CLINICAL STUDY PROTOCOL

Protocol Number	IEDAT-05-2024
Title of Study	An Open-Label Extension Study of EryDex in Patients with Ataxia-Telangiectasia Following Participation in Study IEDAT-04-2022 (NEAT)
Short Study Title - Acronym	Open-Label Extension of EryDex in A-T (OLE NEAT)
Phase	Phase 3
EUCT Number	[redacted]
IND Number	[redacted]
Date of Protocol	Version 3.0 - 10 Sep 2025
Sponsor	Quince Therapeutics S.p.A. Via Meucci, 3 20091 Bresso (MI), Italy [redacted]

Good Clinical Practices Statement

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

Quince Therapeutics S.p.A., Via Meucci 3, 20091 Bresso (MI), Italy

SIGNATURE PAGE

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Protocol Version/Date	Version 3.0 – 10 Sep 2025
Number of Centers	Approximately 21
Sponsor Representative	[redacted] I have read this protocol, and I approve the design of the trial.

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ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACTH	adrenocorticotropic hormone
AE	adverse event
AESI	adverse events of special interest
A-T	ataxia-telangiectasia
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATM	ataxia-telangiectasia mutated
BMD	bone mineral density
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CBC	complete blood count
CD4+	cluster of differentiation 4 positive
CPK	creatine phosphokinase
CRA	clinical research associate
CRO	Contract Research Organization
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP3A4	cytochrome P450 3A4
DEXA	Dual-Energy X-ray Absorptiometry
DSP	Dexamethasone Sodium Phosphate
ECG	electrocardiogram
eCRF	electronic case report form
EDS	EryDex System
eDSP	encapsulated dexamethasone sodium phosphate
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HDL	high-density lipoprotein
IB	Investigator's Brochure
ICARS	International Cooperative Ataxia Rating Scale
ICF	informed consent form
ICH	International Conference on Harmonisation
iDSMB	Independent Data Safety Monitoring Board
IEC	Independent Ethics Committee
IM	intramuscular
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IV	intravenous
LC/MS/MS	liquid chromatography tandem mass spectrometry
LDH	lactate dehydrogenase
LDL	low density lipoprotein
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration

Abbreviation	Definition
MCV	mean corpuscular volume
mICARS	Modified version of the International Cooperative Ataxia Rating Scale excluding oculomotor items (17-19) and items 8-12
OLE	open-label extension
PI	principal investigator
PK	pharmacokinetic(s)
RBC	red blood cell
RDW	red blood cell distribution width
RCL	red cell loader
RmICARS	Rescored Modified version of the International Cooperative Ataxia Rating Scale
RNA-Seq	ribonucleic acid sequencing
RTSM	Randomization and Trial Supply Management
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
TEAE	treatment-emergent adverse events
US	United States
USP	United States Pharmacopeia
WBC	white blood cell

1 PROTOCOL SUMMARY

1.1 Synopsis

Study Title	An Open-Label Extension Study of EryDex in Patients with Ataxia-Telangiectasia Following Participation in Study IEDAT-04-2022 (NEAT)
Brief Study Title	Open-Label Extension of EryDex in A-T (OLE NEAT)
Regulatory Agency Identifier Numbers	[redacted]
Rationale	There are currently no approved therapeutic treatments for ataxia-telangiectasia (A-T); therefore, there is a high unmet medical need. This open-label extension (OLE) trial provides opportunity for participants who complete the full treatment period in Trial IEDAT-04-2022 (A Multi-center, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the ***N****eurological* Effects of ***E****ryDex* on subjects with ***A****taxia-****T****elangiectasia* [***NEAT*** trial]), including participants randomized to the placebo arm, to receive EryDex (dexamethasone sodium phosphate [DSP] encapsulated in autologous erythrocytes [eDSP]) treatment.
Study Objectives	**Safety Objective**: To evaluate the safety and tolerability of eDSP in participants with A-T. **Exploratory Objective:** To evaluate the effects of eDSP on neurological symptoms in participants with A-T.
Study Endpoint Assessments	**Safety Endpoint Assessments**: Evaluation of safety and tolerability in this OLE trial will be based on the assessment of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs), discontinuations due to adverse events (AEs), changes in vital signs, laboratory parameters, physical and neurological examination findings, and the Columbia-Suicide Severity Rating Scale (C-SSRS). Additionally, potential effects associated with the use of eDSP will be assessed by changes in cortisol, glucose, cluster of differentiation 4 positive (CD4+) lymphocyte count, bone mineral density obtained using dual-energy x-ray absorptiometry (DEXA), and growth and development, as applicable. **Exploratory Endpoint Assessments:** Evaluation of the effects of eDSP will be assessed by the International Cooperative Ataxia Rating Scale (ICARS), the modified ICARS (mICARS), and the Rescored mICARS (RmICARS).
Study Design	This is an international, multi-center, prospective, open-label, non-comparative trial to provide eDSP treatment to participants who complete the full trial treatment period and trial assessments (including those receiving placebo) in the IEDAT-04-2022 (NEAT) trial, who do not present safety contraindications to continuation of treatment, and who provide informed consent. The duration of the OLE treatment period will be 24 months. Participants will be considered to have completed the trial when Visit 25 has been performed.

Trial Population	Approximately 100 participants who meet the inclusion and exclusion criteria will be eligible for enrollment. The trial population will include males and females ≥ 6 years of age, with body weight ≥15 kg, who completed the IEDAT-04-2022 trial, including final efficacy assessments (Visit 9), and who do not present with safety contraindications for continuation of treatment, as determined by the investigator. The trial will exclude females who are pregnant or breastfeeding. Females of childbearing potential who are using an adequate birth control method as determined by their healthcare provider, will be eligible. For further details on adequate contraceptive measures, please refer to Section 8.6. Additionally, the trial will exclude participants with the following: • clinically significant immune impairment that in the investigator's opinion precludes further treatment with corticosteroids • current neoplastic disease or previous neoplastic disease not in remission for at least 2 years • confirmed hemoglobinopathies • suicidal ideation • requiring treatment with a systemic corticosteroid (inhaled or intranasal corticosteroids for asthma or allergies, and use of topical corticosteroids are permitted) • requiring concomitant medications prohibited by the protocol, including strong inducers or inhibitors of cytochrome P450 3A4 (CYP3A4).
Study Interventions	The trial treatment, eDSP (encapsulated dexamethasone sodium phosphate, previously referred to as EryDex), is processed ex vivo using the EryDex System (EDS), a drug-device combination product that is used to load DSP into autologous erythrocytes, which are infused into the participant. The eDSP dose to be administered in the IEDAT-05-2024 trial corresponds to that of the IEDAT-04-2022 (NEAT) trial, which was obtained by [redacted] DSP solution) to the EDS and resulted in a mean [redacted] of DSP infused to participants. Trial treatment will be administered by intravenous (IV) infusion approximately every 28 days calculated from the date of the previous dose. There is an allowed window of -7 to +2 days for each treatment visit. The window between an infusion and the subsequent infusion should be kept as consistent as possible, avoiding fluctuations in administration windows. In any case, infusions should not be given fewer than 14 days apart. The [redacted] DSP solution used to prepare eDSP for participants will be provided in sterile, non-pyrogenic [redacted] ampules to be stored at 2°C to 8°C and protected from light. The ex vivo encapsulation of the trial treatment into autologous erythrocytes will be performed using the EDS by means of the red cell loader (RCL), a single-use, disposable kit (EryKit_01), the Syringe Kit, and process solutions, which are all Conformité Européenne (European Conformity; CE)-registered Medical Devices, according to manufacturer instructions. The EDS Version 3.3.2 (or an equivalent version with the same performance and safety) will be used in this trial.

	Trial-related diagnostic and monitoring procedures include: routine (complete hematology, clinical chemistry, and urinalysis) and special (CD4+ lymphocyte counts, alpha-fetoprotein, and C-reactive protein [CRP]) laboratory tests, neurological and physical examinations, vital signs, early morning plasma cortisol tests (and adrenocorticotropic hormone [ACTH] stimulation, as needed), bone mineral density (BMD) assessments, pregnancy tests, administration of scales and questionnaires (ICARS and C-SSRS), biomarker analyses for those who consent, sterility testing of blood and eDSP, DSP concentration testing of eDSP, and ongoing evaluation of concomitant medications and AEs.
Ethical Considerations	A-T is a genetic neurodegenerative disease that causes rapid deterioration in motor function during early childhood, particularly between ages 6 and 9; these children usually become wheelchair-dependent around age 12. In prior clinical studies, eDSP treatment did not raise clinical concerns about the overall safety in A-T participants, nor concern regarding the known long-term side effects of chronic steroid treatment in the A-T population, regardless of the age. Efficacy data suggest that eDSP treatment may reduce the neurological symptoms in patients with A-T. The potential clinical benefit and low incidence of SAEs and treatment-related AEs support the continued investigation of eDSP for the treatment of participants with A-T. Risks associated with trial procedures have been mitigated by selective inclusion and exclusion criteria and safety monitoring, which are tailored to reduce the burden for participants and caregivers (e.g., minimization of blood samples and volume, remote visits, avoidance of long visits when possible, and window intervals for the conduct of trial visits).

1.2 Schedule of Assessments

**For Visits 13 through 25, please see next page*

Visit*	Screening/ Baseline V1[a] Dose 1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Dose		**Dose 2**	**Dose 3**	**Dose 4**	**Dose 5**	**Dose 6**	**Dose 7**	**Dose 8**	**Dose 9**	**Dose 10**	**Dose 11**	**Dose 12**
Visit Window	**Each treatment must be scheduled every 28 days (window -7 days, +2 days), calculated from the previous visit**											
Informed Consent	X											
Medical History/Demographics	X											
Inclusion/Exclusion	X											
eDSP Infusion	1	2	3	4	5	6	7	8	9	10	11	12
Neurological Examination	X			X			X			X		
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[b]	X	X	X	X	X	X	X	X	X	X	X	X
Height, Weight[c]	X	X	X	X	X	X	X	X	X	X	X	X
Early Morning Plasma Cortisol Test[d]	X	**As needed**										
ECG[e]	X											
Routine Laboratory Tests[f]	X			X			X			X		
BMD, where countries allow[g]	X											
ICARS	X						X					
C-SSRS[h]	X	X	X	X	X	X	X	X	X	X	X	X
Special Laboratory Tests[i]	X			X			X			X		
Pregnancy Testing[j]	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for biomarker development[l]	X			X			X			X		
Culture-based Sterility Test on eDSP	X											X
eDSP Sample for CBC, DSP Content[m]	X						X					X
Prior/Concomitant Medications[n]	**Throughout the duration of the trial**											
Adverse Events	**Throughout the duration of the trial**											

Schedule of Assessments (continued)

Visit	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25[o] Trial Completion/ Early Discontinuation
Dose	**Dose 13**	**Dose 14**	**Dose 15**	**Dose 16**	**Dose 17**	**Dose 18**	**Dose 19**	**Dose 20**	**Dose 21**	**Dose 22**	**Dose 23**	**Dose 24**	
Visit Window	**Each treatment must be scheduled every 28 days (window -7 days, +2 days), calculated from the previous visit**												**~ 28 (-7, +2) days after last infusion**
eDSP Infusion	13	14	15	16	17	18	19	20	21	22	23	24	
Neurological Examination	X						X						X
Brief Physical Examination	X			X			X			X			X
Vital Signs[b]	X	X	X	X	X	X	X	X	X	X	X	X	X
Height, Weight[c]	X			X			X			X			X
Early Morning Plasma Cortisol Test[d]	As needed												X
ECG[e]													X
Routine Laboratory Tests[f]	X			X			X			X			X
BMD, where countries allow[g]													X
ICARS	X						X						X
C-SSRS[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Special Laboratory Tests[i]													X
Pregnancy Testing[j]	X	X	X	X	X	X	X	X	X	X	X	X	X
Puberty Status[k]													X
Blood Sample for Biomarker Development[l]	X												X
Culture-based Sterility Test on eDSP												X	
eDSP Sample for DSP Content[m]						X						X	
Prior/Concomitant Medications[n]	**Throughout the duration of the trial**												
Adverse Events	**Throughout the duration of the trial**												

Abbreviations: ACTH = adrenocorticotropic hormone; AE = adverse event; BMD = bone mineral density; BP = blood pressure; CBC = complete blood count; CD4+ = cluster of differentiation 4 positive; C-SSRS = Columbia-Suicide Severity Rating Scale; D = Day; DSP = Dexamethasone Sodium Phosphate; ECG = electrocardiogram; EDS = EryDex System; eDSP = encapsulated dexamethasone sodium phosphate; ICARS = International Cooperative Ataxia Rating Scale; ICF = informed consent form; IV = intravenous; LLN = lower limit of normal; OLE = open-label extension; RNA-Seq = ribonucleic acid sequencing; SAE = serious adverse event; V = visit.

Notes:

Each treatment must be scheduled every 28 days (window -7 to +2 days), calculated from the previous infusion. The window between an infusion and the subsequent infusion should be kept as consistent as possible, avoiding fluctuations in administration windows. Doses should not be given in any case less than 14 days apart.

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

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

At each applicable visit, the ICARS should be the first scale administered. Neurological assessments must be performed before any phlebotomy or IV insertion so that the upper extremity neurological examination is not impeded by an IV line, except at Visit 25 (a non-dosing visit)

Footnotes:

a) The Screening/Baseline visit for this trial may occur concurrently with Visit 9 in the IEDAT-04-2022 trial. The IEDAT-05-2024 ICF should be signed prior to initiating any assessments required for the OLE trial. All assessments required for Visit 9 in the IEDAT-04-2022 trial and the Screening/Baseline IEDAT-05-2024 should be completed only once (neurological examination, ECG, routine laboratory tests, BMD, ICARS, special laboratory tests, early morning cortisol, serum pregnancy test, C-SSRS, physical examination [if performed at Visit 9 in the IEDAT-04-2022 trial on the same day as the Screening/Baseline visit (Visit 1) in the IEDAT-05-2024 trial]) as long as eDSP dosing occurs within 30 days. If the dosing takes >30 days, BMD should not be repeated. For females of childbearing potential, confirmation of a negative urine pregnancy test is required prior to dosing.

b) Vital signs include temperature, pulse, systolic and diastolic BP, and respiratory rate. On the days of treatment, temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic BP, and respiratory rate will be measured within 15 minutes before and within 15 minutes after the IV infusion of the trial treatment. Pulse and BP will be measured after the participant has been in the supine position for at least 5 minutes.

c) Body weight and height and calculation of body mass index (BMI)- Height will be measured by a stadiometer at Screening/Baseline and each applicable subsequent visit and used along with body weight to calculate BMI. Weight will be measured just once per treatment visit, and weight and height will be measured every 3 months after Visit 12.

d) If at any time during the trial a participant exhibits signs or symptoms of adrenal insufficiency, cortisol should be tested via an 8:00 (+30 minutes) AM cortisol sample. If the result is <5 µg/dL (or the LLN of the assay used), the participant should undergo a high dose ACTH stimulation test. Also, if the AM cortisol is between 5-10 µg/dL, and there is a strong suspicion for adrenal insufficiency, the ACTH test should be done. The test should be scheduled as soon as possible, and until normal adrenal function is confirmed, the participant should be monitored and treated following clinical guidelines for suspected adrenal insufficiency. If the result of the ACTH stimulation test is abnormal, the participant should be given appropriate treatment, but can continue in the trial, if the investigator considers it appropriate. Additional details are provided in Appendix 5.

e) ECG is to be performed at Screening and Visit 25 (Trial Completion/Early Discontinuation) only. Results must be available to confirm eligibility before the participant can be treated in the OLE. If the ECG is found to have abnormalities requiring follow-up, it will be repeated (in triplicate) and evaluated to determine eligibility.

f) Routine laboratory assessments include complete hematology, clinical chemistry (including serum creatinine), and urinalysis.

g) The bone mineral density/ DEXA scan will only be performed at Screening if not performed at Visit 9 of the previous trial, even if more than 30 days have elapsed since Visit 9. The BMD will be repeated at Visit 25 only if the participant completed at least 12 months of trial treatment.
h) C-SSRS to be administered at all visits. "Since Last Visit" version should be used at all visits.
i) Special laboratory tests include CD4+ lymphocyte count, alpha-fetoprotein, and C-reactive protein. These tests will be repeated at the end of treatment (Visit 25/Early Discontinuation) only if the participant completed at least 12 months of trial treatment.
j) Female participants noted to be of childbearing potential will have a serum pregnancy test obtained at Screening/Baseline and Visit 25/Early Discontinuation visits. Females noted to be of childbearing potential will have a urine pregnancy test obtained and evaluated before each eDSP infusion at Visits 1 through 24.
k) All participants, including those who have not being identified as having undergone puberty while on study, will have their puberty status documented by the investigator at Visit 25.
l) For participants who have provided specific consent, biomarkers include RNA-seq, cytokine panel, and neurofilament light chain.
m) 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 eDSP sampling point will be used for determination of DSP content and CBC. No CBC is required after Visit 12.
n) Concomitant medications will be recorded for the prior 6 weeks at Screening and at each dosing visit prior to every dose.
o) Participants who withdraw from the trial early or who complete the trial's full treatment period will be requested to perform this Trial Completion/ Early Discontinuation Visit 28 days (-7, +2 days) days after their final infusion.

2 INTRODUCTION

Trial IEDAT-05-2024 is an open-label extension (OLE) of Trial IEDAT-04-2022 (NEAT) and is intended to allow for continued encapsulated dexamethasone sodium phosphate (eDSP) treatment (formerly known as EryDex) and collection of safety and tolerability data beyond the 6-month treatment period in the NEAT trial. (The EryDex encapsulation process is described in more detail in Section 2.1.2, Section 6.2, and in Appendix 2).

The NEAT trial is an international, multi-center, randomized, prospective, double-blind, placebo-controlled, Phase 3 trial to assess the effect of eDSP administered by intravenous (IV) infusion once every 28 days (window -7 to +2 days) on neurological symptoms in participants with ataxia-telangiectasia (A-T). Approximately 86 participants between 6- to 9-years-old (primary analysis population) will be enrolled, and approximately 20 participants ≥10 years old will be enrolled.

Approximately 100 males and females ≥6 years of age, with body weight ≥15 kg, who completed the IEDAT-04-2022 trial, including final efficacy assessments (Visit 9), and who do not present safety contraindications for continued treatment, as determined by the investigator, will be eligible to enroll in the OLE.

2.1 Background Information

Ataxia-telangiectasia (A-T) 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 (in 90%); of patients increased alpha-fetoprotein levels (95%); reduced or absent immunoglobulin A levels (70%), and ataxia-telangiectasia mutated (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 US, the incidence of A-T 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 (www.cancer.net/cancer-types/ataxia-telangiectasia). The world-wide prevalence of A-T is estimated to be between 1 in 40,000 and 1 in 100,000 live births (Rothblum-Oviatt et al, 2016).

Ataxia-telangiectasia is caused by 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 A-T have stable neurologic symptoms for the first 4 to 5 years of life, however, they 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. By the time they are 10 to 12 years of age , A-T patients may be unable to control their muscles, 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. These patients may be restricted to wheelchair use for ambulation, with a recent systematic review of the literature finding a mean age of wheelchair requirement at age 10 (Petley et al, 2022).

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, in patients with classical

A-T, life expectancy is generally 20 to 30 years, with mortality largely due to chronic lung disease or malignancies (Poupard, 2003; Crawford et al, 2006; Petley et al, 2022).

2.1.1 *Overview of the EryDex System*

The EryDex System (EDS) encapsulates dexamethasone sodium phosphate (DSP) into autologous erythrocytes, allowing the slow release of low doses of dexamethasone (active drug) in circulation (plasma) (Mambrini et al, 2017).

The principle used to encapsulate drugs into erythrocytes is based on their ability to become temporarily permeable when exposed to hypotonic (reduced osmolarity) conditions, allowing the diffusion of DSP into the cells. Subsequent addition of a hypertonic solution allows for restoration of physiological osmolarity and permeability, with consequent encapsulation of DSP within the erythrocytes.

This procedure is designed to provide a rapid, short-lived peak, followed by low, slowly declining serum drug concentrations for approximately 4 weeks, avoiding the need for daily administration of higher oral doses of systemic steroids.

Additional details of the EDS are provided in the current version of the eDSP (EryDex) Investigator's Brochure (IB).

2.1.2 *Non-Clinical Studies with EryDex System*

Pharmacokinetics (PK) of DSP differs from that obtained with the ordinary routes of administration (oral, IV, intramuscular [IM], etc.) due to the novel method of administration by ex vivo encapsulation of the drug into human autologous erythrocytes, which are then infused. The PK of the drug product in humans was evaluated in clinical studies. It is not possible to study the PK in animal models because the dephosphorylation rate of the pro-drug, DSP, to the diffusible active drug, dexamethasone, in human erythrocytes is very different from erythrocyte dephosphorylation rates in other species (Zocchi et al., 1991).

2.1.3 *Summary of Ongoing Clinical Studies with EryDex System*

The IEDAT-04-2022 (NEAT) trial is an international, multi-center, randomized, double-blind, placebo-controlled, Phase 3 trial designed to assess the effect of eDSP, administered by IV infusion once every 28 days (-7,+2 days), on neurological symptoms of participants ≥6 years of age with A-T.

In the NEAT trial, a minimum of 86 participants ages 6- to 9-years-old, meeting all inclusion and exclusion criteria, are randomized equally (1:1; 43 patients per group) to receive eDSP or placebo. Approximately 20 patients ≥10 years of age may be enrolled (10 per treatment group). Each patient will receive 6 infusions of eDSP or placebo, given at monthly intervals. After completing treatment in NEAT, eligible patients may receive eDSP treatment in this OLE trial if they meet all inclusion and exclusion criteria described in Section 5 and provide informed consent.

2.2 Risk/Benefit Assessment

2.2.1 *Risk Assessment*

Dexamethasone is a steroid class drug first approved by the United States (US) Food and Drug Administration (FDA) in 1958; therefore, there is a large body of information known about its risk. Dexamethasone is used in the treatment of a number of chronic (long-term) inflammatory diseases. The risks associated with EryDex treatment are similar to those associated with dexamethasone. Typical adverse effects of dexamethasone treatment include osteoporosis, glaucoma, stunting of growth in children, mood

changes, immune suppression, cortisol suppression, vascular disorders, weight gain, Cushingoid appearance, infections, hypercholesterolemia, and hyperglycemia. Adverse effects associated with prolonged therapy and/or high doses of dexamethasone include adrenal suppression, blood/vascular disorders, development of diabetes mellitus, effects on bones and joints, ocular effects, stunting of growth in children, impaired myocardial contractility (prolonged treatment), muscular atrophy, allergic dermatitis, urticaria, erythema, gastrointestinal system effects, euphoric side effects, headache, convulsion, electrolyte imbalance, and hyperglycemia.

Mild to moderate itching has been observed during the eDSP (EryDex) infusion procedure in prior studies.

For additional details, refer to the current eDSP (EryDex) IB.

Participants in this OLE trial will be monitored at each visit through physical examination, vital signs measurements, laboratory testing, and adverse event (AE) surveillance to identify potential eDSP-related side effects.

The safety data from the most recent and largest trial of eDSP (EryDex) in the A-T population (IEDAT-02-2015 ATTeST) were analyzed with particular attention to potentially steroid-related AEs including increased risk of infection, bone density, and Tanner scale as indicators of long-term adverse effects of chronic steroid treatment. The overall conclusion, corroborated by the safety data from the IEDAT-03-2018 (OLE-IEDAT) trial, was that these data did not raise clinical concerns about the overall safety of the eDSP (EryDex) treatment, nor concern regarding the known long-term side effects of chronic steroid treatment.

Risks associated with blood collection for laboratory tests include pain, swelling, bruising, and, on rare occasions, infection at the injection site.

Risks associated with the eDSP (EryDex) infusion are similar to any blood infusion, and therefore may include pain, bruising, infection, hypotension, fever, chills, nausea, hives, rash, itching, swelling of the face or neck, difficulty breathing, and anemia. Pruritus and itching are known side effects of IV administration of steroids and have been reported in prior eDSP (EryDex) studies. It should be noted that itching and pruritus resolve promptly after completing the re-infusion. These side effects were mitigated in previous studies by slowing the infusion rate and, in some instances, pre-medication with Benadryl.

Physical examination must be conducted on the day of eDSP (EryDex) administration and participants will be monitored throughout the infusion process.

Sterility testing will be performed before and after the infusions at the first and last treatment visits (Baseline, V12 and V24), by means of blood culture test.

A bone density test is obtained using dual-energy x-ray absorptiometry (DEXA). This is a non-invasive, painless imaging modality that uses a very small dose of x-rays to measure the density of bones. The scan involves a very low amount of radiation exposure—less than a day's exposure to natural radiation, and less than one-tenth of the dose of a standard chest x-ray.

2.2.1.1 Risks during Pregnancy and Lactation

In pregnant rats, dexamethasone crosses the placenta, but fetal plasma levels are below maternal levels. To a small extent, dexamethasone is distributed into breast milk. The genotoxicity potential of dexamethasone has been evaluated *in vitro* and *in vivo* studies, with both sets of experiments indicating it is devoid of genotoxic potential. Dexamethasone appears to be associated with a teratogenic potential in mice, rats, rabbits, and monkeys. Post-natal development studies indicate that it has the potential to alter the development of the immune system, heart, kidney, bone, brain tissue, lipid profiles, and social behavior in rat pups.

In the clinical trials performed to date with eDSP, women who are pregnant or lactating have been excluded. In the clinical studies in healthy subjects and patients with A-T, females of childbearing potential who are not using adequate contraception methods or are pregnant or lactating are excluded.

2.2.2 *Benefit Assessment*

Results from clinical studies conducted to date with eDSP (EryDex) in participants with A-T suggest that eDSP (EryDex) treatment may reduce the neurological symptoms in patients with A-T.

2.3 Trial Rationale

There is no approved therapeutic treatment for A-T.

The clinical program to assess the efficacy and safety of eDSP (EryDex) for the treatment of A-T has included 1 open-label Phase 2 trial (IEDAT-ERY01-2010), 1 Phase 3 trial (IEDAT-02-2015 [ATTeST]), and 1 OLE (IEDAT-03-2018 [OLE-IEDAT]).

Participants who complete the IEDAT-04-2022 trial and meet the eligibility criteria may participate in this OLE trial.

The principal investigator (PI) will determine each participant's eligibility using their clinical judgement to assess the participant's status and safety.

2.3.1 *Rationale for Exploratory Measures*

The primary efficacy assessment measured in the IEDAT-04-2022 (NEAT) trial RmICARS will continue to be measured in the OLE to collect additional data on the potential effects of eDSP on neurological symptoms.

2.3.1.1 International Cooperative Ataxia Rating Scale (ICARS)

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 internal consistency, criterion-related validity, and internal construct validity of the ICARS have been established in patients with focal cerebellar lesions (Schoch 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; 2006b). The ICARS total score satisfied all psychometric criteria in a validation trial in patients with Friedrich's Ataxia (Cano et al, 2005; Metz et al, 2013).

The Modified ICARS (mICARS) 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.

The Rescored mICARS (RmICARS) is rescored by collapsing categories within specific items; this results in a smaller total sum score across the ICARS domains. The details of this rescoring will be available in the trial statistical analysis plan (SAP).

A comparison of the ICARS, mICARS, and RmICARS is presented in Table 1.

Table 1. Comparison of ICARS, mICARS and RmICARS (items and scores)

Full ICARS **100 points, 19 Items**		**mICARS** **54 points, 11 items**		**RmICARS** **29 Points, 9 items**	
Posture and Gait Disturbance (34 points)		Posture and Gait Disturbance (34 points)		Posture and Gait Disturbance (23 points)	
1. Walking capacities	0-8	1. Walking capacities	0-8	1. Walking capacities	0-4
2. Gait Speed	0-4	2. Gait Speed	0-4	2. Gait Speed	0-3
3. Standing Capacities eyes open	0-6	3. Standing Capacities eyes open	0-6	3. Standing Capacities eyes open	0-4
4. Spread of feet eyes open	0-4	4. Spread of feet eyes open	0-4	4. Spread of feet eyes open	0-3
5. Body sway feet together eyes open	0-4	5. Body sway feet together eyes open	0-4	5. Body sway feet together eyes open	0-3
6. Body sway feet together eyes closed	0-4	6. Body sway feet together eyes closed	0-4	6. Body sway feet together eyes closed	0-3
7. Quality of sitting position	0-4	7. Quality of sitting position	0-4	7. Quality of sitting position	0-3
Kinetic Function (52 points) test left & right except drawing		Kinetic Function (12 points) test left & right except drawing		Kinetic Function (2 points) test left & right except drawing	
8. Knee tibia test (R/L)	0-4				
9. Action tremor (R/L)	0-4				
10. Finger to nose test (dysmetria) (R/L)	0-4				
11. Finger to nose test (intention tremor) (R/L)	0-4				
12. Finger to finger test (R/L)	0-4				
13. Pronation supination (R/L)	0-4	13. Pronation supination (R/L)	0-4		
14. Drawing	0-4	14. Drawing	0-4	14. Drawing	0-2
Speech Disorder (8 points)		Speech Disorder (8 points)		Speech Disorder (4 points)	
15. Fluency of speech	0-4	15. Fluency of speech	0-4		
16. Clarity of speech	0-4	16. Clarity of speech	0-4	16. Clarity of speech	0-4
Oculomotor Disorders (6 points)					
17. Gave evoked nystagmus	0-3				
18. Abnormalities of ocular pursuit	0-2				
19. Dysmetria of the saccade	0-1				
Total	0-100	Total	0-54	Total	0-29

ICARS = International Cooperative Ataxia Rating Scale; L = left; mICARS = modified International Cooperative Ataxia Rating Scale; R = right; RmICARS = Rescored modified International Cooperative Ataxia Rating Scale

3 TRIAL OBJECTIVES

3.1 Safety Objective:

To evaluate the safety and tolerability of eDSP in participants with A-T.

3.2 Exploratory Objective:

To evaluate the effects of eDSP on neurological symptoms in patients with A-T.

4 INVESTIGATIONAL PLAN

4.1 Trial Design

This is an OLE trial to continue to provide eDSP treatment to eligible participants who complete the full treatment period (including those treated with placebo) in the IEDAT-04-2022 trial and to assess the safety and tolerability of eDSP (DSP encapsulated in autologous erythrocytes) administered by IV infusion once every 28 days (window -7 to +2 days) in patients with A-T.

4.1.1 *Collection of Race/Ethnicity*

The participants' race and ethnicity will be collected because analysis of results according to race/ethnicity are required by several Regulatory Authorities (e.g., black population for FDA in the US).

4.1.2 *End of study*

The end of the clinical trial is defined as the date of the last visit of the last participant on Visit 25 in the trial.

Listings of the trial procedures to be performed at each visit are provided in Section 7.

4.2 Rationale for eDSP (EryDex) Dose

The eDSP (EryDex) dose to be used in the IEDAT-05-2024 trial corresponds to the dose administered to participants in the IEDAT-04-2022 (NEAT) trial.

5 TRIAL POPULATION

5.1 Rationale for the Patient Population

Based on the natural history data and results from previous studies, the primary analysis population for the IEDAT-04-2022 (NEAT) trial will be 6- to 9-year-old children with A-T. Approximately 86 participants between 6 to 9 years of age are planned to be enrolled and analyzed as the primary analysis population; approximately 20 participants ≥ 10 years of old are also planned to be recruited for the IEDAT-04-2022 (NEAT) trial. All eligible participants from the IEDAT-04-2022 (NEAT) trial may continue treatment in this OLE trial.

5.2 Inclusion Criteria

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

1. Males and females ≥ 6 years of age, with body weight ≥15 kg, who completed the IEDAT-04-2022 trial, including final efficacy assessments (Visit 9)
2. Participant does not meet any of the criteria for treatment discontinuation and does not present safety contraindications for continuation of treatment as determined by the investigator.
3. In the investigator's opinion, the potential benefit of receiving the investigational treatment in the OLE trial outweighs the potential risks of receiving the investigational treatment in the OLE trial.
4. Participant's body weight ≥15 kg.

5.3 Exclusion Criteria

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

1. Current participation in another clinical trial. Participation in observational, non-interventional studies is allowed as long as trial investigational endpoint raters can remain blinded to the assessments from other studies, and as long as the other trial participation does not interfere with participation in this trial.
2. Females who are pregnant or breastfeeding. Females of childbearing potential using adequate birth control as determined by their healthcare provider will be eligible. For further details on adequate contraceptive measures, please refer to Section 8.6.
3. Participant has clinically significant immune impairment that, in the opinion of the investigator, precludes further treatment with corticosteroids.
4. Current neoplastic disease or previous neoplastic disease not in remission for at least 2 years.
5. Participant has confirmed hemoglobinopathies, e.g., hemoglobin C disease, sickle cell anemia, hereditary spherocytosis, or thalassemia.
6. Participants with suicidal ideation.
7. Participant requires treatment with a systemic corticosteroid. Treatment with inhaled or intranasal corticosteroids for asthma or allergies, as well as use of topical corticosteroids will be permitted.
8. Participant requires any concomitant medication prohibited by the protocol, including strong inducers or inhibitors of cytochrome P450 3A4 (CYP3A4) (refer to Section 7.7).

5.4 Record of Trial Participants and Screening Failures

The investigator will be required to maintain a confidential record of all trial participants, including all participants who were screened for the trial, but were not enrolled. The confidential record must include sufficient information so that it would be possible for the investigators to contact the trial participant.

Information on participants who have signed the ICF/Assent, but failed screening, should be entered on the Screen Failure electronic Case Report Form (eCRF).

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

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

Participants will keep the same screening number assigned during the IEDAT-04-2022 trial.

6 TRIAL TREATMENT

6.1 Description, Labeling and Packaging

6.1.1 *Description of the Supplies*

The study drug, eDSP is a DSP sterile solution encapsulated into human autologous erythrocytes that will be prepared using the EDS process (i.e., the trial treatment).

6.1.1.1 DSP Solution Composition

[redacted]

6.1.1.2 Stability of the DSP Solution

[redacted]

6.1.1.3 EryDex (EDS) System

The EryDex System (EDS) includes the red cell loader (RCL), EryKit_01, Syringe Kit, and process solutions, which are used in combination to process the participant's whole blood for the purpose of encapsulating DSP into autologous erythrocytes. Three sterile process solutions containing only inactive ingredients are used to facilitate encapsulation of DSP into the erythrocytes.

For additional information on the EDS process components and software, refer to Appendix 2 and the current version of the IB.

Details regarding site personnel training requirements for the EDS process are provided in Appendix 6.

6.1.2 *Packaging*

The primary packaging consists of a [redacted] ampule. The secondary packaging is a cardboard box with 1 ampule inside. One ampule will be needed for preparing each dose of EryDex. No opened ampule should be reused, and damaged ampules must not be used.

6.1.3 *Labeling*

Labeling will be done in a manner consistent with the trial design, according to the local requirements. Each box will be labelled with a twin label with a tear-off portion. The tear-off part of the twin label must be attached to the Prescription Form.

The outer packaging will contain the following information in the local language: Investigational New Drug (IND) number, EU Clinical Trial (EUCT) number, Integrated Research Application System (IRAS) ID, study number, site number, participant number, Kit ID number, quantity, content, dosage form and route of administration, Sponsor's name and contact information (address and telephone number), storage conditions (2°C to 8°C), lot number, expiry date, and warnings.

The single use ampules will be labelled with the following information in the local language: study number, Kit ID number, lot number, expiry date, participant number, quantity, content, dosage form and route of administration, warning, and Sponsor name.

6.2 EryDex System Dose Encapsulation Process and Administration

Participants will receive a mean ± standard deviation (SD) IV infusion of [redacted] eDSP (the same dose of DSP used in IEDAT-04-2022). The infusion will be a total volume of approximately [redacted] (final volume of the bag minus the volume transferred into the satellite sample bag) and will be administered over approximately 40 minutes.

A more detailed description of the EDS process is provided in Appendix 2. As an overview, the EDS process will utilize a [redacted] injectable heparin (10,000 IU, anticoagulant) added, along with [redacted] DSP solution ([redacted]), and [redacted] sterile water for injection in the same syringe, for a total of [redacted]. To avoid contamination of the blood used for the EDS process, a "blood diversion" will take place at the time of collection, where at least the first [redacted] of blood will be diverted into a separate collection tube. Note that the blood must be processed with the EDS within [redacted] from collection and at the time of the blood draw, a diversion procedure will occur.

[redacted]

Upon completion of the EDS process at visits specified in the Schedule of Assessments (Section 1.2), the satellite sample bag will be detached and used for sterility culture tests as described in (Appendix 4).

[redacted]

Blood collection and the infusion must be done following standard aseptic procedures for prevention of contamination, minimizing participant discomfort and damage to erythrocytes. [redacted]

The caregiver/participant should be advised to comply with the visit schedule. If the participant is unable to have the infusion performed at the scheduled time, it should be done as soon as is feasible. No infusion should be performed fewer than 14 days after the prior infusion.

[redacted]

[redacted]

6.3 Storage

The eDSP is provided in ampules [redacted] to be stored at 2°C to 8°C. Storage temperatures will be recorded by a data-logger and kept in the trial file. The sponsor will evaluate the temperature excursions beyond the limits set by the manufacturer to determine the appropriate actions to be taken, if any. Temperature excursions that occur during transit will be communicated through an automated trial supply management system. Temperature excursions occurring at the site should be immediately communicated to the clinical research associate (CRA).

Ampules of DSP assigned to a participant must not be used again for other participants; after use, these may be stored at room temperature until accountability is assessed. Upon approximation of the expiry date, and after the CRA performs accountability, the used and unused ampules of DSP will be destroyed at the site following local procedures for the disposition of drugs.

6.4 Accountability

During the course of the trial, the trial pharmacist or site personnel designated by the investigator to manage the trial treatment must record the trial treatment disposition and keep the accountability forms updated. The trial treatment accountability forms will be cross-checked with the Prescription Form and the Randomization and Trial Supply Management (RTSM) system. A copy of the accountability forms must be kept in the trial files at the site, and the other copy will be retained by the clinical research organization (CRO) staff responsible for monitoring the trial treatment. The used and unused eDSP ampules will be kept at the site for accounting and reconciliation by the CRA. The used infusion bags containing any remaining eDSP will be disposed of at the site, with appropriate documentation.

6.5 Overdose

Participants will receive up to 24 infusions of eDSP. Each infusion should contain a maximum of [redacted] DSP 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 than [redacted] will be considered an overdose. Treatment for an overdose should be the same as the clinical management for an overdose of dexamethasone.

6.6 Occupational Safety

There are no risks anticipated related to the trial treatment for the staff involved in administering eDSP to the participants in this trial. Standard procedures and precautions for handling needles and biological samples should be followed.

7 EVALUATIONS AND PROCEDURES

7.1 Written Informed Consent

Written informed consent must be obtained from every participant and parent/caregiver (if below the age of consent) or legal representative (if necessary) at baseline and prior to the initiation of any trial procedures required by the protocol. Every participant and parent/caregiver (if below the age of consent) or a legal representative (if necessary) must provide written consent and sign the informed consent form (ICF); in accordance with local regulations, according to the procedure described in Section 11.1. The details of the trial should be discussed with the participant and parent/caregiver or legal representative (if necessary) prior to obtaining informed consent, and the ICF and Assent Form must be signed and dated by the participant and parent/caregiver or legal representative (if necessary), and by the investigator or designee. A copy of the signed ICF will be provided to the participant, and the original will be retained with the source documents.

A separate section of the ICF will be used to obtain specific consent for the sample for biomarker development.

7.2 Trial Conduct

The structure of this OLE trial, as well as a detailed listing of the assessments and procedures to be performed at each visit is provided in Section 1.2.

7.2.1 *Screening/Baseline*

At IEDAT-04-2022 (NEAT) Visit 9, participants who wish to continue eDSP treatment in the IEDAT-05-2024 OLE trial will be evaluated for eligibility to continue after providing consent/assent, as described in Section 7.1. Final assessments from the IEDAT-04-2022 (NEAT) trial will serve as the screening/baseline evaluations for all other required assessments at this visit.

7.2.2 *Treatment*

The participant may begin trial treatment at the Screening/Baseline visit (Visit 1).

Participants will come to the investigational sites monthly to receive trial treatment and complete the required trial assessments as specified in the Schedule of Assessments (SoA; Section 1.2). Each treatment must be scheduled every 28 days (window -7 to +2 days), calculated from the previous infusion. The window between an infusion and the subsequent one should be kept as consistent as possible throughout the trial, avoiding fluctuations in administration windows. In any case, doses should not be given fewer than 14 days apart. Any instances where it is not possible to administer the infusion within the designated window should be documented as a protocol deviation, and the investigators should immediately contact the medical monitor to discuss whether the participant may continue in the trial, and if so, to agree on the path forward that will best ensure participant's safety and meet the protocol goals.

Due to the length of time required for the encapsulation procedures [redacted], investigators should define the number of participants that can visit and be dosed on the same day, based on the site staff availability and RCL status.

Throughout the trial, investigators may perform any additional safety assessments deemed necessary to assess the participant's safety. The medical management of a participant, outside of the requirements of the protocol, is within the PI's and the PI's delegated medical team's discretion.

7.2.3 *Early Withdrawal*

Participation in the clinical trial is entirely voluntary, and participants may withdraw at any time without providing a reason for withdrawal. Reason for discontinuation (if known) will be entered in the eCRF and in the source documents.

All participants who withdraw from the trial before Visit 25 will be asked to return for a Trial Completion/Early Discontinuation Visit to perform all final safety evaluations as specified in the SOA (Section 1.2).

For those participants who discontinue, an attempt to perform the screening for adrenal insufficiency, via early morning (before 8:00 AM) plasma cortisol testing, should be made as soon as possible following discontinuation of the trial treatment, according to the procedures described in Appendix 5.

7.3 Schedule of Visits and Assessments

An overview of the schedule of visits and assessments for the trial is presented in Section 1.2.

7.4 Visit Schedule and Assessments

7.4.1 *Visit 1: Screening/Baseline*

The Screening/Baseline Visit is designed as a single-day visit but, in case of logistical issues for a particular participant, the visit can be performed over 2 days.

The Screening/Baseline visit may be performed on the same day as Visit 9 of the IEDAT-04-2022 (NEAT) trial. In this case, certain assessments completed during Visit 9 of the IEDAT-04-2022 trial (indicated below) should not be repeated for the Screening/Baseline Visit in IEDAT-05-2024.

If the Screening/Baseline Visit is scheduled separately from Visit 9 of the NEAT trial, then eDSP dosing should occur within 28 days (-7, +2 days) of Visit 9. If dosing does not occur within 30 days of Visit 9 of the NEAT trial, all Visit 1 assessments will be performed, except for the BMD/DEXA scan (note, the DEXA scan should be performed at Visit 9 of the NEAT trial or Visit 1 of this OLE trial, not both). The next scan in this trial will be performed at Visit 25 but only if the participant has completed at least 12 months of prior treatment.

The following procedures should be performed at Visit 1 of this OLE trial even if it coincides with Visit 9 of the NEAT trial:

a) Written informed consent (must be obtained before any trial procedures) by participants and parent/caregiver (if below the age of consent), or a legal representative. In accordance with local regulations, children must provide assent to participate in the trial, to the extent possible.
b) Review of demography
c) Review of medical history
d) Review of inclusion/exclusion criteria and confirmation of eligibility.
e) Pregnancy test – females noted to be of childbearing potential will have a urine pregnancy test obtained and evaluated prior to eDSP infusion.
f) AEs – AEs occurring after the last NEAT visit or after the signing of the ICF for OLE, whichever occurs later, should be reported for the OLE trial. Ongoing AEs from the NEAT trial should be considered medical history in the OLE trial and not recorded as new AEs in the OLE trial.
g) Prior (previous 6 weeks) and concomitant medications – must be reviewed prior to eDSP infusion

h) eDSP infusion – preparation and administration as follows:

[redacted]

- Culture-based sterility test on eDSP– [redacted] sterile sample of eDSP will be stored under refrigeration as a "Retention Sample."
- eDSP sample for complete blood count (CBC) and DSP content – [redacted]

The following procedures performed as part of Visit 9 of the NEAT trial should **not** be repeated if Visit 1 of this trial coincides with Visit 9 of NEAT trial. However, if there are 30 days or more between the two visits, these assessments should be repeated.

a) Neurological examination
b) Physical examination
c) Body weight and height, calculation of body mass index (BMI)
d) Vital signs
   - To be collected within 15 minutes before eDSP infusion - temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic blood pressure (BP), and respiratory rate
   - To be collected within 15 minutes after eDSP infusion – temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic BP, and respiratory rate
e) C-SSRS
f) Plasma cortisol – sample to be collected before 8:00 AM. If the result is <5 µg/dL (or the LLN of the assay used), the participant should undergo a high dose ACTH stimulation test. Also, if the AM cortisol is between 5-10 µg/dL, and there is a strong suspicion for adrenal insufficiency, the ACTH test should be done. The test should be scheduled as soon as possible, and until normal adrenal function is confirmed, the participant should be monitored and treated following clinical guidelines for suspected adrenal insufficiency. If the result of the ACTH stimulation test is abnormal, the participant should be given appropriate treatment, but can continue in the trial, if the investigator considers it appropriate. Additional details are provided in Appendix 5.
g) 12-lead standard ECG
h) Routine laboratory tests to be performed on the diverted blood sample (see Section 7.5), as follows:
   - Hematology – hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential (neutrophils, eosinophils, basophils, lymphocytes, monocytes), platelets, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and RBC distribution width (RDW)

- Clinical chemistry – sodium, potassium, chloride, calcium, phosphorus, serum iron, bicarbonate, glucose, blood urea nitrogen (BUN), serum creatinine, total bilirubin, albumin, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, lactate dehydrogenase (LDH), creatine phosphokinase (CPK), triglycerides, and cholesterol (total, -high-density lipoprotein [HDL], and low-density lipoprotein [LDL])
- Urinalysis (automated) – color, pH, specific gravity, protein, glucose, ketones, nitrites, bilirubin, hemoglobin, urobilinogen, and if indicated, microscopic RBC, WBC, and casts

i) Special laboratory tests to be performed on the diverted blood sample (see Section 7.5.2) as follows:
   - Cluster of differentiation 4 positive (CD4+) lymphocyte count (a local laboratory test)
   - Alpha-fetoprotein
   - CRP

j) Bone mineral density (BMD) – only if not performed at Visit 9 of the NEAT trial, regardless of the number of days elapsed
k) C-SSRS
l) Pregnancy test – participants capable of becoming pregnant will have a serum pregnancy test.
m) Blood sample for biomarker development– to be performed on the diverted blood sample (see Section 7.5) for participants who provide consent
n) ICARS

Participants who initially fail eligibility criteria for the trial may be re-screened in cases where the investigator believes this is appropriate based upon an understanding of the health condition of the participant.

Screening/Baseline may be the day of the first dose, and each subsequent treatment will be calculated from the preceding treatment.

7.4.2 *Visits 2, 3, 5, 6, 8, 9, and 11*

a) Physical examination
b) Weight, height, and BMI
c) Vital signs
   - To be collected within 15 minutes before eDSP infusion - temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic blood BP, and respiratory rate
   - To be collected within 15 minutes after eDSP infusion – temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic BP, and respiratory rate

d) Pregnancy test – females noted to be of childbearing potential will have a urine pregnancy test obtained and evaluated prior to eDSP infusion.
e) C-SSRS
f) AEs – review of AEs as reported by the participant or observed by the investigator
g) Concomitant medications – review of concomitant medications
h) eDSP infusion – preparation and administration as follows:

7.4.3 *Visits 4 and 10*

a) Neurological examination
b) Physical examination
c) Weight, height, and BMI
d) Vital signs
   - To be collected within 15 minutes before eDSP infusion - temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic BP, and respiratory rate
   - To be collected within 15 minutes after eDSP infusion – temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic BP, and respiratory rate
e) Routine laboratory tests to be performed on the diverted blood sample (see Section 7.5), as follows:
   - Hematology – hemoglobin, hematocrit, RBC count, WBC count with differential (neutrophils, eosinophils, basophils, lymphocytes, monocytes), platelets, MCV, MCH, MCHC, and RDW
   - Clinical chemistry – sodium, potassium, chloride, calcium, phosphorus, serum iron, bicarbonate, glucose, BUN, serum creatinine, total bilirubin, albumin, total protein, AST, ALT, alkaline phosphatase, LDH, CPK, triglycerides, and cholesterol (total, HDL, and LDL)
   - Urinalysis – color, pH, specific gravity, protein, glucose, ketones, nitrites, bilirubin, hemoglobin, urobilinogen, and if indicated, microscopic RBC, WBC, and casts
f) Special laboratory tests – to be performed on the diverted blood sample (see Section 7.5) comprising the following tests:
   - CD4+ lymphocyte count (a local laboratory test)
   - Alpha-fetoprotein
   - CRP
g) C-SSRS
h) Pregnancy test – females noted to be of childbearing potential will have a urine pregnancy test obtained and evaluated prior to eDSP infusion.
i) Blood sample for biomarker development– to be obtained from the diverted blood sample (see Section 7.5) for participants who provide specific consent.
j) AEs – review of AEs as reported by the participant or observed by the investigator.
k) Concomitant medications – review of concomitant medications
l) eDSP infusion – preparation and administration as follows:

[redacted]

7.4.4 *Visit 7*

a) Neurological examination
b) Physical examination
c) Weight, height, and BMI
d) Vital signs
   - To be collected within 15 minutes before eDSP infusion - temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic BP, and respiratory rate
   - To be collected within 15 minutes after eDSP infusion – temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic BP, and respiratory rate
e) Routine laboratory tests – to be performed on the diverted blood sample (see Section 7.5) as follows:

- Hematology – RBC, WBC, hemoglobin, hematocrit, platelets, neutrophils, eosinophils, basophils, lymphocytes, monocytes, mean corpuscular volume , mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and red blood cell distribution width
- Clinical chemistry – total protein, albumin, bilirubin, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, serum creatinine, sodium, potassium, chloride, bicarbonate, calcium, phosphorus, serum iron, LDH, alkaline phosphatase, glucose, creatine phosphokinase, triglycerides, and cholesterol (total, high density lipoprotein, and low density lipoprotein)
- Urinalysis – color, pH, specific gravity, glucose, ketones, nitrites, protein, bilirubin, hemoglobin, urobilinogen and if indicated, microscopic RBC, WBC, and casts

f) Special laboratory tests – to be performed on the diverted blood sample (see Section 7.5) comprising the following tests:
   - CD4+ lymphocytes count (a local laboratory test)
   - Alpha-fetoprotein
   - CRP

g) C-SSRS

h) Pregnancy testing – females noted to be of childbearing potential will have a urine pregnancy test obtained and evaluated prior to eDSP infusion.

i) Blood sample for biomarker development to be obtained from the diverted blood sample (see Section 7.5) for participants who provide specific consent.

j) ICARS

k) AEs – review of AEs as reported by the participant or observed by the investigator.

l) Concomitant medications – review of concomitant medications

m) eDSP infusion – preparation and administration as follows:

[redacted]

n) eDSP sample for CBC and DSP content – [redacted]

7.4.5 *Visit 12*

a) Physical examination

b) Weight, height, and BMI

c) Vital signs
   - To be collected within 15 minutes before eDSP infusion - temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic BP, and respiratory rate
   - To be collected within 15 minutes after eDSP infusion – temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic BP, and respiratory rate

d) C-SSRS

e) Pregnancy test – females noted to be of childbearing potential will have a urine pregnancy test obtained and evaluated before eDSP infusion.

f) AEs – review of AEs as reported by the participant or observed by the investigator

g) Concomitant medications – review of concomitant medications
h) eDSP infusion – preparation and administration as follows:

[redacted]

g) Culture-based sterility test on eDSP (EryDex) – [redacted] sterile sample of eDSP (EryDex) will be stored under refrigeration as a "Retention Sample".
h) eDSP sample for CBC and DSP content – [redacted]

7.4.6 *Visit 13*

a) Neurological examination
b) Brief physical examination
c) Weight, height, and BMI
d) Vital signs
   - To be collected within 15 minutes before eDSP infusion - temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic BP, and respiratory rate
   - To be collected within 15 minutes after eDSP infusion – temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic BP, and respiratory rate
e) Routine laboratory tests as follows:
   - Hematology – hemoglobin, hematocrit, RBC count, WBC count with differential (neutrophils, eosinophils, basophils, lymphocytes, monocytes), platelets, MCV, MCH, MCHC, and RDW
   - Clinical chemistry – sodium, potassium, chloride, calcium, phosphorus, serum iron, bicarbonate, glucose, BUN, serum creatinine, total bilirubin, albumin, total protein, AST, ALT, alkaline phosphatase, LDH, CPK, triglycerides, and cholesterol (total, HDL, and LDL)
   - Urinalysis – color, pH, specific gravity, protein, glucose, ketones, nitrites, bilirubin, hemoglobin, urobilinogen, and if indicated, microscopic RBC, WBC, and casts
f) ICARS
g) C-SSRS
h) Pregnancy test – females noted to be of childbearing potential will have a urine pregnancy test obtained and evaluated before eDSP infusion.
i) AEs – review of AEs as reported by the participant or observed by the investigator
j) Concomitant medications – review of concomitant medications
k) eDSP infusion – preparation and administration as follows:

[redacted]

[redacted]

i) Blood sample for biomarker development to be obtained from the diverted blood sample (see Section 7.5) for participants who provide specific consent.

7.4.7 *Visits 14, 15, 17, 20, 21, and 23*

a) Vital signs
   - To be collected within 15 minutes before eDSP infusion - temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic BP, and respiratory rate
   - To be collected within 15 minutes after eDSP infusion – temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic BP, and respiratory rate

b) C-SSRS

c) Pregnancy test – females noted to be of childbearing potential will have a urine pregnancy test obtained and evaluated before eDSP infusion

d) AEs – review of AEs as reported by the participant or observed by the investigator

e) Concomitant medications – review of concomitant medications

f) eDSP infusion – preparation and administration as follows:

[redacted]

7.4.8 *Visits 16 and 22*

a) Brief physical examination

b) Weight, height, and BMI

c) Vital signs
   - To be collected within 15 minutes before eDSP infusion - temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic BP, and respiratory rate
   - To be collected within 15 minutes after eDSP infusion – temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic BP, and respiratory rate

d) Routine laboratory tests as follows:
   - Hematology – hemoglobin, hematocrit, RBC count, WBC count with differential (neutrophils, eosinophils, basophils, lymphocytes, monocytes), platelets, MCV, MCH, MCHC, and RDW
   - Clinical chemistry – sodium, potassium, chloride, calcium, phosphorus, serum iron, bicarbonate, glucose, BUN, serum creatinine, total bilirubin, albumin, total protein, AST, ALT, alkaline phosphatase, LDH, CPK, triglycerides, and cholesterol (total, HDL, and LDL)
   - Urinalysis – color, pH, specific gravity, protein, glucose, ketones, nitrites, bilirubin, hemoglobin, urobilinogen, and if indicated, microscopic RBC, WBC, and casts

e) C-SSRS

f) Pregnancy test – females noted to be of childbearing potential will have a urine pregnancy test obtained and evaluated before eDSP infusion

g) AEs – review of AEs as reported by the participant or observed by the investigator
h) Concomitant medications – review of concomitant medications
i) eDSP infusion – preparation and administration as follows:

[redacted]

7.4.9 *Visit 18*

a) Vital signs
   - To be collected within 15 minutes before eDSP infusion - temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic BP, and respiratory rate
   - To be collected within 15 minutes after eDSP infusion – temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic BP, and respiratory rate
b) C-SSRS
c) Pregnancy test – females noted to be of childbearing potential will have a urine pregnancy test obtained and evaluated before eDSP infusion
d) AEs – review of AEs as reported by the participant or observed by the investigator
e) Concomitant medications – review of concomitant medications
f) eDSP infusion – preparation and administration as follows:

[redacted]

g) EryDex sample for DSP content (see Appendix 3).

7.4.10 *Visit 19*

a) Neurological examination
b) Brief physical examination
c) Weight, height, and BMI
d) Vital signs
   - To be collected within 15 minutes before eDSP infusion - temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic BP, and respiratory rate
   - To be collected within 15 minutes after eDSP infusion – temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic BP, and respiratory rate
e) Routine laboratory tests as follows:
   - Hematology – hemoglobin, hematocrit, RBC count, WBC count with differential (neutrophils, eosinophils, basophils, lymphocytes, monocytes), platelets, MCV, MCH, MCHC, and RDW

- Clinical chemistry – sodium, potassium, chloride, calcium, phosphorus, serum iron, bicarbonate, glucose, BUN, serum creatinine, total bilirubin, albumin, total protein, AST, ALT, alkaline phosphatase, LDH, CPK, triglycerides, and cholesterol (total, HDL, and LDL)
- Urinalysis – color, pH, specific gravity, protein, glucose, ketones, nitrites, bilirubin, hemoglobin, urobilinogen, and if indicated, microscopic RBC, WBC, and casts

f) ICARS
g) C-SSRS
h) Pregnancy test – females noted to be of childbearing potential will have a urine pregnancy test obtained and evaluated before eDSP infusion.
i) AEs – review of AEs as reported by the participant or observed by the investigator
j) Concomitant medications – review of concomitant medications
k) eDSP infusion – preparation and administration as follows:

[redacted]

7.4.11 *Visit 24*

a) Vital signs
   - To be collected within 15 minutes before eDSP infusion - temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic BP, and respiratory rate
   - To be collected within 15 minutes after eDSP infusion – temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic BP, and respiratory rate
b) C-SSRS
c) Pregnancy test – females noted to be of childbearing potential will have a urine pregnancy test obtained and evaluated before eDSP infusion.
d) AEs – review of AEs as reported by the participant or observed by the investigator
e) Concomitant medications – review of concomitant medications
f) eDSP infusion – preparation and administration as follows:

[redacted]

h) Culture-based sterility test on eDSP– [redacted] sterile sample of eDSP will be stored under refrigeration as a “Retention Sample.”

i) EryDex sample for DSP content – [redacted]

7.4.12 *Visit 25: Trial Completion/Early Discontinuation*

a) Brief physical examination
b) Neurological examination
c) Weight, height, and BMI
d) Vital signs
   - To be collected within 15 minutes before eDSP infusion - temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic BP, and respiratory rate
   - To be collected within 15 minutes after eDSP infusion – temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic BP, and respiratory rate
e) Plasma cortisol – sample to be collected before 8:00 AM. If at any time during the trial a participant exhibits signs or symptoms of adrenal insufficiency, cortisol should be tested via an 8:00 (+30 minutes) AM cortisol sample. If the result is <5 µg/dL (or the LLN of the assay used), the participant should undergo a high dose ACTH stimulation test. Also, if the AM cortisol is between 5-10 µg/dL, and there is a strong suspicion for adrenal insufficiency, the ACTH test should be done. The test should be scheduled as soon as possible, and until normal adrenal function is confirmed, the participant should be monitored and treated following clinical guidelines for suspected adrenal insufficiency. If the result of the ACTH stimulation test is abnormal, the participant should be given appropriate treatment, but can continue in the trial, if the investigator considers it appropriate. Additional details are provided in Appendix 5.
f) 12-lead standard ECG
g) Routine laboratory tests as follows:
   - Hematology – hemoglobin, hematocrit, RBC count, WBC count with differential (neutrophils, eosinophils, basophils, lymphocytes, monocytes), platelets, MCV, MCH, MCHC, and RDW
   - Clinical chemistry – sodium, potassium, chloride, calcium, phosphorus, serum iron, bicarbonate, glucose, BUN, serum creatinine, total bilirubin, albumin, total protein, AST, ALT, alkaline phosphatase, LDH, CPK, triglycerides, and cholesterol (total, HDL, and LDL)
   - Urinalysis – color, pH, specific gravity, protein, glucose, ketones, nitrites, bilirubin, hemoglobin, urobilinogen, and if indicated, microscopic RBC, WBC, and casts
h) BMD only after participants complete at least 12 months of trial treatment.
i) C-SSRS
j) ICARS
k) Special laboratory tests to be performed on the diverted blood sample. These tests will be repeated at the end of treatment (Visit 25/Early Discontinuation) only if the participant completed at least 12 months of trial treatment. (see Section 7.5) as follows:
   - CD4+ lymphocyte count (a local laboratory test)
   - Alpha-fetoprotein
   - CRP
l) Pregnancy test – females noted to be of childbearing potential will have a serum pregnancy test obtained.
m) A simplified Puberty Assessment will be documented by the investigator to confirm the date of first menstruation for girls and the date of first voice change for boys if it has occurred while on study.
n) Blood sample for biomarker development to be obtained from the diverted blood sample (see Section 7.5) for participants who provide specific consent.

o) AEs – review of AEs as reported by the participant or observed by the investigator
p) Concomitant medications – review of concomitant medications

7.4.13 *Unscheduled/As Needed Assessments*

Investigators can decide to perform any additional safety assessments deemed necessary to assess participant safety throughout the trial. The medical management of a participant, outside of the requirements of the protocol, is within the discretion of the PI and the PI's delegated medical team.

7.4.14 *Visit Windows*

Each treatment must be scheduled every 28 days (window -7 to +2 days), calculated from the previous infusion. The window between an infusion and the subsequent one should be kept as regular as possible throughout the trial, avoiding fluctuations in administration windows.

Doses should not be given in any case less than 14 days apart. Any instances where it is not possible to administer the infusion within the designated window should be documented as a protocol deviation and the investigators should immediately contact the medical monitor to discuss if the participant may continue in the trial, and if so, to agree on the path forward that will best ensure participant's safety and meet the protocol goals.

7.5 Laboratory Sample Collection

7.5.1 *Aseptic Procedure Guideline*

Aseptic procedures have been implemented to ensure sterility during blood collection for the EryDex process, the various steps of the EryDex process, sample collection for laboratory tests and for sterility testing of EryDex, and administration of eDSP to the participant. Details of these procedures are described in a separate document entitled "Aseptic Procedure Guideline", which will be provided to each site. These 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 participant, disinfected frequently using a bactericidal rub.

[redacted]

7.5.2 *Blood Sampling*

[redacted]

The total amount of blood to be drawn on any single-day or within any 8-week period conforms to the guidelines published by the World Health Organization, relevant to safe limits in blood withdrawal in children.

7.5.3 *Urine Collection*

Urine needed for the urinalysis will be collected at Screening/Baseline (Visit 1) and Visits 4, 7, 10, 13, 16, 19, 22, and 25 (every 3 months).

For females noted to be of childbearing potential at Screening/Baseline, urine pregnancy tests will be performed monthly before every infusion.

All blood and urine samples for safety (hematology/ clinical chemistry/ urinalysis) and special laboratory evaluations will be analyzed by an external (central) laboratory, with the exception of plasma cortisol, ACTH, and sterility tests. In certain circumstances the investigator may choose to utilize a local laboratory if there is an immediate need for the test results.

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

Once the EDS encapsulation procedure has been completed for the first and last dosing visits (Screening/Baseline [Visit 1] and Visit 24), a sample of the contents of the infusion bag will be collected for analysis of the DSP content, so that the actual dose administered to each participant can be determined. DSP content assessment from the eDSP sample is done at Visits 1, 7, 12, 18, and 24 (CBC content assessed only at Visits 1, 7, and 12).

The procedure to be followed for this sample is as follows:

7.7 Concomitant Medications

All participants to be included in the trial must **not** have received **oral or parenteral corticosteroid** therapy other than eDSP within 6 weeks prior to the administration of eDSP. However, treatment with inhaled or intranasal corticosteroids for asthma or allergies, as well as the use of topical corticosteroids, will be permitted. In addition, participants 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 6 weeks prior to Baseline;
- Antipsychotics – unless used at a low, stable dose starting at least 6 weeks prior to baseline, 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 6 weeks prior to baseline; **NOTE: Drugs that are inducers or inhibitors of CYP3A4 may alter the plasma levels of dexamethasone, which is metabolized by this enzyme. Therefore, any drug that is a strong inducer or inhibitor of CYP3A4 will be prohibited from use during the trial. Participants who are taking these drugs at Screening/Baseline should have the medication discontinued upon entry into the trial, if possible, or be switched to another similar medication that does not have this property. A list of drugs that are strong inducers or inhibitors of CYP3A4 can be provided to the investigator upon request and the investigator should refer as well to the local prescriber approved label for dexamethasone.**
- Amphotericin-B within 6 weeks prior to baseline – combination with corticosteroids or corticotropin (ACTH) may induce hypopotassemia.
- Any immunization, vaccination, or skin test, especially using a live, attenuated vaccine, within 4 weeks prior to screening. The use of vaccines that do not contain a live, attenuated virus (e.g. diphtheria, pertussis, and tetanus [DPT], and coronavirus disease 2019 RNA vaccines) during the course of the trial is left to the investigator's clinical judgement and the standard of care at the site.

Participants on stable doses of other drugs, such as antihypertensives, benzodiazepines, antihistamines (histamine receptor blockers), birth control, proton-pump inhibitors, vitamins/multi-vitamins, anti-diabetic agents, and lipid-lowering agents (e.g., statins), will be eligible for the trial. The use of other concomitant medications with central nervous system effects should be discussed with and approved by the medical monitor before prescribing to the participant during the trial. Use of subcutaneous immunoglobulin (SCIG)

is permitted; the investigator should determine the optimal timing of the dose with respect to the eDSP infusion.

During the entire period of the trial, starting with the signing of the ICF, any new treatment that is initiated must be reported in the eCRF 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 – following the instructions included in the eCRF guidelines. After screening, participants should be instructed to contact the investigator before starting any over-the-counter or prescription medication on their own or as prescribed by their physician. The medical monitor should be informed of any new medication started during the trial that may be a prohibited medication, and they will decide whether or not it is acceptable for the participant to continue in the trial.

7.8 ICARS

7.8.1 *Description of the International Cooperative Ataxia Rating Scale*

An exploratory endpoint in this trial will be the mean change of the RmICARS from Baseline to Visit 25 in 6- to 9-year-old participants with A-T.

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 trial; however, for the exploratory endpoint, the rescored 'Modified' ICARS will be used. The 'Modified' ICARS excludes all 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. The Rescored mICARS (RmICARS) is rescored by collapsing categories within specific items as recommended by the US FDA; this results in a smaller total sum score across the ICARS domains. The details of this rescoring will be available in the trial SAP.

7.8.2 *Rater Requirements and Training*

Properly qualified raters will need to be identified by each investigator at each site to perform the ratings on the efficacy measures. The ICARS rater will not be allowed to administer the trial treatment. ICARS ratings must be completed without consulting scores from the previous visit.

Qualification, training, and certification process on the ICARS will be managed by a specialized vendor and will be described in specific guidelines. Additional training and an intra-rater reliability (test-retest) assessment will also be performed during the trial.

To maximize the consistency of the efficacy data, the same site's qualified, trained, and certified raters and with expertise in the field of A-T disorders, will evaluate the same participant at approximately the same time throughout the trial.

7.9 Safety Evaluations

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

a) Physical and neurological examinations
b) Vital signs

c) Standard laboratory tests (clinical chemistry, hematology, and urinalysis)
d) 12-lead standard ECG
e) Special laboratory parameters (CD4+ lymphocyte count [a local laboratory test], alpha-fetoprotein, CRP)
f) Early morning plasma cortisol, ACTH (scheduled and as needed)
g) Pregnancy testing
h) C-SSRS
i) BMD, where country regulations allow
j) Sterility testing of EryDex
k) Subjective reporting of any AE by the participant
l) Objective observation of any AE by the investigator
m) The investigator will be asked to comment on any clinically significant abnormal test results.

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

7.9.1 *Physical and Neurological Examinations*

Physical and neurological examinations will be performed as specified in the SoA (Section 1.2). The physical examination will include an examination of general appearance, skin, neck (including thyroid), eyes and ears, nose, mouth, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and nervous system. Genital, urinary tract, and rectal examinations are not required. The findings will be entered on the Physical Examination section (or AE, as applicable) of the eCRF. Clinically significant changes from baseline should be assessed and should be recorded as an AE. Neurological assessments must be performed before IV insertion, so that upper extremity neurological exam is not impeded by an IV line.

7.9.2 *Height and Weight*

Height will be measured by a stadiometer at Screening/Baseline and each applicable subsequent visit and used along with body weight to calculate BMI. Weight will be measured before the infusion. These assessments will be done at every visit through Visit 13 and then every 3 months (Visits 16, 19, 22 and Visit 25).

7.9.3 *Vital Signs*

Vital signs assessments will be performed at every visit, as specified in the SOA (Section 1.2) and will include temperature (method of recording to be documented in notes and eCRF), pulse, systolic and diastolic BP, and respiratory rate. Pulse and BP will be measured after the participant has been in the supine position for at least 5 minutes. On the days of treatment, the vital signs will be measured within 15 minutes before and within 15 minutes after the IV infusion of the trial treatment.

There were no safety concerns from the vital signs analysis in previous studies. However, each investigator will be allowed to repeat measurements as needed in case previous attempts are not considered reliable or a value is abnormal. Vital signs will be taken pre- and post-infusion, to ensure participant safety.

According to the usual practice in clinical settings, in case of an infusion of blood or derivates, the Sponsor recommends monitoring the participants enrolled in the trial in terms of heart rate and BP with the help of a surveillance monitor, including pulse oximeter. This recommendation should be followed during and after drawing of blood, as well as during reinfusion.

If a **change of clinical relevance** from pre-infusion to post-infusion is observed, the vital signs assessment should be repeated as often as needed, at the discretion of the investigator. Findings should be documented in the Vital Signs eCRF (and AE eCRF, if clinically significant according to investigator's judgement).

7.9.4 *Electrocardiogram*

All participants will have a standard 12-lead ECG performed as specified in the SOA (Section 1.2). If clinically significant abnormal findings are noted at the Screening/Baseline Visit and do not normalize on the repeat ECG evaluation (done in triplicate), the patient will not be enrolled.

Review and interpretation of the ECG will be performed by a cardiologist or qualified physician at the investigational site, using a certified and serviced ECG machine.

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

- Study number
- Site number
- Participant's number and initials
- Date and time ECG obtained

If clinically significant abnormalities are found, the participant'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 beats per minute (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.

7.9.5 *Routine Laboratory Testing*

Blood and urine samples for measurement of standard laboratory parameters will be as specified in the SOA (Section 1.2).

Evaluations of the hematology, clinical chemistry and urinalysis analytes listed in Table 2 will be performed at each of the visits listed in the SOA. Details on aseptic procedure for blood withdrawal and on blood diversion are included in the "Aseptic Procedure Guideline" that will be provided to sites.

Table 2. Summary of Standard Laboratory Analytes

Hematology or Complete Blood Count	Clinical Chemistry		Urinalysis (automated)
Hematocrit	Sodium	Alkaline phosphatase	Color
Hemoglobin	Potassium	Lactate dehydrogenase	pH
RBC count	Chloride	creatine phosphokinase	Specific gravity
WBC count	Calcium	Triglycerides	Protein
Differential white blood cell count	Phosphorus	Total cholesterol	Glucose
Neutrophils	Serum iron	HDL cholesterol	Ketones
Lymphocytes	Bicarbonate	LDL cholesterol	RBC, WBC, casts *
Monocytes	Glucose		Nitrites
Eosinophils	Blood urea nitrogen		Bilirubin
Basophils	Creatinine		Hemoglobin
Platelets	Total bilirubin		Urobilinogen
Mean corpuscular volume	Albumin		
Mean corpuscular hemoglobin	Total protein		
Mean corpuscular hemoglobin concentration	AST		
RBC distribution width	ALT		

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL = high-density lipoprotein
LDL = low density lipoprotein; RBC = red blood cell count; WBC = white blood cell count

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

The investigator must review laboratory values from each evaluation within 24 hours of receipt of the laboratory report. After the review is completed, the investigator must sign and date each laboratory report.

A central laboratory will be used for analyzing samples for routine and special laboratory tests, with the exception of any ACTH testing and all sterility tests (except for the CD4+ lymphocyte counts, which will be measured by a local laboratory). In certain circumstances the investigator may choose to utilize a local laboratory if there is an immediate need for the test results.

The central laboratory will provide 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 central laboratory will provide the normal reference ranges for each parameter and will verify that the result is 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).

The investigator must evaluate any change of clinical relevance in a laboratory test from pre-infusion of trial treatment to post-infusion of trial treatment as to whether it meets the definition of an AE, and repeat, if needed, any clinically significant abnormal laboratory test. Any laboratory abnormalities meeting the definition of an AE should be recorded on the AE eCRF.

For the tests conducted at local level, the same applies but with reference to the normal reference ranges for the laboratory tests on the local laboratory results report.

Refer to Section 8, "Reporting Safety Information" for further instructions.

7.9.6 *Special Laboratory Testing and Plasma Cortisol Testing*

Measurement of selected "special" laboratory parameters has been included in the trial to evaluate potential effects of eDSP treatment. The following special laboratory parameters will be assessed in the trial:

- CD4+ lymphocytes, alpha-fetoprotein, CRP (not repeated at baseline), to be performed at Screening/Baseline and Visits 4, 7, and 10 (every 3 months) and Visit 25/Early Discontinuation only if the participant completed at least 12 months of trial treatment
- Screening/Baseline testing for adrenal insufficiency will be performed in all participants, via early morning (before 8:00 AM) plasma cortisol testing at Screening/Baseline (only if not done at Visit 9 in the NEAT trial) and at Visit 25.
- High dose ACTH stimulation test – In the event that participants show signs or symptoms of adrenal insufficiency (Appendix 5) during the trial, especially following interruption of the trial drug (including loading failures), they will be tested for adrenal insufficiency using a high dose ACTH stimulation test (250 µg given IV or IM). If ACTH testing confirms adrenal insufficiency, the participant will be referred for evaluation and treatment. Blood samples [redacted] for measurement of plasma cortisol will be collected prior to ACTH administration (0 minutes), and at 30- and 60-minutes post ACTH dose. A rise in plasma cortisol level to greater than 18 µg/dL within 60 minutes demonstrates a normal result. A rise in cortisol to less than 18 µg/dL within 60 minutes demonstrates an abnormal response.

7.9.7 *Pregnancy Testing*

Female participants who are noted to have reached childbearing potential at the Screening/Baseline Visit or who display any evidence of childbearing potential will have a serum pregnancy test obtained at Screening/Baseline and undergo urine pregnancy testing prior to eDSP infusion and a serum pregnancy test at Visit 25/Early Discontinuation.

Should the investigator note evidence, or should the parent report any evidence of a female trial participant approaching puberty (e.g., breast development, pubic hair, or onset of menses) after the Screening/Baseline Visit and during the trial, the participant will begin undergoing urine pregnancy testing prior to each eDSP infusion. At Visit 25, the investigator will also document the date of first menstruation for girls and the date of first voice change for boys if it has occurred while on study.

7.9.8 *Blood Samples for Biomarker Development*

These samples will be collected, processed, and stored according to instructions provided in the Laboratory Manual. They will be stored securely and labeled with a code that provides a link to the trial ID number for each participant. Analyses will be performed by commercial and academic laboratories to identify useful biomarkers for the diagnosis and treatment of A-T.

7.9.9 *Bone Mineral Density*

Measurements of BMD will be performed, where country regulations allow, for all participants at Screening/Baseline and repeated at Visit 25/Early Discontinuation (only if the participant completed at least 12 months of trial treatment) 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 trial is dual-energy x-ray absorptiometry. The analysis will be performed with Z-scores following the above guidelines. The same method of assessment will be used for each participant throughout the trial. BMD Z-scores will be evaluated according to the following chart:

BMD Z-Score	Level
- 1 or higher	Normal
Less than -1 to -2.4	Abnormal - osteopenia
-2.5 or lower	Abnormal - osteoporosis

Clinically significant changes from Screening/Baseline to Visit 25/Early Discontinuation should be documented as an AE or SAEs depending on the investigator's judgement. Abnormal values at Screening/Baseline should be recorded as medical history as they underline a pre-existing condition frequent in the A-T population.

7.9.10 *Columbia-Suicide Severity Rating Scale*

The C-SSRS (Posner et al, 2007; 2011) is a standardized suicidal rating system. Important psychometric properties and construct validity of the C-SSRS have been established in multi-center clinical studies.

Site personnel administering the C-SSRS will have been trained to use this assessment tool.

Assessments will be performed using the "Since Last Visit" version of the C-SSRS for all trial visits. Participants with suicidal ideation will be excluded from participating in the trial and referred to a mental health professional as needed.

7.9.11 *Sterility Testing of eDSP (EryDex)*

Once the EryDex process has been completed, the satellite sample bag will be filled with approximately [redacted] of EryDex by gravity (approximately [redacted] if no other samples but the ones for sterility culture test will be collected).

[redacted]

8 REPORTING SAFETY INFORMATION

8.1 Adverse Events

Assessment of AEs will be performed throughout the trial. AEs occurring after the last NEAT visit or after the signing of the ICF for OLE , whichever occurs later, will be reported in the OLE trial and continue to be reported through the final trial visit (Trial Completion/Early Discontinuation [Visit 25]). All AEs will be recorded in the eCRF.

8.1.1 *Glossary*

8.1.1.1 Adverse Drug Reaction

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 AE is at least a reasonable possibility (i.e., the relationship cannot be ruled out).

8.1.1.2 Adverse Event

An AE is any untoward medical occurrence in a participant or clinical investigation participant 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.

8.1.1.3 Serious Adverse Event Including Serious Adverse Drug Reactions

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 participant 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 participant 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 AE. However, the occurrence of new symptoms, or laboratory or instrumental abnormalities, as well as worsening of pre-existing symptoms, are considered AEs.

8.1.1.4 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is an adverse drug reaction of which the nature or severity is not consistent with the applicable product information (i.e, the Reference Safety Information in the IB for an unapproved investigational product).

8.1.1.5 Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is defined as an untoward and unintended response to a study drug, which is not listed in the applicable product information, has a reasonable possibility of a causal relationship and meets one of the following serious criteria: results in death, is life-threatening, requires hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

8.1.1.6 Non-Serious Adverse Event

A non-serious AE is any AE that does not meet the criteria listed above for an SAE.

8.1.2 *Data Collection*

For each event, record the following information on the AE section of the eCRF:

- **Classification of the Event:** Indicate if the event meets serious criteria
- **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 2 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 eCRF.
- **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 AE, 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 AE, 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 AE. The correlation between the study agent and the AE should be classified according to the table that follows, where probably related and possibly related will be considered as having a reasonable causal relationship to the study treatment, and unlikely related and not related will be considered as not having a causal relationship to the study treatment.

Probably Related	The event follows a reasonable temporal sequence from administration of the study treatment. The event follows a known response pattern to the study treatment; The event cannot be reasonably explained by: • the known characteristics of participant's clinical state, or • by other therapy administered, or • by the diagnostic/interventional procedure There is evidence of partial or complete disappearance of the event after withdrawal of the product (positive de-challenge)
Possibly Related	The event follows a reasonable temporal sequence from administration of the study treatment; Causation of the event by the study agent cannot be excluded; The event follows a known response pattern to the study agent, but the event could have been produced by: • the participant's clinical state, or • other therapy administered, or • a diagnostic/interventional procedure
Unlikely Related	The adverse event follows a reasonable temporal sequence from administration of the study agent; however, 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 treatment A causal relationship between the adverse event and the study drug cannot be ruled out *with certainty*.
Not Related	The event is either a pretreatment event or is definitely due to causes separate from the administration of the study treatment, i.e., • documented pre-existing condition • technical and/or manual procedural problems • concomitant medication • participant'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 eCRF)
  2. Non-drug treatment required (a non-drug treatment was prescribed or changed, record under "Comments" in the AE eCRF)
  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 eCRF)
  5. Participant discontinued from the trial

- **Action taken with study treatment:**

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

- **Participant Outcome:**
  1. Recovered without sequelae
  2. Recovered with sequelae (describe the sequelae under "Comments" in the AE eCRF)
  3. Not Recovered, event ongoing (follow the participant until a definite outcome can be determined. When follow-up data are collected, report follow-up information under "Comments" in the AE eCRF; if event is serious, fill in a follow-up SAE Report)
  4. Died (list primary cause of death under "Event Description" of the AE eCRF; if available, attach a copy of the autopsy report to the eCRF and send a copy to the Sponsor)

Comments:

Provide other pertinent clinical information and observations under "Comments" in the AE eCRF. For example, record predisposing or contributing conditions, such as previous history, concomitant diseases or medications, and/or procedural risks.

Events of a positive eDSP (EryDex) culture-based sterility test should be reported as an AE, representing an abnormal laboratory finding, unless a participant shows sign or symptoms of blood borne infection (in this case, the event may be reported as an SAE, depending upon whether it meets that definition). Detailed instructions on the reporting of such cases will be provided as part of the training for the investigators.

8.1.3 *Participant Follow-up*

Every attempt should be made to follow the participant until the AE has resolved or until the investigator determines the participant has returned to an acceptable state of health.

8.1.4 *Reporting Serious Adverse Events*

The investigator must **report all SAEs within 24 hours of event's awareness**, irrespective of the relationship to trial treatment, to the CRO pharmacovigilance department, by completing the dedicated section within the electronic data capture (EDC) system, which will then be automatically sent by the EDC system to the pharmacovigilance department e-mail. Alternatively, if the EDC system is not functional, the investigator may complete the appropriate reporting form and send notification by e-mail to the following address:

PVDS-ROW@premier-research.com.

The CRO pharmacovigilance department will then forward this information to Quince Therapeutics S.p.A. within one business day of receipt. The contact details and e-mail address of the CRO pharmacovigilance department (including back-up contacts) will be communicated to the investigators by the CRO before or during the Site Initiation Visits.

The minimum information required for an initial report of an SAE is as follows:

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

In case of death, a comprehensive narrative report of the case should be prepared by the investigator and sent to the CRO pharmacovigilance department by e-mail together with the SAE Form, retaining a copy onsite. If an autopsy is performed, a copy of the autopsy report should be actively sought by the investigator and sent to the CRO pharmacovigilance department as soon as available. A copy of the autopsy report will be retained onsite.

A follow-up SAE 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 pharmacovigilance department as described above and **within 24 hours of receipt of the follow-up information**.

If the investigator becomes aware of any deaths or SAEs suspected of being causally related to the trial treatment after the end of the window established in the protocol following investigational product administration, they will be reported to the CRO pharmacovigilance department as described above.

8.2 Reporting Events Concerning the Medical Device

Although events concerning the medical device components of the EDS do not necessarily impact on participant safety, investigators are required to inform Quince Therapeutics S.p.A. of any serious or non-serious incident and any device-related AEs and product deficiencies concerning Quince Therapeutics S.p.A. medical devices, through the Medical Device Report Log. Information should be sent to *technicalservice@quincetx.com* immediately and not later than 12 hours from the event.

Quince Therapeutics S.p.A. is responsible for handling and reporting such device events according to applicable country specific regulatory requirements.

8.3 Adverse Events of Special Interest

The following TEAEs are considered to be adverse events of special interest (AESI) due to their potential relationship to the trial treatment:

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

8.4 Safety Reporting to Investigators, Institutional Review Boards/ Independent Ethics Committees, and Regulatory Authorities

The Sponsor or their designee will be responsible for reporting all SAEs to Regulatory Authorities, investigators, and Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs), as applicable, in accordance with national regulations for all the involved countries. The Sponsor or their designee will prepare and distribute expedited safety reports according to all applicable laws and regulations. The investigational site also will forward a copy of all expedited reports to their IRB/IEC.

8.4.1 *Reporting Suspected Unexpected Serious Adverse Reactions (SUSAR)*

A SUSAR is defined as an untoward and unintended response to a study drug that is not listed in the applicable product information, has a reasonable possibility of a causal relationship, and meets one of the following serious criteria: results in death, is life-threatening, requires hospitalization or prolongation of

an existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

When an SAE report form is received and evaluated by the sponsor or designee and this event is considered unexpected and possibly related to the investigational products (therefore qualified as SUSAR), a report must be submitted to all applicable national and local authorities according to national and local laws:

- Within 7 calendar days of the Sponsor's (or designated CRO's) awareness if fatal or life-threatening
- Within 15 calendar days of the Sponsor's (or designated CRO's) awareness for non-fatal or non-life-threatening SUSARs

8.5 Reporting Overdose

If the investigational site staff administering the trial treatment reports that a participant was given more than the specified dose of trial treatment as defined in Section 6.5, this will be considered an overdose and must be reported immediately to the investigator. Any instance of overdose, whether symptomatic or not, must be reported using a process similar to SAE reporting. Details of any signs or symptoms and their management should be recorded including details of any treatments administered.

8.6 Pregnancy

This trial will exclude pregnant and breastfeeding participants. Females of childbearing potential using an adequate birth control method, as determined by their health care provider, will be eligible. Female participants will have a serum pregnancy test obtained at Screening/Baseline, and then females noted to be of childbearing potential at Baseline will have a urine pregnancy test obtained and evaluated before each eDSP infusion and a serum pregnancy test at Visit 25 (Trial Completion/Early Discontinuation).

Following the recommendation of the Heads of Medicines Agencies / Clinical Trials Facilitation and Coordination Group (Recommendations related to contraception and pregnancy testing in clinical trials; Version 1.2, 07 March 2024), adequate birth control methods (i.e., methods that can achieve a failure rate of less than 1% per year when used consistently and correctly) include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

If a participant becomes pregnant during the trial, she will be discontinued from the trial treatment and trial immediately. Participants and their parents/caregivers will be instructed to notify the investigator if it is

determined that, after completion of the trial they have become pregnant, either during the treatment phase of the trial or within 28 days (-7, +2 days) of completing the trial treatment.

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 Quince Therapeutics S.p.A. after delivery.

8.7 Independent Data Safety Monitoring Board

An independent Data Safety Monitoring Board (iDSMB) has been established to review the safety of all participants enrolled in the IEDAT-04-2022 trial and will continue to regularly review safety for participants who continue treatment in the OLE.

9 PARTICIPANT COMPLETION AND WITHDRAWAL

9.1 Definitions

A participant will be considered to have 'completed' the trial at the completion of the Visit 25 in the OLE. 'Early Discontinuation' will refer to any instance of a participant not completing the full treatment period of the trial or up to the time of trial termination by the Sponsor. In the context of the IEDAT-05-2024 trial, the permanent withdrawal of the trial treatment aligns to the discontinuation from the trial.

9.2 Procedures for Handling Withdrawals

A participant or parent/guardian may at any time freely terminate participation in the trial without giving a reason.

Should the participant be withdrawn by the investigator, all efforts should be made to complete all Early Discontinuation (Visit 25) assessments 28 days (-7, +2 days) after their final treatment. The investigator must indicate the primary reason (only one can be reported) for withdrawal as well as the date when the decision was made; these will be specified on the 'End of Study' eCRF form.

A trial participant may be discontinued from the trial at any time for any reason including, but not limited to, the following:

- the participant experiences an AE and/or SAE that in the opinion of the investigator contraindicates the participant continuing to receive the trial treatment and continuation in the trial;
- the participant/caregiver withdraws consent (e.g., participant refuses to have any more blood samples taken for the EryDex process; in this instance a specific reason must be recorded by the investigator)
- the participant becomes pregnant, or a female of childbearing potential will not agree to pregnancy testing or using an adequate birth control method
- General or specific changes in the participant's condition that render them ineligible for further treatment according to inclusion/exclusion criteria
- the participant is lost to follow-up, i.e., the participant did not return to the clinic and attempts to contact the participant were unsuccessful. Attempts to contact the participant must be documented in the medical records
- On the basis of the investigator's clinical judgement
- the Sponsor, IEC/IRB, or regulatory agency terminates the trial.

10 STATISTICAL METHODS

10.1 Safety Objective

To evaluate the safety and tolerability of eDSP in patients with A-T.

10.2 Exploratory Objective

To evaluate the effects of eDSP on neurological symptoms in patients with A-T

10.3 Sample Size

It is expected approximately 100 participants will enter this OLE study. However, there is no formal sample size calculation, as the sample size is dependent on the number of participants who complete the initial double-blind trial (IEDAT-04-2022 [NEAT]), express the desire to continue treatment with the investigational drug, and meet the eligibility criteria defined in Section 5.

Participants who completed the IEDAT-04-2022 (NEAT) study, including final efficacy assessments (Visit 9), and who do not present safety contraindications for continued treatment, as determined by the investigator, will be eligible to enroll in the OLE.

10.4 Populations for Analysis

The following analysis sets will be used:

- Safety Population: any participant that receives at least one dose of eDSP in the OLE and has at least one post-dose safety assessment will be included in the safety analyses.
- Efficacy Population: Any participant that receives at least one dose of eDSP in the OLE

10.5 Background and Demographic Characteristics

The background and demographic characteristics will consist of age, sex, race, ethnicity, height, body weight, BMI, past and current medical conditions, history of disease, and genetic confirmation of A-T. Continuous variables will be summarized by mean, SD, median, and range (minimum, maximum), and discrete variables will be summarized using frequencies and percentages.

10.6 Trial Treatment

The number of participants receiving a dose of eDSP will be reported, and the average dose of eDSP administered to each participant and across all participants, based on measurements of samples taken from the infusion bags prior to dosing, will be summarized by mean, SD, median, and range (minimum, maximum). In addition, the number of infusions will be summarized by mean, SD, median, and range (minimum, maximum)

10.7 Concomitant Medications and Therapy

A listing of concomitant medications administered from the time of dosing of the trial treatment through completion of the final evaluation or early withdrawal will be provided.

10.8 Safety Evaluations

All participants in the Safety Population will be included in the safety analyses. All AEs will be listed and summarized by body system and preferred term. The incidence of AEs (%) and their intensity and relatedness to the trial treatment, as assessed by the investigator, will be reported. SAEs and events which

are newly occurring or worsening after administration of the trial treatment will be summarized. In addition, AEs that result in death or discontinuation of the trial treatment will be listed separately. All AEs experienced after receiving treatment will be considered as TEAEs.

Other safety parameters such as vital signs, laboratory parameters, ECGs, and physical/neurological examination findings will be listed and summarized accordingly, including their changes and summaries of clinically significant changes. Abnormal and clinically notable values will be identified and listed for each parameter, as appropriate.

10.9 Exploratory Analyses

The full statistical analysis details will be provided in an SAP prior to database lock.

10.9.1 *Handling of Dropouts and Missing Data*

Participants who withdraw treatment early will be encouraged to return for assessments at the Early Discontinuation Visit (Visit 25).

As there is to be no formal statistical inference to be performed, no imputation methods will be adopted for presentations in this OLE. Exploratory data will be summarized by visit, with only those participants with data available at that visit being included. This will be apparent in the denominator in the summary tables.

10.9.2 *Exploratory Endpoints: RmICARS, mICARS, and ICARS*

The values of RmICARS, mICARS, and ICARS will be summarized by visit using number of participants with available data at that visit, mean, SD, median, and range (minimum, maximum). All data available at each visit will be summarized. Summaries may also be produced for those participants, aged 6- to 9-years-old and aged ≥10 years old, if numbers allow.

In addition, plots of individual profiles of RmICARS values over time will be produced. Similar plots will also be produced for mICARS and ICARS data.

11 ETHICS

11.1 Ethical Considerations

The trial 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.

In addition, this trial will be conducted in accordance with the following:

- European directive 2005/28/CE dated 8 April 2005 (Good Clinical Practice [GCP]) setting the GCP for biomedical research on drugs for human use.
- Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data.
- Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

11.1.1 *Participant Information and Informed Consent*

The ICF, as well as the Participant Information Sheet, must be approved by the IRB/IEC together with the trial protocol before the start of the trial.

For all participants, their parent/caregiver or legal representative (with assent by the participant), must sign and personally date an approved ICF 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 trial. Each participant/parent/caregiver should be informed that participation in the trial 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 participant is otherwise entitled.

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

No trial procedure can be performed (including the screening procedures) before the ICF has been signed. The informed consent procedure must be done according to the guidelines provided in the Declaration of Helsinki and the International Conference on Harmonisation (ICH) E6 (R3) Guideline for GCP.

The participant/parent/caregiver 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 1), the investigator assures Quince Therapeutics S.p.A. that informed consent will be obtained.

Original signed ICFs will be filed with the Investigator's File.

11.1.2 *Notification of Serious Breach*

The Sponsor may submit different types of notifications in the Clinical Trial Information System (CTIS) as serious breach: this allows the Sponsor to inform about a breach likely to affect, to a significant degree, the safety and rights of a volunteer or the reliability and robustness of the data generated in the clinical trial.

These notifications must be made without undue delay but no later than 7 days from the date on which the Sponsor became aware of the breach (article 52 of the Clinical Trial Regulation).

In the case of a personal data breach, the Sponsor (i.e., Controller) informs the Supervisory Authority without undue delay, and where feasible, no later than 72 hours after becoming aware of it. When the notification is not made within 72 hours, reasons for delay are added to the notification.

11.1.3 *Data Protection*

This trial will be performed in accordance with the standard operating procedures of the Sponsor (or designee), GCP, the European Regulation No. 536/2014, and the Code of Federal Regulations, the guidelines of the ICH, any applicable local regulation, and the most recent guidelines of the Declaration of Helsinki.

All personal data will be processed according to Regulation (EU) 2016/679 on general protection of personal data, and as per local data protection regulations.

The investigator must guarantee the confidentiality of the trial data in the medical files by implementing security measures to prevent unauthorized access to the data and to the computer system.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal trial-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by clinical quality assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IEC members, and by inspectors from Regulatory Authorities .

11.2 IEC/IRB Approval

The protocol, IB, Participant Information Sheet, ICF, and any advertisement for the recruitment of participants 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 also be included in the Final Report. Written IEC/IRB approval must be obtained by the Sponsor prior to shipment of trial treatment or participant enrollment. Any amendments to the protocol, ICF or Participant Information Sheet, other than administrative ones, must be approved by this committee.

12 ADMINISTRATIVE CONSIDERATIONS

12.1 Regulatory Requirements: Sponsor/Investigator Obligations

This trial will be conducted in accordance with the Declaration of Helsinki and the ICH E6(R3) Guideline (GCP). 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 participant's hospital files (the source documents), by authorized individuals.

12.2 Curriculum Vitae

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

12.3 Investigator and Trial Administrative Structure

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

The listing should include:

- The investigator(s);
- 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.

12.4 Investigator's Statement

This document, signed and dated by the PI, describes the investigator's obligations. The standard text is appended to the protocol (Appendix 1).

12.5 Monitoring Procedures

12.5.1 *Trial Monitoring*

A CRO has been selected by the Sponsor to oversee the conduct of the trial. An appropriate representative of the CRO (trial monitor) will maintain contact with the investigator and will visit the trial site for the purpose of discussing and/or retrieving data.

An initiation (pre-trial) visit will be made by the CRA to discuss with the investigator the protocol and the obligations of both the Sponsor and the investigator. The investigator must allow the CRA to perform periodic, interim monitoring visits.

The purposes of these visits are:

- To verify that written informed consent was obtained prior to each participant's participation in the trial.
- To assess the progress of the trial.
- To review the compliance with the trial protocol.
- To determine whether all AEs were appropriately reported.
- To determine whether the investigator is maintaining the essential documents.
- To discuss any emergent problem.
- To check the eCRFs for accuracy and completeness.
- To validate the contents of the eCRFs against source documents.

- 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 confidential. *Violations of and deviations from the protocol must be notified to the CRA as soon as possible.*

The CRA will perform a closeout visit at the time when all eCRFs have been completed as required and all queries have been answered.

12.5.2 *Electronic Case Report Forms*

eCRFs will be provided for each participant. The CRA will review the forms at each site visit according to the monitoring plan. eCRFs must be completed for all participants who sign Informed Consent, even if the participant fails to complete the trial. No section of the eCRFs is to be left blank without an appropriate explanation by the investigator as the lack of such explanation may necessitate discarding an otherwise usable observation. Instructions on how to complete the eCRF will be included in specific eCRF completion guidelines, and investigators will receive adequate training on them and on the electronic system (training will be required to get access to the system). Different access will be granted depending on the individual's role in the trial.

If requested, access to eCRFs is to be granted to the appropriate regulatory agencies.

12.5.3 *Audits and Inspections*

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 confidential. Audits/Inspections may occur any time from start to after conclusion of the trial. When an investigator signs the protocol, he/she agrees to allow Regulatory Authorities and Quince Therapeutics S.p.A. auditors to inspect his/her trial records.

12.6 Archiving of Records

Copies of the protocol, participant identification codes, eCRFs, source data, ICFs, and other documents pertaining to the trial conduct must be kept for the maximum period of time as required by the trial center. This time period must be at least 2 years after the last approval of the marketing application of the trial treatment in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the trial treatment.

No trial 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 trial 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 5 years beyond the lifetime of the trial treatment.

12.7 Final Clinical Study Report

The results of the trial will be reported in a clinical study report (CSR). The CSR will be prepared according to the Sponsor's or delegated CRO's applicable standard operating procedures and according to applicable regulatory guidelines (ICH E3 Structure and Content of Clinical Study Reports [Step 5]).

In compliance with the regulations, the final CSR will be communicated to the member states where the trial was conducted/had investigational sites within one year after the end of the trial.

The final CSR will also be provided to the investigators of the trial.

12.8 Trial Documentation and Publication of Results

12.8.1 *Trial Documentation*

All unpublished documentation (including the protocol, eCRFs and IB) given to the investigator is strictly confidential. Recipients must agree not to disclose the information contained therein to any person not connected with the trial without the prior written authorization of Quince Therapeutics S.p.A. The submission of these documents to the IRB/IEC is expressly permitted. The involved parties agree that the results of this trial 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) is the exclusive property of Quince Therapeutics S.p.A. The investigator will ensure this information is kept strictly confidential by him/her or any other person connected with the trial and shall not be disclosed to any third party without the prior written consent of Quince Therapeutics S.p.A.

12.8.2 *Publication of Results (separate from Final Clinical Study Report)*

Any publication, abstract, paper or material relating to the present clinical trial shall be managed by Quince Therapeutics S.p.A. Prior to initiating any of these activities, Quince Therapeutics S.p.A. will form a trial publication committee to coordinate, develop, and implement a publication policy. The publication committee will decide on the authorship requirements, content, journal, and sequence of publications /presentations as applicable.

12.9 Financial Agreement

A financial agreement (separate from the protocol) will be made and signed by Quince Therapeutics S.p.A., or their designee, and by a representative of the Institution where the trial will be conducted.

12.10 Termination of Trial

In the event that the investigator is unable to continue the trial, 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 CRA within 10 days of the change. Within 6 months of the appointment of the interim investigator, the new investigator must be identified and approved by both Quince Therapeutics S.p.A. and the IRB/IEC for the trial to continue at the site.

If the Sponsor and/or the investigator discover conditions arising during the trial that indicate it should be terminated, an appropriate schedule for termination will be instituted. If the investigator terminates the trial, an explanatory letter will be provided to Quince Therapeutics S.p.A. Should the trial be discontinued due to a decision by Quince Therapeutics S.p.A., the investigator will be reimbursed for reasonable expenses incurred and for the participants actually treated according to the trial protocol.

12.10.1 *Trial Discontinuation by the Sponsor*

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

- failure to enroll participants
- protocol violations or deviations

- inaccurate or incomplete data
- non-GCP compliance
- completion of enrollment
- administrative reasons

12.10.2 *Trial Discontinuation by the Investigator*

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

12.11 Insurance Policy

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

12.12 Financial Disclosure

The 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 trial, and for a period of one year following its completion (last participant last visit).

The trial 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 Code of Federal Regulations (21 CFR part 54) by the US FDA, including requirements for full financial disclosure (US FDA, 2013).

13 REFERENCES

American Society of Clinical Oncology. Ataxia-Telangiectasia. American Society of Clinical Oncology website. https://www.cancer.net/cancer-types/ataxia-telangiectasia. Accessed 14 March 2024.

Boder E. Ataxia-telangiectasia: an overview. In: Gatti RA, Swift M, eds. Ataxia-telangiectasia: Genetics, Neuropathology, and Immunology of a Degenerative Disease of Childhood. Kroc Conference Series. Vol. 19. New York: Alan R. Liss Inc 1985:1-63.

Boehrs JK, He J, Halaby MJ, Yang DQ. Constitutive expression and cytoplasmic compartmentalization of ATM protein in differentiated human neuron-like SH-SY5Y cells. J Neurochem 2007;100(2):337-345.

Cano SJ, Hobart JC, Hart PE, et al. International Cooperative Ataxia Rating Scale (ICARS): appropriate for studies of Friedreich's ataxia? Mov Disord 2005;20(12):1585-91.

Chun HH, Gatti RA. Ataxia-telangiectasia, an evolving phenotype. DNA Repair 2004;3:1187- 1196.

Clinical Trials Facilitation and Coordination Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials; Version 1.1, 21 Sept 2020.

Crawford TO, Skolasky RL, Fernandez R, et al. Survival probability in ataxia telangiectasia. Arch Dis Child 2006;91(7):610-11.

Gordon CM et al., 2013 Pediatric Position Development Conference: Executive Summary and Reflections. Journal of Clinical Densitometry: Assessment and Management of Muscoloskeletal Health, 2014; 17, (2): 219-224.

Hoche F, Seidel K, Theis M, et al. Neurodegeneration in Ataxia Telangiectasia. What is New? What is Evident? Neuropediatrics 2012;43(3):119-29. Epub 2012May21.

Howie SR. Blood sample volumes in child health research: review of safe limits. Bull World Health Organ 2011;89:46-53.

Lee Y, McKinnon PJ. ATM dependent apoptosis in the nervous system. Apoptosis 2000;5(6):523-529.

Mambrini G, Mandolini M, Rossi L, Pierigè F, Capogrossi G, Salvati P, Serafini S, Benatti L, Magnani M. Ex vivo encapsulation of dexamethasone sodium phosphate into human autologous erythrocytes using fully automated biomedical equipment. Int J Pharm. 2017 Jan 30;517(1-2):175-184. doi: 10.1016/j.ijpharm.2016.12.011. Epub 2016 Dec 7. PMID: 27939571.

Metz G, Coppard N, Cooper JM, et al. Rating disease progression of Friedreich's ataxia by the International Cooperative Ataxia Rating Scale: analysis of a 603-patient database. Brain 2013;136(Pt 1):259-68.

Mitchell CD, Richards SM, Kinsey SE, et al.; Medical Research Council Childhood Leukaemia Working Party. Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: results of the UK Medical Research Council ALL97 randomized trial. Br J Haematol 2005;129:734-745.

Orphanet Report Series - Prevalence of rare diseases: Bibliographic data - May 2014 - Number 1 http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_ alphabetical_list.pdf

Perlman S, Becker-Catania S, Gatti RA. Ataxia-telangiectasia: diagnosis and treatment. Semin Pediatr Neurol 2003;10:173-182.

Petley E, Yule A, Alexander S, et. al. The natural history of ataxia-telangiectasia(A-T): A systematic review. PLOS ONE 2022 March 15. doi:10.1371/journal.pone.0264177

Posner K, Oquendo MA, Gould M, et al. Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry 2007; 164:1035-1043.

Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: Initial Validity and Internal Consistency Findings from Three Multisite Studies with Adolescents and Adults. Am J Psychiatry 2011; 168:1266-1277.

Poupard M. Ataxia-telangiectasia. In: Euro-Ataxia: European Federation of Hereditary Ataxia [newsletter 24]. 2003:7-9.

Rothblum-Oviatt C, Wright J, Lefton-Greif MA, McGrath-Morrow SA, Crawford TO, Lederman HM. Ataxia telangiectasia: a review. Orphanet J Rare Dis. 2016 Nov 25;11(1):159.

Schmitz-Hubsch T, du Montcel ST, Baliko L, et al. Reliability and validity of the International Cooperative Ataxia Rating Scale: a study in 156 spinocerebellar ataxia patients. Mov Disord 2006a;21(5):699-704.

Schmitz-Hubsch T, du Montcel ST, Baliko L, et al. Scale for the assessment and rating of ataxia: development of a new clinical scale. Neurology 2006b;66(11):1717-20.

Schoch B, Regel JP, Frings, et al. Reliability and validity of ICARS in focal cerebellar lesions. Mov Disord 2007;22(15):2162-9.

Trouillas P, Takayanagi T, Hallet M, et al. International Cooperative Ataxia Rating Scale for pharmacological assessment of the cerebellar syndrome. The Ataxia Neuropharmacology Committee of the World Federation of Neurology. J Neurol Sci 1997;145(2):205-11.

US Food and Drug Administration. Guidance for Clinical Investigators, Industry and FDA Staff: Financial Disclosure by Clinical Investigators. FDA website. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/financial-disclosure-clinical-investigators. Published 2013. Accessed 14 March 2024.

Weyer A, et al. Reliability and validity of the scale for the assessment and rating of ataxia: a study in 64 ataxia patients. Mov Disord 2007;22(11):1633-7.

Zocchi E, Guida L, Polvani C, et al. Human and Murine Erythrocytes as Bioreactors Releasing the Antineoplastic Drug 5-fluoro-2'-deoxyuridine. In Resealed Erythrocytes as carriers and bioreactors. Advances in the Biosciences (Volume 81), Pergamon Press, R. Green, J.R. DeLoach (1991).

APPENDICES

Appendix 1: Investigator Statement

Investigator Statement

Investigational Medicinal Product:	EryDex System
Protocol Number:	IEDAT-05-2024
Title:	An Open-Label Extension Study of EryDex in Patients with Ataxia-Telangiectasia Following Participation in Study IEDAT-04-2022
Principal Investigator:	
Trial Center:	

COMMITMENTS

By signing this document, I agree to conduct the trial as outlined in the protocol and in accordance with (as applicable) the Declaration of Helsinki, the ICH GCP Guideline as well as all applicable government regulations.

I declare:

1. I am well qualified by scientific training and experience to conduct investigational studies in the clinical area of the proposed trial, and I am affiliated with a recognized medical school or with an independent institution recognized for its excellence.
2. I have received and understood the information about pharmacology, toxicology and possible risks and side effects of the investigational compound (e.g., as described in the eDSP (EryDex) IB).
3. I shall provide information to all staff members involved in the trial about their obligations as described in this document.
4. I shall submit the protocol, ICF/participant information sheet and other required documentation to the IRB/IEC for review and approval.
5. I shall make no changes to the protocol without formal amendment (prepared in agreement with the Sponsor), except when necessary to protect the safety, the rights or welfare of participants. In this last case I will inform the Sponsor of the change.
6. I shall require Informed Consent from each participant prior to enrollment into the trial. The Informed Consent shall be documented by use of a written consent form approved by the Sponsor and the IRB/IEC.
7. I shall use the investigational compound only in compliance with the trial protocol and I shall be responsible for the security and accountability of clinical trial supplies.

8. I shall notify Quince Therapeutics S.p.A. immediately or no later than 24 hours by telephone and/or by fax of serious or unexpected AEs and submit written reports of AEs, as outlined in the protocol, to Quince Therapeutics S.p.A., the IRB/IEC and to Regulatory Authorities (when appropriate).
9. I shall complete the Sponsor's eCRF in a timely and legible manner.
10. I shall maintain accurate source records (hospital or other institutional records), which will support the data entered into eCRF and I shall maintain these as specified in the protocol.
11. I shall allow monitoring visits by Quince Therapeutics S.p.A.'s representatives at a predetermined frequency.
12. I shall allow the authorized Sponsor representative and any Regulatory Authorities to inspect the facilities and pertinent records at reasonable times and in a manner which ensure participant confidentiality.
13. I shall maintain confidentiality about all information concerning the investigational compound, such as patent applications, formulas, manufacturing process, basic scientific data and formulation information supplied by the Sponsor and not previously published, and I shall not disclose this information to a third party without the written consent of the Sponsor.
14. I shall permit the information developed in the clinical trial to be used by the Sponsor in connection with the development of the compound and may be disclosed to the IRB/IEC and Regulatory Authorities.

Following completion of the trial, the data may be considered for reporting at a scientific meeting and/or for publication in a scientific journal. A copy of the manuscript or abstract will be provided to the Sponsor for review before submission to a scientific journal for publication and/or a scientific meeting selection committee for oral or poster presentation. Subgroup or individual Investigator publications must not interfere or compromise publication of the multi-center results of this clinical trial.

_____ _____

Investigator Signature **Date**

_____

Investigator (Printed Name)

Appendix 2: Description of the EryDex System

The EryDex is used for the *ex vivo* encapsulation of the drug DSP into autologous erythrocytes before re-infusion of the drug-encapsulated erythrocytes (final product) into a patient.

EryDex Components:

The EDS is comprised of the following:

- RCL Device (CE Marked)
- EryKit_01 (Single-Use Device CE Marked)
- Syringe Kit (Single-Use Device CE Marked)
- Process Solutions :
  - Hypotonic Solution 1 (CE Marked)
  - Hypotonic Solution 2 (CE Marked)
  - PIGPA Hypertonic Solution (CE Marked)
- Drug: DSP Solution

The components are intended to be marketed for use solely with the EryDex. Some components, such as the EryKit_01, Syringe Kit, Process Solutions and Drug are single-use; the RCL device is reusable.

Red Cell Loader Device

EryKit_01 Device

[redacted]

Syringe Kit Device

[redacted]

Process Solutions

[redacted]

Dexamethasone Sodium Phosphate Solution [redacted]

[redacted]

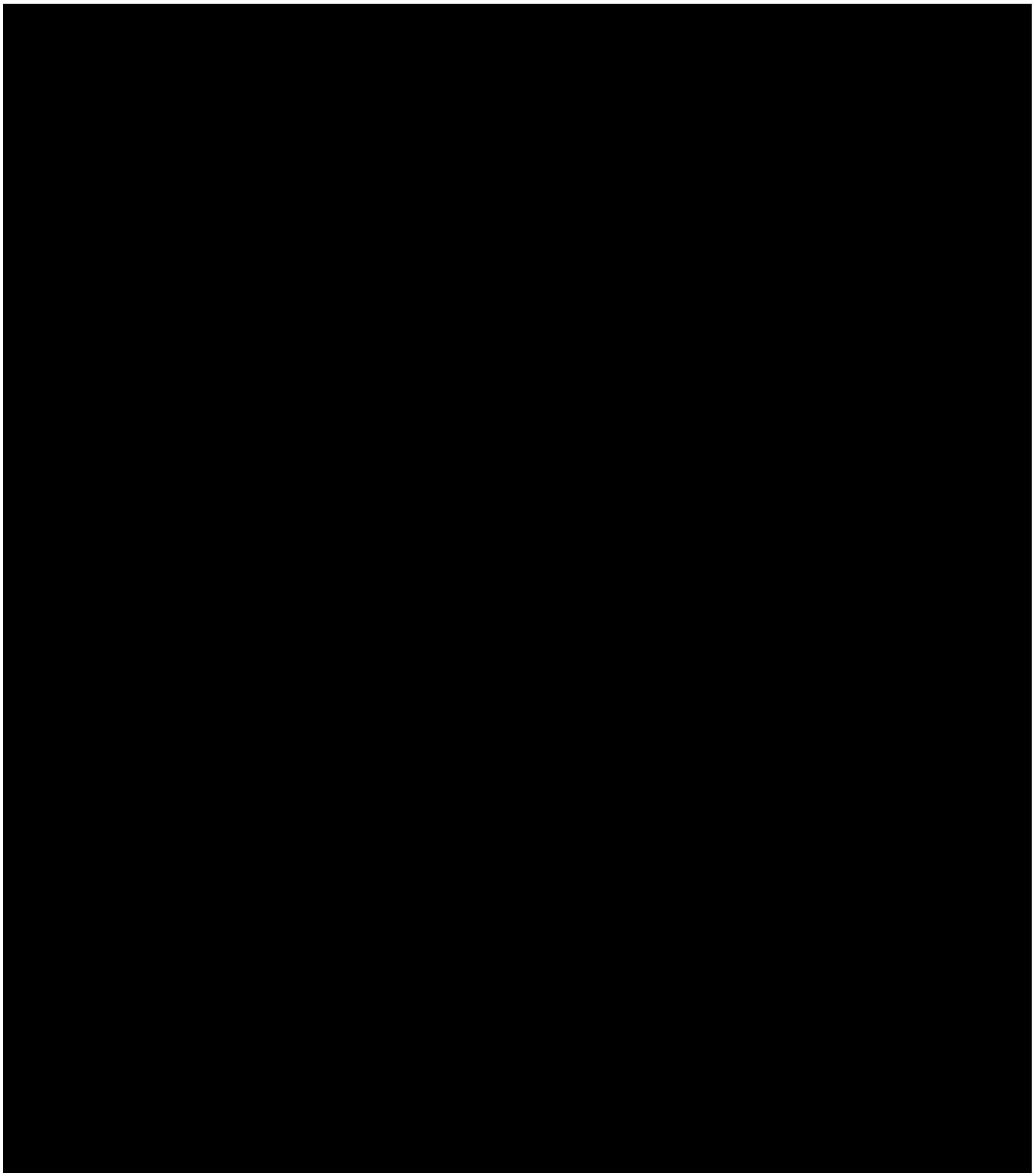
[redacted]

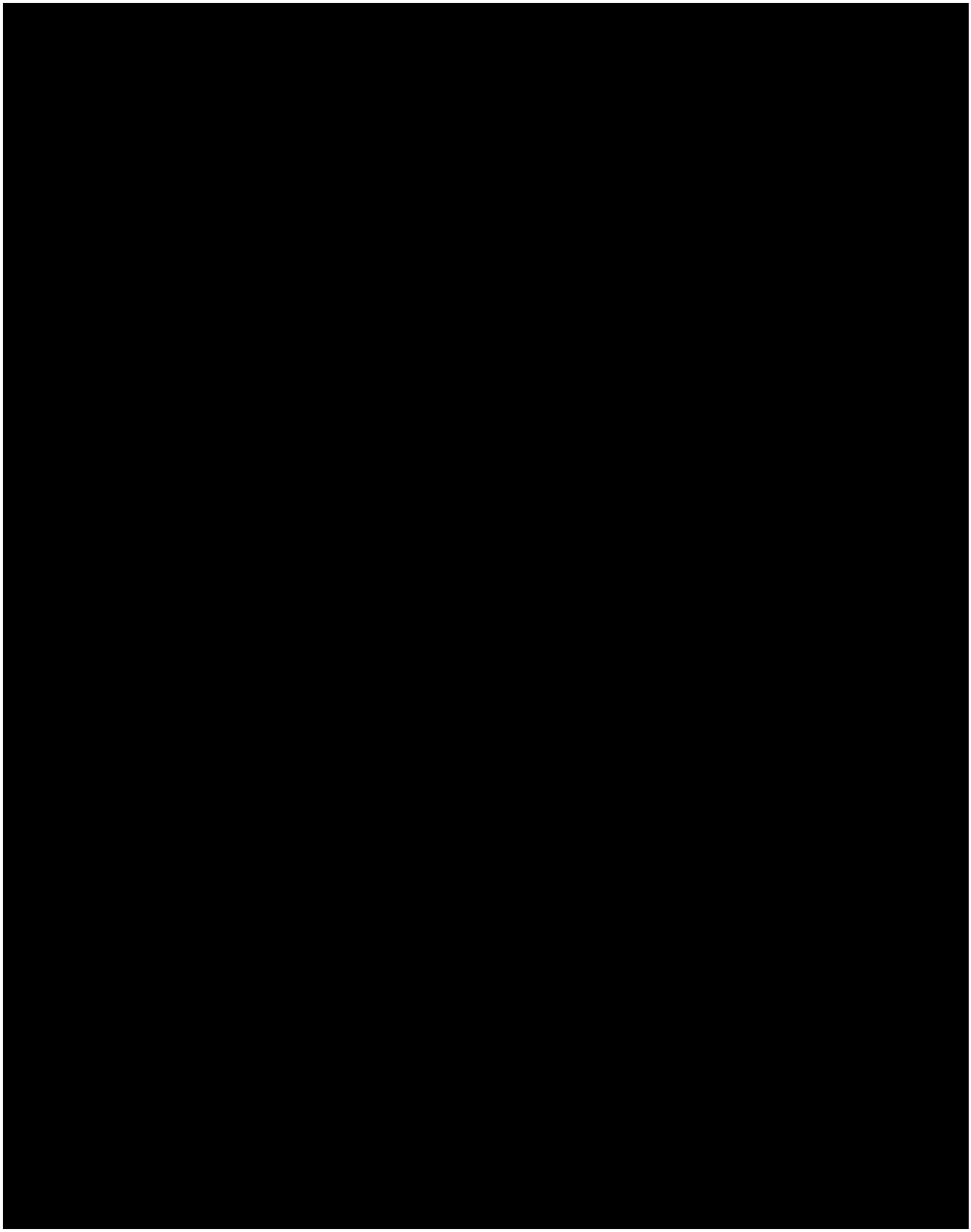
Additional materials

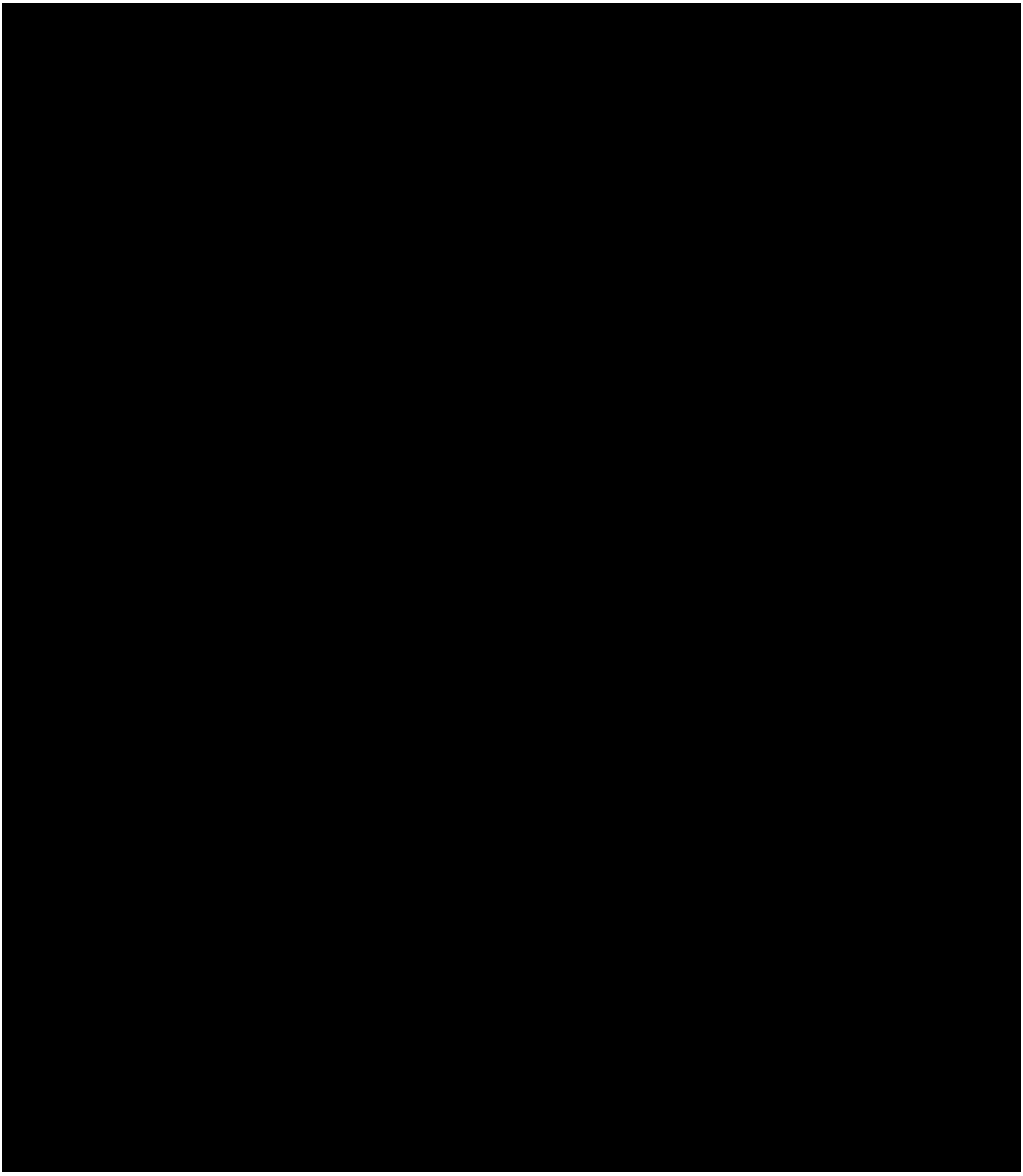
[redacted]

EryDex System Process (or Procedure)

[redacted]

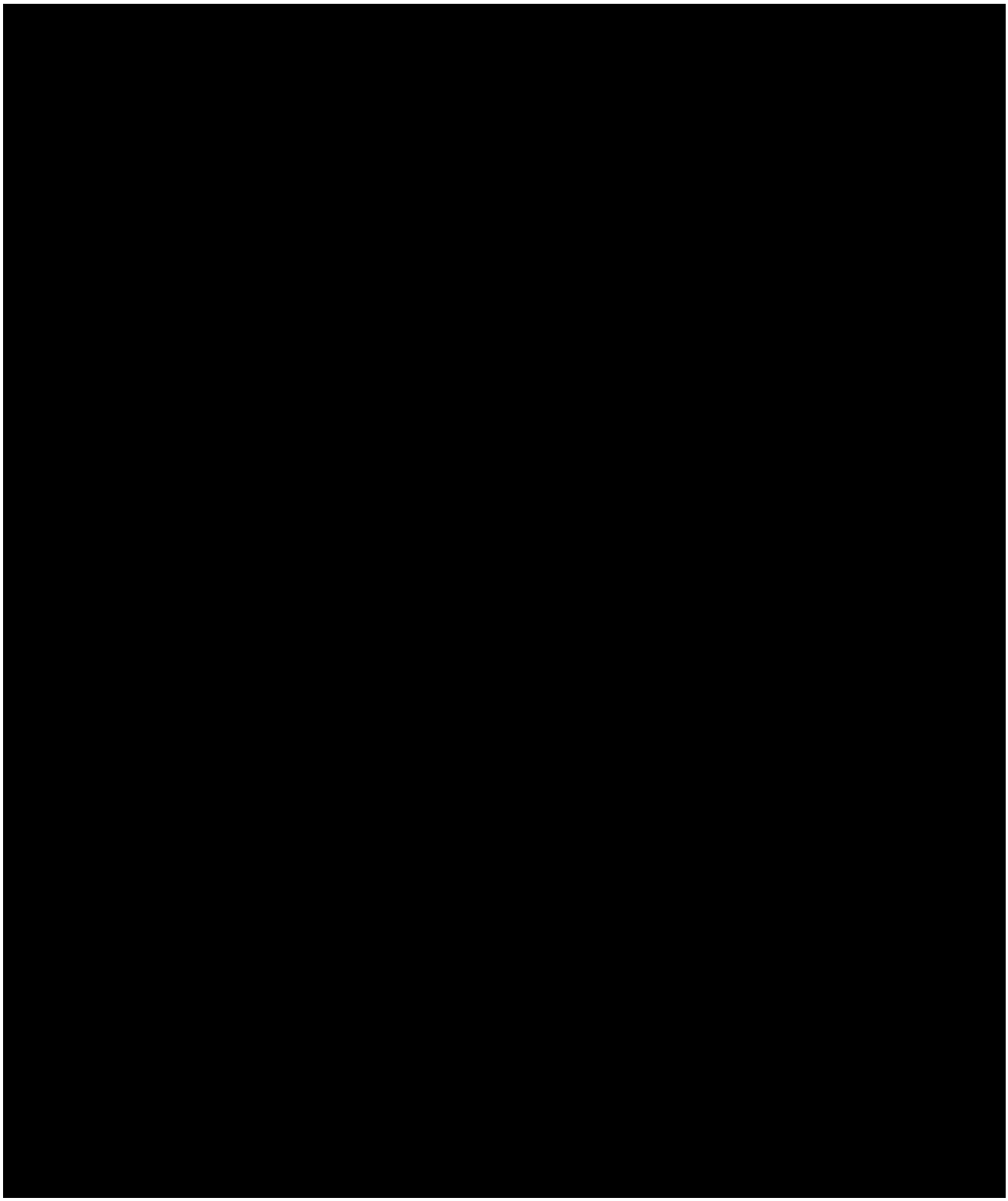






Appendix 3: Method for Measuring Dexamethasone Sodium Phosphate in Samples Taken from Satellite Sample Bag or any other EryDex Sampling Point

Appendix 4: Sterility Test of EryDex Using a Culture-based Method – Sampling Procedure



[redacted]

Results Classification:

- TRUE POSITIVE: Initial positive, confirmed by growth of same bacteria on repeat culture of original specimen.
- FALSE POSITIVE: Initial positive, no growth on repeat culture of original specimen. INDETERMINATE: Initial positive, with no confirmatory test performed or confirmatory test performed but cannot be interpreted.

At the trial's start, investigational sites should collect and provide to the Sponsor/CRO the local procedure that will be followed for the conduct and interpretation of the culture-based method sterility test, including any available quality certificate.

Appendix 5: Signs and Symptoms of Adrenal Insufficiency

Screening for adrenal insufficiency will be performed in all participants, via early morning (before 8:00 AM) plasma cortisol testing, at the following times: (1) during the Screening/Baseline period, (2) when participants are symptomatic, (3) when participants are at most risk for adrenal insufficiency and adrenal crisis, such as following discontinuation or interruptions of dexamethasone dosing (i.e., loading failures and following discontinuation of the trial treatment), and at Visit 25.

The following signs and symptoms will be assessed to screen for adrenal insufficiency:

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

Clinical judgement should be used by the investigator to determine if any of the above signs and symptoms observed are indicative of adrenal insufficiency related to the trial treatment or are symptoms of the underlying neurological disorder.

If the basal (8:00 AM) cortisol level is measured and is within the reference normal range, the participant can continue dosing with eDSP. If at any time during the trial a participant exhibits signs or symptoms of adrenal insufficiency, cortisol should be tested via an 8:00 (+30 minutes) AM cortisol sample. If the result is <5 µg/dL (or the LLN of the assay used), the participant should undergo a high dose ACTH stimulation test. Also, if the AM cortisol is between 5-10 µg/dL, and there is a strong suspicion for adrenal insufficiency, the ACTH test should be done. The test should be scheduled as soon as possible, and until normal adrenal function is confirmed, the participant should be monitored and treated following clinical guidelines for suspected adrenal insufficiency. If the result of the ACTH stimulation test is abnormal, the participant should be given appropriate treatment, but can continue in the trial, if the investigator considers it appropriate.

Appendix 6: EryDex Process Training and Documentation

All site personnel involved in blood collection, processing, testing and administration of eDSP (EryDex) will be trained on the use of the following checklists (will be provided as separate trial documents), to be completed at each treatment visit:

- Encapsulation Procedure and eDSP (EryDex) Infusion Checklist: to collect information on the EryDex process, used materials (including labels from the infusion bag and randomized treatment ampule) and infusion.
- Aseptic Procedure Checklist: to collect information on the correct and full implementation of the aseptic procedures, from collection of blood from the participant through administration of the eDSP (EryDex) to the participant. This checklist will be complemented by the "Instructions for aseptic processing – EryDex System", a stand-alone document that includes detailed description of the actions to be implemented to avoid contaminations in the following steps:
  1. Aseptic procedures for prevention of contamination of EryDex
     - General background information
     - Phase 1: Collection of [redacted] autologous blood cells
     - Phase 2: EryDex Process
     - Phase 3: eDSP (EryDex) administration
  2. Technical instructions for eDSP (EryDex) sterility sampling
     - Samples for sterility culture test, CBC, and determination of DSP content

In addition, the EryDex Operators will be trained and receive copies of the following manuals:

- Operator's Manual EryDex System contains all information required for the use of the RCL and EDS, including:
  - Safety information and warning
  - Product description and technical specifications
  - Instructions for installation of RCL
  - Description of each step of the EryDex process (gather supplies, setup, blood collection, blood connection, EryDex process, eDSP (EryDex) infusion, removal, and disposal)
  - Maintenance instructions and after-sales service
- Quick Reference Guide EryDex System contains a brief guidance related to the use of the EDS including:
  - EryDex process warnings
  - Identification of the parts of the RCL
  - Identification of the parts of the EryKit_01
  - Needed supplies
  - Tips related to setup, blood collection, blood connection, EryDex process, EDS-EP infusion, removal, and disposal.

- Instructions for Use of EryKit_01: contains all information required for the use of EryKit_01, Hypotonic Solutions 1 and 2, PIGPA Hypertonic Solution within the EDS, including:
  - Safety information and warning
  - Product description and technical specifications
- Instructions for Use of Syringe Kit: it contains all information required for the use of Syringe Kit within the EDS, including:
  - Safety information and warning
  - Product description and technical specifications
  - Product use