, in chronological order based on the time of collection.

5.1.5 Handling Data Collected Prior to a Process Event or Interruption

The interruption of an EDS process can result in a repeat EDS process with potentially the repeat of assessments that are scheduled to take place prior to the EDS process at a given visit. If this occurs (a repeat EDS process is conducted and the assessments scheduled to take place prior to an EDS assessment are repeated), the earliest set of assessments that are within the visit window will be used; if both set of assessments are outside of the visit window, then the set of assessments prior to the first EDS process will be used.

5.1.6 Pooling of Investigator Sites

Since the randomization used probabilistic baseline randomization (pBAR) methodology, it was not blocked by site, and the analysis will not be blocked by site.

5.1.7 Determination of Sample Size

Based on the very low prevalence of AT, as well as the high disability, morbidity and mortality, the number of patients available for prospective trials is extremely limited. Furthermore, only aggregate Phase II study results were available (IEDAT-ERY01-2010 Clinical Study Report). Hence, in the absence of a file with the raw item score for each patient, the treatment effect and variability of the 'Modified' ICARS was unknown. Therefore, the parameters needed to identify an appropriate sample size for this study were estimated using the aggregate Phase II results.

Sample size calculations were based on the analysis of the primary efficacy variable (i.e., 'Modified' ICARS) under the following assumptions.

- For aggregate ICARS, a treatment difference of 3.7 - 4.2 for the high dose versus placebo with respect to ICARS measurements is expected, with a standard deviation of 5.0 - 7.4 (IEDAT-ERY01-2010 Clinical Study Report).

- For 'Modified' ICARS, the treatment difference is expected to be less than the aggregate ICARS, therefore instead of examining a treatment effect between 3.7 and 4.2, the range between 3.0 and 3.7 was examined. The decrease in treatment effect is expected given that most of the questions in the Kinetic Function domain are not included in the 'Modified' ICARS and Chessa et al (2014) reported this domain as demonstrating the greatest overall improvement.

- For 'Modified' ICARS, the standard deviation is expected to be more than the aggregate ICARS, therefore instead of examining a standard deviation between 5.0 and 7.4, the range

between 5.0 and 8.0 was examined. This increase is expected given that removing questions from health assessment instruments can decrease precision and increase standard deviations (Awad, 2008; McHorney, 1992; McHorney, 1997).

- The primary efficacy variable will be tested, comparing high dose versus placebo at the 0.05 two-sided significance level. Testing of the low dose versus placebo will only proceed if the high dose is significant for the primary endpoint and the secondary endpoint. Consequently, no adjustment for multiplicity is needed for testing the two dose levels.

Table 3 provides power estimates for the range of potential treatment effects and standard deviations. Estimates had to be based on ranges, since point value estimates for 'Modified' ICARS were not available.

Table 3. Power given treatment effect and standard deviation estimates for a sample size of 54

Treatment Effect	Standard Deviation	Power
3.0	5.0	99.3%
	6.0	95.7%
	7.0	88.3%
	8.0	78.7%
3.2	5.0	99.7%
	6.0	97.5%
	7.0	91.9%
	8.0	83.6%
3.4	5.0	99.9%
	6.0	98.6%
	7.0	94.6%
	8.0	87.8%
3.6	5.0	>99.9%
	6.0	99.3%
	7.0	96.6%
	8.0	91.1%
3.7	5.0	>99.9%
	6.0	99.5%
	7.0	97.3%
	8.0	92.5%

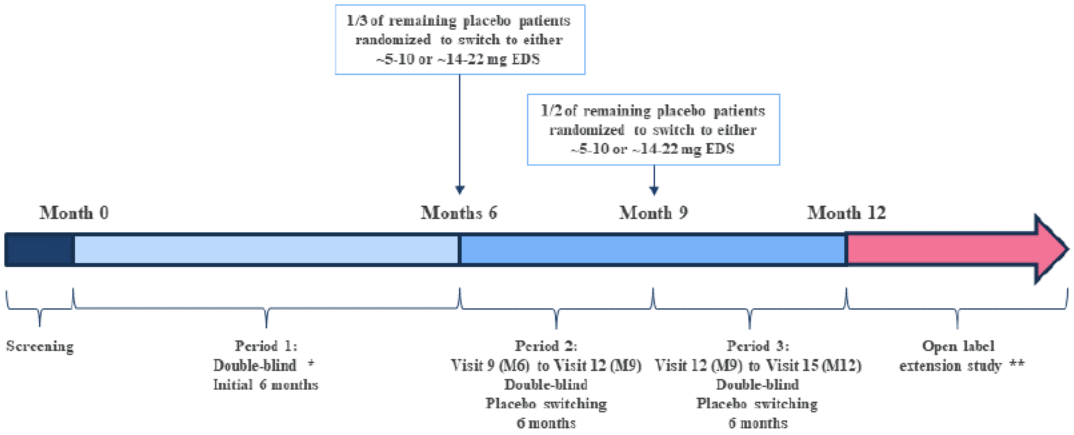
As seen in the above table, a sample size of 54 provides sufficient power for a study design with two repeated measures to assess the primary efficacy endpoint of change from baseline in 'Modified' ICARS between two groups with a two-sided 0.05 significance level, when the treatment effect ranges between 3.0 and 3.7, and the standard deviation ranges between 5.0 and 7.0 (PASS®, Module "Tests for Two Means in a Repeated Measures Design").

The final sample size was adjusted for 10% loss to follow-up, for a final sample size of about 60 per group. It was anticipated that the screen failure rate would be approximately 25%; therefore, at least 240 subjects would need to be screened to enroll 180 eligible subjects.

Sample size was based on the primary efficacy parameter from the Version 10.0, Final, 16 April 2019 IEDAT-02-2015 protocol, the 'Modified' ICARS. The computed sample size is sufficient to maintain at least 80% power for the full ICARS, given the range of treatment differences and range of standard deviations available for the full ICARS from the IEDAT-ERY01-2010 Clinical Study Report described above and the powers computed for the selected ranges of treatment effect and standard deviation for the 'Modified' ICARS.

5.1.8 Randomization

The milestones for the randomization process are depicted in Figure 1 and described in Items 1-4 below.



** Randomization (1:1:1; n=180, i.e. 60 per study arm) to ~5-10 or ~14-22 mg EDS or placebo using a minimization procedure for gender and age (< 10 and ≥ 10 years of age) will be done by IVRS*

*** All remaining placebo patients switch to ~14-22 mg EDS in study IEDAT-03-2018*

NOTE: Due to the impact of COVID-19, the company decided to complete enrollment with 175 patients.

Figure 1. Trial periods and randomization/placebo switching time points.

1. Initial Randomization. This occurred at the start of the double-blind period. Because this trial enrolled subjects with a rare condition, the sample size was limited. Important balancing factors included gender and age (age < 10, age ≥ 10) and region. There are three treatment groups. For this situation, probabilistic baseline randomization (pBAR), or equivalently, probabilistic covariate baseline minimization was desirable. The placebo switches discussed in Items (2)-(4) were assigned at the time of the initial randomization. (See Figure 2)
2. Switching of remaining placebo subjects after 6 months of the Initial Double-Blind treatment assignment. Among subjects initially randomized to placebo who complete their initial 6 months of double-blind dosing, every third such placebo subject was randomized 1:1 to active dose at either the high or low dose level.
3. Switching of remaining placebo subjects after 9 months of the Initial Double-Blind treatment assignment. Among subjects initially randomized to placebo who complete their initial 9 months of double-blind dosing, every other such placebo subject was randomized 1:1 to active dose at either the high or low dose level.
4. Switching of remaining placebo subjects after 12 months of the Initial Double-Blind treatment assignment. For subjects initially randomized to placebo who complete their initial 12 months of double-blind dosing, all such placebo subjects will have been

randomized 1:1 to active dose at either the high or low dose level. These treatment assignments will be made in the open-label extension study (Study IEDAT-03-2016) for those placebo subjects who continue treatment in that study.

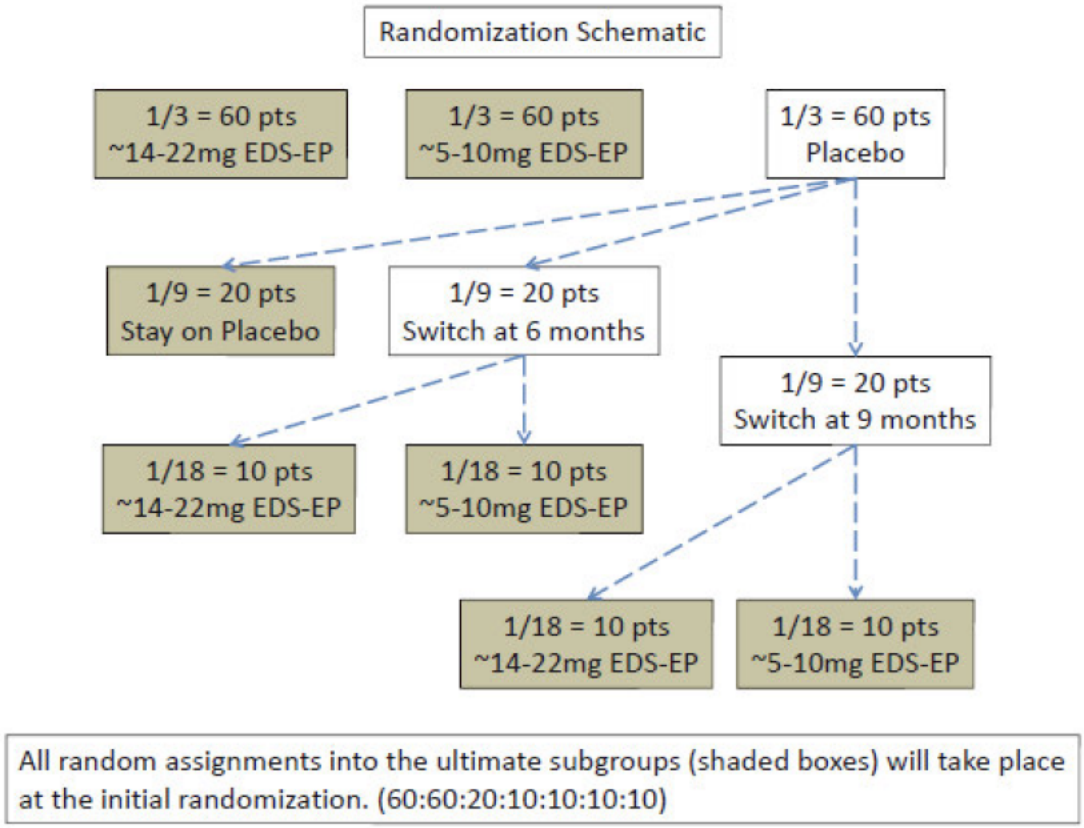


Figure 2. Randomization schematic

When the design of the pBAR randomization was in place, simulations were used to test the randomization system. The simulations were designed

1. to subject the pBAR implementation to conditions beyond the control of the study team, such as the order that subjects arrive for randomization, to assess the robustness of the algorithm. The ability of the system to handle re-ordering of the arrival order of subjects was examined to see how well the desired balance was achieved.
2. to examine the extent to which random fluctuation disturbed the balance, both overall, and within the desired strata.
3. to subject the IVRS system implementation to various stresses, as a validation.

5.1.9 Handling Analysis of Placebo Switching Subjects

As described in the randomization section above (Section 5.1.7), subjects originally randomized to placebo may be switched to EDS-EP treatment during the extension treatment period at Visit 9

("Month 6") or Visit 12 ("Month 9"). This will cause re-distribution of subjects within the analysis populations. For example, the number of ITT subjects in the placebo group will decrease over the course of the study, while the number of ITT subjects in the two EDS-EP treatment groups will increase over the course of the study. Although there will be re-distribution, the total number in each population (ITT, FAS, Safety, PP) will remain consistent. Re-distribution will be presented on the subject disposition table. In order to maintain consistency, subjects who discontinue prior to a switch month, will not be dropped from the total but instead be presented in their intended treatment group. Presentation within intended treatment group is possible because randomization assignments for Visit 9 ("Month 6") and Visit 12 ("Month 9") (the placebo switch months) were identified at the same time as the initial randomization assignment. Because subjects who discontinue prior to Visit 9 ("Month 6") will not have efficacy data past the point of discontinuation, the rules described above for missing data will be applicable for analysis of these subjects (e.g., Jump to Reference, LOCF, and OC) within the initial treatment period. Placebo switching subjects who do not make it to the point at which they would have switched will not appear in related post-switch analyses.

5.1.10 Hypothesis Testing and Handling of Multiple Comparisons

The high dose of the primary efficacy end point will be tested at the two-sided significance level of $\alpha \leq 0.05$. With this requirement, the overall family-wise error rate (FWER) can be no greater than $\alpha = 0.05$, two-sided. The study will be judged statistically significant if the high dose of the primary efficacy endpoint is significant.

For the primary efficacy end point, the low dose will be tested only if the high dose is found statistically significant for the primary and key secondary endpoints. In this way the 0.05 two-sided significance level will be maintained, and no adjustment will be necessary.

The null (H_0) and alternative (H_1) hypotheses are:

> H_0: there is no difference between Group 2-EDS-EP high dose and the placebo group with respect to change from baseline in mICARS
>
> H_1: there is a difference between Group 2-EDS-EP high dose and the placebo group with respect to change from baseline in mICARS

Statistical significance for efficacy and the study as a whole will be declared if:

> The null hypothesis for the primary efficacy analysis (no statistical difference between EDS-EP high dose and placebo) with respect to change from baseline in mICARS is rejected at the 0.05 two-sided significance level.

Following the testing for the primary endpoint for the high dose, analysis of the key secondary endpoint will be performed only if the primary analysis for the high dose level was significant at the two-sided 0.05 level.

Efficacy of the EDS-EP low dose versus placebo:

> If the null hypothesis for the primary efficacy analysis (no statistical difference between EDS-EP high dose and placebo) with respect to change from baseline in mICARS and the null hypothesis for the key secondary endpoint are rejected, the efficacy of EDS-EP low dose versus placebo with respect to change from baseline in mICARS will be tested at the 0.05 two-sided significance level, and testing will proceed hierarchically to the key secondary endpoint also at the 0.05 level.

The analyses for the QOL scale (EQ-5D-5L) and C-SSRS (a safety parameter) will be exploratory and will not be adjusted for multiplicity.

Further analyses will make the same comparisons at Visit 12 ("Month 9") of treatment, and again, at Visit 15 ("Month 12") of treatment. Because these later analyses will be underpowered, these analyses will be for descriptive purposes only and will not follow the sequential testing approach. P-values will be presented strictly as an aid to understanding the results for all comparisons but will provide no basis for statistical inference.

5.2 Subject Characteristics

5.2.1 Subject Disposition

The number and percentage of randomized subjects within each region will be summarized by treatment group and placebo switching subgroups, and regional enrollment will be compared across EDS-EP and pooled placebo treatment groups using the Pearson Chi-square test, or Fisher's Exact test if any cell count is <5. This summarization will be repeated by region and site, with no statistical comparisons performed.

The number of screened subjects, and the number and percentage of randomized subjects who are in the Full Analysis Set, in the Safety Set, and in the Per Protocol Set, and the number and percentage of randomized subjects excluded from the Per Protocol Set by reason for exclusion (including discontinuation due to the COVID-19 pandemic) will be summarized by initial treatment and placebo switch sub-group.

The number and percentage of randomized subjects who are ongoing in the study (at the time of the primary analysis), complete the study, who discontinue the study (overall and by primary reason for discontinuation) will be summarized by treatment group, placebo switching sub-group, and overall. This disposition will also be summarized by region.

The number and percentage of randomized subjects who discontinue the study due to COVID-19 restrictions will be summarized by treatment group, placebo switching sub-group, and overall.

5.2.2 Protocol Violations and Blinded Data Review Meeting

All decisions regarding major deviations and exclusion from the Per Protocol population will be discussed and agreed upon during a Blinded Data Review Meeting (BDRM) prior to breaking the treatment blind and commencing the final analysis on the locked database. The decisions will be documented in the BDRM minutes and signed by the Sponsor and the CRO.

A listing of all subjects with their potential protocol deviations or violations will be presented according to ICH E3. A data listing presenting the eligibility for the analysis populations for each subject will also be presented. Major protocol violations that exclude individual subjects from the per-protocol population will be defined during the BDRM and will be documented prior to data analysis in the meeting minutes.

At least the following checks will be made to identify potential protocol violations by each subject: (1) checks ensuring subjects met all of the inclusion criteria and none of the exclusion criteria (specified in Table 4), (2) checks on visit window deviations, and (3) checks on dosing and the

actual amount of study product received at each infusion versus amount randomized to receive (e.g., identify subjects randomized to receive low dose but instead received 3 mg, also applicable to finding deviations in the high dose group). Other types of protocol violations, which are detected during the course of the study, might lead to additional checks.

Table 4. Inclusion and Exclusion Criteria

Inclusion Criteria	
1	Patient meets clinical criteria for diagnosis of AT. The neurological signs of AT (incoordination of the head and eyes in lateral gaze deflection, gait ataxia associated with an inappropriately narrow base) must be documented. Such signs of AT illustrate the body systems in which changes shall be confirmed but the listed changes are examples and other changes in those systems may be observed and documented to confirm the diagnosis of AT.
2	Patient is in autonomous gait or is helped by periodic use of a support (i.e. local ICARS score for *Item 1 – Walking Capacities* between 0 and 4, included).
3	Patient will be investigated for the proven genetic diagnosis of AT (prior documentation or by central laboratory test report).
4	Patient is at least 6 years of age, of either sex.
5	Body weight > 15 kg.
6	The patient and his/her parent/caregiver (if below the age of consent), or a legal representative, has provided written informed consent to participate. If consent is provided solely by the caregiver in accordance with local regulations, the patient must provide assent to participate in the study.
Exclusion Criteria	
General	
1	Females that are a. pregnant, or are breast-feeding (for EU countries only); b. of childbearing potential, pregnant, or are breast-feeding (for US and Rest of World countries). *Females of childbearing potential using adequate birth control, as determined by their Health Care Provider, will be eligible.*
2	A disability that may prevent the patient from completing all study requirements.
3	Current participation in another clinical study.
Medical History and Current Status	

Table 4. Inclusion and Exclusion Criteria

4	CD4+ lymphocytes count <400/mm3 (for patients 6 years of age) or <150/mm3 (for patients > 6 years). In presence of oral infections, like oral candidiasis, documented at the screening or recurrent as per medical history documentation, the limit increases to <200/mm3 (for patients > 6 years).
5	Loss/removal of 250 mL or more of blood within the past 4 weeks prior to screening.
6	Current neoplastic disease or previous neoplastic disease not in remission for at least 2 years.
7	History of severe impairment of the immunological system.
8	Severe or unstable pulmonary disease.
9	Uncontrolled diabetes. *Patients with diabetes that has been stabilized (i.e. no hypoglycemic or hyperglycemic episodes in the past 3 months) will be eligible.*
10	Any other severe, unstable, or serious disease or condition that in the Investigator's opinion would put the patient at risk for imminent life-threatening morbidity, need for hospitalization or mortality.
11	Any clinically significant abnormality on standard laboratory examinations (hematology, biochemistry, urinalysis) at screening that remains abnormal on repeat testing. Eligibility of patients with abnormal laboratory test values will be determined by the Investigator, in consultation with the Medical Monitor.
12	Confirmed hemoglobinopathies, e.g. hemoglobin C disease, sickle cell anemia, or thalassemia.
13	Moderate or severe renal and/or hepatic impairment.
Prior/Concomitant Medication	
14	Any previous **oral or parenteral** steroid use within 4 weeks before Baseline. *Treatment with inhaled or intranasal steroids for asthma or allergies, as well as use of topical steroids will be permitted.*
15	Chronic condition or prior allergic reaction representing a contraindication to the use of dexamethasone or other steroid drugs.
16	Has participated in any other trial with an investigational drug and received a dose within 30 days or 10 half-lives (whichever is greater) from the start of the 30-day Screening Period.
17	Has participated in a previous trial with EDS.

Table 4. Inclusion and Exclusion Criteria

18	Requires any concomitant medication prohibited by the protocol.
19	Has taken a drug or treatment known to cause major organ system toxicity during the past year.
20	Use of any drug that is a strong inducer/inhibitor of CYP3A4 within 4 weeks before baseline.

5.2.3 Background and Demographic Characteristics

Descriptive summaries of subject demographic and baseline characteristics will be presented by treatment group and overall for the safety population and full analysis set according to treatment during the initial treatment period.

The following demographic data and baseline characteristics will be summarized:

- Age at randomization (years) as a continuous variable and as a categorical variable (6-9 years, ≥10 years);
- Sex
- Ethnicity
- Race
- ICARS total score
- Genetic characteristics
- Disease severity

Categorical age, sex, ethnicity, and race will be compared between treatment groups using the Pearson Chi-square test, or Fisher's Exact test if any cell count is <5.

5.2.4 Extent of Treatment Exposure and Compliance

Unless specified otherwise, extent of exposure and compliance parameters will be summarized for the safety population by treatment received during the initial treatment period, Visits 9 to 12 ("Month 6 to 9"), and Visits 12 to 15 ("Month 9 to 12"), and by treatment scheme received (the seven schemes assigned at randomization) for the total study. Table 5 illustrates how subjects will be allocated to treatment during different periods of the study, under the assumption that no subjects drop out.

Table 5. Planned Subject Allocation to Treatment During Each Study Period

	EDS-EP Low Dose	EDS-EP High Dose	Placebo	Non-switch Placebo	Visit 9 EDS-EP Low Dose	Visit 9 EDS-EP High Dose	Visit 12 EDS-EP Low Dose	Visit 12 EDS-EP High Dose
Initial Treatment Period	60	60	60					

Visit 9 ("Month 6") to Visit 12 ("Month 9")	60	60		40	10	10		
Visit 12 ("Month 9") to Visit 15 ("Month 12")	60	60		20	10	10	10	10

Note: Table presents number of subjects allocated per treatment per period assuming no subjects drop out.

Duration of Treatment and Number of Infusions

Duration of treatment in the initial treatment period will be calculated in days as the date of the last infusion of study treatment during the initial treatment phase (Visit 9) – date of the first infusion of study treatment + 1. Duration of treatment for Visits 9 to 12 ("Month 6 to 9") will be calculated in days as the Visit 12 infusion date – the Visit 9 infusion date + 1, and the duration of treatment for Visits 12 to 15 ("Month 9 to 12") will be calculated in a similar manner. Total duration of treatment (initial treatment period + extension treatment period) will be calculated in days as the date of last infusion of study treatment – date of the first infusion of study treatment + 1.

Duration of treatment and number of infusions received will be summarized by treatment period using summary statistics for continuous variables. The number and proportion of subjects with duration of treatment longer than 228 days in the initial treatment period will be summarized. The exact loaded dose of dexamethasone in Erydex administered to each subject at each dosing visit will be summarized.

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 1 (EryDel definition) is defined as monthly treatments with a maximum of a one monthly treatment interruption at any time during the study. Continuous Exposure 2 (CCI definition) is defined as monthly treatments with no missed treatments.

For each type of treatment (low dose, high dose, and placebo), separately, the number of subjects with each total monthly treatment exposure will be summarized. For each total monthly treatment exposure, the number of subjects in each of the following categories will be summarized:

- Missing ≤1 monthly treatment (Continuous Exposure 1)
- No missed monthly treatments (Continuous Exposure 2)
- Missing ≥ 2 non-consecutive monthly treatments
- Missing ≥ 2 consecutive monthly treatments

Dosing Compliance

Percentage treatment compliance during a given period will be calculated for all treated subjects within the period using the following formula.

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

where for the initial treatment period:

- A = Total number of injections actually administered through Visit 9 ("Month 6")
- P = Total number of injections scheduled to receive up to Visit 9 ("Month 6")

where for the Visits 9 to 12 ("Month 6 to 9") period:

- A = Total number of infusions actually administered from the day after Visit 9 ("Month 6") through the day of Visit 12 ("Month 9")
- P = Total number of infusions scheduled to receive from the day after Visit 9 ("Month 6") through the day of Visit 12 ("Month 9")

where for the Visits 12 to 15 ("Month 9 to 12") period:

- A = Total number of infusions actually administered from the day after Visit 12 ("Month 9") through the day of Visit 15 ("Month 12")
- P = Total number of infusions scheduled to receive from the day after Visit 12 ("Month 9") through the day of Visit 15 ("Month 12")

where for the total treatment period overall (initial plus extension):

- A = Total number of infusions actually administered
- P = Total number of infusions scheduled to receive up to Visit 15 ("Month 12")

Dosing compliance will be summarized using summary statistics for continuous variables. The number and percentage of subjects completing 6 infusions within 228 days during the initial treatment period will also be summarized. Dosing compliance excluding subjects discontinued due to the COVID-19 pandemic will be also be provided.

5.2.5 Prior and Concomitant Medications and Therapies

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary and the Anatomical Therapeutic Chemical (ATC) classification system. Coding will include the drug class and generic drug name.

All prior and concomitant medications will be listed, including verbatim descriptions and coded terms.

Prior medications, concomitant medications during the initial treatment period (through the day prior to Visit 9 ["Month 6"] infusion), concomitant medications from Visit 9 ("Month 6") through the day prior to Visit 12 ("Month 9"), and concomitant medications from Visit 12 ("Month 9") through Visit 15 ("Month 12") will be summarized according to treatment received during the period using the number and percentage of subjects reporting any medication use, and the number and percentage of subjects reporting each drug class and generic drug name. For each subject, multiple records of the same medication will be counted once within a drug class and generic drug name.

Prior and concomitant medications will be presented for the safety population.

5.2.6 Medical History

Past and current medical conditions including disease history will be recorded at screening and will be coded using MedDRA version 19.0. The number and percentage of subjects reporting any medical history and any medical history for each system organ class and preferred term will be summarized by treatment group from the initial treatment period. Subjects will be summarized only once at any level (any history, system organ class, and preferred term) if they have multiple reports at the level. Treatment group differences in the reporting of any medical history will be assessed using the Pearson Chi-square test. Data will be presented for the safety population and FAS.

5.3 Efficacy Analysis

All efficacy analyses will be performed on both the FAS and PP populations.

5.3.1 Primary Efficacy Variable

The modified ICARS total score from the central rater (with speech domain scores from local raters) at baseline and each follow-up visit, and the change and percent change from baseline to each follow-up visit, will be summarized using descriptive summary statistics by treatment group.

The primary efficacy variable, change from baseline to follow-up (Visit 6 ["Month 3"] and Visit 9 ["Month 6"]) in mICARS total score (described above), will be analyzed using a mixed model repeated measures (MMRM) analysis, with the baseline mICARS value as covariate and five fixed effects (treatment, age [6 to <10 years, ≥ 10 years], sex, region, visit) and one interaction term (treatment-by-visit). The treatment effect, together with the associated two-sided 95% CI and p-value will be calculated. Unstructured covariance matrices will be used. Model effect estimation will be based on restricted maximum likelihood (REML). The region-by-treatment interaction can be tested in a separate model and if a significant interaction is found, then a forest plot will be used to present the region-specific treatment effects and associated 95% confidence intervals.

The primary MMRM analysis will assume missing at random (MAR) as a means of handling missing data.

Sensitivity analyses of these primary analyses will consist of ANCOVA at Visit 9 ("Month 6") with missing data imputed using multiple imputations as described in Section 5.1.3, LOCF, and OC. The results from each of the sensitivity analyses will be compared to the primary MMRM analysis.

When applying the multiple imputation methods describe in Section 5.1.3, the regression method will be used, and the imputation model will be the same as the analysis model, based on the factors treatment, sex, age (category), region, and baseline mICARS; the pattern of missing data will be essentially monotonic since none of the factors used in the model are expected to be missing. One hundred iterations of the model will be run, and the results will be combined with SAS PROC MIANALYZE. For Multiple Imputation Method #2, multiple imputation based on subjects taking the same treatment will be applied first to the missing data due to COVID-19 related restrictions, and then Jump to Reference will be applied to the remaining missing data.

For the extension treatment period, the change from baseline will be the change from the last assessment prior to first infusion in the study except for the placebo subjects who switch to EDS-EP at Visits 9 and 12 ("Month 6" and "Month 9", respectively). For these subjects who are switched, the baseline will be the assessment just prior to the switch. The change will be summarized for Visit 12 ("Month 9") and Visit 15 ("Month 12"), using LOCF and OC. Because

of the small sample size and the switch from placebo to EDS-EP, no formal statistical comparisons of treatment groups will be made.

For the FAS only, the mean mICARS score will be plotted over time during the initial treatment period with separate trend lines for each of the three treatment groups. This type of plot will be repeated for mean mICARS score and mean change from baseline in mICARS score over the entire study, with separate trend lines for the seven possible dosing schemes.

For the placebo subjects who switched to EDS-EP at Visit 9 ("Month 6"), the change seen during the initial treatment period, and the change between Visit 9 ("Month 6") and Visit 15 ("Month 12") will be compared with a paired t-test or a non-parametric equivalent. A comparison of the change over 3 months of placebo against 3 months of treatment will also be done using the first 3 months for the subjects who switch at Visit 9 ("Month 6") and those who switched at Visit 12 ("Month 9").

Sensitivity Analyses

The full ICARS will be analyzed using the same methods as for the primary analysis of mICARS. The nominal p-value will be presented, and no adjustments for multiplicity will be made.

5.3.2 Key Secondary Efficacy Variable

The analysis of the key secondary efficacy measure, CGI-C, will be performed using ANCOVA, with age (at 2 levels: <10, ≥10 years), sex, treatment, region, visit, and treatment-by-visit interaction as fixed effects (at Visit 9 ["Month 6"]). The estimate of the treatment effect parameter, together with the associated two-sided 95% CI and p value will be calculated.

The primary analysis of CGI-C will impute missing values using LOCF. Additional sensitivity analyses will be performed with missing values imputed using Multiple Imputation Method 1 (as described in Section 5.1.3) and OC.

For the extension treatment period the same ANCOVA model will be used to estimate the treatment effect for the CGI-C at Visit 12 ("Month 9") and Visit 15 ("Month 12"). Missing data will be imputed using LOCF. Sensitivity analyses will be performed using ANCOVA based on OC.

If the normality assumption of ANCOVA is not met, the alternative methodology of rank score ANCOVA will be used.

Sensitivity analyses of CGI-C will also be performed using a proportional odds model with ordinal logistic regression with age (at 2 levels: <10, ≥10 years), sex, treatment, region, visit, and treatment-by-visit interaction as fixed effects (at Visit 9 ["Month 6"]). The estimate of the treatment effect odds ratio, together with the associated two-sided 95% CI and p value, will be calculated. The primary analysis will impute missing value using LOCF, and additional analyses will be performed with missing values imputed using Multiple Imputation Method 1 (as described in Section 5.1.3) and OC.

In addition, the proportion of subjects with improvement or stable disease (scores of 1, 2, 3, or 4), versus those with worsening (scores of 5, 6, or 7) at Visit 9 will be compared between the EDS-EP high and low doses versus placebo by using a logistic regression model with fixed effects for age, sex, region, and treatment. For the extension treatment period, the same analysis will be repeated at Visit 15 ("Month 12"). Odds ratios and the associated 95% confidence intervals will be reported. Missing values will be imputed using LOCF. Sensitivity analyses will include logistic regression

based on OC. These analyses will be repeated comparing the proportion of subjects with improvement (scores of 1, 2, or 3) versus those with stable or worsening (scores of 4, 5, 6, or 7).

CGI-C scores at all the visits during the initial treatment period and the extension treatment period (Visit 6, Visit 9, Visit 12, and Visit 15) will be summarized using summary statistics appropriate for the analysis (that is, for continuous or categorical data) by treatment group.

For the FAS only, the mean CGI-C score will be plotted over time during the initial treatment period with separate trend lines for each of the three treatment groups. This type of plot will be repeated for mean CGI-C score over the entire study, with separate trend lines for the seven possible dosing schemes.

5.3.3 Other Secondary Efficacy Variables

CGI-S (structured)

The analysis of the change from baseline to Visit 9 ("Month 6") of CGI-S (structured) score will be performed similar to the analysis of the CGI-C score, modifying the approach using baseline as a covariate. The analysis for the extension treatment period will be performed in a similar way. For the extension treatment period, the change from baseline will be the change from the last assessment prior to first infusion in the study except for the placebo subjects who switch to EDS-EP at Visits 9 and 12 ("Month 6" and "Month 9", respectively). For these subjects who are switched, the baseline will be the assessment just prior to the switch.

Ordinal logistic regression analyses will also be performed for CGI-S (structured) in a manner similar to CGI-C, with the exception that baseline CGI-S (structured) score will enter into the analysis.

The CGI-S score at baseline and all visits during the initial treatment period and extension treatment period (Visit 6, Visit 9, Visit 12, and Visit 15) will be summarized using summary statistics appropriate for continuous or categorical data by treatment group. The change from baseline to all visits will also be summarized and compared between treatment groups. Percent change from baseline will be summarized descriptively.

For the FAS only, the mean CGI-S score will be plotted over time during the initial treatment period with separate trend lines for each of the three treatment groups. This type of plot will be repeated for mean CGI-S score and mean change from baseline in CGI-S score over the entire study, with separate trend lines for the seven possible dosing schemes.

VABS

The analysis of the change from baseline (Day 0) to Visit 9 ("Month 6") of VABS score will be performed using ANCOVA with LOCF score from baseline to Visit 9 ("Month 6"). Sensitivity analyses will be based on OC. The analysis for the extension treatment period will be performed in the same way. For the extension treatment period, the change from baseline will be the change from the last assessment prior to first infusion in the study except for the placebo subjects who switch to EDS-EP at Visits 9 and 12 ("Month 6" and "Month 9", respectively). For these subjects who are switched, the baseline will be the assessment just prior to the switch.

The VABS score at baseline and all visits during the initial treatment period and extension treatment period (Visit 6, Visit 9, Visit 12, and Visit 15) will be summarized using summary statistics

appropriate for continuous data by treatment group. The change from baseline to all visits will also be summarized and compared between treatment groups.

For the FAS only, the mean VABS score will be plotted over time during the initial treatment period with separate trend lines for each of the three treatment groups. This type of plot will be repeated for mean VABS score and mean change from baseline in VABS score over the entire study, with separate trend lines for the seven possible dosing schemes.

5.3.4 Tertiary Efficacy Variables

The EQ-5D-5L scale will be used to assess QOL. The analysis of the change from baseline (Day 0) to Visit 9 ("Month 6") of the EQ-5D-5L score will be performed in the same way as the analysis of change of VABS from baseline to Visit 9 ("Month 6").

The EQ-5D-5L score at baseline and all visits during the initial treatment period and extension treatment period (Visit 6, Visit 9, Visit 12, and Visit 15) will be summarized using summary statistics appropriate for continuous data by treatment group. The change from baseline to all visits will also be summarized and compared between treatment groups. For the extension treatment period, the change from baseline will be the change from the last assessment prior to first infusion in the study except for the placebo subjects who switch to EDS-EP at Visits 9 and 12 ("Month 6" and "Month 9", respectively). For these subjects who are switched, the baseline will be the assessment just prior to the switch.

For the FAS only, the mean EQ-5D-5L score will be plotted over time during the initial treatment period with separate trend lines for each of the three treatment groups. This type of plot will be repeated for mean EQ-5D-5L score and mean change from baseline in EQ-5D-5L score over the entire study, with separate trend lines for the seven possible dosing schemes.

5.3.5 Supplemental Analysis

Two methods will be applied for the rescoring of mICARS, Rescored mICARS Method 1 (see Appendix II) and Rescored mICARS Method 2 (see Appendix III). In each case, the rescored mICARS will be analyzed using the MMRM methods as for the primary analysis of mICARS. The nominal p-value will be presented, and no adjustments for multiplicity will be made.

5.3.6 Sub-group Efficacy Analysis

All summarization and analysis of efficacy data during the extension period will be considered exploratory.

The primary efficacy analysis will be repeated for region (India; Europe, Australia, Israel, and Tunisia; United States), age sub-group (6 to <10 years, ≥10 years), sex (male, female), adjudicated genetic disease characteristics, the subset of subjects having a confirmed diagnosis of AT, and baseline disease severity (mild or severe, as determined by an independent adjudication committee).

5.4 Safety Analysis

Safety analysis will be performed for the safety population, unless otherwise noted. No statistical comparisons between groups will be performed.

5.4.1 Adverse Events

Adverse events (AEs) will be coded using MedDRA version 19.0. Coding will include system organ class and preferred term. All verbatim descriptions and coded terms will be listed for all AEs.

Adverse events of special interest include those which are potentially steroid related and those indicative of adrenal insufficiency. These will be summarized separately.

If the assessment of seriousness is missing for an event, then the event will be considered serious as a worst case. The same rule will be applied in case of missing relationship data (the worst relationship will be assumed) and missing severity data (severe will be assumed).

Each AE recorded on the CRF will be classified as either a pre-treatment AE or a treatment-emergent AE (TEAE). Adverse events occurring >60 days after the last dose of study drug will not be considered treatment emergent.

Pre-treatment AEs

Pre-treatment AEs will be defined as AEs that started and either stopped before the first infusion of study treatment or continued after and did not worsen in intensity during the treatment period. Any pre-treatment AEs identified will not be summarized by system organ class and preferred term but they will be flagged on all listings of AEs (all AEs and serious AEs).

Treatment-emergent AEs

Each adverse event will be classified as treatment emergent or not during one of three treatment periods:

- The initial treatment period (Period 1), defined as the day of the first infusion through the day just prior to the day of the Visit 9 ("Month 6") infusion, or <=60 days after last dose if the subject never continued past this period;
- The Visit 9 ("Month 6") to Visit 12 ("Month 9") period (Period 2), defined as the day of the Visit 9 ("Month 6") infusion through the day just prior to the day of the Visit 12 ("Month 9") infusion, or <=60 days after the last dose if the subject never continued past this period; and
- The Visit 12 ("Month 9") to Visit 15 ("Month 12") period (Period 3), defined as the day of the Visit 12 ("Month 9") infusion through 60 days after the last dose.

AEs starting on or after the date/time of the first infusion of a period and prior to the date/time of the first infusion of the next period will be considered TEAEs during the period, for example:

- Events that started on the day of or after the first infusion and are not a continuation of a pre-treatment event.
- Events that started before the first infusion and worsened after the first infusion.
- Events with partial onset dates that indicate that the event could be treatment-emergent during the period.
- Events with completely missing onset dates.

For adverse event reporting, subject events will be allocated to the period of last treatment.

For each treatment period and over all periods, an overall summary of the number and percentage of safety population subjects having pre-treatment AEs and TEAEs will be presented by treatment received, along with the total number of TEAEs. This summary will also include the number and percentage of subjects with related TEAEs, serious TEAEs, serious related TEAEs, TEAEs leading to discontinuation, and TEAEs leading to death. Only subjects treated during the period of interest will be included in the denominator for percentages. For the summarization of AEs over all periods, treatments summarized will include EDS-EP low dose and high dose groups, non-switch placebo, placebo pre-switch, and each active treatment post-switch; placebo subjects who switch to active treatment will have only adverse events emergent during active treatment summarized.

TEAEs will also be summarized as the number and percentage of safety population subjects treated during the period (or the study overall) having any event and any event by MedDRA system organ class and preferred term. For each subject, multiple occurrences of the same event will be counted once within a system organ class and preferred term. Summaries will be prepared for the following types of events:

- TEAEs
- Related TEAEs
- Serious TEAEs
- Related Serious TEAEs
- Potentially steroid-related TEAEs
    - Low bone mineral density
    - Low CD4 count
    - Itching
    - Osteopenia
    - Osteoporosis
    - Weight gain
    - Cortisol suppression
    - Glaucoma
    - Stunt growth
    - Infections
    - Hyperglycemia
- TEAEs indicative of adrenal insufficiency per Protocol Appendix 12 and monitored by a data safety monitoring board
- TEAEs leading to discontinuation
- TEAEs leading to death
- TEAEs by maximum severity
- TEAEs by worst relationship

This summarization will be repeated for Continuous Exposure 2 subjects, and for subjects whose treatment was ended due to COVID-19.

For subjects with treatment interruptions that result in gaps in dosing of greater than 60 days, adverse events will only be considered treatment emergent if they occur within 60 days following the last dose. Adverse events that occurred greater than 60 days following the last dose will not be considered treatment emergent. For this population of subjects (those with long treatment interruptions), and for the sub-population whose long treatment interruption was due to COVID-19, three types of summarization will be prepared:

- On dose (treatment emergent) adverse events – summarized by treatment being taken at the initiation of the interruption
- Off dose (not treatment emergent) adverse events – summarized by treatment being taken at the initiation of the interruption
- Restart (TEAE after restart of treatment) adverse events – summarized by treatment taken when restarted

5.4.2 Physical and Neurological Examination

Physical and neurological examinations will be performed at Screening, at Baseline (pre and post infusion) and prior to dosing at each of the monthly infusions (Visit 4 ["Month 1"], Visit 5 ["Month 2"], Visit 6 ["Month 3"] [also post infusion], Visit 7 ["Month 4"], and Visit 8 ["Month 5"]) and at the final visit (Visit 9 ["Month 6"] or at early discontinuation) during the initial treatment period. For subjects continuing in the extension treatment period, physical and neurological examinations will be performed pre- and post-infusion at Visit 9 ("Month 6") and Visit 12 ("Month 9"), prior to dosing at each of the other monthly infusions (Visit 10 ["Month 7"], Visit 11 ["Month 8"], Visit 13 ["Month 10"], and Visit 14 ["Month 11"]) and at the final visit (Visit 15 ["Month 12"] or at early discontinuation).

If clinically significant abnormal findings are noted at Screening, the examination was to be repeated prior to Baseline. 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 of the CRF.

Physical and neurological examination data will be summarized by treatment period and visit according to the treatment received during the period. Shift tables will be provided for all values and separately for abnormal values (both clinically significant abnormalities and not). Baseline will be defined two ways, as the last assessment prior to the first infusion in the study (Baseline 1), and also as Baseline 1 for non-switch groups and as the last assessment prior to switch for placebo switchers (Baseline 2), and thus summaries will be repeated to reflect the use of each baseline definition.

5.4.3 Vital Signs

Vital signs assessments will be performed at Screening, at Baseline (pre and post infusion) and prior to dosing at each of the monthly infusions (Visit 4 ["Month 1"], Visit 5 ["Month 2"], Visit 6 ["Month 3"] [also post infusion],Visit 7 ["Month 4"], and Visit 8 ["Month 5"]) and at the final visit (Visit 9 ["Month 6"] or at early discontinuation) during the initial treatment period. For subjects

continuing in the extension treatment period, vital signs assessments will be performed pre and post infusion at Visit 9 ("Month 6") and Visit 12 ("Month 9"), prior to dosing at each of the other monthly infusions (Visit 10 ["Month 7"], Visit 11 ["Month 8"], Visit 13 ["Month 10"], and Visit 14 ["Month 11"]) and at the final visit (Visit 15 ["Month 12"] or at early discontinuation).

Vital signs include body weight, temperature, pulse, systolic and diastolic blood pressure, and respiratory rate. Height will be measured at Screening and used along with body weight to calculate Body Mass Index (BMI). Pulse and blood pressure will be measured after the subject has been in the supine position for at least 5 minutes. At Day 0, prior to dosing, measurements of blood pressure and pulse (supine) will be repeated 3 times, at least 10 minutes apart, and the values will be averaged to obtain the baseline values.

The absolute values of the vital signs data will be summarized by treatment period at each visit using the summary statistics for continuous variables according to the treatment received during the period.

Change from baseline to each post-baseline visit will be calculated for each of the vital signs and the change from baseline data summarized by treatment period at each post-baseline visit using the summary statistics for continuous variables according to the treatment received during the period. The number and percentage of subjects at each visit with the abnormalities in Table 6 will be summarized:

Table 6. 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
Weight	kg	≥ 7% Decrease	≥ 7% Increase

Summaries will be repeated to reflect the use of Baseline 1 and Baseline 2, as defined in Section 5.4.2.

5.4.4 12-Lead Electrocardiogram (ECG)

All subjects will have a standard 12-lead ECG performed at Screening (at any time within the 30-day screening period), pre-dose on Day 0 (**optional**; to be performed only to follow up on a clinically significant vital signs abnormality or cardiovascular AE noted at Screening), on Visit 6 ("Month 3"), and at the final visit (Visit 9 ["Month 6"] or at early discontinuation) during the initial treatment period. For subjects continuing in the extension treatment period, ECG evaluations will be done on Visit 12 ("Month 9") and at the final visit (Visit 15 ["Month 12"] or at early discontinuation).

If clinically significant abnormalities are found, the subject's ECG is to be repeated at regular intervals until it returns to normal.

All ECG parameters collected at different visits will be summarized by treatment period according to the treatment received during the period. Shift tables will be provided for clinically significant abnormalities and a categorical analysis evaluating QTc outliers will be performed. Summaries will be repeated to reflect the use of Baseline 1 and Baseline 2, as defined in Section 5.4.2. ECG data will also be listed.

5.4.5 Columbia Suicide Severity Rating Scale

The Columbia Suicide Severity Rating Scale, or C-SSRS, is a suicidal ideation rating scale created by researchers at Columbia University (Posner, 2011). It rates an individual's degree of suicidal ideation on a scale, ranging from "wish to be dead" to "active suicidal ideation with specific plan and intent." At each visit, subjects will be assigned an ideation severity score of 0 (no ideation present) to 5 (active ideation with plan and intent), per scoring instructions (Columbia University).

The scale identifies behaviors which may be indicative of an individual's intent to commit suicide. An individual exhibiting even a single behavior identified by the scale was 8 to 10 times more likely to commit suicide.

Summarization of results will be performed by treatment period separately at each visit, according to the treatment received during the period. Summaries will be repeated to reflect the use of Baseline 1 and Baseline 2, as defined in Section 5.4.2.

For the FAS only, the mean ideation severity score will be plotted over time during the initial treatment period with separate trend lines for each of the three treatment groups. This type of plot will be repeated for mean ideation severity score and mean change from baseline in ideation severity score for each treatment period, with separate trend lines for the treatments during the period. Separate sets of plots will be prepared using each type of baseline (Baseline 1 and Baseline 2).

5.4.6 Laboratory Parameters

Standard Laboratory Evaluations

Hematology, clinical chemistry, and urinalysis will be performed at a central laboratory. Laboratory parameters and special laboratory evaluations that will be measured are listed in Table 7.

Table 7. Laboratory Analytes and Special Laboratory Evaluations

Hematology or CBC	Clinical Chemistry	Urinalysis (automated)	Special Diagnostic Tests	Hemolysis Panel
Hematocrit	Sodium	Color	HbA1c	Free plasma hemoglobin
Hemoglobin	Potassium	pH	CD4+	Haptoglobin
RBC count	Chloride	Specific gravity	Lymphocytes	Total bilirubin
WBC count	Calcium	Protein	α-fetoprotein	Conjugate bilirubin
Differential WBC count	Phosphorus	Glucose	C-reactive protein (CRP)	CBC
o Neutrophils	Serum iron	Ketones	IgG	LDH
o Lymphocytes	Bicarbonate	RBC, WBC, casts *	IgM	Urinalysis
o Monocytes	Glucose	Nitrites	Qualitative Direct Coombs test	
o Eosinophils	BUN	Bilirubin	Cortisol	
o Basophils	Creatinine	Hemoglobin		
Platelets	Total bilirubin	Urobilinogen		
MCV	Albumin			
MCH	Total protein			
MCHC	AST (SGOT)			
RDW	ALT (SGPT)			
	Alkaline phosphatase			
	LDH			
	CPK			
	Triglycerides			
	Total cholesterol			
	HDL cholesterol			
	LDL cholesterol			

* Reflex microscopic analysis to be performed only if other analytes are abnormal on automated testing

Data listings will be presented in two ways:

- Subject Profile: all laboratory data for a subject on a page.
- General Lab listing presented by Visit and Laboratory parameter

Data for each parameter of a continuous nature will be summarized by treatment period 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. The described summarization will be performed by visit according to treatment received during the treatment period.

Shift tables will be provided for all values and separately for abnormal values (both clinically significant abnormalities and not).

Summaries will be repeated to reflect the use of Baseline 1 and Baseline 2, as defined in Section 5.4.2.

An abnormal lab listing will be produced by using clinical significance flags.

Shift tables will also be created for the EDS-EP Complete Blood Count local laboratory parameters collected at the time of EDS-EP infusions, in a manner similar to shift tables created for the standard, central laboratory evaluations. Since local labs are collected with different units, only shift tables can be created with each value classified low, normal, or high relative to the local normal range.

5.4.7 Bone Mineral Density

Bone mineral density z-scores will be summarized and analyzed in a manner similar to the standard laboratory evaluations.

5.4.8 Tanner Staging

The number and percentage of safety population subjects at each Tanner stage will be summarized treatment period and by visit according to treatment received during the period. Summaries will be repeated to reflect the use of Baseline 1 and Baseline 2, as defined in Section 5.4.2.

5.4.9 Sterility Testing of EDS-EP

The number and percentage of potentially contaminated infusions at any time and potentially contaminated infusions by visit will be summarized by treatment period and visit, according to treatment received during the period and in total.

5.4.10 Process Events/Interruptions

The number of subjects with infusions, the number and percentage of subjects with infusions who experienced at least 1 process event, the number of process events, and the number and percentage of process events by root cause will be summarized by treatment period and visit, according to the treatment received during the period.

5.5 PK/PD Analysis

PK/PD analysis is not part of this statistical analysis plan.

5.6 Analysis of Other Assessments

Not applicable.

5.7 Interim Analysis

No interim efficacy analysis will be conducted in this study. Interim review of safety data is described in Section 5.9.

5.8 Primary Analysis

The primary analysis based on 6-month initial treatment period (Visit 1 to Visit 9) data from all subjects will determine the success or failure of the trial. However, as per the design, subjects will continue in the trial beyond the initial treatment period (approximately six months), until subjects have been followed through the extension treatment period (Visit 9 – Visit 15). This will provide efficacy data beyond the primary analysis and will be considered exploratory, due at least in part to the placebo switching that will limit the power. To clarify, Section 11.2 of the protocol describes procedures "if one of the doses has been eliminated following the Interim Analysis." This description relates to interim safety analyses and DSMB actions, not actions taken based on review of an interim efficacy analysis.

The blind will be broken after all subjects have completed the double-blind, Initial Treatment Period, and the database for this period has been locked, so that the primary efficacy analysis can be performed. The biostatistics team will prepare and quality check a blinded version of the primary analysis output, and then a second biostatistics team, otherwise uninvolved in the study and who will remain uninvolved in the study until after final database lock and unblinding, will run the quality checked primary analysis under unblinded conditions and distribute the results as instructed; all unblinded outputs will be generated into a restricted network area. To further ensure that the blind is maintained for the extension period, the following restrictions on communications within the CRO, and between the CRO and the Sponsor, will be put in place:

- The second, unblinded biostatistics team conducting the primary efficacy analysis will have no direct communication with any blinded personnel within the CRO or at EryDel, other than for purposes of oversight (such as providing any programming issues back to the blinded biostatistics team to address).
- Any communications or documentation generated during the primary efficacy analysis will be filed outside the Trial Master File (TMF) and will be incorporated into the TMF after final database lock (of extension treatment period data) to meet requirements of GCP. The nature of this repository will be agreed with the Sponsor in advance of the primary efficacy analysis.
- The Unblinded Biostatistics team conducting the primary efficacy analysis can only discuss with and provide results to the Chief Medical Officer and Head of Regulatory Affairs from EryDel.

Conduct of the primary efficacy analysis by the team who is to be unblinded will be conducted according to the PPD standard operating processes for determination of analysis populations and release of randomization codes and interim analysis.

5.9 Data Monitoring

An independent Data Safety Monitoring Board (DSMB) was established by EryDel to review the safety of all subjects enrolled in this trial, on an ongoing basis. No EryDel employee or investigator involved in the EDS-EP clinical studies is a member of this board. The DSMB periodically reviews the safety data accrued.

The DSMB met regularly to assess the safety from the emerging data. The first DSMB meeting was conducted prior to the start of the trial, and the DSMB decided when the first data review safety DSMB meeting would occur. DSMB meetings were held when 9 patients completed 30 days of treatment. In January 2020, the DSMB agreed to quarterly meetings.

The DSMB will be regularly notified of the occurrence of any fatal or life-threatening events within 7 calendar days and any other serious adverse events within 15 calendar days. The DSMB will also receive updates on any adverse dropouts on a regular basis (once per month). The DSMB will have access to the blinded safety data including serious AEs and adverse dropouts, as well as clinically significant abnormal laboratory tests, vital signs, and ECGs at periodic intervals. The DSMB may request an unblinding of the treatment groups if there is a safety concern.

The DSMB will review all of the safety data on an ongoing basis, with special emphasis on the incidence and severity of steroid related events, new infections, and serious AEs and deaths, in addition to the standard safety parameters. The Board will make a recommendation to EryDel to (a) amend the ongoing study (e.g., increase safety monitoring), (b) terminate the EDS program (e.g., the EDS-EP safety profile is unacceptable), or (c) continue the clinical program as designed. The current study protocol will not be amended or changed (this includes the study design and entry criteria) unless mandated by the emerging (unblinded) safety profile of EDS-EP.

Details of the DSMB charter (separate document) will be submitted to regulatory authorities and will be available to Ethics Committees/IRBs upon request.

5.10 Changes to Methods Planned in the Protocol

Per protocol, sensitivity analyses are planned using three methods: LOCF, OC, and OC+RDO (observed cases plus retrieved dropouts). Each method handles missing values differently. LOCF imputes missing values by using last observation carried forward, while OC does not impute values but instead uses only observed cases. Per protocol, "Those patients who discontinue treatment prematurely but return for scheduled efficacy assessments at 6, 9 and 12 months are defined as RDOs." According to this definition, none of these subjects would be excluded from any of the four analysis populations, and since all have efficacy assessments at three of the four ICARS time points (only missing Visit 6 ["Month 3"]), they would be included in the OC analysis (as well as all other analyses). Although RDO subjects with missing evaluations at the Visit 6 ("Month 3") ICARS time point will not contribute a Visit 6 ("Month 3") ICARS evaluation in the OC analysis, they will be included in the LOCF analysis. Hence, the use of the LOCF and OC methods will sufficiently incorporate the RDO subjects, and therefore the third sensitivity analysis (OC+RDO) will not be employed.

Due to deviations in the timing of the visits, the total months of treatment and assessments exceeded the 12 months as described in the protocol. The data as collected by the investigators will still be included and analyzed.

6. TABLES, FIGURES, AND LISTINGS

The mock tables, listings, and figures (including a TOC) will be presented in a separate document.

The general layout of the tables, figures, and listings (TFLs) will be as follows.

Orientation	Landscape
Paper Size	A4
Margins	Top: 3.2 cm Bottom: 2.5 cm Left: 2.5 cm Right: 2.5 cm
Font	Courier New 9 pt
Headers (alignment)	Sponsor name and Protocol number (Center) Page X of Y (Right) TFL Number and Title (Center)
Footers (alignment)	SAS program path and file name (Left) Date output generated (Right)

The font size may be reduced as necessary to allow additional columns to be presented, but not at the expense of clarity. Also, the orientation may be changed to portrait, if appropriate.

6.1 Preparation of Tables

Certain data will be collated into summary tables. A table of contents for the summary tables planned is presented in Section 6.3. It may be necessary to change the table layouts, as appropriate, upon review of the data available.

6.2 Preparation of Data Listings

A table of contents, including the listing order and content of the data listing appendices, is presented in Section 6.3. It may be necessary to change the listing layouts, as appropriate, upon review of the data available.

Data will be presented within the data listings according to the following order:

- Treatment group
- Subject number
- Visit

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6.3.3 Safety Data

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