CLINICAL STUDY PROTOCOL

Protocol Number	IEDAT-03-2018
Study Title	**Open-label, Long-term, Extension Treatment using Intra-Erythrocyte Dexamethasone Sodium Phosphate in Patients with Ataxia Telangiectasia Who Participated in the IEDAT-02-2015 Study**
Short Study Title - Acronym	**OLE-IEDAT**
Phase	Phase III
EudraCT Number	**2018-000338-36**
IND Number	115929
Date of Protocol	Version 1.0: 25 January 2018, Final Version 2.0: 29 March 2018, Final Version 3.0: 30 April 2018, Final Version 4.0: 19 March 2019, Final Version 5.0: 29 April 2019, Final Version 6.0: 22 May 2020, Final Version 7.0: 01 December 2020, Final
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Trial Protocol Version	Version 7.0: 01 December 2020, Final

GCP Statement

This study will be performed in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments) and local legal and regulatory requirements.

1 SYNOPSIS

Title of the Study	Open-label, Long-term, Extension Treatment using Intra-Erythrocyte Dexamethasone Sodium Phosphate in Patients with Ataxia Telangiectasia Who Participated in the IEDAT-02-2015 Study.
Protocol Number	IEDAT-03-2018
Phase of Development	III
Center(s)/ Country(ies)	20-25 centers in North America, Europe, Africa, Asia and Australia
Planned Trial Period (first subject enrolled - last subject out)	First Subject In (FSI): 12 June 2018 Last Subject In (LSI): 3rd Quarter 2021
Study Objectives	**Primary Objective:** • To monitor and evaluate the long-term safety and tolerability of EDS-EP in AT patients. **Exploratory 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), and Clinical Global Impression of severity and change (CGI-S/C). **Secondary Objective:** • To evaluate the long-term effect of EDS-EP on health related Quality of Life (QoL; EQ-5D-5L scale).
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 contraindication to continuation of treatment, and provided informed consent. The study aims to collect information on the long-term safety and efficacy of the trial treatment. Moreover, patients who were discontinued from the ATTeST study during the COVID-19 pandemic will be eligible to receive the EryDex treatment in the context of the OLE-IEDAT study, in the absence of safety contraindications to continuation of the treatment, and subject to the provisions of the informed consent. Patients meeting all selection criteria will receive monthly infusions of EDS-EP (CCI [redacted]). If this dose of EDS-EP is not tolerated, the patient should be discontinued from the study. During the study, long-term efficacy assessments will be performed approximately every 6 months, while safety parameters will be assessed at each monthly visit. The ICARS, EQ-5D-5L and the CGI-C/S will be administered by a site rater. As a result of the COVID-19 pandemic, temporary changes to the protocol have been implemented. These changes are described in Appendix 13.

Planned Number of Patients	All patients enrolled in this study will have participated in Study IEDAT-02-2015, and there will be no *de novo* enrollment of new patients. It is estimated that a maximum of 150 patients from the prior study will enter this study.
Inclusion and Exclusion Criteria	**Inclusion Criteria** 1. Patient completed the double-blind period in the IEDAT-02-2015 trial and must have completed the final (Visit 15/Month 12) efficacy assessments of IEDAT-02-2015 or discontinued the study during the COVID-19 pandemic. 2. Patient tolerated the study medication, without any evidence of steroid adverse events, or treatment-related severe/ serious adverse events. 3. Body weight > 15 kg. 4. The patient and his/her parent/caregiver (if below the age of consent), or a legal representative, has provided written informed consent to participate. If consent is provided solely by the caregiver in accordance with local regulations, the patient must provide assent to participate in the study. 5. Patient does not present safety contraindication for continuation of treatment, as determined by the Principal Investigator (PI) according to the procedures described below. **Procedure for selecting patients for further treatment in IEDAT-03-2018** • The Principal Investigator will ask all patients who meet the above requirements, and determine their interest in continuing to receive treatment with the study medication in a new protocol. The Principal Investigator will then determine the eligibility of the patients on the basis of his/her clinical judgement of patients' status and their safety. **Exclusion Criteria** *General* 1. Females that are a. pregnant, or are breast-feeding (for EU countries only); b. of childbearing potential, pregnant, or are breast-feeding (for US and Rest of World countries). *Females of childbearing potential using adequate birth control, as determined by their Health Care Provider, will be eligible.* 2. A disability that may prevent the patient from completing all study requirements. 3. Current participation in a clinical study with another investigational drug. *Medical History and Current Status* 4. CD4+ lymphocytes count <400/mm3 (for patients 6 years of age) or <150/mm3 (for patients > 6 years). In presence of oral infections, like oral candidiasis, documented at the screening or recurrent as per medical history documentation, the limit increases to <200/mm3 (for patients > 6 years). 5. Current neoplastic disease. 6. Severe impairment of the immunological system. 7. Severe or unstable pulmonary disease. 8. Uncontrolled diabetes. *Patients with diabetes that has been stabilized (i.e. no hypoglycemic or hyperglycemic episodes in the past 3 months) will be eligible.* 9. Any other severe, unstable, or serious disease or condition that in the Investigator's opinion would put the patient at risk for imminent life-threatening morbidity, need for hospitalization, or mortality. 10. Eligibility of patients with abnormal laboratory test values will be determined by the Investigator. 11. Confirmed hemoglobinopathies, e.g. hemoglobin C disease, sickle cell

	anemia, or thalassemia. 12. Moderate or severe renal and/or hepatic impairment. 13. Patients who experienced moderate/ severe steroid side effects, or moderate/ severe adverse events associated with the study medication administered in the IEDAT-02 study. *Prior/Concomitant Medication* 14. Requires treatment with an oral or parenteral steroid. *Treatment with inhaled or intranasal steroids for asthma or allergies, as well as use of topical steroids will be permitted.* 15. Requires any other concomitant medication prohibited by the protocol. 16. Use of any drug that is a strong inducer/inhibitor of CYP3A4.
Schedule of Visits and Assessments: Baseline visit (Visit 1)	Final evaluations for IEDAT-02-2015 study (Visit 15/Month 12) will serve as baseline evaluations for patients continuing in IEDAT-03-2018 study. Patients providing informed consent or assent and meeting the eligibility criteria will receive study treatment prepared and administered as follows: • Vital signs • CCI [redacted] (see Section 11.5), CCI [redacted]. • CCI [redacted] • Addition of the assigned study medication (DSP) to the EDS process • CCI [redacted]

	CCI [redacted] Before the EDS-EP infusion, patients (women of childbearing potential) must undergo a urine pregnancy test. All patients should undergo assessment of prior and concomitant medication and AEs. After completion of the IV infusion of the study treatment, the following assessments will be performed on Day 1: • Vital signs • Physical examination • Assessment of AEs • Assessment of concomitant medications Applicable only for patients which will be enrolled without completing the ATTeST trial (i.e. who discontinued 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) After providing the informed consent or assent, as applicable, patients will enter the screening phase. The screening phase will last at maximum 30 days for those patients who are in treatments with other corticosteroid compounds (washout from previous treatment), while for other patients the screening phase will 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 the eligibility is confirmed, the patients can undergo the baseline visit as described at the beginning of this section. The following screening evaluations will be conducted: • Medical history and demographics • Physical examination • Vital signs (including height and weight in triplicate) • Neurological examination • Tanner staging of the breasts in pre-menarchal females and of the scrotum in males who have not completed puberty. Post-menarchal females and males who have completed puberty will be excluded from this growth analysis. • ICARS (administered by the qualified site-specific rater). • CGI-S • 12-lead standard Electrocardiogram (ECG) • Routine laboratory tests, on the diverted blood sample (see Section 11.5) • Special laboratory tests: HbA1c, CD4+ lymphocytes count, and CRP, on the diverted blood sample (see Section 11.5) • Serum pregnancy test (women of childbearing potential), on the diverted blood sample (see Section 11.5) • BMD • CSSRS • EQ-5D-5L • Blood collected to assess RBC osmotic resistance (in selected centers) • Plasma cortisol – sample to be collected before 8:00 AM. If the basal cortisol level is within the reference normal range, the patient can be enrolled in the study. If the 8:00 AM cortisol level is below 3-5 µg/dL

	(depending on assay) regardless of symptoms, or the patient exhibits signs or symptoms of adrenal insufficiency (see Appendix 12) and has a cortisol <10 µg/dL, the patient will receive a high dose ACTH stimulation test, regardless of weight, within 24 hours. If the ACTH stimulation test is normal, the patient can be enrolled after the effects of the ACTH have dissipated (e.g., 30 days after ACTH administered). If the patient fails the ACTH stimulation test they will be excluded from the study and referred to a pediatric endocrinologist, with a recommendation to prescribe stress dose steroids. • Assessment of prior and concomitant medications • Assessment of AEs 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. Adverse events, reported by the patient or observed by the investigator, and the use of concomitant medication will be recorded from the time of signing of informed consent through the end of the study.
Schedule of Visits and Assessments: Months 1-5 and 7-11	At Months 1-5 and 7-11, the following assessments will be performed: • Vital signs • Laboratory tests: serum creatinine, on the diverted blood sample (see Section 11.5) • Routine laboratory tests, on the diverted blood sample (see Section 11.5) • Urine pregnancy test will be performed before every infusion (for women of childbearing potential) • C-SSRS • Assessment of prior and concomitant medication • Assessment of AEs • CCI [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • **Study treatment administration by IV infusion, within 30 min after the EDS process has been completed.** • CCI [redacted] • [redacted]

	CCI • After completion of the IV infusion of the study treatment the following assessments will be performed: o Physical examination and vital signs 1-2 hr after the end of infusion; o Assessment of AEs and concomitant medications.
Schedule of Visits and Assessments: Months 6 and 12	At Months 6 and 12 the following assessments will be performed before treatment administration (unless specified otherwise): • Physical examination • Vital signs • Neurological examinations • ICARS • CGI-S and CGI-C • EQ-5D-5L • C-SSRS • BMD • 12-lead standard ECG • Routine laboratory tests, on the diverted blood sample (see Section 11.5) • Special laboratory tests: HbA1c, CD4+ lymphocytes count, and CRP, on the diverted blood sample (see Section 11.5) • Serum pregnancy test (women of childbearing potential), on the diverted blood sample (see Section 11.5) • Urine pregnancy test will be performed before every infusion for women of childbearing potential. • Assessment of physical development, sexual maturation, and the effect of treatment with dexamethasone on these aspects. Tanner staging of the breasts in pre-menarchal females and of the scrotum in males who have not completed puberty, will be performed at Months 6 and 12. Post-menarchal females and males who have completed puberty will be excluded from this growth analysis. • Assessment of concomitant medications • Assessment of AEs • CCI • **Study treatment administration by IV infusion, within 30 min after the EDS process has been completed.** • CCI

	CCI • After completion of the IV infusion of the study treatment the following assessments will be performed: o Physical examination and vital signs 1-2 hr after infusion; o Assessment of concomitant medications; o Assessment of AEs. The schedule of visits and assessments for the first 12 months - as described above- will be replicated for the second year onwards, if patients continue treatment for more than 12 months. *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, pregnancy status (for women of childbearing potential), 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.
Investigational Medicinal Product(s): dose, mode of administration, and dosing schedule	The study treatment consists of a CCI dexamethasone sodium phosphate (DSP) administered via *ex vivo* encapsulation into autologous erythrocytes (EDS) that are infused into the patient with AT. The dose of EDS-EP has been selected to allow collection of long-term safey data on a high dose. However, if this dose is associated with significant tolerability issues that do not resolve, then the patient should be discontinued from the study. Autologous whole blood CCI to be used for the EDS process will be collected according to the instructions provided in Section 11.5. Details of these procedures are described in a separate document entitled "Study Procedures on Sterility Testing for Study IEDAT-03-2018 (OLE-IEDAT)", which will be provided to each site (see Appendix 9). The study medication will be prepared with a CCI Study treatment will be administered by monthly IV infusion. CCI

Planned Treatment Duration per Patient	The open-label treatment period is planned for 12 months, but may be extended further and continue until patients eventually withdraw consent or the Investigator decides to discontinue treatment based on a risk/ benefit assessment.
Statistical Methods	Descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum) will be provided for all continuous efficacy measures for actual values and changes from baseline of Study IEDAT-03-2018 at each time-point. For categorical variables, the number and percentage of patients in each category will be presented at each time-point. The analysis of long-term efficacy of EDS-EP is an exploratory objective of this extension study, and will be based on the results for the "Modified" International Cooperative Ataxia Rating Scale (mICARS), and the Clinical Global Impression of severity and change (CGI-S/C). The mean (SD) change from baseline at each time-point will be evaluated for the mICARS and the CGI-S. 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. 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. As a secondary objective, similar descriptive analyses will be performed to evaluate the long-term effects of EDS-EP on health-related Quality of Life (QoL), as assessed by the EQ-5D-5L scale. Descriptive statistical analyses of changes from baseline will be performed for all safety parameters. Abnormal and clinically notable values will be identified and listed for each parameter, as appropriate.
Analysis Populations	The following analysis sets will be used: 1) *Efficacy Population (EP)*: 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 primary efficacy variable in this extension study. 2) *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.

Schedule of Visits and Assessments: 1st year of open-label extension treatment (Visit 1 to Visit 13 to be replicated for the second year onwards)

Visit (V)	Screening Phase *	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 who will be enrolled without completing the ATTeST trial (i.e. which 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 bagor, 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)"; 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 sterile sample of the EDS-EP will bestored 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 Appendix 13.

(pre) Pre EDS-EP infusion procedure

(post) Post EDS-EP infusion procedure

2 SIGNATURE PAGE

Study Title:	Open-label, Long-term, Extension Treatment using Intra-Erythrocyte Dexamethasone Sodium Phosphate in Patients with Ataxia Telangiectasia Who Participated in the IEDAT-02-2015 Study
Study Code:	IEDAT-03-2018
Protocol Version/Date:	Version 1.0: 25 January 2018, Final Version 2.0 (including Amendment 1): 29 March 2018, Final Version 3.0 (including Amendment 2): 30 April 2018, Final Version 4.0 (including Amendment 3): 19 March 2019, Final Version 5.0 (including Amendment 4): 29 April 2019, Final Version 6.0 (including Amendment 5): 22 May 2020, Final Version 7.0 (including Amendment 6): 01 December 2020, Final
Number of Centers:	20-25

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Date of Signature (dd / mm / yyyy)

Sponsor Representative

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Email: PPD

I have read this protocol and I approve the design of the trial.

PPD 18 DEC 2020
Sign *Date of Signature (dd / mm / yyyy)*

Signature Pages (cont'd)

Investigator

Center No. _____

I agree to conduct the clinical trial in accordance with this Protocol and in compliance with Good Clinical Practice and all applicable regulatory requirements.

_____ _____
Investigator's Name (Printed) *Title*

_____ _____
Signature *Date of Signature (dd / mm / yyyy)*

Clinical Research Organization

PPD

Italy

The Sponsor has transferred all responsibilities for the conduct of the trial to the CRO or other designated vendors for specific services.

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4 ABBREVIATIONS AND DEFINITIONS OF TERMS

ACTH	Adrenocorticotropic hormone
AEs	Adverse Events
ALT (SGPT)	Alanine-aminotransferase
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
AST (SGOT)	Aspartic-aminotransferase
AT	Ataxia Telangiectasia
ATM	Ataxia Telangiectasia Mutated
ATP	Adenosine triphosphate
AUC	Area under the plasma drug concentration vs. time curve
BARS	Brief Ataxia Rating Scale
BMD	Bone mineral density
BMI	Body Mass Index
BP	Blood Pressure
bpm	Beats per minute
BUN	Blood Urea Nitrogen
CBC	Complete blood count
CD4+ lymphocytes	Cluster differential 4 positive lymphocytes
CGI-S / CGI-C	Clinical Global Impression of Severity / Change
CF	Cystic fibrosis
C_{max}	Maximum plasma drug concentration after dosing
CNS	Central Nervous System
COPD	Chronic obstructive pulmonary disease
CPK	Creatine phosphokinase
^{51}Cr	Chromium-51
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-Reactive Protein
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical Study Report
CV	Coefficient of variation
CYP3A4	Cytochrome P450 3A4
D	Day
2,3-DPG	2,3-Diphosphoglyceric acid
DSP	Dexamethasone sodium phosphate
ECG	Electrocardiogram
EDS	EryDex System
EDS-EP	EryDex System end product
EIA	Enzyme immunoassay
EP	Evaluable Population
EQ-5D-3L	EuroQol 5D Three-level version
EQ-5D-5L	EuroQol 5D Five-level version
ESI-MS	Electrospray mass spectrometry
FAS	Full Analysis Set

FSI	First Subject In
FWER	Family-wise error rate
G6PD	Glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
SGOT (AST)	Serum Glutamic-Oxaloacetic Transaminase
SGPT (ALT)	Serum Glutamic-Pyruvic Transaminase
HbA1c	Blood glycosylated haemoglobin
Hct	Hematocrit
HDL	High density lipoprotein
Hb	Hemoglobin
HbA1c	Blood glycosylated hemoglobin
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
hr	Hour
IBD	Inflammatory bowel disease
ICARS	International Cooperative Ataxia Rating Scale
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICSH	International Committee for Standardization in Hematology
IEC	Independent Ethics Committee
IMP	Investigation Medicinal Product
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intention-to-Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
IU	International Unit
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LOCF	Last observation carried forward
LSI	Last Subject In
LSLV	Last Subject Last Visit
M	Month
MAO	Monoamine oxidase
MAR	Missing at random
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
µCi	Microcuries
mCi	Millicuries
min	Minute
mmHg	Millimeters of mercury (blood pressure)
MMRM	Mixed Model Repeated Measures
mICARS	Modified version of the International Cooperative Ataxia Rating Scale excluding oculomotor items (17-19) and items 8-12
NSAID	Non-steroidal anti-inflammatory drug

OC	Observed cases
OTC	Over-the-counter
pBAR	Probabilistic baseline randomization
PK	Pharmacokinetic(s)
RBCs	Red Blood Cells
RCL	Red Cell Loader
RDW	Red blood cell distribution width
RMANOVA	Repeated Measures Analysis of Variance
RT	Room Temperature
SAEs	Serious Adverse Events
SARA	Scale for Assessment of Rating of Ataxia
SD	Standard Deviation
SNRI	Serotonin-norepinephrine reuptake inhibitor
SOPs	Standard Operating Procedures
SP	Safety Population
SSRI	Selective serotonin reuptake inhibitor
$t_{1/2}$	Half-life
T50	Time to disappearance of 50% of the labelled red blood cells from the circulation
^{99m}Tc	Technetium-99m
TCA	Tricyclic antidepressant
TEAEs	Treatment Emergent Adverse Events
t_{max}	Time to maximum plasma concentration after dosing
ULN	Upper limit of normal
WBC	White Blood Cells

5 TITLE OF STUDY

Open-label, Long-term, Extension Treatment using Intra-Erythrocyte Dexamethasone Sodium Phosphate in Patients with Ataxia Telangiectasia Who Participated in the IEDAT-02-2015 Study.

6 PROTOCOL NUMBER

This study is being conducted under Protocol No. IEDAT-03-2018.

7 BACKGROUND AND STUDY RATIONALE

7.1 Background Information

7.1.1 *Overview of the CCI System (EDS)*

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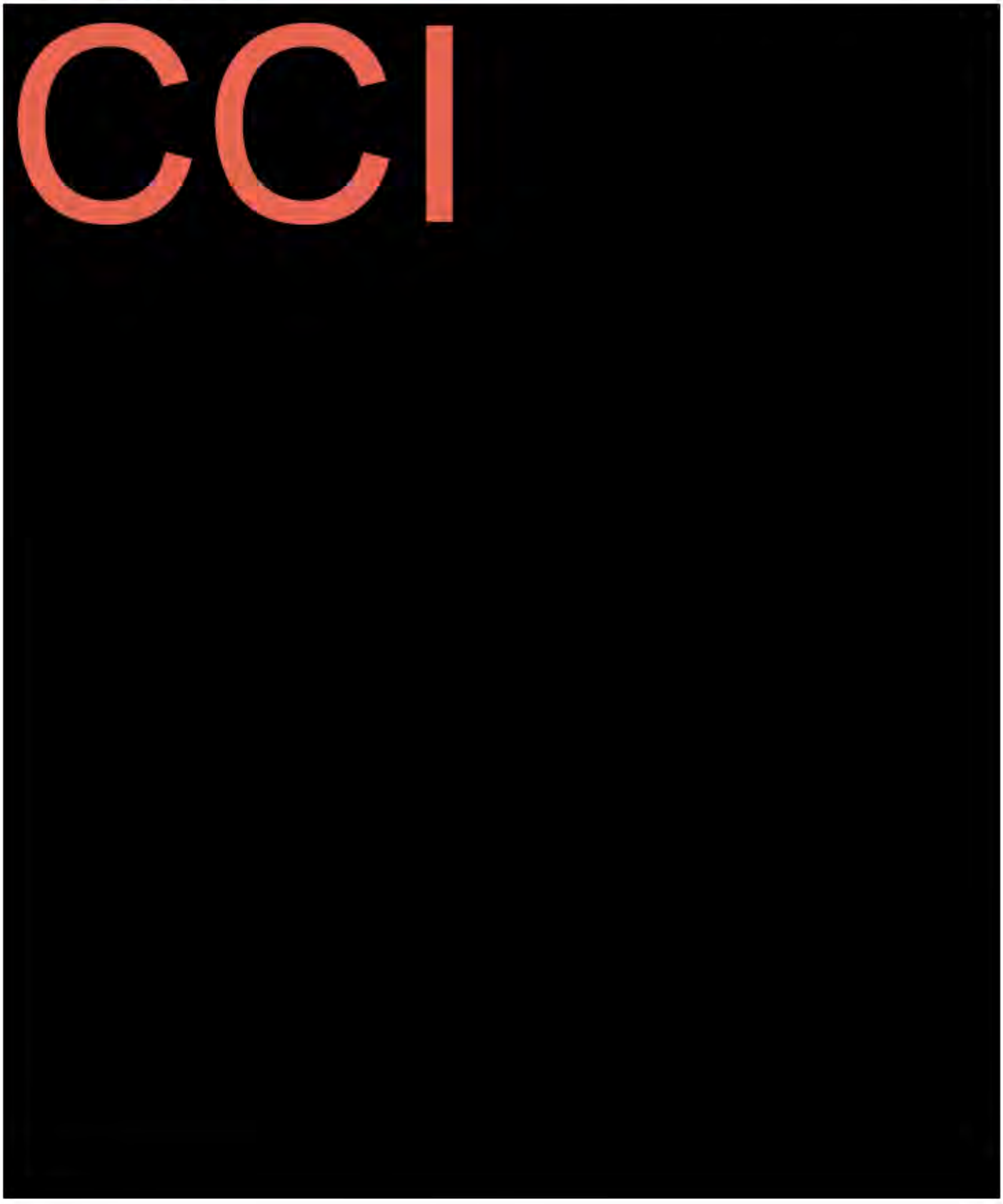
7.1.2 *Non-Clinical Trials with EDS*

Pharmacokinetics is the only characteristic of the drug product (dexamethasone sodium phosphate; DSP) pharmacology that differs from that obtained with the ordinary routes of administration (oral, intravenous, intramuscular, etc.) due to the novel method of administration by *ex vivo* encapsulation of the drug into human autologous red blood cells which are then infused. The pharmacokinetics of the drug product in humans was evaluated in clinical trials. It is not possible to study the pharmacokinetics in animal models because the dephosphorylation rate of the pro-drug, DSP, to the diffusible active drug, dexamethasone, in human RBCs is very different from RBC dephosphorylation rates in other species (Zocchi et al. 1991).

7.1.3 *Summary of Human Clinical Trials with EDS*

A total of 209 subjects have received at least one dose of EDS-EP. Of these, 115 participated in Investigator-initiated and 89 in Sponsor-initiated studies. A total of 1827 EDS-EP infusions have been administered; 366 of these infusions were performed in the 89 patients enrolled in Sponsor-initiated studies. Twenty-two patients with AT were administered 344 EDS-EP infusions in a phase II study (IEDAT-01-2010) and in subsequent compassionate use.

Table 1 below lists the trials performed to date, the indication, the number of subjects, the doses administered, the treatment duration, and key safety findings.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A total of 1827 EDS-EP infusions of EDS-EP have been administered to the subjects in the completed studies, and no toxicity related to RBCs processed for dexamethasone dosing has been observed. These include 51 pediatric patients (< 18 years) suffering from cystic fibrosis (n=11), Crohn's disease (n=19) or AT (n=22, one patient was 19 years of age at inclusion); some of these patients have been exposed to EDS for up 36 months. There was no consistent pattern of dexamethasone-related adverse findings reported in these pediatric populations.

Additional detailed information on pre-clinical and clinical studies evaluating the EDS can be found in the current version of the Investigator's Brochure.

7.1.3.1 Clinical Study IEDAT-ERY01-2010: Pilot Proof of Concept Phase II Trial in Patients with Ataxia Telangiectasia [Chessa et al, 2014]

Title: Evaluation of Effects of **I**ntra-**E**rythrocyte **D**examethasone Sodium Phosphate on Neurological Symptoms in **A**taxia-**T**elangiectasia Patients

Study Design and Patient Population

This was a single-arm, open-label, 6-month, Phase II study to assess the effect of the EryDex System end product (EDS-EP; dexamethasone sodium phosphate [DSP] encapsulated in autologous erythrocytes by the EDS process) on neurological symptoms of patients with Ataxia Telangiectasia (AT) enrolled in two centers in Italy. Males and females, > 3 years of age, with neurological signs of AT (un-coordination of the head and eyes in lateral gaze deflection, gait ataxia associated with an inappropriately narrow base), an autonomous gait (or helped by support), and a genetic diagnosis of AT (at least one ATM mutation) and/or ATM protein deficiency by Western blot, were included. Patients with low CD4+ lymphocytes counts, current/previous neoplastic disease, history of severe impairment of the immunological system, chronic conditions representing a contraindication to the use of steroid drugs, or any other significant disease that could have put the patient at risk were excluded. Females of childbearing potential that were pregnant, breastfeeding or not using adequate contraception were also excluded. Eligible patients could not have participated in a trial with another investigational agent within 30 days of the start of the Screening Period, and must have discontinued prior steroid medication at least 30 days before the first dose of EDS-EP.

Objectives

The primary objective of the trial was to evaluate the effect of EDS-EP in improving neurological symptoms of AT patients over a 6-month treatment period, assessed by means of the ICARS (Trouillas et al., 1997). The ICARS is a 100-point semi-quantitative scale offering a compartmentalized quantification of the following 4 sub-scores: Posture and gait disturbances, kinetic functions, speech disorders, and oculomotor disorders. The ICARS rating was performed by a trained neurologist at baseline (before the first dose) and at 1, 3 and 6 months after the first EDS-EP administration; analysis of the change from baseline at each visit was performed on the ITT population using Repeated Measures Analysis of Variance (RMANOVA). Secondary objectives of the trial were to evaluate the safety profile of EDS-EP through the assessment of TEAEs, including steroid-dependent adverse reactions, SAEs, standard laboratory parameters, physical examination, vital signs, ECGs and concomitant medications and procedures. Additionally, the effects of EDS-EP were assessed on the patients' global health status (IGA), ocular motility, and adaptive behaviour (VABS). The effect of EDS-EP on special laboratory parameters, i.e. total cholesterol, HDL, LDL, blood glycosylated hemoglobin (HbA1c), $CD4^+$ lymphocytes counts, α-fetoprotein, urinary cortisol and plasma cortisol, was also measured.

Methods

Patients providing informed consent (along with consent of their parents or legal guardian, as required) entered a 30-day screening period, during which any prior corticosteroid treatment was withdrawn. Medical history and demographic information was collected, and physical and neurological examinations, vital signs, ECG and standard laboratory tests were performed. Patients meeting all selection criteria were enrolled in the treatment period and CCI [redacted]

A physical examination, vital signs and routine laboratory tests were performed at each monthly visit. The primary efficacy measure (ICARS) was assessed at one month, and at the 3-month visit, all efficacy assessments were done, along with the special laboratory tests (before drug infusion). A final evaluation was performed at 6 months after the initial infusion (one month after the last dose), during which all efficacy and safety assessments were performed. The occurrence of any AEs and the use of concomitant medication were recorded from the time of signing of the consent form until the end of the study. Blood samples for the PK analysis were collected from selected patients prior to dosing (0 hr), and at 4 hours and 15 and 30 days post-dose for the first and fourth infusions.

Disposition

A total of 26 patients with AT were screened and 22 were enrolled in the study, representing the ITT population. Four subjects discontinued prematurely; one withdrew consent, another patient was dropped due to a protocol violation (CD+4 lymphocytes below cut-off at baseline), and 2 patients experienced laboratory abnormalities (decrease in CD4+ lymphocytes count) that led to their withdrawal.

Demographics and Disease Characteristics

The mean (SD) age of the AT patients was 11.2 (3.5) years, with 11 (50%) patients being males. All patients were Caucasian with a mean weight of 29.1 (9.5) kg and BMI of 15.6 (2.6). The average age of diagnosis of AT was 60.0 (35.2) months, with a mean age of symptom onset of 25.9 (17.5) months. The mean baseline scores for the ICARS and VABS were 50.6 (12.8) and 5.5 (2.0), respectively. Mean baseline scores on the sub-scales of the ICARS were as follows: posture/gait disturbance – 20.9 (7.1); kinetic function – 23.1 (6.2); speech disorders – 3.5 (1.4); and oculomotor disorders – 3.2 (1.0). Two patients were on inhalational steroids at screening, and these medications were discontinued.

Efficacy Results

Sixteen patients (72.7%) received all 6 infusions of EDS-EP, as planned. Results for the primary efficacy measure (change from total baseline ICARS score) for the ITT population (n=22) indicated an overall statistically significant (p=0.02, RMANOVA) improvement with EDS-EP treatment. Significant improvement was observed after 3 and 6 months of treatment with EDS-EP for the kinetic sub-score of the ICARS, the clinician rated the Investigator Global Assessment (IGA), adaptive behavior (as assessed by the VABS) and ocular motility.

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Safety Results

The safety population included all 22 patients. Overall, 15 (68.2%) of patients experienced at total of 29 TEAEs, most of which were rated as mild (~60% of subjects) and not related to the study medication (> 90% of patients), with the exception of 1 patient with a mild hypercholesterolemia. Two SAEs were reported during the study, including one case of severe pneumonia and a second patient with bronchopneumonia, and bronchiectasis and bleeding; both patients required hospitalisation. Both cases were considered unrelated to study medication and resolved with treatment.

Two patients had a > 20% decrease in CD4+ lymphocytes count during the study period which resulted in premature discontinuation, and were considered related to study medication.

There were no clinically meaningful changes in mean values for routine laboratory parameters with EDS-EP treatment, except for serum iron, which showed a > 20% mean decrease from baseline value, with 8 patients having newly occurring abnormal (low) values at the final visit (one reported as a TEAE). For the special laboratory parameters, no clinically meaningful changes were observed, except for urinary cortisol, which showed an approximately 30% decrease from baseline to the final visit (statistically significant, p=0.016). Although this could indicate an effect of EDS-EP on the hypothalamo-pituitary-adrenal axis, a comparison of blood and urinary cortisol levels versus dose did not indicate any relationship. No clinically significant changes with EDS-EP treatment were observed for vital signs, ECGs, or physical examination findings.

Conclusions

In this open-label study in AT patients > 3 years of age, EDS-EP treatment for 6 months led to a statistically significant improvement in the primary efficacy measure, the ICARS, which assesses key symptoms of the disease. Additional statistically significant benefits of EDS treatment were noted in the Kinetic Function sub-scale of the ICARS, IGA, adaptive behavior (VABS), and ocular motility (ad hoc scale). EDS-EP was generally well tolerated in this subject population, with only two patients discontinuing prematurely due to adverse events. Two patients experienced serious adverse events related to pulmonary infections; most AEs were mild in intensity and considered unrelated to study medication.

Laboratory findings indicated a low serum iron levels in approximately one third of patients and a mean reduction in urinary cortisol, which did not appear to be related to the dose administered.

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Pilot observation that higher DSP load appears to be associated with improved response of the ICARS has led the Sponsor to target higher DSP doses in future efficacy studies.

7.1.3.2 Clinical Study IED-PK01-2013

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Pharmacokinetic Results

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Safety Results

Adverse events. There were no SAEs, or discontinuations due to AEs in either group. Five of 9 (55.6%) subjects in Group 1 reported a total of 5 TEAEs, all of mild intensity. In Group 2, 5 subjects (55.6%) reported a total of 6 TEAEs, 4 of mild and 3 of moderate intensity. Two subjects had TEAEs that required drug treatment, one with abdominal discomfort (treated with an antacid) and the other with gastrointestinal pain (treated with anti-gas agent) and gingival pain (treated with analgesics). All of the TEAEs resolved without any sequelae. No Group 1 subjects received a concomitant medication during the study and only two Group 2 subjects received one or more concomitant medications for their TEAEs (abdominal discomfort, gingival pain, and gastrointestinal pain).

Standard laboratory tests. A number of small but statistically significant transient changes in hematological (absolute eosinophils, hematocrit, hemoglobin, lymphocytes, monocytes, RBC count, MCH, neutrophils, platelet, and WBC count) and biochemical (AST, creatine phosphokinase, CO_2, creatinine, glucose, cholesterol, potassium, sodium, LDH, HDL and BUN) parameters associated with DSP administration were observed. Sporadic abnormal values (high/low) were noted for some of the laboratory hematology and biochemistry parameters at Day 2 and/or the final visit (Day 42); however, none of these were considered to be clinically significant. No meaningful changes from baseline were observed in any urinalysis parameter throughout the study. Both increases and decreases compared to baseline were observed for laboratory analytes in Groups 1 and 2, without any consistent pattern of change.

Other laboratory tests. Serum cortisol levels were significantly reduced up to the 48-hour time point in Group 1, while in Group 2 a significant decrease in serum cortisol levels was observed through the 7-day time point and at Day 42, but not at Day 14. Urinary cortisol showed no significant reduction at any time point.

All 9 patients in each of the treatment groups had normal RBC osmotic resistance values at NaCl concentrations from 0.55% up to 0.85% on Day 1 before the EDS process. The majority of the patients had normal RBC osmotic resistance values at NaCl concentrations between 0.30% and 0.50%; however, 4 patients (2 in Group I and 2 in Group II) showed a pattern of decreased lysis while one subject had a pattern of borderline increase. Results for RBC osmotic resistance for the sample taken from the infusion bag, following the EDS process, confirmed a pattern of decreased lysis at the 0.40%-0.50% concentration range in 3 (1 in Group I and 2 in Group II) out of 4 patients that had this pattern before the procedure. All other patients exhibited RBC osmotic fragility within the normal range.

Free hemoglobin values were above normal (high) on Day 1 (prior to infusion) in 4 of 9 patients in Group 1 and in 6 of 9 patients in Group 2. The mean value for free hemoglobin before infusion in the 9 patients in Group 1 was 6.79 mg/dL (median 5.30 mg/dL) with a maximum subject value of 12.60 mg/dL, and the mean value for the 9 patients in Group 2 was 23.62 mg/dL (median 16.20 mg/dL) with a maximum subject value of 76.00 mg/dL. Free hemoglobin was detected sporadically also after infusion during this trial.

Analysis of plasma samples (taken for PK determination) indicated the presence of free hemoglobin in samples at baseline prior to the EDS end product infusion. The presence of free plasma hemoglobin may have resulted from the blood drawing technique used to collect the samples (e.g., use of IV catheter with a 22-gauge needle). Analysis of urine samples for hemoglobin, bilirubin, urobilinogen, urine clarity and color did not detect any pattern suggestive of hemoglobinuria or associated findings in any subject.

Other safety parameters. Abnormalities in vital signs that were reported as TEAEs included a mild increase in diastolic blood pressure (DBP) on the day of study drug infusion, two reports of mild 'orthostatic tachycardia' on the day of dosing, and mildly rapid heartbeat/palpitations; all resolved without sequelae. Small statistically significant mean changes ($p < 0.05$) were observed for systolic blood pressure, diastolic blood pressure and pulse rate, primarily at early time-points (Days 2 and 3), in both groups, but did not indicate any pattern of adverse change. No statistically significant mean changes from Baseline were observed at any time point for supine respiratory rate, body temperature measures or body weight.

The overall interpretation of the ECG did not indicate any adverse cardiac effects of EDS-EP treatment, as no newly occurring abnormalities were observed post-baseline. In addition, no statistically significant changes in any ECG parameter were noted at Day 42. One physical examination finding was reported (Day 42) as a TEAE (mild severity right eye upper lid inflammation that was not considered to be clinically significant by the Investigator), and one subject had a new abnormality in reflexes reported on the neurological examination (Day 42).

7.1.3.3 Clinical Study Ery51Cr-01-2014

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Results

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Summary of Safety Data

No consistent pattern of changes of a magnitude that led to values that were abnormal, or were deemed clinically notable, was detected in subjects receiving EDS-processed erythrocytes containing DSP or saline for measures evaluating a pre-specified hemolysis panel of tests, or other routine laboratory hematology, biochemistry, and urinalysis parameters. Similarly, there was no evidence of a systematic effect on vital signs, weight, or ECGs, and no pattern of adverse events was detected with the trial treatments. There were no discontinuations due to AEs, serious adverse events (SAE), or AEs rated severe or unexpected.

7.1.3.4 Clinical Study IEDAT-02-2015

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

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The initial treatment period will be considered complete when the endpoint assessment (at Visit 9or at early discontinuation) has been performed for all patients. Patients who are not experiencing severe side-effects, and have not deteriorated significantly while on the treatment, and provide informed consent will be eligible to continue treatment for an additional 6 months in a double-blind, placebo-controlled extension treatment period. Patients meeting all entry criteria will be treated as follows:

- Patients originally randomized to EDS-EP treatment groups (Group 1 or Group 2) will continue on the same treatment;
- Patients originally randomized to the Placebo group (Group 3) will be re-randomized in equal proportions (1:1) to receive either the CCI DSP/infusion or ~CCI DSP/infusion, as follows:
    - Following the initial (approximately) 6 months of treatment, one third of the originally randomized placebo patients will be re-randomized to treatment with EDS-EP, as described above;
    - After (approximately) 9 months of treatment, one third of the originally randomized placebo patients will be re-randomized to treatment with EDS-EP, as described above;
    - At (approximately) 12 months, all remaining placebo patients who continue open-label treatment will receive treatment with EDS-EP, as described above.

A minimum of 180 patients meeting all selection criteria will be enrolled and randomized to one of the 3 treatment groups (approximately 60 patients per group).

The objectives of the Study are the following:

Initial Treatment Period

Primary Efficacy Objective:

- To evaluate the effect of twoCCI end product [EDS-EP; the EDS is a combination product that is used to load dexamethasone sodium phosphate (DSP) into autologous erythrocytes, creating the EDS end product, which is infused into the patient], compared to placebo, on central nervous system (CNS) symptoms measured by the 'Modified' International Cooperative Ataxia Rating Scale (mICARS) in patients with ataxia telangiectasia (AT).

Key Secondary Efficacy Objective:

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

Safety Objective:

- To evaluate the safety and tolerability of EDS-EP compared to placebo in AT patients, 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 Efficacy Objectives:

- To evaluate the effect of EDS-EP, compared to placebo, in this population on the following efficacy measures:
  - Clinical Global Impression of Severity (CGI-S) of neurological symptoms of AT;
  - Adaptive behavior measured by the Vineland Adaptive Behavior Scales (VABS);

Tertiary Objectives:

- To evaluate the effect of EDS-EP on health-related Quality of Life (QoL) using the EQ-5D-5L scale;
- To assess the pharmacokinetic and pharmacodynamic relationships between dexamethasone administered through EDS-EP and safety, tolerability, and demographic variables.
- To evaluate the pharmacokinetic (PK) profile of dexamethasone administered through EDS-EP at two dose levels based on pooled data from all patients in each treatment group.

A determination of individual PK parameters will be performed for patients with an adequate number of PK blood samples after the initial infusion.

Exploratory Objective:

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

Extension Treatment Period

Primary Objective:

- To evaluate the efficacy of two dose ranges CCI compared to placebo in treating CNS symptoms in AT patients during long-term treatment (up to 12 months), as measured by the 'Modified' ICARS.

Secondary Objectives:

- To evaluate the long-term (up to 12 months) safety and tolerability of EDS-EP in AT patients;
- To compare the effects of the two dose ranges of EDS-EP on the clinician's global impression (CGI-C and CGI-S), adaptive behavior (VABS), and QoL (EQ-5D-5L scale).

Results

The study is ongoing at the time of the finalization of the IEDAT-03-2018 Study Protocol, so no data are currently available. At the time of the finalization of the IEDAT-03-2018 Study Protocol Version 1.0, 131 adverse events occurred in 55 randomized patients, and 3 of these have been reported as SAEs. At the time of the finalization of the IEDAT-03-2018 Study Protocol Version 1.0, the Data Safety Monitoring Board didn't express any concern and the outcome of the DSMB review of the ongoing data was to continue the trial without modification.

7.2 Drug Product and Delivery System

Generic Name

Drug: Dexamethasone sodium phosphate solution (CCI), referred to as DSP Solution
Process Solutions: Hypertonic/hypotonic sterile solutions
Devices: Blood processing equipment and kit of single use sterile disposable device accessories

Proprietary Name

Drug: Not determined (a proprietary name for dexamethasone sodium phosphate solution CCI has not yet been proposed)
Process Solutions: PIGPA Hypertonic Solution, Hypotonic Solution 1, and Hypotonic Solution 2
Devices: Red Cell Loader and EryKit_01

The CCI System (EDS)

The CCI 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.

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7.3 Study Rationale

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 contraindication to continuation of treatment, and provided informed consent. The study aims at collecting information on the long-term safety and efficacy of the trial treatment.

The study aims to collect information on the long-term safety and efficacy of EDS-EP treatment in patients who have completed the full treatment period in the IEDAT-02-2015 study.

Rationale for Using the EDS in Treating AT Patients

AT is considered a *rare disease* by the Office of Rare Diseases of the National Institutes of Health (US), as well as by *Orphanet*, the consortium of European partners. There is no marketed drug approved to treat AT, and there is no treatment available that slows down or stops the progression of AT patients to early debilitating disability and mortality. Symptomatic, preventive, and supportive management of the key disabilities and symptoms of the disease has provided limited benefit. Immune deficiencies are managed by administration of immunoglobulins, and infections are managed by both preventive and symptomatic use of antibiotics. Developmental deficiencies are managed by physical therapies, education, or targeted treatments (Hoche et al, 2012).

Neurological degeneration is the major contributor to the severe outcome of the disease. The progression of the neurologic problems is currently unstoppable. Anti-parkinson and antiepileptic drugs provide limited benefit in the management of extrapyramidal symptoms. The serendipitous discovery of the benefit of short-term betamethasone in a patient with AT (Buoni et al, 2006), and further pilot, uncontrolled, short–term treatment trials in small numbers of patients have suggested that betamethasone at doses of 0.03 mg/kg, but not 0.01 mg/kg, given for a short period has beneficial effects on the neurological impairment of AT patients (Russo et al, 2009; Broccoletti et al, 2008). Treatment discontinuation in these studies was accompanied by the reappearance of symptoms, suggesting that long-term administration may be required to preserve the benefit.

These early findings with administration of betamethasone prompted the search for steroids that could be given at low plasma concentrations for an extended period of time without the associated steroid-like effects. The EDS, consisting of dexamethasone sodium phosphate (DSP) encapsulated in autologous erythrocytes, allows the administration of dexamethasone at low plasma concentrations that are associated with approximately 80-85% occupation of the glucocorticoid receptor (GR), similar to the GR occupancy that occurs with the betamethasone plasma concentrations reported by Broccoletti et al, 2011. The EDS provides the benefit of low and constant plasma delivery of dexamethasone without the associated steroid

side effects, despite long-term use in the pediatric population (Rossi et al, 2001; Lucidi et al, 2006; Annese et al, 2005; Bossa et al, 2008; Castro et al, 2007).

The mechanism of action of glucocorticoids in producing the benefits observed in A-T patients was postulated to occur through regulation of expression of corticosteroid-responsive genes, suppression of inflammatory cytokines, or its effect as an antioxidant (Russo L. et al., 2009). Recently, an effect of dexamethasone on ATM (Ataxia Telangiectasia Mutated) gene splicing in an AT lymphoblastoid cell line, leading to production of a new active ATM protein variant, has been demonstrated (Menotta M. et al., 2012). This may explain in part the beneficial effect of treatment with glucocorticoid analogues in AT patients. The results show, for the first time in mammalian cells, a short direct repeat-mediated non-canonical splicing event induced by dexamethasone that leads to the skipping of mutations upstream of nucleotide residue 8450 of *ATM* Coding DNA Sequence (CDS).

A pilot, open-label, 6-month study was performed with EDS-EP in AT patients (Chessa et al, 2014). In this study, statistically significant (p=0.02; RMANOVA) improvement (reduction) in the ICARS score from baseline to endpoint (~4 points; ITT population; n=22) was observed. The decision to initiate the ongoing IEDAT-02-2015 double-blind, placebo-controlled study in AT patients was based on the results from the above mentioned pilot study, as well as the other evidences of the benefit of steroids in treating the disease, as described above.

Rationale for the Patient Population

Only patients who participated in the IEDAT-02-2015 trial and meet the following selection criteria will be eligible for this trial: completed the full treatment period in the IEDAT-02-2015 trial, completed the study assessments, do not present safety contraindications to continuation of treatment, and provided informed consent. During the COVID-19 pandemic, some patients had to be discontinued from the IEDAT-02-2015 trial; for this reason, the eiligibility 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 contraindication to continuation of treatment, and provision of informed consent.

Procedure for selecting patients for further treatment

The Principal Investigator will ask all patients who meet the above requirements, and determine their interest in continuing to receive treatment with the study medication in a new protocol.

The Principal Investigator will then determine the eligibility of the patients on the basis of his/her clinical judgement of patients' status and their safety.

A brief description of the important features of AT is provided prior to discussing the selection criteria.

Ataxia telangiectasia (AT) is a rare inherited autosomal recessive, multisystem disorder, characterized by the following: progressive neurologic disease, including cerebellar ataxia and oculomotor apraxia; cutaneous and ocular telangiectasia (90%); increased alpha-feto-protein levels (95%); reduced or absent IgA levels (70%) and ATM protein (98%); increased susceptibility to chronic nasal and pulmonary infections (70%); delayed organ maturation; and increased susceptibility to X-rays and malignancies (Hoche et al, 2012). In countries where marriage between cousins is uncommon, such as in the U.S., the incidence of AT is about 1 in 40,000 live births. However, among ethnic groups where cousin-cousin marriages are common, the incidence increases significantly. The carrier frequency is approximately 1 in 100 persons (https://www.ataxia.org/pdf/Ataxia%20Telangiectasia.pdf). The estimated prevalence in Europe is 1 in 100,000 population (Orphanet. 2014). Ataxia telangiectasia is due to mutations in the ATM gene located on human chromosome 11 (11q22.3). These defects in the ATM gene reduce or eliminate the function of the ATM protein that controls cell division and is involved in double-strand DNA repair (Lee and McKinnon, 2000; Boehrs et al, 2007), thus leading to repeated infections and malignancies.

The onset of symptoms becomes evident in early childhood when children demonstrate unsteadiness while walking, or swaying when standing still or sitting. Most children with AT have stable neurologic symptoms for the first 4 to 5 years of life, but begin to show increasing problems in early school years. Oculomotor apraxia, slurred speech, and difficulties in swallowing appear in late pre-school and early school age children. AT patients are unable to control their muscles by the time they are 10 to 12 years of age, and this may lead to problems with fine motor functions (writing, coloring, and using utensils to eat), and slurring of speech (dysarthria) that usually stop progressing after the age of about 12 to 15 years. Most AT patients are restricted to wheelchair use for ambulation around this age. Involuntary movements such as tremors, myoclonic jerks, dystonia, chorea, athetosis, etc., are variable in the age of onset and rate of progression. (Boder, 1985; Perlman et al, 2003; Chun and Gatti, 2004) The immune system becomes progressively weaker, and recurrent respiratory infections and blood cancers are noted in late-stage patients. There is high variability in life-expectancy; however, most patients die around the age of 25 years, largely due to chronic lung disease or malignancies. (Poupard, 2003; Crawford et al, 2006)

The exclusion criteria for the study are designed to exclude patients who would be at increased risk for an adverse outcome related to treatment with EDS-EP or their participation in the trial due to their medical history/current status or use of concomitant medication. Dexamethasone has teratogenic potential in rodents; therefore, females of childbearing potential will be included only if they are practicing adequate contraception, as described at Section 9.2.2. Pregnant women will be excluded. Dexamethasone is excreted in breast milk; therefore, patients who are breast-feeding are also excluded. Patients with AT are at increased risk of neoplastic and immunological diseases due to the decreased ability of the ATM gene to repair DNA; therefore, patients with these conditions are excluded.

Rationale for the Study Design

Open-label Design

The open-label design allows patients who completed the full treatment period in the IEDAT-02-2015 and all its assessments (or were discontinued from the Study IEDAT-02-2015 during the COVID-19 pandemic), to continue treatment as long as their physician determines they are not experiencing any adverse effects that would necessitate discontinuation of treatment and do not present safety contraindications to continuation of treatment. This study also gives patients who were receiving placebo treatment in the prior study the opportunity to start treatment with EDS-EP.

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.

Exploratory Endpoint

The exploratory objective is to evaluate the long-term effect of EDS-EP in treating CNS symptoms as measured by the International Cooperative Ataxia Rating Scale (ICARS), 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) persist during long-term treatment.

Secondary 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).

Rationale for EDS Dose

CCI

[redacted]

CCI [redacted]

Rationale for Efficacy Measures

The the long term efficacy measures for this trial were selected based on feedback from Regulatory Authorities and on the previous study IEDAT-02-2015. The efficacy measures to be used in the study are described below.

International Cooperative Ataxia Rating Scale (ICARS)

The ICARS will be used to measure efficacy in the study. The internal consistency, criterion-related validity, and internal construct validity of the ICARS have been established in patients with focal cerebellar lesions (Schoch B et al, 2007). The inter-rater reliability, test-retest reliability and internal consistency have also been validated in patients with spinocerebellar ataxia (Weyer et al, 2007, Schmitz-Hubsch et al , 2006a). The ICARS total score satisfied all psychometric criteria in a validation study in patients with Friedrich's Ataxia (Cano et al, 2005; Metz et al 2013) The ICARS has been used as an outcome measure in interventional studies in patients with ataxia, but there are no clinical data to suggest the magnitude of change on the ICARS that would correspond to a clinically relevant improvement, due to the absence of any drug producing such a benefit. The ICARS has been used in several studies in patients with Friedreich's Ataxia over the age of 8 years, in phase 3 potentially pivotal trials (Lynch et al, 2010), as well as in open-label long-term studies (Meier et al, 2012).

The ICARS was used also in two interventional studies in children with AT. Zanolli et al, 2012 showed a statistically significant decrease in the ICARS total score in a placebo-controlled crossover study in 13 children with AT treated with oral betamethasone (Zannolli et al, 2012). Nissenkorn et al, using ICARS as a secondary endpoint, showed improvement in the static and kinetic subscales in a short-term open-label study in 17 children (from 4 years of age) treated with amantadine (Nissenkorn et al, 2013).

Incoordination of eye movements, nystagmus and loss in saccadic eye movement control is observed early in the AT disease process (Hoche et al, 2012). The ICARS items relating to ocular motility do not provide a comprehensive assessment of this domain. Also, no scale has been validated for the measurement of ocular motility in AT patients. The investigator will be asked to assess the ocular motility item based on the site's clinical paradigm and the instructions for rating the ICARS.

As AT is a severe, relentlessly progressive disorder that leads to loss of independent movement in most patients by the age of 10 to16 years, any statistically significant difference from placebo over a 6-month period should be considered as a treatment success.

Most of the developmental and validation studies of the ICARS were performed in patients who were 10 years of age or older. An international study has been completed (ClinicalTrials.gov: NCT01942850) to extend its validity to patients in the age-range of 5 to10 years. Data collected from this validation study in selected centers [Data on file, EryDel S.p.A] indicated that the distribution of scores for the ICARS for patients with AT under 10 years of age was similar to the scores for these patients on other validated scales such as the SARA (Schmitz-Hubsch et al, 2006b) and the BARS (Schmahmann et al, 2009). Data collected from the validation study in selected centers confirmed that the severity of AT increased with age in patients under the age of 10 years, as demonstrated by a significant correlation of the total scores on the ICARS, SARA, and the BARS, but not for patients above 10 years. Overall, the distribution of scores for the ICARS for 5 to 10 year-old patients with AT was similar to the scores for other validated scales such as the SARA, BARS, CGI-S and CGI unstructured.

These local rater ratings will be used in the analysis of the exploratory endpoint.

Although the ICARS will be rated in its entirety, the primary analyses will be limited to the 'Modified' ICARS; this version excludes Items 8-12 related to kinetic function and Items 17-19 related to oculomotor functions that are required for visual control, as these items are not directly predictive of change in functioning.

CGI-C and CGI-S

The Clinical Global Impression (CGI) consists of two 7-point, clinician-rated, Likert-type scales assessing change from baseline (CGI-C) and severity of illness (CGI-S) (Guy, 1976). In the current study, an overall assessment of the change in the patient's neurological symptoms of AT, compared to the status at baseline, will be performed at each visit and used as the key secondary efficacy measure. To ensure independence of this rating from the rating of the ICARS (the primary efficacy measure), a different rater will perform the CGI-C.

In addition, the severity of illness at baseline and at each subsequent timepoint will be assessed using the CGI-S. No version of the CGI-S exists which has been specifically adapted for use in AT patients; therefore, a 5-point structured version was developed which takes into account the severity of the following symptoms of AT: ataxia (walking), dysarthria, dysmetria, extrapyramidal symptoms (chorea, myoclonus, dystonia, and tremor), and eye movements. Ratings of none, mild, moderate, severe, and very severe are selected based on the level of symptomatology. A pilot validation study has been performed in AT patients using the CGI-S scale, and the results indicate that the CGI–S adequately discriminated patients with mild, moderate, or severe disease [Data on file, EryDel S.p.A.]. The distribution of patients to different scores on the CGI-S of AT was similar using the ICARS, BARS, and SARA in 6 to 9 year-olds. The CGI-S for patients ≥10 years of age was greater than in 6 to 9 year-old patients; however, the distribution of scores on the ICARS, BARS, and SARA was similar across severity categories.

*QoL Scale (EQ-5D-*5L)

Improvements in quality of life (QoL) are an important goal for treatment of patients with AT. Therefore, the EQ-5D-5L scale assessing QoL has been included as a secondary efficacy measure. The EQ-5D is a standardized instrument for assessing health-related QoL in a variety of health conditions (Rabin and de Charro, 2001). The EQ-5D-5L is a newer version of the scale, which includes five levels of severity for each of the five EQ-5D dimensions (Herdman et al, 2011), and has been validated in a diverse patient population in 6 countries, including 8 patient groups with chronic conditions and a student cohort (Janssen et al, 2013). For children and adolescents, the EQ-5D-5L administrators will be trained to help the younger population in the study complete the scale. Assessment of the EQ-5D-5L will be performed by the patient, or the patient's parent/caregiver, at regular intervals throughout the study.

8 STUDY OBJECTIVES

Primary Objective:

- To monitor and evaluate the long-term safety and tolerability of EDS-EP in AT patients

Exploratory 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), and Clinical Global Impression of severity and change (CGI-S/C)

Secondary Objective:

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

9 INVESTIGATIONAL PLAN

9.1 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. During the COVID-19 pandemic, some patients had to be discontinued from the IEDAT-02-2015 trial; for this reason, the eiligibility 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.

The study aims at collecting information on the long-term safety and efficacy of the trial treatment.

Patients meeting all selection criteria will receive monthly infusions of EDS-EP (CCI [redacted] CCI [redacted]). During the Study, long term efficacy assessments will be evaluated every 6 months, while the safety parameters will be assessed at each monthly visit.

The ICARS, EQ-5D-5L and the CGI-C/S will be administered by a site rater.

Listings of the study procedures to be performed at each visit are provided in Section 11.0.

9.2 Study Population

9.2.1 *Inclusion Criteria*

To be eligible, the patient must meet all of the following criteria:

1. Patients completed the double-blind period in the IEDAT-02-2015 trial and have completed the final (Visit 15/Month 12) efficacy assessments of IEDAT-02-2015 or discontinued the study during the COVID-19 pandemic
2. Patients tolerated the study medication without any evidence of steroid adverse events, or treatment - related severe/ serious adverse events.
3. Body weight > 15 kg.

4. The patient and his/her parent/caregiver (if below the age of consent), or a legal representative, has provided written informed consent to participate. If consent is provided solely by the caregiver in accordance with local regulations, the patient must provide assent to participate in the study.
5. Patient does not present safety contraindications for continuation of treatment, as determined by the Principal Investigator (PI) according to the procedures described below.

Procedure for selecting patients for further treatment

The Principal Investigator will ask all patients who meet the above requirements, and determine their interest in continuing to receive treatment with the study medication in a new protocol. The Principal Investigator will then determine the eligibility of the patients on the basis of his/her clinical judgement of patients' status and their safety.

9.2.2 *Exclusion Criteria*

To be eligible, the patient must not meet any of the following criteria:

General

1. Females that are
   a. pregnant, or are breast-feeding (for EU countries only);
   b. of childbearing potential, pregnant, or are breast-feeding (for US and Rest of World countries).

   Females of childbearing potential using adequate birth control, as determined by their Health Care Provider, will be eligible.
2. A disability that may prevent the patient from completing all study requirements.
3. Current participation in another clinical study with another investigational drug.

Medical History and Current Status

4. CD4+ lymphocytes count <400/mm3 (for patients 6 years of age) or <150/mm3 (for patients > 6 years). In presence of oral infections, like oral candidiasis, documented at the screening or recurrent as per medical history documentation, the limit increases to <200/mm3 (for patients > 6 years).
5. Current neoplastic disease.
6. Severe impairment of the immunological system.
7. Severe or unstable pulmonary disease.
8. Uncontrolled diabetes.

   Patients with diabetes that has been stabilized (i.e. no hypoglycemic or hyperglycemic episodes in the past 3 months) will be eligible.
9. Any other severe, unstable, or serious disease or condition that in the Investigator's opinion would put the patient at risk for imminent life-threatening morbidity, need for hospitalization, or mortality.
10. Eligibility of patients with abnormal laboratory test values will be determined by the Investigator.
11. Confirmed hemoglobinopathies, e.g. hemoglobin C disease, sickle cell anemia, or thalassemia.
12. Moderate or severe renal and/or hepatic impairment.
13. Patients who experienced moderate/ severe steroid side effects, or moderate/ severe adverse events associated with the study medication administered in the IEDAT-02 study.

Prior/Concomitant Medication

14. Requires treatment with an oral or parenteral steroid. *Treatment with inhaled or intranasal steroids for asthma or allergies, as well as use of topical steroids will be permitted.*
15. Requires any other concomitant medication prohibited by the protocol.
16. Use of any drug that is a strong inducer/inhibitor of CYP3A4.

9.3 Premature Discontinuation

Patients who discontinue from the study prematurely must have their reason for discontinuation entered in the Case Report Forms (CRFs). Patients who discontinue from the study after having received a dose of study medication will not be replaced.

All patients who discontinue prematurely will be asked to return for the Safety follow up visit.

9.4 Record of Study Participants and Screening Failures

The investigator will be required to maintain a confidential record of all study participants, including all patients who were screened for the study, but were not enrolled to treatment. The confidential record must include sufficient information so that it would be possible to contact the study patient. Information on patients who have signed ICFs, but have failed screening, should be entered on the Screen Failure CRF.

The primary reason for screen failure will be recorded using the following categories:

- Did not meet entry criteria
- Major protocol deviation
- Pre-treatment Event/Adverse Event
- Lost to follow-up
- Voluntary withdrawal (specify reason)
- Study termination
- Other (specify reason).

Patients will keep the same screening number assigned during the IEDAT-02-2015 Study.

10 STUDY MEDICATION

10.1 CCI

CCI

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10.1.2 CCI

CCI

10.1.3 CCI

CCI

CCI

CCI

CCI

10.2 CCI

CCI

A description of the EDS and details of the procedure for the encapsulation process are provided in Appendix 5.

CCI

[redacted]

10.4 Accountability

During the course of the study, the study pharmacist or site personnel designated by the Investigator to manage the study medication must record the study drug disposition and keep the accountability forms updated. The study drug accountability forms will be cross-checked with the Encapsulation Procedure Check-List (Appendix 7). A copy of the accountability forms must be kept in the study files at the site, and the other copy will be withdrawn by the CRO staff responsible for monitoring the study medication. The used and unused dexamethasone vials, as well as the Encapsulation Procedure Check-List, will be kept at the site for accounting and reconciliation by the CRA vs. the study documentation. The used infusion bags containing any remaining erythrocytes (with DSP encapsulated) will be disposed of at the site, with appropriate documentation.

10.5 Overdose

Each infusion should contain a [redacted] encapsulated in autologous RBCs. However, based upon results of prior studies, some inter-individual variability in loaded dose is expected; therefore, administered doses of DSP greater [redacted] will be considered an overdose. Treatment for an overdose should be the same as the clinical management for an overdose of dexamethasone.

10.6 Occupational Safety

There are no risks anticipated related to the study medication for the staff involved in administering EDS to the patients in this study. Standard procedures and precautions for handling needles and biological samples should be followed.

11 EVALUATIONS AND PROCEDURES

11.1 Written Informed Consent

Written Informed Consent must be obtained from the patient and his/her parent/caregiver (if below the age of consent), or legal representative (if necessary), at baseline prior to initiating any study procedures required by the protocol, according to the procedure described in Section 17.

This process should be performed at screening 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 who may not have final evaluations for IEDAT-02-2015 study (Visit 15/Month 12); these patients will have to undergo a screening phase before the baseline visit, therefore consenting should be performed before any screening related procedure takes place.

If consent is provided solely by the caregiver in accordance with local regulations, the patient must provide assent to participate in the study. The details of the study should be discussed with the patient and parent/caregiver or legal representative (if necessary) prior to obtaining informed consent, and the Informed Consent Form (ICF) must be signed and dated by the patient, parent/caregiver/ legal representative (if necessary), and by the Investigator or his/her designee. A copy of the signed ICF will be provided to the patient, and the original will be retained with the source documents.

11.2 Study Conduct

The structure of this study open-label extension treatment study, as well as a detailed listing of the assessments and procedures to be performed at each visit is provided in Section 11.4. The same scheme and assessments will be replicated for the second year onwards.

As a results of the COVID-19 pandemic, temporary changes to the protocol have been implemented. These changes are described in Appendix 13.

Screening phase

Applicable only for patients which will be enrolled without completing the ATTeST trial.

After providing consent/assent, as described in Section 11.1, patients will enter the screening phase. The screening phase will last at maximum 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.

The screening evaluation described in Section 11.4 will be performed.

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. Adverse events, reported by the patient or observed by the investigator, and the use of concomitant medication will be recorded from the time of signing the informed consent through the end of the study.

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 Vist 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; VABS: EQ-5D-5L; C-SSRS; BMD; review of AEs and concomitant medications.

After providing consent/assent, as described in Section 11.1, each patient will undergo evaluation of the eligibility criteria at the baseline visit, and if eligible, will proceed with the EDS-EP infusion. Demographic information will be rolled over from the IEDAT-02-2015 eCRF and rechecked by the Investigators for consistency, as well as medical history.

Before the EDS-EP infusion, all patients will undergo vital signs evaluation, hemolysis panel (on the diverted blood sample, see Section 11.5) and assessment of prior and concomitant medication and AEs. Women of childbearing potential must undergo a urine pregnancy test. .

CCI [redacted]

Study treatment administration by IV infusion will be performed within 30 min after the EDS process has been completed.

CCI [redacted]

After completion of the IV infusion of the study treatment the following assessments will be performed on Day 0 (Baseline/Visit 1): Vital signs, physical examination (1-2 hr after infusion), assessment of AEs, and assessment of concomitant medications.

Months 1-5 and 7- 11

Before the EDS-EP infusion, patients must undergo to laboratory tests: the diverted blood sample (see Section 11.5) will be collected for measurement of serum creatinine and routine tests. Women of childbearing potential must undergo a pregnancy urine test.

A C-SSRS assessment, will be performed at each of these visits, as well as a vital signs assessment. In addition, a hemolysis panel on diverted blood sample (see Section 11.5) will be done at the Month 4 and Month 8 visits.

All patients should undergo assessment of prior and concomitant medication and AEs.

CCI [redacted]

CCI [redacted]

Study treatment administration by IV infusion, will be performed within 30 min after the EDS process has been completed.

The satellite sample bag will be detached and used for sterility culture tests: a sample of the EDS-EP (approximately 1 ml per inoculum for a total of 2 mL) will be collected to perform a sterility test using a culture-based method as presented in Appendix 10. A 1-mL sterile sample of the EDS-EP will be stored under refrigeration as a "Retention Sample". In case of positive/contaminated post-release sterility results, an action plan has been established as presented in Section 13.6 and in Appendix 11.

After completion of the IV infusion of the study treatment the following assessments will be performed: Vital signs, physical examination (1-2 hr after infusion), assessment of AEs, and assessment of concomitant medications

Months 6 and 12

At Months 6 and 12 the following assessments will be performed before treatment administration: all assessments of efficacy (ICARS, CGI-C, CGI-S and EQ-5D-5L) and safety (vital signs, ECG, routine laboratory tests on the diverted blood samples (see Section 11.5), physical and neurological examinations, C-SSRS, BMD and assessments of AEs and concomitant medication use), as well as special laboratory tests (HbA1c, CD4+ lymphocytes count and CRP), on the diverted blood samples (see Section 11.5). A serum (on the diverted blood samples, see Section11.5) and urine pregnancy test will be performed for women of childbearing potential. Physical development, sexual maturation, and the effect of treatment with dexamethasone on these aspects will be assessed (Tanner scale). Tanner staging of the breasts in pre-menarchal females and of the scrotum in males who have not completed puberty, will be performed at Months 6 and 12. Post-menarchal females and males who have completed puberty will be excluded from this growth analysis.

CCI [redacted]

Study treatment administration by IV infusion, will be performed within 30 min after the EDS process has been completed.

CCI [redacted]

After completion of the IV infusion of the study treatment, a physical examination and vital signs will be performed (1-2 hr after infusion), as well as assessments of AEs and concomitant medication use.

A Month 12 infusion, and all of the associated procedures, would only be done in patients who are continuing open label treatment past one year. The schedule of visits and assessments for the first 12 months - as described above- will be replicated for the second year onwards.

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.

Evaluation and Infusion Schedule

The monthly infusions should be performed every 21-28 days. A window of + 10 days will be perimitted 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 administrationInfusions should not be skipped; therefore, if necessary, the infusion schedule can be modified to conform to the above guidelines.

11.3 Schedule of Visits and Assessments

An overview of the schedule of evaluations for the study is presented in Table 2 for the first 12 months will be replicated for the second year onwards.

Table 2. Schedule of Visits and Assessments: 1st year of open-label extension treatment (to be replicated for the second year onwards)

Visit (V)	Screening Phase *	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; VABS: 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)"; 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 Appendix 13.

(pre) Pre EDS-EP infusion procedure

(post) Post EDS-EP infusion procedure

11.4 Visit Schedule and Assessments

11.4.1 *Screening phase (D -30 to -1)*

Applicable only for patients which will be enrolled without completing the ATTeST trial.

After providing consent/assent, as described in Section 11.1, patients will enter the screening phase. The screening phase will last at maximum 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.
The following screening evaluations will be conducted:

a) Medical history and demographics
b) Physical examination
c) Vital signs (including height and weight in triplicate)
d) Neurological examination
e) Tanner staging of the breasts in pre-menarchal females and of the scrotum in males who have not completed puberty. Post-menarchal females and males who have completed puberty will be excluded from this growth analysis.
f) ICARS (administered by the qualified site-specific rater).
g) CGI-S
h) 12-lead standard Electrocardiogram (ECG)
i) Routine laboratory tests, on the diverted blood sample (see Section 11.5)
j) Special laboratory tests: HbA1c, CD4+ lymphocytes count, and CRP,, on the diverted blood sample (see Section 11.5)
k) Serum pregnancy test (women of childbearing potential), on the diverted blood sample (see Section 11.5)
l) BMD
m) CSSRS
n) EQ-5D-5L
o) Blood collected to assess RBC osmotic resistance (in selected centers)
p) Plasma cortisol – sample to be collected before 8:00 AM. If the basal cortisol level is within the reference normal range, the patient can be enrolled in the study. If the 8:00 AM cortisol level is below 3-5 µg/dL (depending on assay) regardless of symptoms, or the patient exhibits signs or symptoms of adrenal insufficiency (see Appendix 12) and has a cortisol <10 µg/dL, the patient will receive a high dose ACTH stimulation test, regardless of weight, within 24 hours. If the ACTH stimulation test is normal, the patient can be enrolled after the effects of the ACTH have dissipated (e.g., 30 days after ACTH administered). If the patient fails the ACTH stimulation test they will be excluded from the study and referred to a pediatric endocrinologist, with a recommendation to prescribe stress dose steroids
q) Assessment of prior and concomitant medications
r) Assessment of AEs

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. BMD abnormalities at screening visit should be reported in the Medical History, as it would underline a pre-existing condition.
Adverse events, reported by the patient or observed by the investigator, and the use of concomitant medications, will be recorded from the time of signing of informed consent through the end of the study.

11.4.2 *Baseline visit (Visit 1/ Day 0)*

Final evaluations for IEDAT-02-2015 study (Visit 15/Month 12) will serve as baseline evaluations for patients continuing in 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.

a) Obtaining written informed consent (before any study procedures)
b) Check of the demographic information, medical history, previous and concomitant medications, ongoing adverse events and non-drug therapies and procedures (demographic information, medical history rolled over from IEDAT-02-2015 eCRF)
c) Vital signs [including height and weight measurements in triplicate at baseline; calculation of BMI, temperature (oral or tympanic, according to the specific medical practice of the Center), pulse, systolic and diastolic BP, and respiratory rate].
d) Hemolysis panel (including urinalysis), on the diverted blood samples (see Section 11.5)

Patients providing informed consent or assent and meeting the eligibility criteria will receive study treatment prepared and administered as follows:

e) 1 mL blood collected, after blood diversion (see Section 11.5), for aerobic culture
f) Autologous blood collection for EDS processing
g) Addition of the assigned study medication (DSP) to the EDS process
h) Upon completion of the EDS process, fill the satellite sample bag CCI [redacted] if no other samples but the ones for sterility culture test will be collected).
i) Study treatment administration by IV infusion, within 30 min after the EDS process has been completed.
j) CCI [redacted]

Before the EDS-EP infusion, patients (women of childbearing potential) must undergo a pregnancy urine test. All patients should undergo assessment of prior and concomitant medication and AEs.

After completion of the IV infusion of the study treatment the following assessments will be performed on Day 0:

k) Vital signs - body weight and height in triplicate, calculation of BMI, temperature (oral or tympanic, according to the specific medical practice of the Center), pulse, systolic and diastolic BP, and respiratory rate

l) Physical examination

m) Assessment of AEs occurring after giving informed consent – reported by the patient or observed by the Investigator

n) Assessment of concomitant medications

11.4.3 *Months 1-5 (Visits 2-6) and 7- 11 (Visits 8-12)*

At Months 1- 5 and 7- 11, the following assessments will be performed:

a) Laboratory tests, on the diverted blood sample (see Section 11.5): serum creatinine
b) Routine laboratory tests, on the diverted blood sample (see Section 11.5):
   - hematology
   - clinical chemistry
   - urinalysis
c) Hemolysis panel (including urinalysis), on the diverted blood sample (see Section 11.5): only at Month 4 and 8
d) Urine pregnancy test will be performed before every infusion (for women of childbearing potential)
e) C-SSRS
f) Assessment of prior and concomitant medication
g) Assessment of AEs - reported by the patient or observed by the Investigator
h) 1 mL blood collected, after blood diversion (see Section 11.5), for aerobic culture
i) Autologous blood collection for EDS processing
j) Addition of the assigned study medication (DSP) to the EDS process
k) Upon completion of the EDS process, fill the satellite sample bag with CCI [redacted] if no other samples but the ones for sterility culture test will be collected).
l) Study treatment administration by IV infusion, within 30 min after the EDS process has been completed.
m) CCI [redacted]

After completion of the IV infusion of the study treatment the following assessments will be performed:

n) Physical examination and vital signs (body weight and height, calculation of BMI, temperature - oral or tympanic, according to the specific medical practice of the Center - pulse, systolic and diastolic BP, and respiratory rate) 1-2 hr after the end of infusion
o) Assessment of AEs and concomitant medications

11.4.4 *Months 6 (Visit 7) and 12 (Visit 13)*

At Months 6 and 12 the following assessments will be performed before treatment administration (unless specified otherwise):

a) Physical examination
b) Vital signs (body weight and height in triplicate, calculation of BMI, temperature - oral or tympanic, according to the specific medical practice of the Center - pulse, systolic and diastolic BP, and respiratory rate)
c) Neurological examinations
d) ICARS
e) CGI-S and CGI-C
f) EQ-5D-5L
g) C-SSRS
h) BMD
i) 12-lead standard ECG
j) Routine laboratory tests, on the diverted blood sample (see Section 11.5)
k) Special laboratory tests, on the diverted blood sample (see Section 11.5): HbA1c, CD4+ lymphocytes count and CRP.
l) Serum pregnancy test (women of childbearing potential), on the diverted blood sample (see Section 11.5).
m) Urine pregnancy test will be performed before every infusion for women of childbearing potential.
n) Assessment of physical development, sexual maturation, and the effect of treatment with dexamethasone on these aspects. Tanner staging of the breasts in pre-menarchal females and of the scrotum in males who have not completed puberty. Post-menarchal females and males who have completed puberty will be excluded from this growth analysis.
o) Assessment of concomitant medications
p) Assessment of AEs - reported by the patient or observed by the Investigator
q) 1 mL blood collected, after blood diversion (see Section 11.5), for aerobic culture
r) Autologous blood collection for EDS processing
s) Addition of the assigned study medication (DSP) to the EDS process.
t) Upon completion of the EDS process, fill the satellite sample bag with approximately CCI [redacted] if no other samples but the ones for sterility culture test will be collected).
u) Study treatment administration by IV infusion, within 30 min after the EDS process has been completed.
v) CCI [redacted]

CCI [redacted]

After completion of the IV infusion of the study treatment the following assessments will be performed:

w) Physical examination and vital signs 1-2 hr after infusion
x) Assessment of concomitant medications
y) Assessment of AEs - reported by the patient or observed by the Investigator

11.4.5 *Safety Follow-up Visit (Visit 16)*

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.

11.4.6 *Visit Windows*

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..

11.5 **Laboratory Sample Collection**

Study procedures to ensure sterility of the EDS-EP
Aseptic procedures should be implemented to ensure sterility during blood collection for the EDS process, the various steps of the EDS process, sample collection for routine laboratory tests, sample collection from the EDS-EP for sterility testing, and administration of the EDS-EP to the patient. Details of these procedures are described in a separate document entitled "Study Procedures on Sterility Testing for Study IEDAT-03-2018 (OLE-IEDAT)", which will be provided to each site (see Appendix 9). These new procedures include the following measures that must be performed to ensure sterility:

- Blood sampling under sterile conditions.
- Careful hand washing and use of fresh (non-sterile) gloves for each patient, disinfected frequently using a bactericidal rub.
- Frequent and repeated use of a bactericidal solution, including the mandatory use of 2% chlorhexidine in 70% isopropyl alcohol for disinfection of the skin at the venipuncture site, or during handling of the venous catheter (if used), and for disinfecting ports, connectors and working surfaces/environments.
- CCI [redacted]

CCI

Blood sampling

Venous blood samples will be drawn for routine safety evaluations to be performed at local level, according to Sites' clinical practice and local regulations.

The total amount of blood to be drawn on any single day or within any 8-week period must conform to the guidelines specified for pediatric patients by the World Health Organization (Howie, 2011).

Urine collection

Urine needed for the urinalysis will be collected at Baseline visit, Month 4, Month 8, Safety follow up visits -as part of hemolysis panel and according to local laboratory guidelines.

Pregnancy test

All female patients of childbearing potential will have a blood sample drawn at Month 6 and Month 12 for a serum pregnancy test. "Non-childbearing potential" is defined as follows:

- surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral tubal ligation), or
- patient is pre-pubertal, with confirmation that menstruation has not started.

Results of the serum pregnancy test must be negative at the IEDAT-02-2015 study final visit for the patient to be included in the IEDAT-03-2018 study.

A urine pregnancy test will be performed montly before every infusion, starting from baseline visit. Results of the urine pregnancy test must be negative at Baseline (Day 0) for the patient to be eligible.

All blood and urine samples for safety (hematology/ clinical chemistry/ urinalysis) and special laboratory evaluations will be analyzed by the local laboratory.

11.6 Measurement of Dexamethasone Sodium Phosphate and Other Analytes in Infusion Bag Sample

CCI

11.7 Concomitant Medications

All patients to be included in the study must not have received oral or parenteral steroid therapy within 4 weeks prior to the administration of EDS. Treatment with inhaled or intranasal steroids for asthma or allergies, as well as the use of topical steroids, will be permitted. In addition, patients with a history of use or currently using any of the following medications will be excluded from participation, according to the guidelines specified:

- Narcotic analgesics – use within 4 weeks prior to baseline, unless the intake is stable since IEDAT-02-2015 study;
- Antipsychotics - unless used at a low, stable dose since IEDAT-02-2015 study, in which case they will be permitted;
- Drugs that are strong inducers (e.g. carbamazepine, St. John's wort) or inhibitors (e.g. clarithromycin, grapefruit juice) of CYP3A4 within 4 weeks prior to baseline;

  Drugs that are inducers or inhibitors of Cytochrome P450 3A4 (CYP3A4) may alter the plasma levels of dexamethasone, which is metabolized by this enzyme. Therefore, in the current study, any drug that is a strong inducer or inhibitor of CYP3A4 will be prohibited from use during the trial. Patients who are taking these drugs upon entry into the screening period should have the medication discontinued, if possible, or be switched to another similar medication that does not have this property. A link to a website with a list of drugs that are strong inducers or inhibitors of CYP3A4 will be provided to the Investigator as a reference.
- Amphotericin-B – combination with corticosteroids or corticotropin (ACTH) may induce hypopotassemia;
- The use of live or attenuated vaccines is prohibited. However, the use of a vaccine that contains killed viruses is left to the clinical judgement of the Principal Investigator, and the standard of care at the site. The requirements for the vaccination will be based on the local/site clinical standard of care practices, SPC (Summary of Product Characteristics) of the given product/vaccine and general considerations relating to the timing gap the infusion and the vaccination. This decision is up to the Investigator`s medical judgment and discretion.

Patients on stable doses of other drugs, such as antihypertensives, benzodiazepines, antihistamines (histamine receptor blockers), birth control, proton-pump inhibitors, vitamins/multi-vitamins, anti-diabetics agents and lipid-lowering agents (e.g. statins), will be eligible for the study. The use of other concomitant medications with CNS effects should be discussed with and approved by the Medical Monitor at the CRO before prescribing to the patient during the study. Use of immunoglobulins either administered by IV or IM

route is permitted; the Investigator should determine the optimal timing of the dose with respect to the EDS infusion.

During the entire period of the study, starting with the signing of the ICF, any new treatment that is initiated must be reported in the CRF using the pharmacological name (not the trade name, with the exception of medicines in fixed combination), specifying daily dose, route, duration of treatment, reason for use. After screening, patients should be instructed to contact the Investigator before starting any OTC or prescription medication on their own or as prescribed by their physician. The Medical Monitor at the CRO should be informed of any new medication that may be a prohibited medication and is started during the study, and will make a decision whether or not it is acceptable for the patient to continue in the trial.

The current participation in a clinical trial with another investigational drug is an exclusion criterion.

12 EFFICACY EVALUATIONS

12.1 ICARS

12.1.1 *Description of the ICARS*

The primary efficacy endpoint in the AT study will be the mean change from baseline to endpoint (Month 6 or early discontinuation) in the total score on the 'Modified' International Cooperative Ataxia Rating Scale (ICARS).

The ICARS (Trouillas et al, 1997), the most frequently used clinician-(neurologist) rated measure in patients with ataxias, was developed by a Committee of the World Federation of Neurology to help standardize common manifestations of syndromes that lead to cerebellar dysfunction. The ICARS is a 100-point, semi-quantitative scale offering a compartmentalized quantification of the following 4 sub-scores: Posture and Gait Disturbances (34 points), Kinetic Functions (52 points), Speech Disorders (8 points), and Oculomotor Disorders (6 points).

The complete ICARS will be rated in the current study; however, for the primary efficacy endpoint, the 'Modified' ICARS will used. The 'Modified' ICARS excludes all of the Oculomotor Disorders items (items 17-19) and items 8-12 in the Kinetic Functions domain, as these items do not directly contribute to functioning.

12.1.2 *Validity of ICARS in AT Patient Population*

The internal consistency, criterion-related validity, and internal construct validity of the ICARS have been established in patients with focal cerebellar lesions (Schoch B et al, 2007). The inter-rater reliability, test-retest reliability and internal consistency have also been validated in patients with spinocerebellar ataxia (Weyer et al, 2007, Schmitz-Hubsch et al , 2006a). The ICARS total score satisfied all psychometric criteria in a validation study in patients with Friedrich's Ataxia (Cano et al, 2005; Metz et al 2013) The ICARS has been used as an outcome measure in interventional studies in patients with ataxia, but there are no clinical data to suggest the magnitude of change on the ICARS that would correspond to a clinically relevant improvement, due to the absence of any drug producing such a benefit. The ICARS has been used in several studies in patients with Friedreich's Ataxia over the age of 8 years, in phase III potentially pivotal trials (Lynch et al, 2010), as well as in open-label long-term studies (Meier et al, 2012).

The ICARS was used also in two interventional studies in children with AT. Zanolli et al, 2012 showed a statistically significant decrease in the ICARS total score in a placebo-controlled crossover study in 13 children with AT treated with oral betamethasone (Zannolli et al, 2012). Nissenkorn et al, using ICARS as a secondary endpoint, showed improvement in the static and kinetic subscales in a short-term open-label study in 17 children (from 4 years of age) treated with amantadine (Nissenkorn et al, 2013). As AT is a severe, relentlessly progressive disorder that leads to loss of independent movement in most patients by the age of 10 to 16 years, any statistically significant difference from placebo over a 6-month period should be considered as a treatment success.

Most of the developmental and validation studies of the ICARS were performed in patients who were 10 years of age or older; an international study has been completed (ClinicalTrials.gov: NCT01942850) to extend its validity to patients in the age-range of 5 to10 years. Data collected from the validation study in selected centers [Data on file, EryDel S.p.A] indicated that the distribution of scores for the ICARS for patients with AT under 10 years of age was similar to the scores for these patients on other validated scales such as the SARA (Schmitz-Hubsch et al, 2006b) and the BARS (Schmahmann et al, 2009). Data collected from the validation study in selected centers confirmed that the severity of AT increased with age in patients under the age of 10 years, as demonstrated by a significant correlation of the total scores on the ICARS, SARA, and the BARS, but not for patients above 10 years. Overall, the distribution of scores for the ICARS

for 5 to 10 year-old patients with AT was similar to the scores for other validated scales such as the SARA, BARS, CGI-S (structured and unstructured versions).

12.1.3 *Standardization of Ratings*

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 ICARS will be performed at Month 6 and Month 12.

12.2 Clinical Global Impression {CGI-C and CGI-S (structured)}

The CGI (Guy, 1976) is the general name for two scales, the CGI - Change scale (CGI-C) and CGI- Severity scale (CGI-S). 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, and the mean rating of change at Endpoint (Month 6 or early discontinuation) 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. A guideline for performing the rating of change using the CGI-C is provided below.

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. VABS, 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.

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.

A pilot validation study has been performed in AT patients using the CGI-S scale, and the results indicate that the CGI-S adequately discriminated patients with mild, moderate, or severe disease [Data on file, EryDel S.p.A.]. The distribution of patients to different scores on the CGI-S of AT was similar using the ICARS, BARS, and SARA in 6 to 9 year olds. The CGI-S for patients 10 years of age or older was greater than in 6 to 9 year old patients; however, the distribution of scores on the ICARS, BARS, and SARA was similar across severity categories.

12.3 Quality of Life Scale

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 (Rabin and de Charro, 2001). The scale was originally designed for use in adult populations, 18 years of age and older. The EQ-5D includes single item measures of five health dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each item has three possible response options that allow the subject to rate (no problems/some or moderate problems/extreme problems) their current state with respect to each of the 5 domains. 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 is cognitively simple, and provides a score that can be compared across different conditions (http://www.euroqol.org/).

The EQ-5D-5L that will be used in this study is a newer version of the scale, which 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 (Herdman et al, 2011); rather than the three levels included in the previous version (EQ-5D-3L). The EQ-5D-5L has been validated in a diverse patient population in 6 coutries, including 8 patient groups with chronic conditions (e.g. cardiovascular disease, respiratory disease, depression, diabetes, liver disease, personality disorders, arthritis, stroke) and a student cohort (Janssen et al, 2013).

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 he/she has questions related to scale completion. If the patient is unable to complete the scale, it will be completed by the patient's parent/cargiver.

12.4 Rater Requirements and Training

Properly qualified raters will need to be identified at each site to perform the ratings on the efficacy measures. The ICARS rater must remain blinded to other assessments and will not have access to the safety data. The CGI rater will not have access to the ICARS ratings or safety data, but may refer to other scales in scoring the CGI. Training and certification on the ICARS and CGI will take place at the Investigator's meeting and additional training and an intra-rater reliability (test-retest) assessment will be performed during the study.

12.5 **Order of Test Performance**

The ICARS should be the first scale administered. The sequence of performance for the other efficacy assessments is not fixed across the study; however, the order in which these tests are performed for an individual patient should be kept constant throughout the trial.

13 SAFETY EVALUATIONS

The assessment of safety and tolerability will be based on the following:

a) Vital signs (body weight, temperature [oral or tympanic], pulse, systolic and diastolic blood pressure, and respiratory rate

b) Standard laboratory tests (clinical chemistry, hematology, and urinalysis)

c) 12-lead standard ECG

d) Physical and neurological examinations

e) Special laboratory parameters

f) C-SSRS

g) BMD

h) Culture-based sterility test on EDS-EP

i) Tanner staging

j) Subjective reporting of any AE by the patient

k) Objective observation of any AE by the Investigator

l) The investigator will be asked to comment on any clinically significant abnormal test results.

The frequency of investigations that involve blood draws have been verified to ensure that the volume of blood taken from patients conforms to the guidelines specified for pediatric patients by the World Health Organization (Howie, 2011).

13.1 Physical and Neurological Examinations

Physical and neurological examinations will be performed as specified on the Schedule of Visits and Assessments. The physical examination will include an examination of general appearance, skin, neck (including thyroid), eyes and ears, nose, mouth, throat, lungs, heart, abdomen, back, lymph nodes, extremities and nervous system. Genital, urinary tract and rectal examinations are not required. The findings will be entered on the Physical Examination section of the CRF.

13.2 Vital Signs

Vital signs assessments will be performed as specified on the Schedule of Visits and Assessments and will 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.

If a change *of clinical relevance* from pre-dose to post-dose is observed, the vital signs assessment should be repeated as often as needed, at the discretion of the Investigator. Guidelines for clinically notable vital signs values are provided in Appendix 4. Findings should be documented on the Vital Signs section of the Case Report Form.

13.3 Electrocardiogram (ECG)

All patients will have a standard 12-lead ECG performed locally, as specified on the Schedule of Visits and Assessments. The ECG will be done at Month 6 and 12 in triplicate, at least 10 min apart, and the values will be averaged to obtain the baseline values.

The review and interpretation of the 12-lead ECGs will be performed by a cardiologist or qualified physician at the investigational site. The report from the local ECG service must be reviewed by the Investigator, initialed and dated, and copies inserted in the patient's records and attached to the CRF. If clinically significant abnormalities are found, the patient's ECG should be repeated at regular intervals until it returns to normal.

Each ECG tracing must have the following information entered on it:

- Study number,
- Site number,
- Subject's number and initials,
- Date and time ECG obtained.

If clinically significant abnormalities are found, the patient's ECG should be repeated at regular intervals until it returns to normal. The cardiologist or qualified physician reviewing the ECGs should use the following guidelines in determining the clinical significance of any abnormal findings:

- PR interval: < 100 msec or > 210 msec
- QRS interval: < 50 msec or > 120 msec
- QTc interval: > 450 msec
- Heart rate: < 50 bpm (sinus bradycardia) or > 120 bpm (sinus tachycardia)
- Morphology: presence of T-wave inversion, abnormal R-waves, pathological Q-waves, or significant ST elevation or depression.

13.4 Standard Laboratory Evaluations and Screening Tests

Blood and urine samples for measurement of standard laboratory parameters will be as specified on the Schedule of Visits and Assessments.

Evaluations of the hematology, clinical chemistry and urinalysis analytes listed in Table 3 will be performed at each of the visits listed above. In addition, a serum pregnancy test will be performed for women of childbearing potential at Month 6 and Month 12. For women of childbearing potential also a monthly urine pregnancy test will be performed before every infusion throughout the study. For details on the aseptic procedure for blood withdrawal and on blood diversion see "Study Procedures on Sterility Testing for Study IEDAT-03-2018 (OLE-IEDAT)" (Appendix 9)

Table 3. Summary of standard laboratory analytes

LABORATORY ANALYTES			
Hematology or CBC	**Clinical Chemistry**		**Urinalysis (automated)**
Hematocrit	Sodium	Alkaline phosphatase	Color
Hemoglobin	Potassium	LDH	pH
RBC count	Chloride	CPK	Specific gravity
WBC count	Calcium	Triglycerides	Protein
Differential WBC count	Phosphorus	Total cholesterol	Glucose
• Neutrophils	Serum iron	HDL cholesterol	Ketones
• Lymphocytes	Bicarbonate	LDL cholesterol	RBC, WBC, casts *
• Monocytes	Glucose		Nitrites
• Eosinophils	BUN		Bilirubin
• Basophils	Creatinine		Hemoglobin
Platelets	Total bilirubin		Urobilinogen
MCV	Albumin		* Reflex microscopic analysis to be performed only if other analytes are abnormal on automated testing
MCH	Total protein		
MCHC	AST (SGOT)		
RDW	ALT (SGPT)		
Special Diagnostic Tests: *Serum pregnancy test* (to be performed at Month 6, Month 12 and safety follow up visit for women of childbearing potential). For women of childbearing potential also a monthly urine pregnancy test will be performed before every infusion throughout the study.			

The Investigator must review the final IEDAT-02-2015 values, prior to the first administration of the study drug in IEDAT-03-2018, to ensure that the patient meets the protocol's inclusion/exclusion criteria. The Investigator must review laboratory values from each subsequent evaluation within 24 hours of receipt of the laboratory report. After the review is completed, the Investigator must sign and date each laboratory report.

The local laboratory should provide quality certifications/accreditations and normal reference ranges for the laboratory tests on the laboratory results report. A value is considered **normal** when it falls on or within the upper and lower limits of the reference range for the laboratory. A value is considered **abnormal** when it exceeds the upper or lower limit of the reference range. The local laboratory should verify that abnormal results are not due to pre-analytical problems (e.g., sample taken improperly, sample stored incorrectly, sample labeled incorrectly) or to analytical problems (e.g., machine not accurately calibrated, technical problems with equipment or reagents, or deterioration of analyte). If there are any conflicts between reference ranges in Appendix 4 and the reference ranges for the local laboratory, the local laboratory reference ranges will have precedence in the determination of AEs.

The Investigator must evaluate any change *of clinical relevance* in a laboratory test as to whether it meets the definition of an adverse event, and repeat, if needed, any clinically significant abnormal laboratory test. Any laboratory abnormalities meeting the definition of an adverse event should be recorded on the Adverse Events CRF.

Refer to Section 14, "Reporting Safety Information" for further directions.

13.5 Special Laboratory Evaluations

Measurement of selected "special" laboratory parameters has been included in the study to evaluate potential effects of dexamethasone (EDS-EP) treatment (for details on aseptic procedure for blood withdrawal and on blood diversion see "Study Procedures on Sterility Testing for Study IEDAT-03-2018 (OLE-IEDAT)"; Appendix 9). The following special laboratory parameters will be assessed in the study:

- Blood glycosylated hemoglobin (HbA1c, %), CD4+ lymphocytes and C-reactive protein (CRP)– to be performed at Months 6 and 12.
- Screening for adrenal insufficiency will be performed in all patients, regardless of weight, via early morning (before 8:00 AM) plasma cortisol testing 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). If the 8:00 AM cortisol level is below 3-5 µg/dL (depending on assay) regardless of symptoms, or the patient exhibits signs or symptoms of adrenal insufficiency (Appendix 12) and has a cortisol <10 µg/dL, the patient will receive a high dose ACTH stimulation test, regardless of weight, within 24 hours. If the ACTH stimulation test is normal, the patient can continue dosing with EDS-EP, after the effects of the ACTH have dissipated (e.g., 30 days after ACTH administered). If the patient fails the ACTH stimulation test they will be discontinued from the study and referred to a pediatric endocrinologist, with a recommendation to prescribe stress dose steroids.
- High dose ACTH stimulation test – In the event that patients show signs or symptoms of adrenal insufficiency (Appendix 12) during the study, especially following interruption of the study drug (including loading failures), they will be tested for adrenal insufficiency using a high dose ACTH stimulation test (250 µg given i.v. or i.m.), regardless of weight. If ACTH testing confirms adrenal insufficiency, the patient will be referred for evaluation and treatment. Blood samples (2.0 mL) for measurement of plasma cortisol will be collected prior to ACTH administration (0 min), and at 30 and 60 min post-dose. A rise in plasma cortisol level to greater than 18 µg/dL within 60 min demonstrates a normal result. A rise in cortisol to less than 18 µg/dL within 60 min demonstrates an abnormal response.

13.6 Sterility Testing of EDS-EP

CCI [redacted]

13.7 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS (Posner et al, 2007; Posner et al, 2011) is a standardized suicidal rating system that has provided data for the pediatric suicidal risk analysis of antidepressants conducted by the Food and Drug Administration (FDA). The pediatric version of the scale will be used for patients who are less than 12 years of age at the baseline visit (and will be used throughout the study, even if a patient turns 12 during the course of the study). The test assessments will be performed using the "Since Last Visit" version of the C-SSRS. Subjects with suicidal ideation will be excluded from participating in the trial.

13.8 Bone Mineral Density (BMD)

Measurements of BMD will be performed for all patients at at 6 and 12 months to assess potential steroid-related changes. Bone mass will be measured in the spine and total body (less the head), following the guidelines provided in the 2013 International Society for Clinical Densitometry Official Pediatric Position (Gordon et al, 2014). The suggested method for assessing BMD in the study is dual energy x-ray absorptiometry (DXA). The analysis will be performed with Z-scores following the above guidelines. The same method of assessment will be used for each patient throughout the study.

13.9 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 (Marshall and Tanner 1969, 1970) 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.

14 REPORTING SAFETY INFORMATION

14.1 Adverse Events

Assessment of Adverse Events (AEs) will be performed throughout the study, from the time of signing of the ICF at baseline through the final study visit (Month 12 or early discontinuation). All Adverse Events will be recorded in the CRF. In addition, all subjects will be followed up through 30 days after the final visit (Month 12 or early discontinuation) or at least 60 days after the final infusion, whichever is longer, for the occurrence of any AEs or SAEs.

14.1.1 *Glossary*

Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "response to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at last a reasonable possibility, i.e., the relationship cannot be ruled out.

Adverse Event (AE)

An AE is 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.

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)

Any untoward medical occurrence 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.

Symptoms or medically significant laboratory or instrumental (e.g., electrocardiographic) abnormalities of a pre-existing disease, such as cancer or other disease, should not be considered an adverse event. However, the occurrence of new symptoms, or laboratory or instrumental abnormalities, as well as worsening of pre-existing symptoms, are considered adverse events.

Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is an adverse event, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or Package Insert/Summary of Product Characteristics for an approved product).

Non-Serious Adverse Event

A non-serious adverse event is any adverse event that does not meet the criteria listed above for a serious adverse event.

14.1.2 *Data Collection*

For each event, record the following information on the Adverse Event section of the Case Report Form:

- **Classification of the Event:** Classify the event as either serious or non-serious
- **Description of Signs or Symptoms:** Whenever possible, record a specific diagnosis for the event. If a diagnosis cannot be made, then record each sign or symptom separately, e.g., record nausea and vomiting as two events. If multiple episodes of an event occur, separated by an appropriate time interval to justify considering the subsequent episodes as a repeat occurrence, record each episode separately on the Case Report Form.
- **Onset Date and Time:** Record the date and time the event started. If a change from baseline/previous evaluation in a laboratory test is reported as an adverse event, record the start date as the date of collection of the first lab sample that shows the change.
- **Stop Date and Time:** Record the date and time the event resolved. If a change from baseline/previous evaluation in a laboratory test is reported as an adverse event, record the stop date as the date of collection of the first sample that shows a return to the previous level.
- **Intensity:**
    1. **Mild:** Event not resulting in disability/incapacity, which resolves without treatment.
    2. **Moderate:** Event not resulting in disability/incapacity, which requires treatment.
    3. **Severe:** Event resulting in temporary and mild disability/incapacity, which requires treatment.
- **Relationship to the Study Agent:** Every effort should be made to determine the cause of each adverse event. The correlation between the study agent and the adverse event should be classified as follows:

1. **Probable**
    a) The event follows a reasonable temporal sequence from administration of the study agent;
    b) The event follows a known response pattern to the study agent;
    c) The event <u>cannot be</u> reasonably explained by:
        - the known characteristics of subject's clinical state, or
        - by other therapy administered, or
        - by the diagnostic/interventional procedure;
    d) There is evidence of partial or complete disappearance of the event after withdrawal of the product (positive de-challenge)

2. **Possible**
   a) The event follows a reasonable temporal sequence from administration of the study agent;
   b) Causation of the event by the study agent cannot be excluded;
   c) The event follows a known response pattern to the study agent but the event could have been produced by:
      - the subject's clinical state, or
      - other therapy administered, or
      - a diagnostic/interventional procedure.

3. **Unlikely**
   a) The adverse event follows a reasonable temporal sequence from administration of the study agent;
   b) Other reasons are more likely to be the cause of the adverse event, based on the present knowledge of the
      - disease under treatment, or
      - other therapy administered, or
      - study drug;
   c) A causal relationship between the adverse event and the study drug cannot be ruled out with certainty.

4. **Not Related** The event is either a pre-dose event or is definitely due to causes separate from the administration of the study agent, i.e.,
      - documented pre-existing condition
      - technical and/or manual procedural problems
      - concomitant medication
      - subject's clinical state.

- **Action Taken, in relation to treatment of the AE:**

0. **None**
1. **Drug treatment required** (a medication was prescribed or changed; record on the Concomitant Medication section of the Case Report Form)
2. **Non-drug treatment required** (a non-drug treatment was prescribed or changed, record under "Comments" in the Adverse Event section of the Case Report Form)
3. **Hospitalization or prolonged hospitalization** (fill out an SAE report)
4. **Diagnostic or clinical test(s) conducted** (attach a copy of the results to the Case Report Form)
5. **Subject discontinued from the study**

- **Action taken with study treatment**

  0. **Dose not changed**
  1. **Drug interrupted**
  2. **Drug withdrawn**
  3. **Not applicable**

- **Subject Outcome:**

  1. **Recovered without sequelae**
  2. **Recovered with sequelae** (describe the sequelae under "Comments" in the Adverse Event section of the Case Report Form)
  3. **Not Recovered, event on-going** (follow the subject until a definite outcome can be determined. When follow-up data are collected, report follow-up information under "Comments" in the Adverse Event section of the Case Report Form; if event is serious, fill in a follow-up Serious Adverse Event Report)
  4. **Died** (list primary cause of death under "Event Description" of the Adverse Event section of the Case Report Form; if available, attach a copy of the autopsy report to the Case Report Form and send a copy to the Sponsor)

- **Comments:**

  Provide other pertinent clinical information and observations under "Comments" in the Adverse Event section of the Case Report Form. For example, record predisposing or contributing conditions, such as previous history, concomitant diseases or medications, and/or procedural risks.

14.1.3 *Subject Follow-up*

Every attempt should be made to follow the subject until the adverse event has resolved or until the Investigator determines the subject has returned to an acceptable state of health.

14.1.4 *Reporting Serious Adverse Events (SAEs)*

The Investigator must report **all serious adverse events within 24 hours**, irrespective of the relationship to study medication, to the CRO, by fax or by e-mail (as back-up option), completing the appropriate reporting form. The CRO will then forward this information to **EryDel** within one business day of receipt. The names of the CRO contact will be communicated to the investigators by the CRO prior to the start of subject enrollment.

The minimum information required for an initial report of a Serious AE is as follows:

- Sender of report (name, address of Investigator, site number),
- Subject identification (screening number),
- Protocol number,
- Reportable event.

All SAE reports and any case of overdose leading to an AE or SAE must be faxed using the appropriate reporting form to the following number within 24 hours:

Materiovigilance and Pharmacovigilance Unit

PPD

In case of fax failure, all sites can use the following email address as back-up option:

Email: PPD

In case of death, a comprehensive narrative report of the case should be prepared by the Investigator and sent to the CRO by mail together with the Serious AE Form, retaining a copy on-site. If an autopsy is performed, a copy of the autopsy report should be actively sought by the Investigator and sent to the CRO as soon as available. A copy of the autopsy report will be retained on-site.

A follow-up Serious Adverse Event Report will be completed by the Investigator if important follow-up information (i.e., diagnosis, outcome, causality assessment, results of specific investigations) are made available after submission of the initial form. The follow-up form will be sent to the CRO as described above.

If the Investigator becomes aware of any deaths or Serious Adverse Events after the end of the 60-day follow-up window established in the protocol following investigational product administration, they will be reported to the CRO as described above.

14.2 Safety Reporting to Investigators, IRBs/IECs, and Regulatory Authorities

The Sponsor or their designee will be responsible for reporting all SAEs to regulatory authorities, investigators, and Independent Ethics Committees / Institutional Review Boards (IRBs/IECs), as applicable, in accordance with national regulations for the United States. For all active investigators located in the United States, the Sponsor or their designee will prepare an expedited report for all SAEs that are unexpected and potentially related to the study drug, and copies will be distributed according to all applicable laws and regulations. The investigational site also will forward a copy of all expedited reports to their IRB/IEC.

14.3 Reporting Overdose

If the investigational site staff administering the study medication reports that a subject was given more than the specified dose of study medication, this will be considered an overdose and must be reported immediately to the Investigator. Any instance of overdose, whether symptomatic or not, must be communicated to the CRO within 24 hours and be fully documented as a Serious Adverse Event. Details of any signs or symptoms and their management should be recorded including details of any antidote(s) administered.

14.4 Pregnancy

This study will exclude pregnant and breast-feeding patients, and females of childbearing potential, unless they are practicing adequate contraception, as determined by their Health Care Provider. As a further precaution, a serum pregnancy test will be performed at Months 6, 12 and safety follow up visits for all young women who have had a menstrual period within the past year. Results of the pregnancy tests at IEDAT-02-2015 final visit must be negative for the patient to be randomized to treatment.

If a patient becomes pregnant during the study, she will be discontinued from the study immediately. Patients and their parents/caregivers should be instructed to notify the Investigator if it is determined that, after completion of the study they have become pregnant, either during the treatment phase of the study or within 30 days of completing the study. Whenever possible a pregnancy should be followed to term, any premature terminations reported, and the status of the mother and child should be reported to the CRO or EryDel after delivery.

Based on the estimated half-life of dexamethasone given with the EDS, i.e. less than 4 days, a period of one month of continued contraception should follow after study conclusion or early termination due to any reason.

14.5 Independent Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be established by EryDel to review the safety of all patients enrolled in this trial, on an ongoing basis. No EryDel employee or investigator involved in the EDS clinical studies will be a voting member of this board. The DSMB will regularly review the safety data as it accrues.

The Board will be regularly notified of the occurrence of any fatal or life threatening events immediately (within 7 calendar days) and any other serious adverse events within 15 calendar days. The Board will also receive updates on any adverse dropouts on a regular basis (once per month). The Board will have access to the safety data including serious AEs and adverse dropouts, as well as clinically significant abnormal laboratory tests, vital signs and ECGs at periodic intervals.

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

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

15 SUBJECT COMPLETION AND DISCONTINUATION

15.1 Definitions

'Discontinuation' will refer to any subject who does not complete the full 12 months (±30 days) of this extension.

15.2 Procedures for Handling Withdrawals

In the absence of a medical contraindication or significant protocol violation, every effort should be made by the Investigator to keep the patient in the study. All efforts should be made to report the observations as thoroughly as possible at the time of the patient's withdrawal, with an explanation of why the subject is withdrawing from the study.

The criteria for discharging a patient from the study are listed below. The Investigator must indicate the primary reason (only one can be reported) for discontinuation, as well as the date when the decision was made; these will be specified on the 'End of Study' form.

A patient may be withdrawn from study participation if:

- Any hypersensitivity or allergic reaction, clearly linked to the study medication, has occurred;
- the patient experiences an AE sufficiently severe, in the opinion of the investigator, that it contraindicates the patient continuing in the study;
  If the patient experiences a systemic illness considered unrelated to the study medication, it still must be reported as an AE.
- the patient/caregiver withdraws consent (e.g. subject refuses to have any more blood samples taken for the EDS process; in this instance a specific reason must be recorded by the investigator);
- a major protocol deviation that jeopardizes the continued well-being of the patient or poses an risk to the patient's health;
  If the patient is able to abstain in the future from activities/behaviors that constituted a major protocol violation, the patient should be allowed to continue.
- the patient is lost to follow-up, i.e., the subject did not return to the clinic, and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented;
- the Sponsor, IEC/IRB, or regulatory agency terminates the study.

Dropouts will not be replaced.

The Investigator may terminate a patient's study participation at any time during the study if a patient meets the study termination criteria described above. In addition, a patient or his/her parent/guardian may discontinue the patient's participation without giving a reason at any time during the study. Should a patient's participation be discontinued, the primary reason for termination must be recorded. For patients who discontinue prior to Month 12, an attempt should be made to perform the safety follow up visit on the patient, and to follow up on any safety issues until resolution.

Patients who discontinue prematurely should be followed up for 60 days after their final infusion regarding the occurrence of any Serious Adverse Events.

16 STATISTICAL METHODS

16.1 Analysis of Efficacy

Primary Endpoint

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

Exploratory Endpoint

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

Secondary Endpoint

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

16.2 Statistical Methods

16.2.1 *Sample Size*

There is no formal sample size calculation, as the sample size is dependent on the number of patients who complete the double-blind extension study (Protocol IEDAT-02-2015), express the desire to continue treatment with the investigational drug, and meet the selection criteria defined in Section 9.2 of the Study IEDAT-03 protocol. It is expected that a maximum of 150 patients will enter this open-label extension.

The following analysis sets will be used:

1) *Efficacy Population (EP)*: 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 primary efficacy variable in this extension study.
2) *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.

16.2.2 *Background and Demographic Characteristics*

The background and demographic characteristics will consist of age, sex, height, body weight, BMI, past and current medical conditions, and history of disease. Continuous variables will be summarized by mean, standard deviation, median, and range (minimum, maximum), and discrete variables will be summarized using frequencies and percentages.

16.2.3 *Study Medication*

The number of patients receiving a dose of study treatment will be reported, and the average dose of EDS-EP (RBC-encapsulated DSP) administered to each patient and across all patients, based on measurements of samples taken from the infusion bags prior to dosing, will be summarized by mean, standard deviation, median, and range (minimum, maximum).

16.2.4 *Concomitant Medications and Therapy*

A listing of concomitant medications administered from the time of dosing of the study medication through completion of the final evaluation (Month 12 or early discontinuation) will be provided.

16.2.5 *Safety Evaluations*

All patients in the Safety Population will be included in the safety analyses. All adverse events will be listed and summarized by body system and preferred term. The incidence of AEs (%) and their intensity and relatedness to the study drug, as assessed by the Investigator, will be reported. Serious adverse events (SAEs) and events which are newly occurring or worsening after administration of the study medication will be summarized. In addition, adverse events that result in death or discontinuation (ADO) of the study medication will be listed separately.

Other safety parameters such as vital signs, standard laboratory parameters, ECGs, physical/neurological examination findings, and special laboratory parameters will be listed and summarized accordingly. Abnormal and clinically notable values will be identified and listed for each parameter, as appropriate.

16.2.5.1 Interim Safety Review

The independent Data Safety Monitoring Board (DSMB) that was established by EryDel to review the safety of all patients enrolled in the IEDAT-02 study, will continue to monitor the safety of all patients continuing in this trial, on an ongoing basis. No EryDel employee or investigator involved in the EDS-EP clinical studies will be a member of this board. The DSMB will meet regularly to assess the safety from the emerging data. The time between successive meetings should not be more than three months.

After reviewing the emerging safety profile for EDS-EP, the DSMB will make a recommendation to EryDel to (a) amend the ongoing EDS-EP study, (b) terminate the EDS-EP, or (c) continue the clinical program as designed. The current study will not be amended or changed (this includes the study design and entry criteria) unless mandated by the emerging safety profile of EDS-EP.

A separate DSMB Statistical Analysis Plan will be developed for specifying the analyses, tables, listings and figures to be prepared for DSMB meetings.

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

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

16.2.6 *Efficacy Analyses*

Descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum) will be provided for all continuous efficacy measures for actual values and changes from baseline of Study IEDAT-03 at each time-point. For categorical variables, the number and percentage of patients in each category will be presented at each time-point.

The analysis of long-term efficacy of EDS-EP is an exploratory objective of this extension study, and will be based on the results for the "Modified" International Cooperative Ataxia Rating Scale (mICARS), and the Clinical Global Impression of severity and change (CGI-S/C). Descriptive statistics will be performed to determine the proportion of patients who improve, maintain their current state, or worsen after one year of treatment with EDS-EP in this open-label extension study, compared to their baseline status at entry into the IEDAT-03-2018 trial. The mean (SD) change from baseline at each time-point will be evaluated for the mICARS and the CGI-S. 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.

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. As a secondary objective, similar descriptive analyses will be performed to evaluate the long-term effects of EDS-EP on health-related Quality of Life (QoL), as assessed by the EQ-5D-5L scale.

The details of the statistical analyses will be presented in a separate Statistical Analysis Plan.

Handling of Dropouts and Missing Data

Patients who discontinue treatment prematurely, i.e. prior to the Month 12 visit, are defined as dropouts. All final Month 12 (Visit 13) evaulations should be performed at the time of discontinuation.

17 ETHICS

17.1 Ethical Considerations

The study will be carried out in accordance with the Declaration of Helsinki, as amended by the 64th General Assembly of the World Medical Association, Fortaleza, Brazil, October 2013 (Appendix 1).

Subject Information and Informed Consent

The Informed Consent Form, as well as the Subject Information Sheet, must be approved by the IRB/IEC together with the Study Protocol, before the start of the study.

All subjects, or if necessary their parent/caregiver or legal representative (with assent by the subject), must sign and personally date an approved Informed Consent Form after receiving detailed written and verbal information about the reason, the nature, the required procedures, the intended duration and the possible risks and benefits and any discomfort associated with the study. Each subject should be informed that his/her participation in the study is voluntary and that he/she may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

The language used in the oral and written information about the trial, including the written Informed Consent Form should be as non-technical as practical and should be understandable to the subject. The subject must be given ample time to read and to understand the Subject Information Sheet and opportunity to inquire and ask any clarification about the trial before signing the Informed Consent Form.

No study procedure can be performed (including the baseline visit) before the informed consent form has been signed. The informed consent procedure must be done according to the guidelines provided in the Declaration of Helsinki and the ICH E6 Guideline for Good Clinical Practice.

The subject must be made aware and agree that personal information may be scrutinized during audit / inspection by competent authorities and properly authorized persons. However, personal information will be treated as strictly confidential and will not be publicly available.

By signing the Investigator Statement (Appendix 3), the Investigator assures **EryDel Pharmaceuticals** that Informed Consent will be obtained.

Original signed Informed Consent Forms will be filed with the Investigator's File.

17.2 IEC/IRB Approval

The protocol, Investigator's Brochure, Subject Information Sheet, Informed Consent Form and any advertisement for the recruitment of subjects must be reviewed and approved by an appropriately constituted IEC/IRB, as required in Chapter 3 of the ICH E6 Guideline. A copy of the Committee's dated approval and a list of the members of the IEC/IRB will be given to the Sponsor for the Sponsor's files. A copy will be also included in the Final Report. Written IEC/IRB approval must be obtained by the Sponsor prior to shipment of study agent or subject enrollment. Any amendments to the protocol, Informed Consent Form (ICF) or Subject Information Sheet, other than administrative ones, must be approved by this committee.

18 ADMINISTRATIVE CONSIDERATIONS

18.1 Regulatory Requirements: Sponsor/Investigator Obligations

This study will be conducted in accordance with the Declaration of Helsinki and the ICH E6 Guideline (Good Clinical Practice, see Appendix 2). To ensure compliance the Investigator agrees, by written consent to this protocol, to fully cooperate with compliance checks by allowing access to all documentation, including subjects' hospital files (the source documents), by authorized individuals.

18.2 Curriculum Vitae

The Investigator and any co-Investigator(s) must provide the Sponsor with current copies of their own curriculum vitae.

18.3 Investigator and Study Administrative Structure

The administrative structure of the study (e.g., Investigators, monitoring and evaluation personnel, laboratory facilities, clinical trial supply management) is presented in the Trial Master File.

The listing should include:

a) The Investigator(s);

b) Any other person carrying out observations of primary or other major efficacy or safety variables, such as a nurse, physician's assistant, clinical psychologist, clinical pharmacist or house staff physician.

18.4 Investigator's Statement

This document, signed and dated by the Principal Investigator, describes the Investigator's obligations. The standard text is appended to the protocol (Appendix 3).

18.5 Monitoring Procedures

18.5.1 *Study Monitoring*

A CRO will be selected by the Sponsor to oversee the conduct of the trial. An appropriate representative of the CRO (Study Monitor) will maintain contact with the Investigator and will visit the study site for the purpose of discussing and/or retrieving data. An initiation (pre-study) visit will be made by the Study Monitor to discuss with the Investigator the protocol and the obligations of both the Sponsor and the Investigator. The Investigator must allow the Study Monitor to perform periodic, interim monitoring visits. The purposes of these visits are:

- To verify that written Informed Consent was obtained prior to each subject's participation in the trial.
- To assess the progress of the study.
- To review the compliance with the study protocol.
- To determine whether all adverse events were appropriately reported.
- To determine whether the Investigator is maintaining the essential documents.
- To discuss any emergent problem.
- To check the Case Report Forms (CRFs) for legibility, accuracy and completeness.
- To validate the contents of the CRFs against source documents.

- To collect completed CRFs.
- To assess the status of drug storage, dispensing and retrieval.

The Investigator will make available the source documents for inspection. This information will be considered as confidential. *Violations of and deviations from the protocol must be notified to the Study Monitor as soon as possible.*

The Study Monitor will perform a closeout visit at the time when all CRFs have been retrieved and all queries have been answered.

18.5.2 *Case Report Forms (CRFs)*

Electronic Case Report Forms (eCRFs) will be provided for each subject. The study Monitor will review the forms at each site visit.

Case Report Forms must be completed for all subjects who sign Informed Consent, even if the subject fails to complete the study. No section of the CRFs is to be left blank without an appropriate explanation by the Investigator, since the lack of such explanation may necessitate discarding an otherwise usable observation.

If requested, copies of the CRFs are to be made available to the appropriate regulatory agencies.

18.5.3 *Auditing/Inspecting*

The Investigator will make all pertinent records available, including source documentation, for inspection by regulatory authorities and for auditing by the Sponsor. This information will be considered as confidential. Audits/Inspections may occur any time from start to after conclusion of the study. When an Investigator signs the protocol, he/she agrees to allow regulatory authorities and **EryDel** auditors to inspect his/her study records.

18.6 **Archiving of Records**

Copies of the protocol, subject identification codes, eCRFs, source data, Informed Consent Forms and other documents pertaining to the study conduct must be kept for the maximum period of time as required by the study center. This time period must be at least two years after the last approval of the marketing application of the study agent in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least two years have elapsed since the formal discontinuation of clinical development of the study agent.

No study document should be destroyed without prior written agreement between the Sponsor and the Investigator. Originals of all documentation and copies of outgoing correspondence concerning the study will be stored and retained by the Sponsor in a safe area in the Trial Master File for the lifetime of the product. In particular, the final report sent by the Investigator to the IRB/IEC must be retained by the Sponsor, or the subsequent owner, for five years beyond the lifetime of the study agent.

18.7 **Final Clinical Study Report**

The Final Clinical Study Report (CSR) will be written by the CRO, according to specifications to be defined by **EryDel**.

18.8 **Study Documentation and Publication of Results**

Study Documentation

All unpublished documentation (including the protocol, CRFs and Investigator's Brochure) given to the Investigator is strictly confidential. All recipients must agree not to disclose the information herein

contained to any person not connected with the study without the prior written authorization of **EryDel S.p.A**. The submission of these documents to the IRB/IEC is expressly permitted. The involved parties agree that the results of this study will be used in their original form and/or in a global report for submission to governmental and regulatory authorities of any country.

All information communicated to the investigator(s) by **EryDel** is the exclusive property of **EryDel S.p.A**. The Principal Investigator will ensure this information shall be kept strictly confidential by him/her or any other person connected with the study and shall not be disclosed to any third party without the prior written consent of **EryDel**.

Publication of Results

Any formal presentation or publication of the data from this trial will be considered as a joint publication by the Investigator(s) and EryDel. Authorship will be determined by a Publication Committee consisting of the lead investigator(s) from the trial, representatives from EryDel, and an external consultant with expertise in the field. For multi-center studies, it is mandatory that the first publication is based on data from all centers, analyzed as stipulated in the protocol by a statistician designated by EryDel. Investigators participating in this study agree not to present or publish data gathered from a single center or sub-group of centers before the full initial publication, unless agreed to by all other investigators and EryDel. Authorship of any publication resulting from this trial will include members of each of the contributing centers and key contributors to the design and execution of the study, including EryDel personnel.

EryDel will form a study publication committee to coordinate and develop a publication policy and help in its implementation. The publication committee will be comprised of the Principal Investigators from each of the countries (to be determined by EryDel), based on their contributions to study conduct and their status in the field. The other members of the publication committee will include a representative of EryDel and an external consultant. Members of the publication committee cannot serve as first authors of more than one primary publication.

The authorship of the first multicenter paper will be comprised of members of the publication committee, Principal Investigators of the three sites with the highest numbers of valid patients, and EryDel representatives who have made significant contributions to the design, conduct and analysis of the results. The Principal Investigators of all contributing centers will be acknowledged in the publication. The Publication Committee will decide on the content, journal, and sequence of publications /presentations.

Any publication, abstract, or paper of any information or material relating to or arising out of the present clinical study shall be sent to EryDel for review at least sixty (60) days before presentation at any congress, or publication of the final form(s) by any journal. EryDel will inform the Investigator of any changes or deletions necessary to preserve EryDel's confidential and proprietary technical information. All rights and interests worldwide in any inventions, know-how or other intellectual or industrial property rights, which arise during the course and/or as a result of the present clinical study or which arise from the information or materials supplied under this Agreement, shall be assigned to, vest in and remain the property of EryDel S.p.A.

18.9 Financial Agreement

A financial agreement (separate from the protocol) will be made and signed by **EryDel S.p.A.** or their designee and by a representative of the Institution where the study will be conducted.

18.10 Termination of Study

In the event that the Investigator is unable to continue the study, another suitable sub-Investigator at the site will be designated to serve as the Investigator in the interim, until a new Investigator can be identified. This interim Investigator, if approved by the site IRB/IEC will carry out the responsibilities of the

Investigator. Documentation testifying to this will be submitted to the Study Monitor within 10 days of the change. Within 6 months of the appointment of the interim Investigator, the new Principal Investigator must be identified and approved by both **EryDel S.p.A.** and the IRB/IEC for the study to continue at the site.

If the Sponsor and/or the Investigator should discover conditions arising during the study that indicate it should be terminated, an appropriate schedule for termination will be instituted. If the Investigator terminates the study, an explanatory letter will be provided to **EryDel**. Should the study be discontinued due to a decision by **EryDel**, the Investigator will be reimbursed for reasonable expenses incurred and for the subjects actually treated according to the study protocol.

18.10.1 *Study Discontinuation by the Sponsor*

The Sponsor may terminate the entire study, or the study at an individual site, at any time, for any of the following reasons:

- failure to enroll subjects;
- protocol violations or deviations;
- inaccurate or incomplete data;
- non GCP compliance;
- completion of enrolment;
- administrative reasons.

18.10.2 *Study Discontinuation by the Investigator*

The Investigator may terminate his/her participation in the study in consultation with the Sponsor due to the occurrence of significant adverse events and/or adverse drug reactions endangering the health of subjects, which make it ethically unacceptable to continue.

18.11 Insurance Policy

EryDel S.p.A., or its designee, will provide insurance coverage for damages emerging from the trial and involving the subjects treated with the test compound, provided that the Investigator(s) have adhered to the terms and provisions of the protocol. The principal Investigator will be supplied with all data concerning the insurance company and policy number for a maximum sum insurable.

18.12 Financial Disclosure

The Principal Investigator and sub-Investigators will provide the Sponsor with adequate and accurate financial information (PD35) to ensure that the Sponsor can make complete and accurate financial certification of disclosure statements to concerned regulatory authorities. It is the duty of the Investigator to promptly update previous information provided to the Sponsor if there are salient changes that occur during the course of the study, and for a period of one year following its completion (last patient last visit).

The study will be performed under a US IND; therefore, all Investigators/sub-Investigators, contractors, etc., are expected to comply with the obligations as specified in the CFR (21 CFR part 54) by the US FDA, including requirements for full Financial Disclosure (Guidance for Clinical Investigators, Industry and FDA Staff: Financial Disclosure by Clinical Investigators, February 2013).

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