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EryDel S.p.A.

Open-label, **L**ong-term, **E**xtension Treatment using **I**ntra-**E**rythrocyte **D**examethasone Sodium Phosphate in Patients with **A**taxia **T**elangiectasia Who Participated in the IEDAT-02-2015 Study

(OLE-IEDAT)

Protocol No: IEDAT-03-2018

EudraCT No: 2018-000338-36

Statistical Analysis Plan

Version 4.0

Final

25-January-2023

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Signature Page

Signatures for EryDel

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Signatures for CROMSOURCE

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1. SOPs to be followed

The statistical analysis is carried out according to the following PPD SOPs:

SOP number	SOP title
SOP-ST-03	Statistical Analysis Plan
SOP-ST-04	SAS Programming and Validation
SOP-ST-05	Data Review Meeting
SOP-ST-08	Trial Statistics File

2. Abbreviations

ACTH	Adrenocorticotropic Hormone
ADaM	Analysis Data Model
AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
AT	Ataxia Telangiectasia
BMD	Bone mineral density
BMI	Body Mass Index
bpm	Beats per minute
BUN	Blood Urea Nitrogen
CBC	Complete blood count
CD4+ lymphocytes	Cluster differential 4 positive lymphocytes
CDISC	Clinical Data Interchange Standards Consortium
CGI-C	Clinical Global Impression of Change from Baseline
CGI-S	Clinical Global Impression of Severity (structured)
CNS	Central Nervous System
COVID-19	Disease caused by SARS-CoV-2
CPK	Creatinine Phosphokinase
CRP	C-Reactive Protein
CRF	Case Report Form
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	Diastolic Blood Pressure
DSP	Dexamethasone sodium phosphate
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDS	EryDex System
EDS-EP	EryDex System end product
EQ-5D-5L	EuroQol 5D Five-level version
FAS	Full Analysis Set
HbA1c	Hemoglobin A1C
HDL	High Density Lipoprotein
HLGT	High Level Group Term
HLT	High Level Term

ICARS	International Cooperative Ataxia Rating Scale
ICH	International Conference on Harmonization
IMP	Investigation Medicinal Product
IU	International Unit
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LLT	Lower-Level Term
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mICARS	Modified International Cooperative Ataxia Rating Scale
mmHg	Millimeters of mercury (blood pressure)
OLE-IEDAT	Open-label Long-term Extension (this study)
PT	Preferred Term
Q1	1st quartile
Q3	3rd quartile
QC	Quality Control
RBC	Red Blood Cell
RDW	Red Cell Distribution Width
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard deviation
SDTM	Study Data Tabulation Model
SGOT (AST)	Serum Glutamic-Oxaloacetic Transaminase
SGPT (ALT)	Serum Glutamic-Pyruvic Transaminase
SI	Système International
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TLF	Tables, Listings and Figures
TOT	Total Set
WBC	White Blood Cell

WHO-DD	World Health Organization Drug Dictionary
WHO-ATC	World Health Organization Anatomical Therapeutic Chemical

3. Protocol

This study is being conducted under the sponsorship of EryDel. The clinical monitoring, data management, statistical analysis and medical writing are performed by PPD under contract and in collaboration with EryDel.

This Statistical Analysis Plan (SAP) provides a complete, expanded and detailed description of the statistical methods outlined in the protocol IEDAT-03-2018 (OLE-IEDAT) version 7.0 (dated 01-DEC-2020). Text that has been copied from the protocol is formatted in italics to indicate that it is identical to the protocol, which should ease the review and avoid unnecessary alterations to text approved in the protocol.

All TLFs (Tables, Listings and Figures) of the final analysis, for inclusion in the CSR (Clinical Study Report) are produced by PPD.

3.1 Study Objectives

Primary Objective:

To monitor and evaluate the long-term safety and tolerability of EDS-EP in Ataxia Telangiectasia (AT) patients.

Secondary Objective:

To evaluate the long-term effect of EDS-EP in treating CNS symptoms as measured by the "Modified" International Cooperative Ataxia Rating Scale (mICARS), "Rescored, Modified" International Cooperative Ataxia Rating Scale(RmICARS) *and Clinical Global Impression of* change and severity *(CGI*-C/S).

Tertiary Objective:

To evaluate the long-term effect of EDS-EP on health-related Quality of Life (QoL; EQ-5D-5L scale).

3.2 Study Design

This is an international (North America, Europe, Africa, Asia and Australia), multi-center, prospective, open-label treatment study, designed to continue to provide the study medication to all patients who completed the full treatment period (including those treated with placebo) in the IEDAT-02-2015 trial, completed the study assessments, do not present safety contraindications to continuation of treatment and provided informed consent.

The IEDAT-02-2015 trial is also referred to as the ATTeST study.

During the COVID-19 pandemic, some patients had to be discontinued from the IEDAT-02-2015 trial; for this reason, the eligibility of the IEDAT-03-2018 (OLE-IEDAT) trial has been amended to allow patients which were discontinued from the ATTeST study, to receive the EryDex treatment in the context of the OLE-IEDAT study. Eligibility is subject to the absence of safety contraindications to continuation of treatment, and provision of the informed consent.

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3.3 Study Schedule

Screening phase

The screening phase is *applicable only for patients which will be enrolled without completing the ATTeST trial. The screening phase will last a maximum of 30 days. Any previous treatments with corticosteroid compounds will be withdrawn (washout from previous treatment), while for other patients the screening phase may coincide with the screening visit (1 day long, provided that all the required laboratory reports are available and reviewed before the eligibility confirmation at the baseline). As soon as all screening assessments/procedures have been performed and eligibility is confirmed, the patients can undergo the baseline visit.*

If any abnormal laboratory test results, vital sign measurements, or ECG findings of clinical significance are noted at the screening visit, these must be repeated during the 30-day screening period and the results made available prior to making the final decision on a patient's eligibility for the study at Baseline.

Baseline

Final evaluations for the IEDAT-02-2015 trial will serve as baseline evaluations for patients continuing in the IEDAT-03-2018 study. The following "baseline" assessments for IEDAT-03-2018 will be done as part of the final Visit 15 evaluation in Study IEDAT-02-2015: physical/neurological examination; 12-lead standard ECG; laboratory evaluations [including hematology, clinical chemistry, urinalysis, serum pregnancy test (women of childbearing potential); special laboratory tests: HbA1c, CD4+ lymphocytes count and CRP]; assessment of physical development, sexual maturation, and the effect of treatment with dexamethasone on these aspects (Tanner scale); ICARS; CGI-S; CGI-S; EQ-5D-5L; C-SSRS; BMD; review of AEs and concomitant medications.

Monthly Follow-Up and treatment visits

The regular follow-up and treatment visits are to be performed approximately once a month. Every 6 months (Month 6, Month 12 etc.) additional examinations and efficacy measurements are to be performed.

Safety Follow-up Visit

All patients who discontinue will be required to return for a Safety Follow-up Visit approximately 60 days (± 7 days) after their last infusion. At this visit, plasma cortisol, hemolysis panel, pregnancy status (for women of childbearing potential), C-SSRS, and vital signs will be assessed, as well as the occurrence of any AEs or Serious AEs (SAEs) reported by the patient/caregiver or observed by the Investigator since the previous visit.

An overview of the schedule of evaluations for the study is presented in Table 1: Schedule of Visits and Assessments: 1st year of open-label extension treatment *for the first 12 months* and *will be replicated for the second year onwards.*

Table 1: Schedule of Visits and Assessments: 1st year of open-label extension treatment
(To be replicated for the second year onwards)

Visit (V)	Screening Phase *	OLE-IEDAT Baseline /V1 (&)	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	Safety follow up visits (e)
Study Day or Month (D/M) (i)	**D -30 to -1**	**D0**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Month 7**	**Month 8**	**Month 9**	**Month 10**	**Month 11**	**Month 12 (l)**	**~60 days after last infusion**
Procedure (§)															
Informed Consent Signature	X	X (pre)													
Inclusion/Exclusion Criteria	X	X (pre)													
EDS-EP Infusion (h)		1	2	3	4	5	6	7	8	9	10	11	12	13	
Culture-based sterility test (j)		X (post)	X (post)	X (post)	X (post)	X (post)	X (post)	X (post)	X (post)	X (post)	X (post)	X (post)	X (post)	X (post)	
Neurological Examination	X							X (pre)						X (pre)	
Physical Examination (k)	X	X (post)	X(post)	X(post)	X(post)	X (post)	X(post)	X (pre; post)	X(post)	X(post)	X(post)	X(post)	X(post)	X (pre; post)	
Tanner Scale	X							X (pre)						X (pre)	
Vital Signs (h)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X							X (pre)						X (pre)	
Routine Laboratory Tests (a)	X		X (pre)	X (pre)	X (pre)	X (pre)	X (pre)	X (pre)	X (pre)	X (pre)	X (pre)	X (pre)	X (pre)	X (pre)	
Serum creatinine (g)			X (pre)	X (pre)	X (pre)	X (pre)	X (pre)		X (pre)	X (pre)	X (pre)	X (pre)	X (pre)		
Bone Mineral Density	X							X (pre)						X (pre)	
Serum($)/Urine(*) Pregnancy Test (d)	X($,*;pre)	X(*, pre)	X(*; pre)	X(*; pre)	X(*; pre)	X(*; pre)	X(*; pre)	X($,*;pre)	X(*; pre)	X(*;pre)	X(*;pre)	X(*;pre)	X(*;pre)	X($,*;pre)	X($)
ICARS	X							X (pre)						X (pre)	
CGI-C								X (pre)						X (pre)	
CGI-S	X							X (pre)						X (pre)	
Quality of Life (EQ-5D-5L)	X							X (pre)						X (pre)	
C-SSRS	X		X (pre)	X (pre)	X (pre)	X (pre)	X (pre)	X (pre)	X (pre)	X (pre)	X (pre)	X (pre)	X (pre)	X (pre)	X
Hemolysis panel (m)		X (pre)				X (pre)				X (pre)					X (pre)
Special Laboratory Tests (b; c)	X							X (pre)						X (pre)	
EDS end product sample (f)		X (post)	X (post)	X (post)	X (post)	X (post)	X (post)	X (post)	X (post)	X (post)	X (post)	X (post)	X (post)	X (post)	
Prior/Concomitant Treatments	Throughout the duration of the study														
Adverse Events	Throughout the duration of the study														

* Applicable only for patients which will be enrolled without completing the ATTeST trial (i.e., who were discontinued from the Study IEDAT-02-2015 during the COVID-19 pandemic), and which may not have final evaluations for IEDAT-02-2015 study (Visit 15/Month 12). Patients signing the informed consent form or assent, as applicable, at this visit do not need to reconsent at baseline visit.

&) The following "baseline" assessments for IEDAT-03-2018 will be done as part of the final Month 12 evaluation in Study IEDAT-02-2015: physical/neurological examination; 12-lead standard ECG; laboratory evaluations [including hematology, clinical chemistry, urinalysis, serum pregnancy test (women of childbearing potential); special laboratory tests: HbA1c, CD4+ lymphocytes count and CRP]; Tanner scale; ICARS; CGI-S; CGI-C; EQ-5D-5L; C-SSRS; BMD; Review of AEs and concomitant medications.

a) Routine laboratory assessments to include complete hematology, biochemistry, and urinalysis.

b) Special laboratory tests include HbA1c, CD4+ lymphocytes count and CRP.

c) Blood sample to be collected before 8:00 AM for measurement of plasma cortisol at the following times: (1) when patients are symptomatic, and (2) when patients are at most risk for adrenal insufficiency and adrenal crisis, such as following discontinuation or interruptions of dexamethasone dosing (i.e., loading failures and following discontinuation of the study drug).

d) For women of childbearing potential only. The test results must be negative at baseline (urine) for the patient to be eligible for the study. Urine pregnancy test will be performed before every infusion, while serum pregnancy test will be performed at Month 6, 12 and safety follow up visit.

e) A Safety Follow-up assessment will be performed approximately 60 days (±7 days) after the final infusion; at this visit, plasma cortisol, pregnancy status (for women of childbearing potential), vital signs will be assessed, as well as the occurrence of any AEs or Serious AEs since the final evaluation will be reported.

f) Upon completion of the EDS process, the remaining sample in the satellite sample bag or, if this is not available, a sample collected from another EDS-EP sampling point, will be used for determination of DSP content and CBC.

g) Blood sample for serum creatinine measurement to be taken before infusion.

h) Vital signs to be performed at each visit pre and post infusion (at safety follow up visit, only once). Vital signs to include height and weight measurements in triplicate at screening, baseline, Month 6 and 12.

i) The monthly infusions should be performed every 21-28 days. A window of + 10 days will be permitted on each of the scheduled monthly visits. Therefore, no EDS-EP infusion should be performed less than 21 days or more than 38 days after the previous infusion. The window between an infusion and the subsequent one should be kept as regular as possible throughout the study, avoiding fluctuations in administration windows. The date of an infusion is not bound to the date of the initial treatment but to the date of the previous IMP administration.

j) 1 mL blood collected, after blood diversion, for aerobic culture, before EDS process (see "Study Procedures on Sterility Testing for Study IEDAT-03-2018 (OLE-IEDAT)"; protocol Appendix 9). Moreover, a sample of the EDS-EP (approximately 1 ml per inoculum for a total of 2 mL) will be collected from satellite sample bag, to perform a culture-based sterility test. A 1 mL sterility sample of the EDS-EP will be stored under refrigeration as a "Retention Sample".

k) At Month 1-5 and 7-11 visits, physical examination and vital signs 1-2 hr after the end of infusion. At Month 6 and 12 visits, the physical examination will be performed pre-dose as well.

l) Month 12 infusion, and all of the associated procedures, would only be done in patients who are continuing open label treatment past one year.

m) Hemolysis panel, including urinalysis.

(§) As a results of the COVID-19 pandemic, temporary additional safety assessments may be requested at some visits. These changes are described in protocol Appendix 13.
(pre) Pre EDS-EP infusion procedure
(post) Post EDS-EP infusion procedure

3.4 Efficacy and Safety Variables

Primary Endpoint

The primary objective is to monitor and evaluate the long-term safety and tolerability of EDS-EP in AT patients. This will be done based on the occurrence of Treatment-Emergent Adverse Events (TEAEs), including Serious AEs and discontinuations due to AEs, and changes in vital signs, laboratory parameters, ECGs and physical/neurological examination findings.

Secondary Endpoints

The exploratory objective is to evaluate the long-term effect of EDS-EP in treating CNS symptoms as measured by the "Modified" *International Cooperative Ataxia Rating Scale (mICARS),* Rescored mICARS, *Clinical Global Impression of severity and change (CGI-S/C). This will allow assessment of whether the benefits observed in the prior study (IEDAT-02-*2015*) persist during long-term treatment.*

Tertiary Endpoint

The secondary objective is to evaluate the long-term effect of EDS-EP on health-related Quality of Life (QoL; EQ-5D-5L scale).

Efficacy and safety variables are defined in sections 7.4.7 and 7.4.8.

3.5 Interim Analyses

The protocol does not foresee any interim analyses.

3.6 Changes in the Conduct of Study or Planned Analysis compared to protocol

According to section 16.2.1 of the protocol the safety analysis set should be defined as follows:

Safety Population (SP): All subjects who receive a dose of study medication and have at least one post-dose safety assessment will be included in the safety analyses.

However, to be in line with general guidance like ICH E9 it was decided to include all patients who received any dose of study medication during this OLE-IEDAT study into the safety analysis set, regardless of the presence of post-dose safety assessments.

The schedule of events in Section 3.3 of this SAP is a copy from the protocol apart from one difference: To clarify that in this SAP also uses baseline from the ATTeST study the column "Baseline" has been renamed to "OLE-IEDAT Baseline".

Section 16.2.6 of the protocol states: *Additional analyses will be performed to determine the change in each of the efficacy measures compared to the baseline of the IEDAT-02-2015 study, comparing patients who were treated with EDS-EP throughout the double-blind and open-label treatment periods vs. those who received placebo for varying periods in Study IEDAT-02-2015, before being switched to the active treatment.*

However, as described in Section 6.3 of this SAP this comparison will not be limited to efficacy or the protocol defined groups and all summaries in this study will display the 7 treatment groups from the ATTeST study. Subgroups for Age (<10 years, ≥ 10 years) and Region (India; Europe, Australia, Tunisia; United States) are also included.

Section 12.1.1 of the protocol outlines the ICARS assessment, including a description of the "Modified" ICARS (mICARS). As described in Section 3.4 of this SAP, the "Rescored" mICARS is also considered as an endpoint in the analysis.

A definition of continuous exposure is added to Section 7.1 to support future analysis.

Visit periods of 12 months is assessed to Section 7.1 and these are used in summary of Adverse Events described in Section 10.7.1. To investigate Adverse Events by the period in which they occur.

4. General Definitions

4.1 Report Language

The output of the analyses (tables, figures, listings, and inferential analyses) is prepared in English.

4.2 Analysis Software

The statistical analysis is performed using the SAS® statistical software package (Statistical Analysis System, Version 9.3 or later).

5. Data Preparation

5.1 Data Handling and Medical Coding

For data quality control, medical coding and data provided by third parties which is not contained in the clinical database (e.g., central lab, DSP concentrations, data coming from the ATTeST study for data reconciliation), please refer to the Data Management Plan, including the Data Validation Plan, in its most recent version.

ADaM datasets from the ATTeST study containing the treatment subgroups and the ATTeST baseline values are provided by EryDel.

Determination of Adverse Events of Special Interest (described in Section 7.4.8) is based on an Excel spreadsheet provided by EryDel documenting the outcome of a manual review of Adverse events contained within the clinical database.

For the definition of Adverse Events During COVID-19 treatment interruptions (described in Section 7.4.8) the times to be considered as treatment interruptions due to Covid-19 are provided by EryDel in form of an Excel spreadsheet.

The following coding dictionaries are used in the analysis:

MedDRA version 22.0 for Adverse Events, Medical History and Non-drug Therapies and Procedures. This comprises the datasets: 1) MH, 2) AE and 3) NDRP.

The verbatim event terms are coded to a Lower-Level Term (LLT), Preferred Term (PT), High Level Term (HLT), High Level Group Term (HLGT) and a System Organ Class (SOC). Only PT and SOC are used in the analysis.

WHO-DD version of March 2019 for Prior and Concomitant Medications. This concerns the dataset CM.

The Investigator Terms (Generic Medication Name, and Indication) are coded to a WHO-ATC Drug class, a WHO-ATC Drug number, a WHO Drug Name (Preferred Term) and Anatomic Therapeutic Chemical (ATC) level classification to all levels from 1 to 4.

5.2 CDISC

All output as defined in the SAP is generated based on CDISC ADaM datasets, as per contract with EryDel. Specifications for the ADaM datasets as well as the underlying SDTM datasets are described in separate documents. CDISC SDTM datasets are produced based on SDTM version 1.4 with the SDTM implementation guide version 3.2, CDISC ADAM datasets are produced based on ADaM version 2.1 with the ADaM implementation guide version 1.0. Define.xml is produced based on version 2.0.

5.3 SAS-Programming Quality Level

The following quality level of programming deliverables is applied, as per contract with EryDel. All statistical output receives a tailored Quality Control (QC) approach by:

Deliverable	**Double Programming?**
CDISC SDTM datasets	
Including QC against the applicable CDISC guidelines.	YES
CDISC ADaM datasets	
Including QC against the SAP and applicable CDISC guidelines.	YES
Tables and Figures (including in-text tables and in-text figures)	YES
Inferential analyses	YES

Listings	
○ Listings for Data Review Meeting that do not need complex selection	NO
○ Listings for Data Review Meeting that do need complex selection*	YES
* The selection of the data is double programmed from the source dataset.	

All TLFs undergo the following by the Quality Control (QC) team:

- Comparison with specifications (i.e., SAP and shells)
- Cross checking with other TLFs for consistency and correctness
- Sensibility review
- SAS log review
- In addition, a Principal/Senior Statistician or the Head of Programming and Biostatistics Unit (independent of the study team) performs a senior review of all data and TLFs to pre-empt customer comments allowing points of interest to be highlighted and discussed at EryDel handover.

6. Analysis Populations and Subgroups

6.1 Analysis Populations

Total Set (TOT)

The Total Set consists of all patients who provided informed consent or assent as documented by a date of informed consent or date of assent on the 'Informed Consent' Electronic Case Report form (eCRF) page.

Screening Failures

Screening Failures are defined as patients who provided informed consent or assent but did not receive any Study Treatment during this OLE-IEDAT study (no "Date performed" on the "EDS-EP Infusion" eCRF page at any visit). Any data collected for Screening Failures are listed.

Safety Analysis Set (SAF)

The Safety Analysis Set consists of all patients who provided informed consent or assent and who received any dose of study medication during this OLE-IEDAT study (i.e., "Date performed" given on the "EDS-EP Infusion" eCRF page at any visit). The Safety Analysis Set is used for all safety analyses.

Full Analysis Set (FAS)

The Full Analysis set comprises *all patients who enter study IEDAT-03, have a baseline efficacy assessment in study IEDAT-03, and who received at least one dose of study medication and had at least one post-baseline efficacy assessment of the* ICARS *in this extension study.*

6.2 Treatment Misallocation

Not applicable for this single arm study.

6.3 Subgroup Definitions

Patients are grouped by their treatment group in the ATTeST study: EDS-EP Low Dose, EDS-EP High Dose, Non-switch Placebo, Visit 9 Low Dose, Visit 9 High Dose, Visit 12 EDS-EP Low Dose, and Visit 12 High Dose. All outputs contain columns to display these groups.

The following endpoints are also summarised by subgroups for Age (<10; ≥10 years) and Region (India; Europe, Australia, and Tunisia; United States):

- ICARS
- mICARS
- RmICARS
- CGI-C
- CGI-S
- EQ-5D-5L

Patients with a treatment gap of greater than 76 days between the ATTeST study and the OLE-IEDAT study are presented as a separate subgroup for outputs as outlined in Section 10.

7. Definition of Time Points and Analysis Variables

7.1 Definition of Time Points

The monthly infusions should be performed every 21-28 days. A window of + 10 days will be permitted on each of the scheduled monthly visits. Therefore, no EDS-EP infusion should be performed less than 21 days or more than 38 days after the previous infusion. The window between an infusion and the subsequent one should be kept as regular as possible throughout the study, avoiding fluctuations in administration windows. The date of an infusion is not bound to the date of the initial treatment but to the date of the previous IMP administration. Infusions should not be skipped; therefore, if necessary, the infusion schedule can be modified to conform to the above guidelines.

All patients who discontinue will be required to return for a Safety Follow-up Visit approximately 60 days (± 7 days) after their last infusion.

Data collected outside of the per-protocol windows are included in the analyses based on the nominal visit label in the CRF.

'Table 2: Study Visits' shows how the Visits are labelled in all TLF outputs.

Table 2: Study Visits

Scheduled Visit	Scheduled Visit Label	Scheduled Study Day	Visit Window
Visit 0	Screening	-30 - -1	Study day =< -1
Visit 1	Baseline	0	Study day = 0
Visit 2	Month 1	28	Study day in [21 – 38]
Visit 3	Month 2	56	Visit 2 + [21 – 38] days
Visit 4	Month 3	84	Visit 3 + [21 – 38] days
...	...	...	...
Visit x	Month x-1	28(x-1)	Visit x-1 + [21 – 38] days
Safety follow-up visit	Safety FU	60 days after last infusion	Last Infusion + [53 - 67] days
The visit schedule of the first 12 months is repeated for subsequent visits. Unscheduled Visits are labelled as "Unscheduled Visit y" with y in (1, 2, 3,). Data from unscheduled visits are presented in listings.			

Date of First OLE-IEDAT Infusion

The Date of First OLE-IEDAT Infusion is defined as the earliest value of the "Date performed" recorded on the 'EDS-EP Infusion' eCRF page, provided "Was EDS-EP infusion started within 30 min of completion of the EDS Process?" is answered with "Yes".

Date of Last Infusion

The Date of Last Infusion is defined as the latest value of the "Date performed" recorded on 'EDS-EP Infusion' eCRF page, provided "Was EDS-EP infusion started within 30 min of completion of the EDS Process?" is answered with "Yes".

Date of First Infusion of Active Treatment

The Date of First Infusion of Active Treatment is defined as the earliest infusion of active study drug, including infusions from the ATTeST study. For patients in the Non-Switch Placebo group

this will equal the date of first OLE-IEDAT Infusion. For all other patients this date will be received by CROMSOURCE in ADaM datasets from ATTeST.

Intervals from First Infusion of Active Treatment

Efficacy analysis outlined in Section 7.4.7 is displayed in 6-month intervals from first dose of active study drug, using data from the ATTeST Study.

These are derived by calculating day since First Infusion of Active Treatment:

> Day since First Infusion of Active Treatment = (Date of visit - Date of First Infusion of Active Treatment)

This is then mapped to 6 months intervals as follows:

Interval	Window
6 months	Day in [91, 273]
12 months	Day in [274, 456]
18 months	Day in [457, 638]
24 months	Day in [639, 821]
…	…

Any day since First Infusion of Active Treatment < 91 will not be mapped to a 6-month interval.

Intervals from First OLE-IEDAT Infusion

Adverse Event analysis outlined in Section 10.7.1 is displayed overall and in 12 month intervals from first OLE-IEDAT Infusion.

These are derived by calculating day since First OLE-IEDAT Infusion:

> Day since First OLE-IEDAT Infusion = (Date of event - Date of First OLE-IEDAT Infusion)

This is then mapped to 12 months intervals as follows:

Interval	Window
0 to 12 months	Day in [0, 364]
12 to 24 months	Day in [365, 729]
24 to 36 months	Day in [730, 1094]
36 to 48 months	Day in [1095, 1459]
48 to 62 months	Day in [1460, 1824]
…	…

Continuous Exposure

Continuous exposure is derived in 12-month intervals with a patient being determined to have continuous exposure if they have a maximum of one month treatment interruption within any 12 month interval. The 12-month interval of continuous exposure may start at any dosing visit. Data on continuous exposure may be used for future exploratory analysis.

Study Day

For event type data the Study Day of an event is calculated relative to the Date of First OLE-IEDAT Infusion as defined above. The Study Day of events occurring before the Date of First OLE-IEDAT Infusion is calculated as:

Study Day = (Date of event - Date of First OLE-IEDAT Infusion).

For events/assessments occurring on or after the date of First OLE-IEDAT Infusion , Study Day is calculated as:

Study Day = (Date of event - Date of First OLE-IEDAT Infusion).

OLE-IEDAT Baseline

Final evaluations for the IEDAT-02-2015 trial will serve as baseline evaluations for patients continuing in the IEDAT-03-2018 study. The following "baseline" assessments for IEDAT-03-2018 will be done as part of the final Visit 15 evaluation in Study IEDAT-02-2015: physical/neurological examination; 12-lead standard ECG; laboratory evaluations [including hematology, clinical chemistry, urinalysis, serum pregnancy test (women of childbearing potential); special laboratory tests: HbA1c, CD4+ lymphocytes count and CRP]; assessment of physical development, sexual maturation, and the effect of treatment with dexamethasone on these aspects (Tanner scale); ICARS; CGI-S; CGI-S; EQ-5D-5L; C-SSRS; BMD; review of AEs and concomitant medications.

If values are missing at the baseline visit, and the data are also recorded at screening, then the screening value are used in the summaries and calculations of change from baseline. Otherwise, the baseline value is missing for safety and efficacy endpoints.

ATTeST Baseline

For some analyses a comparison with the baseline value of the ATTeST study is to be performed. PPD receives datasets where it is clearly marked which values are to be regarded as ATTeST baseline for these analyses.

Repeated evaluations

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 set of assessments recorded under the nominal visit label are used.

7.2 Event Dates

Medical events are defined as medical history, prior and concomitant medication, non-drug therapy and procedures, and adverse events.

7.2.1 Event Days

All types of events have a Start/Onset Day calculated and, if not 'Ongoing', have a Stop/Resolution Day calculated equivalent to Study Day as defined in 7.1.

7.2.2 Missing Dates and/or Times

Missing and/or incomplete dates/times for events are imputed for calculating Start Day and Stop Day only. Dates are listed as missing/incomplete [with "-" replacing missing information] but the Start/Stop Day/Time are listed between square brackets to denote it is calculated based on missing data (i.e. [-28], [1], [Ongoing]).

Missing and/or incomplete dates/times are imputed in a manner that assumes the worst-case scenario (i.e., Start as close as possible to the First Study Treatment Administration and stopped such that it is assumed to have lasted for the longest possible duration, taking into account that the Start date/time should not be after the Stop date/time).

Technically, this is done as follows for Stop Day/Time:

- For a completely missing stop year (regardless of minute, hour, day or month response) the event is assumed to be ongoing.
- For a missing stop hour (and the event is not 'Ongoing'):
  - it is assumed to have ended on hour 23 (11pm) of that day
- For a missing stop minute (and the event is not 'Ongoing'):
  - it is assumed to have ended 59 minutes past the hour
- For a missing stop day (and the event is not 'Ongoing'):
  - it is assumed to have ended on the last day of the month, if the month is given
  - it is assumed to have ended on the 31st of December of that year, if the month is also missing

Technically, this is done as follows for Start Day/Time:

- For a completely missing Start date (day, month and year regardless of the minute and hour recorded)
  - the Start Day of the event is "[Pre-Treat]" if the stop date or partial stop date concludes the event stopped before First Study Treatment Administration (i.e., assumed to be prior or pre-treatment as is applicable).
  - in all other instance (i.e., inconclusive stop date or Ongoing event) the Start Day of the event is assumed to be the same date and time as First Study Treatment Administration (i.e., assumed to be concomitant or treatment emergent as applicable.)
- For a missing start hour:
  - it is assumed to have started on hour 00 (midnight) of that day.
  - or at the time (hour and minute) of First Study Treatment Administration if the start date (day, month and year) is the same as the First Study Treatment Administration date.
- For a missing start minute:
  - it is assumed to have started on minute 00 of that hour.
  - or at the time (hour and minute) of First Study Treatment Administration if the start date (day, month and year) is the same as the First Study Treatment Administration date.
- For a missing Start day but given month:
  - it is assumed to have started on the first day of the month.
  - or at the date of First Study Treatment Administration if the start month and the year is the same as the First Study Treatment Administration month and year.
- For a missing start month:
  - it is assumed to have started on the first of January of that year.
  - or at the date of First Study Treatment Administration if the start year is the same as the First Study Treatment Administration year.

7.3 Study Medication

All patients are treated with EDS-EP.

7.4 Analysis Variables

7.4.1 Disposition

Patient disposition data is collected on the 'End of Study' eCRF page when a patient completes or discontinues the study. The date of completion/discontinuation and the reason for discontinuation are recorded. If a patient dies the date of death and if an autopsy was performed is recorded.

For sites in Italy and USA who note the patient as having completed the study this is summarised as "Study Terminated by Sponsor" as the patients participation in the study ended when the study was terminated. This was confirmed by the respective Principal Investigators in writing and confirmations were filed in eTMF.

For sites in India the study was terminated by the sponsor due to the impact of the COVID-19 pandemic. For patients who were discontinued due to such specific COVID-19 related study termination the reason for discontinuation is displayed in summary tables and listings as "Study terminated by sponsor due to COVID-19".

7.4.2 Demographic and Other Baseline Characteristics

Age

Age (years) is calculated at Baseline based on the date of informed consent as recorded on the 'Informed Consent' eCRF page and the date of birth as collected on the 'Demography' eCRF page as:

INT(date of informed consent - date of birth)/365.25).

Where INT denotes the integer part of the calculation. In case of incomplete dates, missing days are set to 16th and missing months are set to June. If, as a result of this imputation, the age of the patient is 5 years, then the age is set to 6 years.

Age categories

Age is classified into the following categories:

- 6 to <10 years,
- ≥ 10 years]

Region

Region is derived from the location of the Site and is classified into the following categories:

- India
- Europe, Australia, Tunisia
- United States

Sex

As recorded on the 'Demography' eCRF page.

Ethnicity

"Hispanic or Latino" or "Not Hispanic or Latino" as recorded on the 'Demography' eCRF page.

Race

"White", "Black", "American Indian or Alaska native", "Asian" or "Native Hawaiian or other pacific islander" as recorded on the 'Demography' eCRF page. Multiple answers are possible.

Height

As recorded on the 'Vital Signs' eCRF pages. Where triplicate measurements are available the mean of the three values is used for summary statistics at that visit/timepoint.

Weight

As recorded on the 'Vital Signs' eCRF page. Where triplicate measurements are available the mean of the three values is used for summary statistics at that visit/timepoint.

BMI

As recorded on the 'Vital Signs' eCRF page. Where triplicate measurements are available the mean of the three values is used for summary statistics at that visit/timepoint.

7.4.3 Medical History

Past and current medical conditions including Adverse Events resolved in study IEDAT-02-2015 are recorded at screening on the 'Medical History' and 'Medical History Open Label' eCRF pages. For each CRF-requested body system the investigator's assessment of normal/abnormal is recorded, and in case of abnormal the following parameters are recorded: Diagnosis (coded using MedDRA), start date and end date/ongoing.

AT Disease History is recorded at IEDAT-02-2015 study screening visit and verified with proven genetic diagnosis of AT (prior documentation or by central laboratory test report). No additional information is recorded in the OLE-IEDAT study eCRF.

7.4.4 Concomitant Medication

Prior and Concomitant medication data are collected throughout the study on the 'Prior / Concomitant Medications' eCRF page. For each Medication (coded using WHO-DD) the start date (or "Not known"), the end date (or "Not known") / Ongoing, Dose, Unit, Frequency, Route and Indication (with corresponding AE number, if applicable) are recorded.

All medications have a start day and end day calculated as described in section 7.2, 'Prior medications' are medications that were stopped before first Study Treatment administration. All other medications are regarded as 'Concomitant medications.

7.4.5 Non-drug Therapy and Procedures

Data on Non-drug Therapy and Procedures are collected throughout the study on the 'Non-drug Therapy and Procedures' eCRF page. For each therapy or procedure (coded using MedDRA) the start date, the end date/ Ongoing, and the reason for use are recorded.

7.4.6 Measurements of Exposure and Treatment Compliance

The EryDex System (EDS) is used to load dexamethasone sodium phosphate (DSP), a marketed drug, into autologous erythrocytes, creating the EDS end product (EDS-EP), which is infused once per month into the patient. The study treatment consists of a dose range of ~14-22 mg dexamethasone sodium phosphate (DSP) administered via ex vivo encapsulation into autologous erythrocytes (EDS) that are infused into the patient.

Data on EDS-EP infusions are recorded on the 'EDS-EP Infusion' eCRF page. Data on the DSP concentration in µg/mL are provided directly from a third-party vendor. Data on DSP concentration is converted to mg/bag using the following formula:

- Result (mg/bag) = Result (µg/mL)*78.7/1000.

Number of infusions received

Number of infusions received is derived as the total number of infusions completed, as determined by response to "Was EDS-EP infusion completed", during the OLE-IEDAT study. This count includes unscheduled visits.

In addition, as the number of infusions during the ATTeST study varies with the original treatment arm, and the timing of the switch from placebo to active, the total number of infusions from the ATTeST baseline is also calculated.

Duration of treatment

Duration of treatment on OLE-IEDAT study is derived as:

- Date of Last Infusion – Date of First OLE-IEDAT Infusion + 1.

The overall duration of active treatment from ATTeST baseline is derived as:

- Date of Last Infusion – Date of First Infusion of Active Treatment + 1.

For a definition of Date of first/last OLE-IEDAT infusion and date of first infusion of active treatment, see section 7.1.

7.4.7 Efficacy Variables

The "Modified" International Cooperative Ataxia Rating Scale (mICARS) is the most important of the secondary efficacy endpoints.

ICARS

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). (Trouillas, et al., 1997)

To maximize the consistency of the data obtained from the ICARS, the same site's neurologist, qualified, trained, and certified in the use of the ICARS and with expertise in the field of AT disorders, will evaluate the same patient at approximately the same time throughout the study. ICARS ratings should be completed without consulting scores from the previous visit.

The primary efficacy endpoint is 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.

The modified ICARS is rescored, collapsing categories within specific items. This method results in a smaller total sum score across the ICARS domains. This is referred to as Rescored mICARS, to prevent confusion with modified ICARS. The rescoring method is outlined in Appendix 2 (Section 13.2) of this SAP.The ICARS is collected on the ICARS eCRF page. For the purpose of analysis, the total scores will be derived. If any of the individual ICARS scores contributing to the total score of interest are missing, then the total score will be set to missing.

The endpoints are the change of the mICARS and RmICARS scores from baseline to Visit 7 (6 Months) and all subsequent measures in 6-month intervals. These endpoints are repeated for all 6-month intervals since start of active treatment as outlined in Section 7.1.

The change in the full ICARS, which is the validated scale and the preference of European Regulators, from baseline to Visit 13 is presented as a sensitivity analysis.

Modified ICARS score (mICARS)

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 FDA request. The 'Modified' ICARS score ranges from 0 to 54, with higher scores indicative of more severely affected outcome.

Modified ICARS score - absolute change from OLE-IEDAT baseline

For any follow-up visit (FU) the absolute change from OLE-IEDAT baseline is calculated as:

- mICARS absolute change from OLE-IEDAT baseline = mICARS score at FU - mICARS score at OLE-IEDAT baseline.

Modified ICARS score - absolute change from ATTeST baseline

For any follow-up visit (FU) the absolute change from the baseline of the ATTeST study is calculated as:

- mICARS absolute change from ATTeST baseline = mICARS score at FU - mICARS score at ATTeST baseline.

Rescored Modified ICARS score (RmICARS)

The Rescored 'Modified' ICARS (RmICARS) score is the total sum of the sub scores using the (FDA) scoring approach. The scoring method is presented in Appendix 2 (section 13.2) of this document.

The Rescored 'Modified' ICARS score ranges from 0 to 29, with higher scores indicative of more severely affected outcome.

Rescored Modified ICARS score - absolute change from OLE-IEDAT baseline

For any follow-up visit (FU) the absolute change from OLE-IEDAT baseline is calculated as:

- RmICARS absolute change from OLE-IEDAT baseline = RmICARS score at FU - RmICARS score at OLE-IEDAT baseline.

Rescored Modified ICARS score - absolute change from ATTeST baseline

For any follow-up visit (FU) the absolute change from the baseline of the ATTeST study is calculated as:

- RmICARS absolute change from ATTeST baseline = RmICARS score at FU - RmICARS score at ATTeST baseline.

Full ICARS score

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.

Full ICARS score - absolute change from OLE-IEDAT baseline

For any relevant follow-up visit (FU, every 6 months) the change from the baseline of this OLE-IEDAT study is calculated as:

Full ICARS change from OLE-IEDAT baseline = ICARS score at FU - ICARS score at OLE-IEDAT baseline.

Clinical Global Impression CGI-C

The CGI (Guy, 1976) is the general name for two scales, the CGI - Change scale (CGI-C) and CGI - Severity scale (CGI-S) (Guy, 1976)*.*

The CGI-C scale assesses the change in the patient's clinical status from baseline using a 7-point scale, ranging from 1 (very much improved) to 7 (very much worse), with a score of 4 indicating no change. In the current study, the change from the patient's baseline condition will

be assessed at all post-baseline visits, will be the key secondary efficacy measure the rater performing the CGI-C will be different from the rater performing the ICARS rating, and will assess the patient without access to the ICARS ratings or safety data.

For the CGI-C rating, clinicians will be required to conduct a full clinical interview and examination of the patient, if necessary, with the caregiver present. The interview and examination should assess various aspects of the patient's appearance (grooming, evidence of falls, etc.), ataxia, cognition (orientation, calculation ability, language, ability to follow commands, memory, etc.), apraxia, dysarthria, extrapyramidal motor symptoms, activities of daily living and mood. The CGI-C rating should be based on a holistic assessment of the patient and should not be anchored to specific change or cut-off scores of performance-based measures. It is not necessary for the rater to use specific scales or be guided by their scores for severity; however, the rater may review findings on other measures that are assessed in the trial, e.g. quality of life scale (EQ-5D-5L), to guide their assessments. The raters may also use additional scales or measures to assess specific domains; however, it is important that the raters use the same methods at baseline and at all subsequent visits.

In the current study, an overall assessment of the change in the patient's neurological symptoms of AT, compared to the status at baseline, are made using the CGI-C. CGI-C scores range from 1 (very much improved) through 7 (very much worse).

The CGI-C score is assessed every 6 months on the 'CGI-C' eCRF page.

Clinical Global Impression CGI-C - categories

The CGI-C is classified into the following categories:

- Improved (CGI-C score 1-3)
- No change or worsened (CGI-C score 4-7)

Clinical Global Impression CGI S (structured)

The CGI-S scale measures global severity of illness at a given point in time, and is usually rated on a 7-point, Likert-type scale ranging from 1 (normal, not ill at all) to 7 (among the most extremely ill patients). However, no version of the CGI-S exists which has been specifically adapted for use in AT patients; therefore, a 5-point version was developed that 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. Ratings of none (0), mild (1), moderate (2), severe (3) and very severe (4) are selected based on the level of symptomatology. Two independent versions of the CGI-S scale were developed, a structured scale, based on the 5 disease-related anchors and an unstructured scale based on the clinical judgment of an experienced physician. Both the structured and unstructured versions were field-tested. The final structured CGI-S score is based on the severity of the symptoms in each domain, as indicated below:

- *A rating of 0 (not ill/asymptomatic) can be made only if there are no symptoms, or a rating of mild on only one symptom domain;*
- *A rating of 1 (mild) can be made only if there are not more than 2 domains rated greater than mild;*
- *A rating of 2 (moderate) can be made only if there are not more than 2 domains rated greater than moderate;*
- *A rating of 3 (severe) can be made only if there are not more than 2 domains rated greater than severe;*

- *A rating of 4 (very severe) can be made only if there are at least 2 domains rated as severe and at least 2 rated as very severe.*

The final structured CGI-S score is captured on the "CGI-S" eCRF Form as "CGI-S overall rating".

EQ-5D-5L

A patient/caregiver-rated assessment of quality of life (QoL) will be performed using the EQ-5D-5L scale. The EQ-5D is a standardized instrument for assessing health-related QoL, which provides a simple descriptive profile and a single index value for health status in a variety of health conditions. The EQ-5D includes single item measures of five health dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In addition, EQ-5D includes a global rating of current health using a visual analogue scale (VAS) ranging from 0 (worst imaginable) to 100 (best imaginable).

The EQ-5D-5L [...] includes five levels of severity (i.e., no problems, slight problems, moderate problems, severe problems, and extreme problems) for each of the five EQ-5D dimensions. These levels are scored from 1=no problems to 5= extreme problems. (EuroQol Research Foundation, 2019)

For children and adolescents, the EQ-5D-5L administrators will be trained to help the younger population in the study complete the scale. The EQ-5D-5L administrator will explain in detail the scale to the younger patients and will confirm that they understand how the scale should be completed. They will explain what each domain measures in a child friendly manner and will confirm that the respondent understands how to complete the scale. With regards to the usual activities' domain, the administrator will explain that this domain measures if a subject has difficulties going to school, or with hobbies, sports, playing and doing things with family or friends. The administrator will be present during the completion and will be available to help the child if he/she does not understand a question or has questions related to scale completion. If the patient is unable to complete the scale, it will be completed by the patient's parent/caregiver.

Replies to the EQ-5D-5L questionnaire are recorded on the 'Quality of Life (EQ-5D-5L)' eCRF page.

EQ-5D-5L health state

The scores (1-5) for the five dimensions are concatenated into a 5-digit code (in the order mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that describes the patient's health state.

EQ-5D-5L index

From the EQ-5D-5L health state the EQ-5D-5L index values are calculated based on the Crosswalk Value Set for the US. If one of the dimensions has a missing score, the EQ-5D-5L index value is derived as missing.

EQ-5D-5L index - change from OLE-IEDAT baseline

The EQ-5D-5L index - change from OLE-IEDAT baseline is calculated at each relevant FU visit as:

- EQ-5D-5L index - change from baseline = EQ-5D-5L index at FU
  - EQ-5D-5L index at OLE-IEDAT baseline.

7.4.8 Safety Variables

Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Adverse events data are collected from the time that informed consent is given until *30 days after the final visit (Month 12 or early discontinuation) or at least 60 days after final infusion, whichever is longer*, on the 'Adverse Events' eCRF page.

The AE Description (Investigator term) is coded to a Lower-Level Term (LLT), a Higher Level Term (HLT), a Preferred Term (PT) and a System Organ Class (SOC) using MedDRA.

AEs' intensity is recorded as "Mild", "Moderate" or "Severe". any AE with a missing intensity is considered "Severe".

Treatment-emergent adverse events (TEAEs)

A treatment-emergent adverse event (TEAE) is defined as an AE that started or increased in severity on or after the date of first Study Treatment Administration. All AEs that occur during this OLE-IEDAT study are defined as TEAE as all patients received study treatment in the IEDAT-02-2015 study.

Serious Adverse Events

A Serious Adverse Event (SAE) is any adverse event *that at any dose:*

- *Results in death,*
- *Is life-threatening, i.e., an event which, in the view of the Investigator, places the subject at immediate risk of death from the event as it occurred (it does not include an event which hypothetically might have caused death if it were more severe)*
- *Requires inpatient hospitalization or prolongation of existing hospitalization,*
- *Results in persistent or significant disability/incapacity,*
- *Is a congenital anomaly/birth defect (if exposure to product just before conception or during pregnancy resulted in an adverse outcome in the child), or*
- *Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.*

Treatment-emergent SAEs (TEAEs) are derived as any TEAE flagged as serious on the 'Adverse Events eCRF' page. Any TEAEs with a missing serious flag are regarded as serious.

Adverse Events of Special Interest (AESIs)

Adverse Events of Special Interest include the following:

- 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
  - Extreme fatigue
  - Weight loss and decreased appetite
  - Darkening of skin (hyperpigmentation)
  - Low blood pressure, even fainting
  - Salt craving
  - Hyponatremia
  - Hyperkalemia
  - Low blood sugar (hypoglycemia)
  - Nausea, diarrhea or vomiting
  - Abdominal pain
  - Muscle or joint pains
  - Irritability
  - Depression
  - Confusion
  - Body hair loss or sexual dysfunction in women

These are identified by a manual review of all AEs.

The findings of the manual review are documented in an excel spreadsheet provided by EryDel which is used to select AESIs from the clinical database.

Adverse Events resulting in treatment discontinuation

TEAEs are derived as resulting in treatment discontinuation if the “Action taken with Study Treatment” is recorded as “Drug Withdrawn”.

Adverse Events related to study treatment

A TEAE is classified as ‘Related’ to Study Treatment if the relationship to study medication is recorded as ‘Unlikely’, ‘Possible’ or ‘Probable’. A TEAE is classified as unrelated to study medication if the relationship to study medication is recorded as ‘Not Related’. TEAEs with unknown relationship to Study Treatment are counted as ‘Related’ to Study Treatment.

Adverse Events Leading to Death

A TEAE is derived as leading to death if the outcome is recorded as “Died”.

Adverse Events During COVID-19 treatment interruptions

For patients with treatment interruptions that result in gaps in dosing of greater than 60 days, adverse events are only 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 patients whose long treatment interruption was due to COVID-19, three types of summarizations will be prepared:

- On dose (treatment emergent) adverse events
- Off dose (not treatment emergent) adverse events. Off dose events are those that occur during a period >60 days following a dose and prior to the immediately following dose.
- Restart (TEAE after restart of treatment) adverse events. Restart events are those that occur on/after the first dose after an off-dose period and prior to the start of any following off dose period.

Times to be considered as treatment interruptions due to Covid-19 are provided by EryDel in form of an excel spreadsheet.

Laboratory variables

There are two types of laboratory assessment defined: 'Standard Laboratory' evaluations and 'Special Laboratory' evaluations. Standard Laboratory evaluations include all parameters outline in Table 3 and are performed in accordance with the Schedule of Study Events (Section 3.3). Special Laboratory evaluations include parameters to evaluate the potential effects of dexamethasone treatment, these parameters and the timing for their assessment are outlined in Table 4. Additionally, serum creatinine is measured at each monthly visit except for the visits at Month 6, Month 12 etc.

Table 3: Standard Laboratory Evaluations

Hematology		**Clinical Chemistry**		**Urinalysis (Categorical)**
Parameter	**Reporting unit**	**Parameter**	**Reporting unit**	**Parameter**
Hematocrit	L/L	Sodium	mmol/L	Color
Hemoglobin	g/L	Potassium	mmol/L	pH
Red Blood Cell (RBC) count	x10E12/L	Chloride	mmol/L	Specific Gravity
White Blood Cell (WBC) count	x10E9/L	Calcium	mmol/L	Protein
Differential WBC count: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	 % % % % %	Phosphorus Serum Iron Bicarbonate Glucose BUN Creatinine	mmol/L µmol/L mmol/L mmol/L mmol urea /L µmol/L	Glucose Ketones RBC,WBC, casts* Nitrites Bilirubin Hemoglobin
Platelets	x10E9/L	Total Bilirubin	µmol/L	Hemoglobin
MCV	fL	Albumin	g/L	Urobilinogen *Reflex microscopic analysis to be performed only if other analytes are abnormal on automated testing
MCH	pg	Total Protein	g/L	
MCHC	g/L	AST (SGOT)	IU/L	
RDW	%	ALT (SGPT)	IU/L	
Hemolysis		Alkaline phosphatase	IU/L	
Haptoglobin (Hemolysis Panel)	g/L	LDH	IU/L	
Free plasma hemoglobin (Hemolysis Panel)	g/L	CPK	IU/L	
		Triglycerides	mmol/L	
		Total cholesterol	mmol/L	
		HDL cholesterol	mmol/L	
		LDL cholesterol	mmol/L	
		Hemolysis		
		Bilirubin, direct	µmol/L	

Table 4: Special Laboratory Evaluations

Parameter	**SI Unit**	**Timepoints**
Blood Glycosylated Hemoglobin (HbA1c)	mmol/L	Month 6 and Month 12
C-reactive Protein (CRP)	mg/L	Month 6 and Month 12

CD+4 Lymphocyte count	x10E9/L	Month 6 and Month 12
Early morning Plasma Cortisol testing for Adrenal Insufficiency	µg/dL	As needed: *when patients are symptomatic, and when patients are at most risk for adrenal insufficiency and adrenal crisis, such as following discontinuation or interruptions of dexamethasone dosing*
High dose ACTH stimulation test	µg/dL	As needed: *In the event that patients show signs or symptoms of adrenal insufficiency during the study*

All laboratory assessments are performed at local laboratories. Quantitative laboratory results are converted to their respective Reporting units for use in summary tables. Assessment of results as being within the normal range are made by the local laboratory. *Any laboratory abnormalities meeting the definition of an adverse event should be recorded on the Adverse Events CRF.*

Clinically notable values of standard laboratory are derived based on SI units as outline in Appendix 13.1.

If repeat tests are performed at any visit the result documented under the nominal visit label is used in all summaries and analyses for that Visit.

Baseline is as described in Section 7.1.

The change from baseline is calculated for quantitative laboratory tests at each scheduled post-baseline visit as:

- Change from baseline = Scheduled Visit result (measured or derived) – Baseline value.

Special Laboratory: Adrenal Insufficiency Screening

As part of the Special Laboratory evaluations, patients are screened for adrenal insufficiency. The results are recorded on the 'Screening for Adrenal Insufficiency' eCRF page.

Special Laboratory: Early Morning Plasma Cortisol and ACTH Stimulation Test

Patients' Early Morning Plasma Cortisol levels are recorded on the 'Early Morning Plasma Cortisol' eCRF page and ACTH Stimulation Test data are recorded on the 'ACTH Stimulation Test' eCRF page.

Pregnancy Testing

A serum pregnancy test is performed every 6 months and at the Safety follow up visit for women of childbearing potential. A monthly urine pregnancy test is also performed before every infusion throughout the study. Results are recorded on the 'Serum Pregnancy Test' or 'Urine Pregnancy Test' eCRF pages.

Culture-based sterility test on EDS-EP

CCI

Process Events

The EDS-EP process is derived as being not fully complete if the response to "Was EDS-EP infusion completed?" is recorded as "No" on the 'EDS-EP Infusion' page.

Vital Signs

Vital signs assessments are performed pre- and post-infusion at all visits with additional triplicate pre- and post-infusion assessments every 6 months *as specified on the Schedule of Visits.* Vital Sign assessments include *body weight, temperature (oral or tympanic, according to the specific medical practice of the Center) , pulse, systolic and diastolic blood pressure, and respiratory rate. Height will be measured by a stadiometer in triplicate at each required visit and used along with body weight (also measured in triplicate at each required visit) to calculate Body Mass Index (BMI). Pulse and blood pressure will be measured after the patient has been in the supine position for at least 5 minutes.* All results are recorded on the 'Vital Signs Pre-Infusion' or 'Vital Signs Post Infusion' eCRF pages.

The baseline value is as described in Section 7.1. The arithmetic mean of all triplicate values is calculated for use in summary tables. Results are converted for summary tables as follows:

- Temperature: Results measured in Fahrenheit converted to Celsius as
  - Temperature (°C) = (Temperature (°F) – 32) * 5/9
- Weight: Results measured in pounds converted to kilograms as
  - Weight (kg) = Weight (lb) / 2.205
- Height: Results measured in inches converted to centimetre as
  - Height (cm) = Height (in) * 2.54

The change from baseline is calculated for vital signs with a continuous response at each scheduled post-baseline visit:

- Change from baseline = Scheduled Visit result (measured or derived) – Baseline value.

At each scheduled post-baseline visit each vital sign with a continuous response is derived as having a clinically notable change using the rules in Table 5.

Table 5: Clinically Notable Values for Vital signs

Parameter	Unit	Decrease	Increase
Systolic Blood Pressure (SBP)	mmHg	Value ≤ 90 and ≥ 20 Decrease	Value ≥ 180 and ≥ 20 Increase
Diastolic Blood Pressure (DBP)	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
Weight	kg	≥ 7% Decrease	≥ 7% Increase
Respiration Rate	breaths/ minute	< 12	> 25
Temperature	°C	NA	Value ≥ 38.3 and ≥ 1.1 Increase
Temperature	°F	NA	Value ≥ 101 and ≥ 2.0 Increase

"Decrease" and "Increase" refer to change from baseline. Respiration Rate is based on recorded value only and not change from baseline.

Physical and Neurological Examination

Physical examinations are performed as specified on the Schedule of Visits. Physical examination includes 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. Abnormal results are identified by the investigator and specified as clinically significant or not clinically significant. All results are recorded on the 'Physical Examination Pre-Infusion' or 'Physical Examination Post Infusion' eCRF pages. Neurological Examination results are recorded on the 'Neurological Examination' eCRF page.

Physical Examinations are performed post infusion at all visits with additional pre-infusion assessments at Month 6, Month 12 etc. Neurological Examinations are performed pre-infusion at Month 6, Month 12 etc.

ECG variables

Electrocardiogram (ECG) evaluations are performed every 6 months in accordance with the Schedule of Study Events. At each evaluation, three ECG assessments are performed in succession, approximately 10 minutes apart. The investigator's interpretation of ECG results ('normal'; 'abnormal, clinically significant'; 'abnormal, not clinically significant') is recorded on the 'ECG' eCRF page.

C-SSRS

The Columbia Suicide Severity Rating Scale (C-SSRS) is a suicidal ideation rating scale which rates individual's degree of suicidal ideation on a scale, ranging from "wish to be dead" to "active suicidal ideation with specific plan and intent." (Posner, et al., 2011). At each visit, patients are assigned an ideation severity score of 0 (no ideation present) to 5 (active suicidal ideation with plan and intent) based on their most severe suicidal ideation since the last visit as recorded in the eCRF. This is derived as 0 if the question "Wish to be dead" is marked as "No" and is derived as 1 to 5 based on the response to "Most severe ideation (Type#(1-5))". If one of the two variables is missing for a visit, the ideation severity score is also regarded as missing.

Patients under the age of 12 years at the baseline visit would use the pediatric version of the scale throughout the study. Results are recorded on the 'C-SSRS Children's Since Last Visit' or 'C-SSRS Adult's Since Last Visit' eCRF page as appropriate.

Bone Mineral Density

Measurements of Bone Mineral Density (BMD) will be performed for all patients at 6 and 12 months to assess potential steroid-related changes. Results of BMD, including investigator's interpretation, are recorded on the 'Bone Mineral Density' eCRF page.

Tanner Staging

Assessment of physical development, sexual maturation, and the effect of treatment with dexamethasone on these aspects will be evaluated using the Tanner scale at 6 and 12 months. The scale defines physical measurements of development in children, adolescents and adults based on external primary and secondary sex characteristics, such as the size of the breast, genitals, testicular volume and development of pubic hair. Due to natural variation, individuals pass through the Tanner stages at different rates, depending in particular on the timing of puberty. Tanner staging of the breasts in pre-menarchal females and of the scrotum in males who have not completed puberty, will be performed. Post-menarchal females and males who have completed puberty will be excluded from this growth analysis.

Results of Tanner Staging assessments are recorded on the 'Tanner Scale' eCRF page.

7.4.9 Pharmacokinetic Variables

Not applicable.

7.4.10 Pharmacodynamic Variables

Not applicable.

7.4.11 Pharmacoeconomic Variables

Not applicable.

8. Analysis Methods

8.1 General Methods

For continuous variables, the mean, standard deviation (SD), minimum, median and maximum as well as 1st and 3rd quartile (Q1, Q3) are presented, together with the total number of observations and the number of non-missing values. Unless otherwise specified minimum and maximum values are reported to the same number of decimal places as the recorded measurements, mean, median, 1st and 3rd quartile are reported to one more decimal place and standard deviation one additional decimal place more than the mean.

For categorical variables, absolute and relative frequencies are reported. Relative frequencies are based on all observations and reported as a percentage to one decimal place. Unless otherwise specified percentages are based on the number of patients with data and are not calculated for missing categories.

Adverse events, medical histories and concomitant medications are reported on a patient basis, i.e. if a patient reported several events coded to the same coding term the patient is counted only once at the respective level of display. The percentages are calculated using the number of patients in the population Analysis Set as the denominator.

8.2 Specific Methods for Efficacy Analyses

All Efficacy Data are summarized by descriptive statistics as described in section 8.1.

8.2.1 Statistical/Analytical Issues

8.2.1.1 Adjustments for Covariates

Not applicable.

8.2.1.2 Handling of Dropouts or Missing Data

Dropouts are not replaced.

Missing data are handled as described in section 7.

8.2.1.3 Blind Review

Not applicable since this is an open label study.

8.2.1.4 Multicentre Studies

This study is performed in Australia, Belgium, Germany, India, Italy , Norway, Poland, Spain, Tunisia , the UK and the US. Analyses are performed over all centres.

8.2.1.5 Multiple Comparisons/Multiplicity

Not applicable.

8.3 Specific Methods for Safety Analyses

All Safety Data are summarized by descriptive statistics as described in section 8.1.

8.4 Specific Methods for Pharmacokinetic Analyses

Not applicable.

8.5 Specific Methods for Pharmacodynamic Analyses

Not applicable.

8.6 Specific Methods for Pharmacoeconomic Analyses

Not applicable.

9. Interim analyses

An analysis will be produced to support the New Drug Application Submission. This is comprised of two parts: a Briefing Book submission and then the NDA submission.

As this study is open label and there are no hypothesis tests, no consideration is required for masking or Type I error control.

The outputs to be presented as part of the Briefing Book and NDA analysis are outlined in a separate document. For both analysis the subgroup of treatment gap outlined in Section 7.1 is not required.

10. Overview of Tables, Listings and Figures

Unless otherwise stated summary tables are produced based on the complete analysis set mention in the respective section. The treatment groups from the ATTeST study are presented on all outputs.

10.1 Disposition of Patients

A listing presents study completion data, including the primary reason for study discontinuation, for the Total Set (TOT).

A table summarizes the disposition of patients in the Total Set. This includes a summary of the number of patients who completed the study, the number of patients who had a treatment interruption due to COVID-19, the number of patients who discontinued the study, and the primary reason for discontinuation.

The number of patients who attended Scheduled Visits is summarized (Visit Attendance) by absolute counts (n) and percentages (%) for the SAF.

10.2 Protocol Deviations

A listing presents all protocol deviation data as recorded in the course of the study.

10.2.1 Inclusion and Exclusion Criteria

Listings present all patients who failed to meet at least one of the Inclusion or Exclusion criteria, along with all the failing Inclusion and Exclusion responses for the TOT.

10.3 Data Sets Analysed

The number of patients in each Analysis Set defined in Section 6.1 is summarized by absolute counts (n) and percentages (%) for the TOT. Percentages are based on the TOT.

A listing presents the inclusion into each Analysis Set, including the primary reason for exclusion from the FAS for the TOT.

10.4 Demographic and Other Baseline Characteristics

10.4.1 Demographic Characteristics

A listing presents all demographic data for the SAF.

A table summarizes all demographic data, and additionally height, weight and BMI at baseline by summary statistics and absolute counts (n) and percentages (%) for the SAF.

10.4.2 Medical History

The medical history data are listed as recorded in the CRF together with the MedDRA SOC and PT.

The number and percentage of patients reporting any medical history and any medical history for each system organ class and preferred term are summarized. Patients are summarized only once at any level (any history, system organ class, and preferred term) if they have multiple reports at the level. Data are presented for the SAF.

10.4.3 Concomitant Medications, Therapies and Procedures

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

Prior medications, concomitant medications are summarized using the number and percentage of patients reporting any medication use, and the number and percentage of patients reporting each ATC drug class and generic drug name (WHO-DD preferred term). For each patient, multiple records of the same medication are counted once within a drug class and generic drug name.

Prior and concomitant medications are presented for the SAF.

All Non-drug Therapies and Procedures are listed, including verbatim descriptions and coded terms.

10.5 Exposure to Study Medication

A listing presents all Exposure to Study Medication data for the SAF (including overall duration, total number of completed infusions and data on each individual infusion).

Exposure to Study Medication data, including number of infusions received and duration of treatment are summarized by summary statistics for the SAF. The dexamethasone concentration data at each visit is summarized separately for the SAF.

10.6 Efficacy Results

10.6.1 Efficacy Analysis

(m)ICARS and RmICARS

The individual items of the ICARS are listed as well as the Full ICARS score, the “Modified” ICARS score, The Rescored “Modified” ICARS scores, and their respective changes from OLE-IEDAT baseline and ATTeST baseline. The listing is produced based on the SAF.

The modified ICARS score at baseline and each relevant follow-up visit (every 6 months), and the absolute change from OLE-IEDAT baseline and from ATTeST baseline to each relevant follow-up visit are summarized using summary statistics appropriate for continuous data as described in section 8.1.

The modified ICARS score at baseline and each 6-month interval from initiation of active treatment, and the absolute change from OLE-IEDAT baseline and from ATTeST baseline to each relevant 6 month interval are summarized using summary statistics appropriate for continuous data as described in section 8.1.

The Rescored modified ICARS scores at baseline and each relevant follow-up visit (every 6 months), and the absolute change from OLE-IEDAT baseline and from ATTeST baseline to each relevant follow-up visit are summarized using summary statistics appropriate for continuous data as described in section 8.1. Each scoring method is summarized separately.

The Rescored modified ICARS scores at baseline and each 6-month interval from initiation of active treatment, and the absolute change from OLE-IEDAT baseline and from ATTeST baseline to each relevant 6 month interval are summarized using summary statistics appropriate for continuous data as described in section 8.1. Each scoring method is summarized separately.

The full ICARS score at baseline and each relevant follow-up visit, and the absolute change from baseline to each relevant follow-up visit are summarized using summary statistics appropriate for continuous data as described in section 8.1.

The above summaries are presented for the FAS and repeated for the subgroups Age (<10 years, ≥10 years) and Region (India; Europe, Australia, Tunisia; United States).

For the FAS, the mean mICARS and Rescored mICARS (both methods) scores are plotted separately over time with a trend line. These plots are repeated displaying only patients in the EDS-EP High Dose treatment group from ATTeST.

CGI-C

The results of the CGI-C assessments are presented in a listing together with the categories based on the SAF.

For the CGI-Change, the proportion [n(%)] of patients rated as improved, as well as those showing no change or worsening, at each time-point will be calculated. This analysis is performed on the FAS as described in section 8.1 and repeated for the subgroups Age (<10 years, ≥10 years) and Region (India; Europe, Australia, Tunisia; United States).

The CGI-C scores are plotted over time within stacked bar charts on the FAS.

CGI-S

The individual items of the CGI-S are listed including the CGI-S overall rating (CGI-S structured) for the SAF.

The CGI-S score is analysed as a categorical variable as described in section 8.1. The summary statistics are presented for the FAS and repeated for the subgroups Age (<10 years, ≥10 years) and Region (India; Europe, Australia, Tunisia; United States).

The CGI-S (structured) scores are plotted over time with stacked bar charts for the FAS.

EQ-5D-5L

The individual items of the EQ-5D-5L are listed including the values of the VAS, as well as the EQ-5D-5L index and its change from baseline. The listing is presented for patients in the SAF.

The EQ-5D-5L index at baseline and each relevant follow-up visit (every 6 months), and the change from OLE-IEDAT baseline and from ATTeST baseline to each relevant follow-up visit are summarized using summary statistics appropriate for continuous data as described in section 8.1. These summary statistics on the change from ATTeST baseline to each relevant follow-up visit are repeated for the subgroups of placebo patients and non-placebo patients of the ATTeST study. These summary statistics are presented for the FAS.

For the FAS, the mean EQ-5D-5L index is plotted over time with a trend line.

10.6.1.1 Confirmatory Analysis

Not applicable in this single arm study.

10.6.1.2 Sensitivity Analysis

Not applicable in this single arm study.

10.7 Safety Results

10.7.1 Adverse Events

Brief Summary of Adverse Events

An overview of AEs (including the number of patients with at least one TEAE, at least one TESAE, at least one TEAE leading to Death, at least one AESI, the number of patients who permanently withdrew the Study Treatment due to a TEAE, AEs during COVID-19 interruption, the worst intensity of any TEAE experienced by each patient with at least one TEAE and the closest relationship to Study Treatment of any TEAE experienced by each patient with at least one TEAE) is summarized for the SAF.

This summary is repeated for each 12-month period as described in Section 7.1.

Display of Adverse Events

Adverse events are summarized on a per-patient basis (i.e. if a patient reported the same event repeatedly the patient is counted only once at the specific level of display) and on a per event basis. Absolute counts (n) and percentages (%) are presented for the number of patients with at least one Adverse event, and per SOC and per PT within SOC, for the SAF. Percentages are based on the number of patients in the population.

Descriptive tables are ordered by descending frequency of the overall number of patients within each SOC, and then ordered within each SOC by the number of patients within each PT. In the event of equal frequencies, tables are ordered by number of events in the respective category and, in the event of a tie, alphabetically.

AEs are summarized for the SAF as follows:

- Treatment-Emergent Adverse Events
- Treatment-Related Treatment-Emergent Adverse Events
- Adverse Events of Special Interest
- Treatment-Emergent Adverse Events by worst intensity
- Treatment-Emergent Adverse Events leading to death
- Treatment-Emergent Serious Adverse Events
- Treatment-Emergent Adverse Events that led to discontinuation of Study Treatment.
- On dose Treatment-Emergent Adverse Events During COVID-19 Treatment Interruption.
- Off dose Treatment-Emergent Adverse Events During COVID-19 Treatment Interruption.
- Restart Treatment-Emergent Adverse Events After COVID-19 Treatment Interruption.

Listing of Adverse Events

Listings present all Adverse Event data (raw, derived, and coded) for the SAF, ordered within patient by onset date and time and end date and time of the event.

Serious Adverse Events

A listing presents all Adverse Event data (raw, derived, and coded, equivalent to the format for the AE listings) ordered within patient by onset date and time and end date and time of the event, for Serious AEs.

Deaths

A listing presents all Adverse Event data (raw, derived, and coded, equivalent to the format for the AE listings) ordered within patient by onset date and time and end date and time of the events with outcome Death.

Adverse Events that led to discontinuation of Study Treatment

A listing presents all Adverse Event data (raw, derived, and coded, equivalent to the format for the AE listings) ordered within patient by onset date and time and end date and time of the events that led to discontinuation of Study Treatment.

10.7.2 Clinical Laboratory Evaluation

Separate listings for hematology, chemistry, urinalysis, hemolysis panel and the special laboratory parameters present the raw values, normal ranges, investigators interpretation (for special laboratory parameters only) and, for all quantitative tests, the results converted to SI units for the SAF. Special laboratory data for adrenal insufficiency screening, early morning plasma cortisol and ACTH stimulation test are listed separately for the SAF.

Data for each parameter of a continuous nature are summarized, separately for hematology, chemistry and the special laboratory parameters, for the SAF. The change from baseline to each visit is calculated and summarized. Data for each parameter of a categorical nature is summarized descriptively using absolute counts (n) and percentages (%).

Clinically notable changes in laboratory values are summarized separately for hematology, chemistry and urinalysis using absolute counts (n) and percentages (%).

Results of the investigators interpretation of special laboratory parameters are presented as a shift table comparing each visit to Baseline for the SAF.

10.7.3 Pregnancy Testing

Results of serum and urine pregnancy tests are listed for the SAF.

10.7.4 Culture-based sterility Test on EDS-EP

The absolute count (n) and percentage (%) of potentially contaminated infusions at any time and potentially contaminated infusions by visit is summarized for the SAF. All sterility test data and process data are listed for the SAF.

10.7.5 Process Events

The absolute count (n) and percentage (%) of EDS process failures at any time and potentially contaminated infusions by visit is summarized for the SAF. All EDS process data is listed for the SAF as outlined in section 10.5.

10.7.6 Vital Signs

All Vital Sign data are included in a listing for the SAF.

Vital Sign results and change from baseline are summarized by summary statistics on scheduled visits for the SAF. The absolute counts (n) and percentages (%) of patients with clinically notable findings are included in a separate summary for the SAF. The absolute counts (n) and percentages (%) of patients with at least one clinically notable change from baseline and summary statistics of the most extreme clinically notable increase and decrease from baseline are presented in separate summaries for the SAF.

10.7.7 Physical and Neurological Examination

All physical and neurological examination data are included in separate listings for the SAF. Neurological examination data is listed by type in separate listings (Cranial Nerves, Motor, Sensory, Reflexes and Cerebellar and Other)

Investigator assessment of the examination of physical and neurological examination data are summarized as categorical data as described in section 8.1 by visit for the SAF.

10.7.8 ECGs

All ECG data are included in a listing for the SAF.

Absolute counts (n) and percentages (%) of investigator interpretation of ECG results are summarized for each scheduled visit for the SAF.

10.7.9 C-SSRS

All recorded C-SSRS data are included in listings for the SAF.

The ideation summary score is summarized at each scheduled visit as a continuous variable, Additionally the ideation summary score is analysed as a categorial variable. Both analyses are performed separately for the Children's scale and the Adult's Scale as described in section 8.1 on the SAF.

10.7.10 Bone Mineral Density

All recorded BMD data are included in a listing for the SAF.

BMD z-scores, including change from baseline, are summarized at each scheduled visit. Results of the investigator's interpretation are presented as a shift table comparing each visit to Baseline for the SAF.

10.7.11 Tanner Staging

All recorded Tanner Staging data are included in a listing for the SAF.

The absolute counts (n) and percentage (%) of patients at each Tanner stage is summarized by visit for the SAF.

10.8 Pharmacokinetics

Not applicable.

10.9 Pharmacodynamics

Not applicable.

10.10 Pharmacoeconomics

Not applicable.

11. References

EuroQol Research Foundation, 2019. *EQ-5D-5L User Guide.* s.l.:Available from: https://euroqol.org/publications/user-guides.

Guy, W., 1976. *Clinical Glocal Impressions. ECDEU Assessment Manual for Psychotherapy.* s.l.:National Institute of Mental Health.

Posner, K. et al., 2011. The Columbia-Suicide Severity Rating Scale: Initial Validity and Internal Consistency Findings from Three Multisite Studies with Adolescents and Adults. *American Journal of Psychiatry,* Issue 168, pp. 1266-1277.

Trouillas, P. et al., 1997. International Cooperative Ataxia Rating Scale for Pharmacological Assessment of the Cerebellat Syndrome. *Journal of the Neurological Sciences,* Volume 145, pp. 205-211.

12. Tables, Listings and Figures

U=Unique TLF (or first instance of a table to be repeated) or R=Repeat item.

12.1 Post-text Tables

Patient Disposition & Protocol Deviations		**Population**	
Table 14.1-1.1	Summary of Patient Disposition	TOT	U
Table 14.1-1.2	Summary of Visit Completion	SAF	U
Analysis Sets			
Table 14.1-2.1	Summary of Analysis Sets	TOT	U
Demographics			
Table 14.1-3.1	Summary of Demographic Data	SAF	U
Baseline Patient Characteristics			
Table 14.1-4	Summary of Medical History at Baseline	SAF	U
Concomitant Medication			
Table 14.1-5.1	Summary of Prior Medications	SAF	U
Table 14.1-5.2	Summary of Concomitant Medications	SAF	R
Treatment Compliance			
Table 14.1-6.1	Summary of Overall Exposure	SAF	U
Table 14.1-6.2	Summary of Dexamethasone 21-Phosphate disodium salt Concentration Data by Visit	SAF	U
Efficacy Data			
Table 14.2-1.1	Summary of Modified ICARS	FAS	U
Table 14.2-1.2	Summary of Modified ICARS (Subgroup: Age < 10 years	FAS	R
Table 14.2-1.3	Summary of Modified ICARS (Subgroup: Age ≥ 10 years)	FAS	R
Table 14.2-1.4	Summary of Modified ICARS (Subgroup: Region = India)	FAS	R
Table 14.2-1.5	Summary of Modified ICARS (Subgroup: Region = Europe, Australia, Tunisia)	FAS	R
Table 14.2-1.6	Summary of Modified ICARS (Subgroup: Region = United States)	FAS	R
Table 14.2-1.7	Summary of Modified ICARS by time from initiation of active treatment	FAS	U
Table 14.2-1.8	Summary of Modified ICARS by time from initiation of active treatment (Subgroup: Age < 10 years	FAS	R
Table 14.2-1.9	Summary of Modified ICARS by time from initiation of active treatment (Subgroup: Age ≥ 10 years)	FAS	R
Table 14.2-1.10	Summary of Modified ICARS by time from initiation of active treatment (Subgroup: Region = India)	FAS	R
Table 14.2-1.11	Summary of Modified ICARS by time from initiation of active treatment (Subgroup: Region = Europe, Australia, Tunisia)	FAS	R
Table 14.2-1.12	Summary of Modified ICARS by time from initiation of active treatment (Subgroup: Region = United States)	FAS	R

Table 14.2-2.1	Summary of Rescored Modified ICARS	FAS	R
Table 14.2-2.2	Summary of Rescored Modified ICARS (Subgroup: Age < 10 years)	FAS	R
Table 14.2-2.3	Summary of Rescored Modified ICARS (Subgroup: Age ≥ 10 years)	FAS	R
Table 14.2-2.4	Summary of Rescored Modified ICARS (Subgroup: Region = India)	FAS	R
Table 14.2-2.5	Summary of Rescored Modified ICARS (Subgroup: Region = Europe, Australia, Tunisia)	FAS	R
Table 14.2-2.6	Summary of Rescored Modified ICARS (Subgroup: Region = United States)	FAS	R
Table 14.2-2.7	Summary of Rescored Modified ICARS by time from initiation of active treatment	FAS	R
Table 14.2-2.8	Summary of Rescored Modified ICARS by time from initiation of active treatment (Subgroup: Age < 10 years)	FAS	R
Table 14.2-2.9	Summary of Rescored Modified ICARS by time from initiation of active treatment (Subgroup: Age ≥ 10 years)	FAS	R
Table 14.2-2.10	Summary of Rescored Modified ICARS by time from initiation of active treatment (Subgroup: Region = India)	FAS	R
Table 14.2-2.11	Summary of Rescored Modified ICARS by time from initiation of active treatment (Subgroup: Region = Europe, Australia, Tunisia)	FAS	R
Table 14.2-2.12	Summary of Rescored Modified ICARS by time from initiation of active treatment (Subgroup: Region = United States)	FAS	R
Table 14.2-3.1	Summary of ICARS	FAS	R
Table 14.2-3.2	Summary of ICARS (Subgroup: Age < 10 years)	FAS	R
Table 14.2-3.3	Summary of ICARS (Subgroup: Age ≥ 10 years)	FAS	R
Table 14.2-3.4	Summary of ICARS (Subgroup: Region = India)	FAS	R
Table 14.2-3.5	Summary of ICARS (Subgroup: Region = Europe, Australia, Tunisia)	FAS	R
Table 14.2-3.6	Summary of ICARS (Subgroup: Region = United States)	FAS	R
Table 14.2-4.1	Summary of CGI-C	FAS	U
Table 14.2-4.2	Summary of CGI-C (Subgroup: Age < 10 years)	FAS	R
Table 14.2-4.3	Summary of CGI-C (Subgroup: Age ≥ 10 years)	FAS	R
Table 14.2-4.4	Summary of CGI-C (Subgroup: Region = India)	FAS	R
Table 14.2-4.5	Summary of CGI-C (Subgroup: Region = Europe, Australia, , Tunisia)	FAS	R
Table 14.2-4.6	Summary of CGI-C (Subgroup: Region = United States)	FAS	R
Table 14.2-5.1	Summary of CGI-S	FAS	U
Table 14.2-5.2	Summary of CGI-S (Subgroup: Age < 10 years)	FAS	R
Table 14.2-5.3	Summary of CGI-S (Subgroup: Age ≥ 10 years)	FAS	R
Table 14.2-5.4	Summary of CGI-S (Subgroup: Region = India)	FAS	R

Table 14.2-5.5	Summary of CGI-S (Subgroup: Region = Europe, Australia, Tunisia)	FAS	R
Table 14.2-5.6	Summary of CGI-S (Subgroup: Region = United States)	FAS	R
Table 14.2-6.1	Summary of EQ-5D-5L	FAS	U
Table 14.2-6.2	Summary of EQ-5D-5L (Subgroup: Age < 10 years)	FAS	R
Table 14.2-6.3	Summary of EQ-5D-5L (Subgroup: Age ≥ 10 years)	FAS	R
Table 14.2-6.4	Summary of EQ-5D-5L (Subgroup: Region = India)	FAS	R
Table 14.2-6.5	Summary of EQ-5D-5L (Subgroup: Region = Europe, Australia, , Tunisia)	FAS	R
Table 14.2-6.6	Summary of EQ-5D-5L (Subgroup: Region = United States)	FAS	R
Adverse Events			
Table 14.3.1-1.1.1	Summary of Adverse Events	SAF	U
Table 14.3.1-1.1.2	Summary of Adverse Events by 12 Month Period	SAF	U
Table 14.3.1-1.2	Treatment Emergent Adverse Events by System Organ Class and Preferred Term	SAF	U
Table 14.3.1-1.3	Treatment Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term	SAF	R
Table 14.3.1-1.4	Adverse Events of Special Interest by System Organ Class and Preferred Term	SAF	R
Table 14.3.1-1.5	Treatment Emergent Adverse Events by Worst Intensity by System Organ Class and Preferred Term	SAF	R
Table 14.3.1-1.6	Treatment Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term	SAF	R
Table 14.3.1-1.7	Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term	SAF	R
Table 14.3.1-1.8	Treatment Emergent Adverse Events That Led to Discontinuation of Study Treatment by System Organ Class and Preferred Term	SAF	R
Table 14.3.1-1.9	On Dose Treatment Emergent Adverse Events During COVID-19 Treatment Interruption by System Organ Class and Preferred Term	SAF	R
Table 14.3.1-1.10	Off Dose Adverse Events During COVID-19 Treatment Interruption by System Organ Class and Preferred Term	SAF	R
Table 14.3.1-1.11	Restart Treatment Emergent Adverse Events After COVID-19 Treatment Interruption by System Organ Class and Preferred Term	SAF	R
Laboratory Values			
Table 14.3.2-1.1	Summary of Hematology Laboratory Parameters	SAF	U
Table 14.3.2-1.2	Summary of Clinical Chemistry Laboratory Parameters	SAF	R
Table 14.3.2-1.3	Summary of Special Laboratory Parameters	SAF	R
Table 14.3.2-1.4	Summary of Urinalysis Laboratory Parameters	SAF	U

Table 14.3.2-2.1	Summary of Clinically Notable Hematology Laboratory Parameters	SAF	U
Table 14.3.2-2.2	Summary of Clinically Notable Clinical Chemistry Laboratory Parameters	SAF	R
Table 14.3.2-2.3	Summary of Clinically Notable Urinalysis Laboratory Parameters	SAF	R
Table 14.3.2-3.1	Summary of Shift in Special Laboratory Parameters from Baseline	SAF	U
Other Safety			
Table 14.3.3-1.1	Summary of Culture-Based Sterility Test	SAF	U
Table 14.3.-1.2	Summary of Process Events	SAF	U
Table 14.3.3-2.1	Summary of Vital Sign Data	SAF	U
Table 14.3.3-2.2	Summary of Clinically Notable Change from Baseline Vital Signs	SAF	U
Table 14.3.3-3.1	Summary of Physical Examination Data	SAF	U
Table 14.3.3-3.2	Summary of Neurological Examination Data	SAF	R
Table 14.3.3-4	Summary of ECG Data	SAF	U
Table 14.3.3-5.1	Summary of Columbia-Suicide Severity Rating Scale (C-SSRS) Children's	SAF	U
Table 14.3.3-5.1	Summary of Columbia-Suicide Severity Rating Scale (C-SSRS) Adult's	SAF	R
Table 14.3.3-6.1	Summary of Bone Mineral Density z-scores	SAF	U
Table 14.3.3-6.2	Summary of Shift in Bone Mineral Density z-scores from Baseline	SAF	U
Table 14.3.3-7.1	Summary of Tanner Staging data	SAF	U

12.2 Post-Text Figures

Efficacy Data		**Population**	
Figure 14.2.3-1.1.1	Figure of Mean mICARS Over Time	FAS	U
Figure 14.2.3-1.1.2	Figure of Mean mICARS Over Time, High Dose Group Only	FAS	R
Figure 14.2.3-1.2.1	Figure of Mean RmICARS Over Time	FAS	U
Figure 14.2.3-1.2.2	Figure of Mean RmICARS Over Time, High Dose Group Only	FAS	R
Figure 14.2.3-1.3.1	Figure of Mean ICARS Over Time	FAS	U
Figure 14.2.3-1.3.2	Figure of Mean ICARS Over Time, High Dose Group Only	FAS	R
Figure 14.2-3.2.1	Figure of CGI-C Scores Over Time	FAS	U
Figure 14.2-3.2.2	Figure of CGI-S Overall Scores Over Time	FAS	R
Figure 14.2-3.2.3	Figure of Mean EQ-5D-5L Over Time	FAS	R

12.3 Post-Text Listings

Patient Disposition & Protocol Deviations		**Population**	
Listing 16.2.1-1.1	Listing of Study Disposition	TOT	U
Listing 16.2.2-1.1	Listing of Protocol Deviations	TOT	U
Listing 16.2.2-1.2	Listing of Inclusion/Exclusion Criteria	TOT	U
Analysis Sets			
Listing 16.2.3-1.1	Listing of Analysis Sets with Reason for Exclusion	TOT	U
Demographic Data and Other Baseline Characteristics			
Listing 16.2.4-1.1	Listing of Demographic Data	SAF	U
Listing 16.2.4-2	Listing of Medical History at Baseline	SAF	U
Listing 16.2.4-3.1	Listing of Prior Medications	SAF	U
Listing 16.2.4-3.2	Listing of Concomitant Medications	SAF	R
Listing 16.2.4-3.3	Listing of Non-drug Therapy and Procedures	SAF	R
Exposure Data			
Listing 16.2.5-1	Listing of Study Drug Administration and Exposure	SAF	U
Efficacy Data			
Listing 16.2.6-1.1	Listing of ICARS data – Individual Item Responses	SAF	U
Listing 16.2.6-1.2	Listing of ICARS data – Total Scores	SAF	U
Listing 16.2.6-2.1	Listing of Global Clinical Impression of Change data	SAF	U
Listing 16.2.6-2.2	Listing of Global Clinical Impression of Severity data	SAF	U
Listing 16.2.6-3.1	Listing of EQ-5D-5L data	SAF	U
Adverse events			
Listing 16.2.7-1.1	Listing of Adverse Events	SAF	U
Listing 16.2.7-1.2	Listing of Serious Adverse Events	SAF	R
Listing 16.2.7-1.3	Listing of Serious Adverse Events with Outcome Death	SAF	R
Listing 16.2.7-1.4	Listing of Adverse Events that led to Discontinuation of Study Treatment	SAF	R
Clinical Laboratory Evaluation			
Listing 16.2.8-1.1	Listing of Hematology Data	SAF	U
Listing 16.2.8-1.2	Listing of Clinical Chemistry Data	SAF	R
Listing 16.2.8-1.3	Listing of Urinalysis Data	SAF	U
Listing 16.2.8-1.4	Listing of Special Laboratory Data	SAF	R
Listing 16.2.8-1.5	Listing of Early Morning Plasma Cortisol	SAF	U
Listing 16.2.8-1.6	Listing of ACTH Stimulation Test	SAF	U
Listing 16.2.8-1.7	Listing of Adrenal Insufficiency Screening	SAF	U
Listing 16.2.8-1.8	Listing of Pregnancy Test Data	SAF	U
EDS-EP Infusion			
Listing 16.2.9-1.1	EDS-EP Infusion – EryDex system (EDS) process before Infusion	SAF	U

Listing 16.2.9-1.2.1	EDS-EP Infusion – Staining Test on EDS-End Product	SAF	U
Listing 16.2.9-1.2.2	EDS-EP Infusion – Pre-infusion Aerobic Blood Culture	SAF	U
Listing 16.2.9-1.3.1	EDS-EP Infusion – 14-Day Sterility Test Sampling	SAF	U
Listing 16.2.9-1.3.2	EDS-EP Infusion – RBC Osmotic Resistance	SAF	U
Listing 16.2.9-1.4	EDS-EP Infusion – EryDex system End Product before Infusion	SAF	U
Listing 16.2.9-1.5	Listing of 14-Day Sterility Test Positive Staining Test	SAF	U
Listing 16.2.9-1.6.1	Listing of Positive post-Release Sterility Test	SAF	U
Listing 16.2.9-1.6.2	Listing of Positive Post-Release Sterility Test – Retention Sample	SAF	U
Listing 16.2.9-2.1.1	EDS Process - Encapsulation Procedure Checklist – Part 1	SAF	U
Listing 16.2.9-2.1.2	EDS Process - Encapsulation Procedure Checklist – Part 2	SAF	U
Vital Signs			
Listing 16.2.10-1.1	Listing of Vital Sign Data	SAF	U
Physical and Neurological Examination			
Listing 16.2.10-2.1	Listing of Physical Examination Data	SAF	U
Listing 16.2.10-2.2.1	Listing of Neurological Examination Data – Cranial Nerves	SAF	U
Listing 16.2.10-2.2.2	Listing of Neurological Examination Data – Motor	SAF	U
Listing 16.2.10-2.2.3	Listing of Neurological Examination Data – Sensory	SAF	U
Listing 16.2.10-2.2.4	Listing of Neurological Examination Data – Reflexes	SAF	U
Listing 16.2.10-2.2.5	Listing of Neurological Examination Data – Cerebellar and Other	SAF	U
Electrocardiogram			
Listing 16.2.10-3	Listing of ECG Data	SAF	U
C-SSRS			
Listing 16.2.10-4.1	Listing of C-SSRS (Children's) Data – Ideation and Intensity	SAF	U
Listing 16.2.10-4.2	Listing of C-SSRS (Children's) Data – Behaviour and Lethality	SAF	U
Listing 16.2.10-4.3	Listing of C-SSRS (Adults) Data – Ideation	SAF	U
Listing 16.2.10-4.4	Listing of C-SSRS (Adults) Data – Intensity	SAF	U
Listing 16.2.10-4.5	Listing of C-SSRS (Adults) Data – Behaviour and Lethality	SAF	U
Bone Mineral Density			
Listing 16.2.10-5	Listing of Bone Mineral Density Data	SAF	U
Tanner Staging			
Listing 16.2.10-6	Listing of Tanner Staging Data	SAF	U