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Clinical Research Protocol

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Protocol CLI-06814AA1-01

Phase IV

Single Arm, Open-Label, Multicenter, Registry Study of Revcovi (elapegademase-lvlr) Treatment in ADA-SCID Subjects Requiring Enzyme Replacement Therapy

Version 5.0

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2 STUDY SYNOPSIS

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USA</td><td>No. of centers:
13</td><td>Expected Study Duration: A minimum of 24 months per subject</td></tr>
<tr><td colspan="3">Study Objectives:
To conduct a registry study on patients with adenosine deaminase severe combined immune deficiency (ADA-SCID) treated with Revcovi™ and have periodic clinical and biochemical assessments for safety and dose adjustment based on adenosine deaminase (ADA) activity and erythrocyte deoxyadenosine nucleotide (dAXP) levels.</td></tr>
<tr><td colspan="3">Study Design and Methodology:
Protocol CLI-06814AA1-01 is designed as a single arm, open-label, multicenter registry study. The study will include ADA-SCID patients requiring Revcovi as Enzyme Replacement Therapy (ERT). This is inclusive of:
• patients currently receiving chronic ERT with Adagen®; and transitioned/transitioning to Revcovi
• infants diagnosed via newborn screening and/or definitive testing for ADA deficiency prescribed Revcovi
• patients receiving Revcovi while preparing for Hematopoietic Stem Cell Transplant (HSCT) or Hematopoietic Stem Cell Gene Therapy (HSC-GT)
• subjects who decline, are ineligible or do not respond to HSCT or HSC-GT and resume/start Revcovi.
Subjects for whom written informed consent/assent is obtained will be assigned an identification number and undergo enrollment procedures. The date of ICF signature is considered the date of</td></tr>
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Study Drug: Revcovi (elapegademase-lvlr)		**IND No.:** 100,687
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enrollment into the registry. Subjects should have initial, trough erythrocyte dAXP levels and plasma ADA activity measurements collected prior to start of Revcovi as part of standard of care. Additionally, at enrollment, physical examination, vital signs, and laboratory values for total lymphocytes and subset analysis, as well as quantitative immunoglobulins, should be collected as per standard of care. Subjects who started treatment with Revcovi before enrollment should have data collected retrospectively in accordance with the Suggested Schedule of Assessments.

Subjects/Parents/Caregivers/Health Care Providers will administer weekly intramuscular (IM) dose(s) of Revcovi and will be followed according to the Suggested Schedule of Assessments for trough dAXP and ADA activity as deemed appropriate by the provider. Treatment dosing and monitoring will be individualized per provider and subject characteristics in adherence with each study sites' standards of care.

The Phase III Study STP-2279-002 was an open-label, multicenter, single-arm, one-way crossover study to determine the safety, efficacy, and PK of Revcovi (EZN2279; Succinimidyl Carbamate-Polyethylene Glycol Recombinant Adenosine Deaminase [SC-PEG rADA]; elapegademase) in patients with ADA-SCID who were currently being treated with Adagen. All participants from the Phase III Study, who are now under treatment with commercial Revcovi, are permitted to enroll and proceed directly to the Treatment Month 6 Visit of this study protocol (CLI-06814AA1-01).

Enrolled subjects will be followed until the last enrolled patient has reached a minimum of 24 months of Revcovi treatment or until undergoing HSCT or HSCGT, whichever occurs first. Subjects undergoing HSCT or HSCGT will be followed one month and again at 6 months after last Revcovi dose to assess adverse events (AEs) and survival.

Study Drug: Revcovi (elapegademase-lvlr)		**IND No.:** 100,687
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Throughout the duration of the study, subjects will be assessed continually for AEs. An interim analysis will be performed approximately two years after study initiation.		
Sample Size: No formal sample size is calculated for this study. The study will enroll all eligible patients over a minimum of 2 years.		
Patient Selection Criteria: <u>*Inclusion Criteria*</u> • Patients currently receiving chronic ERT with Adagen®; and transitioned/transitioning to Revcovi; • Infants diagnosed via newborn screening and/or definitive testing for ADA deficiency prescribed Revcovi; • Patients receiving Revcovi while preparing for Hematopoietic Stem Cell Transplant (HSCT) or Hematopoietic Stem Cell Gene Therapy (HSC-GT); • Patients who decline, are ineligible or do not respond to HSCT or HSC-GT and resume/start Revcovi. <u>*Exclusion Criteria*</u> • Any condition that, in the opinion of the Investigator, makes the subject unsuitable for the study.		
Study Duration: Enrolled subjects will be followed until the last enrolled patient has reached 24 months of Revcovi treatment or until undergoing HSCT or HSCGT, whichever occurs first. Subjects undergoing HSCT or HSCGT will be followed one month and again at six months after final Revcovi dose to assess for AEs and survival.		

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Revcovi - Dose, Route of Administration, and Duration of Administration:

Subjects previously treated with Adagen and Adagen-naïve subjects (newborn) should be dosed in accordance with the Revcovi Package Insert (PI) recommendation. Subjects who started Revcovi treatment prior to study enrollment should continue to be dosed in accordance with provider or Revcovi PI recommendation.

Subjects transitioning from Adagen to Revcovi:

For subjects currently receiving Adagen at ≤ 30 U/kg/wk or an unknown Adagen dose, the recommended weekly IM dose of Revcovi is 0.2 mg/kg.

For subjects currently receiving Adagen at > 30 U/kg/wk an equivalent Revcovi dose (mg/kg) can be calculated using the following equation:

$$\text{Revcovi dose in mg/kg} = \frac{\text{Adagen dose in U/kg}}{150}$$

The total weekly dose may be divided and administered in multiple IM injections per week. The weekly Revcovi dose may be increased by increments of 0.033 mg/kg, if trough ADA activity is under 30 mmol/hr/L, dAXP is above 0.02 mmol/L, and/or the immune reconstitution is inadequate based on the clinical assessment of the subject by the investigator.

Adagen-naïve subjects: The starting weekly IM dose with Revcovi is 0.4 mg/kg based on ideal body weight, divided into two doses (0.2 mg/kg twice a week), for a minimum of 12 to 24 weeks until immune reconstitution is achieved. After that, the dose may be gradually adjusted to maintain trough ADA activity over 30 mmol/hr/L, dAXP under 0.02 mmol/L, and/or to maintain

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adequate immune reconstitution based on clinical assessment of the subject.

The optimal long-term dose and schedule of administration should be established by the treating physician for each subject individually and may be adjusted based on the laboratory values for trough plasma ADA activity, trough erythrocyte dAXP level, and/or on the treating physician's medical assessment of the subject's clinical status.

Reference Therapy, Dose Route of Administration and Duration of Administration: Not applicable

Criteria for Evaluation:

Biochemical Variables and Immune Status: Total erythrocyte dAXP from a trough blood sample; trough plasma ADA activity; immune status (B-, T-, and natural killer (NK) lymphocyte subset analysis; quantitative immunoglobulin concentration [IgA, IgG, IgM]); and immune function measurement, as indicated (phytohaemagglutinin [PHA] stimulation or equivalent).

Safety Variables: AEs, serious adverse events (SAEs), vital signs and safety laboratory evaluations will be assessed in accordance with the Investigator's standard of care. Immunogenicity of Revcovi should be assessed based on the Revcovi PI recommendations.

Clinical Status: Clinical signs and symptoms from physical examination (including height and weight for growth assessment), incidence and duration of hospitalizations, infections (clinically and microbiologically documented, including opportunistic infections), and survival (follow up visits and/or phone calls to confirm subject status).

Quality of Life: Quality of life (QOL) will be assessed for subjects up to and including those who are 18 years old using the age-specific Pediatric Quality of Life Inventory (PedsQL). Subjects over 18 years old will be assessed using the SF-36 and Primary

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Antibody Deficiency Quality of Life Questionnaire (PADQOL). QOL assessment data will be collected from study participants via scripted phone calls by the study call center and the QOL responses will be entered directly into the electronic data capture (EDC) system. QOL assessments will be collected prospectively for 24 months after starting Revcovi.

Statistical Methodology:

As this is a registry study, analyses will be descriptive, with data listings, graphical presentations, frequency tabulations, and summary statistics as appropriate.

Biochemical Analysis:

Following recommendations from the Revcovi PI, Erythrocyte dAXP concentration should be maintained at ≤ 0.02 μmol/mL and trough plasma ADA activity at ≥ 30 μmol/h/mL for Adagen-treated subjects transitioning to Revcovi and for Adagen-naïve subjects.

Analyses of the following biochemical parameters will be primarily descriptive, with data listings, graphical presentations, frequency tabulations, and summary statistics as appropriate: total erythrocyte dAXP, trough plasma ADA activity, absolute lymphocyte count, B-, T-, and NK-lymphocyte subset analysis; quantitative immunoglobulin concentration, and immune reconstitution data. Change from baseline will be calculated and summary statistics provided for all applicable parameters.

Safety Analysis:

- AEs will be coded according to most recent version of Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized in frequency tables displaying counts and percentage by body system, preferred term, and treatment groups as naïve patients or patients transitioning from Adagen. In

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addition, AEs will be summarized by relationship to Revcovi and by severity. All SAEs will also be summarized in a frequency table.

- Safety laboratory parameters (chemistry, hematology, and urinalysis) will be summarized descriptively at each time point; out-of-range values will be listed.
- Vital sign parameters will be summarized descriptively at each time point.

Clinical Status: These endpoints will be summarized descriptively:

- Incidence of infection
- Incidence and duration of hospitalizations
- Growth: Height-for-age and weight-for-age Z-scores
- Survival: Descriptive summary of subject status.

Quality of Life Analysis:

Quality of Life: QOL will be assessed for subjects up to and including those who are 18 years old using the age-specific Pediatric Quality of Life Inventory (PedsQL). Subjects over 18 years old will be assessed using the SF-36 and Primary Antibody Deficiency Quality of Life Questionnaire (PADQOL). Data will be summarized by age and stratified by previous participation in the Phase III study STP-2279-002. Subjects that age out of PedsQL and into PADQOL will be summarized only in the PedsQL while their PADQOL will be listed.

3 LIST OF ABBREVIATIONS

Abbreviation	Term
ADA	adenosine deaminase
ADA-SCID	adenosine deaminase severe combined immunodeficiency
AE	adverse event
aPTT	activated partial thromboplastin time
AUC	area under the curve
C_{max}	maximum concentration
CMV	cytomegalovirus
CRF	case report form
Cys74	cysteine at position 74
C74S	Cys74 mutated to serine
d-adenosine	2′-deoxyadenosine
d-ATP	2′-deoxyadenosine 5′-triphosphate
dAXP	deoxyadenosine nucleotides
DCF	data clarification forms
dCydK	deoxycytidine kinase
d-inosine	2′-deoxyinosine
DNA	deoxyribonucleic acid
DSMC	Data and Safety Monitoring Committee
EDTA	ethylenediaminetetraacetic acid
ERT	Enzyme Replacement Therapy
FACS	fluorescence-activated cell sorter
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIPAA	Health Insurance Portability and Accountability Act
HLA	human leukocyte antigen
HSC-GT	hematopoietic stem cell gene therapy

HSCT	hematopoietic stem cell transplantation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IM	intramuscular
IND	Investigational New Drug
IP	intraperitoneal
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
mPEG	monomethoxypolyethylene glycol
Mg	milligram
MPV	mean platelet volume
NK	natural killer
NOAEL	no observed adverse effect levels
PADQOL	Primary Antibody Deficiency Quality of Life Questionnaire
PD	pharmacodynamic
PedsQL	Pediatric Quality of Life Inventory
PEG	polyethylene glycol
PHI	protected health information
PI	package insert
PK	pharmacokinetic
QC	quality control
rADA	recombinant adenosine deaminase
SAE	serious adverse event
SC	succinimidyl carbamate
SF-36	Short Form 36 Health Survey
SS	succinimidyl succinate
SST	serum separator tube
$t_{1/2}$	Terminal elimination half life
TSE	transmissible spongiform encephalopathy

4 GENERAL STUDY INFORMATION

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5 INTRODUCTION

Leadiant Biosciences, Inc. (Leadiant Biosciences) developed and received Food and Drug Administration (FDA) approval (BLA 761092) for Revcovi™ (elapegademase-lvlr), a polyethylene glycol recombinant adenosine deaminase [PEG-rADA], for the treatment of pediatric and adult subjects with adenosine deaminase severe combined immunodeficiency (ADA-SCID) on October 2017. In November 2020 Chiesi Farmaceutici S.p.A (Chiesi) bought the rights of Revcovi™ from Leadiant Biosciences. The change in IND ownership has been communicated to FDA with notification submitted to the IND by Chiesi on 23 Nov 2020.

5.1 Disease Background

Adenosine deaminase (ADA)-deficient combined immunodeficiency disease is a rare, inherited, and often fatal disease. It is characterized by severe and recurrent opportunistic infections, failure to thrive, profound lymphopenia with absent or severely impaired cellular and humoral immune function, and metabolic abnormalities (Booth and Gaspar 2009, Gaspar et al., 2009). These patients are lymphopenic at birth and predisposed to recurrent illnesses caused by pathogens and opportunistic organisms that often begin within a few weeks. The average age at diagnosis for patients with ADA-SCID is within first few months of life (Arredondo-Vega et al., 1998). The incidence of ADA deficiency is estimated to be between 1:200,000 and 1:1,000,000 live births (Gaspar et al., 2009).

ADA deficiency can be categorized into four phenotypes (Booth and Gaspar 2009):

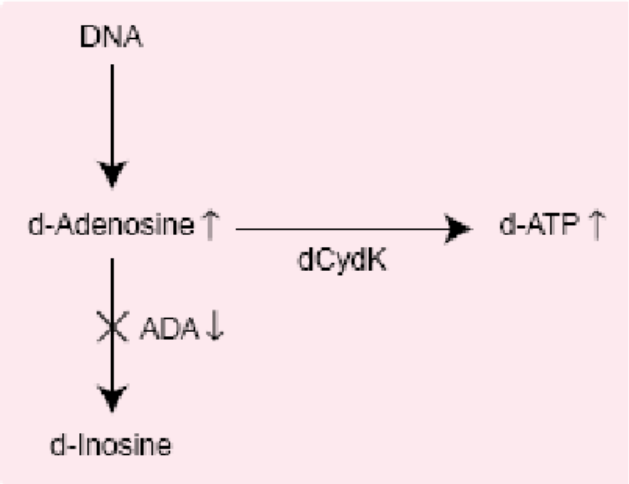
- **Early onset**: The largest number of patients with ADA deficiency (about 85% to 90%) present with early onset ADA-SCID, which is the most severe form of the immunodeficiency. Patients are usually diagnosed within first few months of life and almost always by the age of 1 year.
- **Delayed onset ADA deficiency** has been identified in 10% to 15% of patients with ADA deficiency. The disease presents itself after the first year of life and is most likely related to the specific ADA mutation that in such cases results in some residual ADA activity and less profound lymphopenia and immune function.
- **Late (or adult) onset ADA deficiency** has been identified in some individuals but is less common than early or delayed-onset forms.
- **Partial ADA deficiency** can be an incidental finding in a healthy individual who has normal immune function and abnormal ADA expression in erythrocytes. Partial ADA deficiency is extremely rare.

Patients with ADA-SCID are unable to produce sufficient ADA enzyme in their cells because of mutations in the ADA gene on chromosome 20q. ADA deficiency is a disorder of purine salvage (Booth et al., 2007). In the absence of this enzyme, the purine substrates adenosine, 2′-deoxyadenosine, and their metabolites reach unusually high levels in cells and are toxic to lymphocytes (see Figure 1) (Qasim et al., 2004). Thus, deficiency of the ADA enzyme is the underlying defect that leads to the buildup of toxic metabolites, which in turn affect different organ systems, most notably the immune system (Gaspar et al., 2009). It is still not entirely clear whether ADA-deficient patients have intrinsically abnormal lymphocytes or whether the

defects seen are secondary to the effect of accumulation of 2′-deoxydenosine and adenosine (Gaspar et al., 2009). In addition, accumulation of toxic metabolites also may interfere with thymic stroma development, maturation, and function, resulting in impaired ability to support T-cell development (Gaspar et al., 2009). Finally, the decrease in S-Adenosyl homocysteine hydrolase also has some impact as a result of the ADA deficiency on critical transmethylation cellular reactions contributing to lymphocyte dysfunction.

Absence of the enzyme ADA allows accumulation of toxic metabolites, resulting in complete or partial deficiency of both cell-mediated and humoral immunity (Booth and Gaspar 2009).

Figure 1 Biochemical Defects in ADA Deficiency



ADA is expressed in all tissues of the body. In normal cells, DNA turnover is mediated by ADA catalyzing the deamination of d-adenosine to d-inosine. In ADA-deficient cells, there is an accumulation of d-adenosine, which is then converted by dCydK to d-ATP. The build-up of these two metabolites has profound effects on lymphocyte development and function – through effects on DNA synthesis, impaired cell division, and apoptosis – causing immunological defects.
Source: (Qasim et al., 2004)
ADA = adenosine deaminase; d-adenosine = 2′-deoxyadenosine; d-ATP = 2′-deoxyadenosine 5′-triphosphate; dCydK = deoxycytidine kinase; d-inosine = 2′-deoxyinosine; DNA = deoxyribonucleic acid.

Patients with ADA deficiency are unable to produce the ADA enzyme in their cells. Without treatment, ADA-SCID is usually fatal in the first year of life, and therefore early intervention is required (Gaspar et al., 2009). ADA enzyme therapy is key to the successful detoxification of metabolic substrates and promotion of immune recovery in these patients (Gaspar et al., 2009). The ADA enzyme can be delivered in the form of allogeneic wild-type cells (donor stem cell transplantation), gene-modified autologous cells, or exogenous direct enzyme replacement therapy (ERT) (Gaspar et al., 2009).

Hematopoietic stem cell transplantation (HSCT) from a human leukocyte antigen (HLA)-identical sibling donor is the treatment of choice for ADA-SCID as it is well tolerated and results in long-term correction of the immunodeficiency in ADA deficiency. However, HSCT does not prevent non-immune complications of the disease (Gaspar et al., 2009). In the absence of a suitable matched donor, parental haploidentical transplants are associated with greater complications and sometimes, poorer long-term immune recovery (Gaspar and Thrasher

2005). Completing a successful bone marrow transplant depends upon finding a matched donor, but the probability of this is relatively low. ADA enzyme therapy is thus considered for patients lacking HLA-matched bone marrow donors and for patients whose clinical status places them at high risk for transplant-associated morbidity (Taupin 2006).

Hematopoietic stem cell gene therapy (HSC-GT) using gamma retroviral vectors for the treatment of ADA-SCID has been under clinical investigation for more than 20 years (Cavazzana-Calvo et al., 2005, Engel et al., 2003) . Clinical trials since the year 2000 have employed an approach that was first reported from two subjects treated in Milan, Italy and has recently been updated with 10 subjects (Aiuti et al., 2002, Aiuti et al., 2009). This approach involves discontinuing Adagen® (in subjects receiving Adagen as an ERT) and administering non-myeloablative conditioning prior to the infusion of ADA vector-transduced autologous CD34+ stem cells. In addition to the Milan study, variations on this protocol are currently under investigation in the UK, US, and Japan. More than 40 affected individuals (most of whom had been receiving Adagen) have been treated at these centers (Aiuti et al., 2002, Aiuti et al., 2009, Candotti et al., 2012, Cappelli and Aiuti 2010, Engel et al., 2007, Gaspar et al., 2006, Gaspar et al., 2013). Reconstitution of immune function is generally slow and may take 1 year or more. In most (but not all) affected individuals, stable ADA expression in lymphoid cells has been achieved, along with correction of metabolic abnormalities in erythrocytes, which has resulted in maintenance of good health without the need for ERT. In contrast to the experience with gene therapy for X-linked SCID, no subjects with ADA deficiency have thus far been reported to develop leukemia as a result of vector-associated insertional mutagenesis following gene therapy (Aiuti et al., 2007, Cappelli and Aiuti 2010). However, because of this concern and in order to achieve more effective ADA expression, the clinical investigation of gene therapy using lentiviral vectors is now underway (Farinelli et al., 2014).

5.2 Description of the Study Product

Revcovi is approved by the FDA for the treatment of ADA-SCID in pediatric and adult subjects. Revcovi is a recombinant adenosine deaminase (rADA) based on bovine amino acid sequence, conjugated to monomethoxypolyethylene glycol (mPEG). rADA is manufactured in *E.coli* and is covalently conjugated to mPEG with a succinimidyl carbamate (SC) linker to produce methoxypolyethylene glycol recombinant adenosine deaminase. The approximate molecular weight of Revcovi is 113 KDa.

Revcovi was developed to replace the bovine-derived ADA in Adagen with recombinant ADA. Similar to Adagen, Revcovi provides an exogenous source of ADA enzyme that is associated with a decrease in toxic adenosine and deoxyadenosine nucleotides (dAXP) levels as well as an improvement in lymphocyte number and function.

The polyethylene glycol (PEG) used for manufacturing Revcovi is similar to the PEG used to manufacture Adagen. However, the succinimidyl succinate (SS) linker used to link PEG to ADA in Adagen has been replaced by the more stable SC linker in Revcovi.

The enzyme used for manufacturing Revcovi is recombinant and based on the same sequence as Adagen. Native bovine ADA undergoes post-transcriptional modification, with C-terminal processing (removal of the last six amino acids) and oxidation of cysteine at position 74 (Cys74). Therefore, rADA in SC-PEG rADA has been engineered so that the sequence

encoding the last six amino acids of ADA have been deleted, and in addition, Cys74 has been mutated to serine (C74S), which reduces oxidative degradation of the molecule at this site without decreasing enzymatic activity of the protein.

Replacing Adagen with Revcovi eliminates any risk of transmission of transmissible spongiform encephalopathy (TSE) or adventitious mammalian viruses (e.g. bovine spongiform encephalopathy) to patients as well as guarantees a more consistent, stable, and indefinite supply of drug for the ADA-SCID patient population. Revcovi will also resolve the instability of Adagen (9-month shelf life) determined by the spontaneous dePEGylation during storage and protein degradation caused by the presence of protease impurities in the Adagen drug product. Additional details for Revcovi are provided in the Revcovi Package Insert (PI).

5.3 Product Background Information

Revcovi provides an exogenous source of ADA enzyme that is associated with a decrease in toxic adenosine and dAXP, thereby correcting the metabolic abnormalities and cellular toxicity associated with the absence of ADA. This section provides a summary of nonclinical and clinical experience with Revcovi.

Additional details are provided in the Revcovi PI.

5.3.1 Non-Clinical Experience

The pharmacodynamic (PD), pharmacokinetic (PK), and toxicologic properties of Revcovi were evaluated in animal models [Leadiant Biosciences data on file]. Where appropriate, comparisons were made with Adagen. The ability of the drug to generate antibodies that bind and neutralize Revcovi was studied together with the PK analysis.

5.3.1.1 Pharmacology

ADA-/-mice were used to compare the efficacy of Adagen and Revcovi. ADA-/- mice were generated and genotyped. ADA-/- mice were injected IM or intraperitoneally (IP) in several dosing regimens with selected doses of Adagen or Revcovi. Compounds were given on the same schedule (once every 4 days × 5 starting on postnatal Day 1 until postnatal Day 21, and followed, if needed, once each week until postnatal Day 42) and at equivalent doses (5 U/mouse injected IM or IP). Both untreated ADA+/+ and ADA-/- mice as well as ADA-/- mice treated with Revcovi or Adagen were sacrificed 18 days to 6 weeks following injection. Bronchial alveolar lavage fluid, thymus, and spleen were collected for the analysis of adenosine concentrations using reversed-phase high-performance liquid chromatography as well as for total cell counts and cellular differentials. Blood was obtained from the circulation or thoracic cavity at the time of sacrifice to measure ADA enzymatic activity using zymogram or spectrophotometric analysis, respectively. Survival and body weight also were assessed.

Results of the pharmacology and PD studies performed in the ADA-/- mouse model suggest Revcovi behaves very similarly to Adagen and both compounds are highly effective. Consistent with this, when Adagen and Revcovi were given at equivalent doses and schedules, both PEG-ADA compounds 1) were delivered to the circulatory system with equal efficiency in both ADA+/+ and ADA-/- mice; 2) increased ADA plasma levels to similar, clinically relevant levels; 3) decreased abnormally high adenosine levels found in the lung, spleen, or thymus to a similar extent; 4) maintained thymus and spleen cellularity, including total cell

numbers and T- and B-cell populations; and 5) promoted the survival of ADA-/- mice. There is a suggestion that Revcovi may be more efficacious than Adagen in the ADA-/- mouse model. The results tended to show Revcovi-treated ADA-/- mice having statistically lower adenosine levels in the thymus compared with Adagen, as well as a consistent trend toward better improvement of most PD endpoints (body weight, survival, and thymocyte and splenocyte cell number, as well as adenosine levels in spleen) when compared with Adagen. These effects correlated with 35% higher plasma levels of ADA activity derived from Revcovi compared with Adagen when analyzed either 24 or 72 hours after the last dose; the higher plasma levels of ADA activity are likely due to the longer half-life of Revcovi.

5.3.1.2 Pharmacokinetics

Revcovi demonstrated improved in vitro stability in human plasma in comparison with Adagen. Two single-dose intravenous studies in rats were conducted. In these studies, PK parameters for ADA activity were markedly increased for Revcovi as compared with unPEGylated Revcovi and were equivalent to or slightly different than those for Adagen (i.e., in one experiment, Revcovi had lower clearance, longer half-life, and higher area under the curve [AUC] compared to Adagen).

Single IM doses of Revcovi or Adagen were given to rats or dogs at two dose levels (30 and 150 U/kg). AUC and maximum concentration (C_{max}) values for ADA activity increased in proportion to dose for both rats and dogs. The AUC values for Revcovi were statistically significantly higher (approximately 45% in rats, 55% in dogs) compared with Adagen. Terminal elimination half-lives ($t_{1/2}$) also were increased approximately 30% in rats and 80% in dogs when Revcovi was compared with Adagen. The calculated mean $t_{1/2}$ in rats after a single dose was 49 to 61 hours for Revcovi and 36 to 50 hours for Adagen. In dogs, these values were 128 to 154 hours for Revcovi and 68 to 79 hours for Adagen.

In multiple-dose studies, Revcovi was given every 3 to 4 days for 4 weeks (total of 9 doses) at three dose levels (30, 100, and 300 U/kg). These studies were conducted under Good Laboratory Practice (GLP) guidance. AUC and C_{max} values for ADA activity were higher on Day 29 as compared with Day 1 for rats that received 300 U/kg Revcovi and dogs that received 30, 100, or 300 U/kg Revcovi. In contrast, likely due to detectable anti-drug antibodies, marked reductions in Day 29 exposure values for ADA activity occurred for male rats that received 30 U/kg Revcovi or 30 U/kg Adagen, female rats that received 30 U/kg Revcovi, and male rats that received 100 U/kg Revcovi. In dogs, Day 29 AUC values were markedly reduced for 1 of 5 males that received 30 U/kg Revcovi and 1 of 5 females that received 100 U/kg Revcovi. Anti-drug binding antibodies were present in the plasma of rats that received Revcovi or Adagen and in most dogs that received Revcovi at the end of the 4-week treatment periods and/or recovery periods. In rare cases, neutralizing antibodies were detected that reduced the enzymatic activity of ADA in experimental assays.

In conclusion, the PK (ADA activity) following single-dose IM administration to rats and dogs demonstrate that AUC and $t_{1/2}$ were significantly higher for Revcovi compared to Adagen. Repeat doses of 30 U/kg Revcovi or 30 U/kg Adagen in rats, as well as 30 U/kg or 100 U/kg in dogs, resulted in the formation of anti-drug antibodies in some animals and markedly reduced exposure to ADA activity in comparison with single-dose administration. Despite the

presence of anti-drug binding antibodies in rats and dogs in the repeat-dose studies, there was no evidence for clinical anaphylactic reactions to Revcovi or Adagen in either species.

5.3.1.3 Toxicology

The single-dose studies of Revcovi and Adagen in rats and dogs were conducted primarily for PK assessment. Revcovi and Adagen were dosed intramuscularly. Toxicology evaluations including clinical signs, body weight, and food consumptions were done for up to 14 days after injection, after which animals were sacrificed. The experiments were performed under non-GLP conditions.

The toxicity profile of Revcovi also was evaluated in Sprague-Dawley CD® rats and Beagle dogs in 4-week repeat-dose IM GLP toxicology studies. Animals were administered 30, 100, or 300 U/kg of Revcovi every 3 or 4 days for 4 weeks (9 doses total) with a 4-week recovery period. Microscopic pathology evaluations were performed on approximately 40 tissues/animals.

Revcovi given IM was well tolerated in rats and dogs in single- and repeat-dose studies. No mortality was observed in any of these studies, and no adverse effects on clinical condition, body weight, food consumption, electrocardiograms (dogs), or microscopic pathology were evident in either species at any dose. Adagen was similarly well tolerated in rats and dogs at single doses of 30 and 150 U/kg and in rats at 30 U/kg given every 3 or 4 days for 4 weeks as part of a PK study.

Compound-related findings were seen in the repeat-dose IM studies after 4 weeks of treatment (9 doses) and were limited to slight increases in mean platelet volume (MPV) values (3% to 7%) for male rats that received 30, 100, or 300 U/kg Revcovi; slightly prolonged mean values for activated partial thromboplastin time (aPTT) for male and female rats that received 300 U/kg Revcovi (5 to 6 seconds); slightly prolonged aPTT for male dogs that received 30, 100, and 300 U/kg Revcovi (6 to 20 seconds) and female dogs that received 100 and 300 U/kg Revcovi (8 and 14 seconds); and red foci at the injection sites for 2 of 10 male rats that received 100 U/kg Revcovi. The increased MPV and aPTT values were considered compound related but not adverse because of the small magnitude of change and lack of correlative changes. Partial or complete recovery was evident in both species for all of the changes after 4 weeks of recovery. These clinical pathology changes could not be compared to effects associated with Adagen because Adagen was not administered in these studies.

The no observed adverse effect levels (NOAELs) were the highest doses given in each of the IM studies, which were 150 U/kg Revcovi in the single-dose rat and dog studies and 300 U/kg Revcovi in the repeat-dose rat and dog studies. Despite the presence of anti-drug binding antibodies, which were present in the rat plasma following repeated doses of Revcovi or Adagen and in most dogs that received repeated doses of Revcovi, no clinical observations were suggestive of an anaphylactoid response in any of the studies. The Day 29 $AUC_{0-\infty}$ values at the NOAEL doses of 300 U/kg in the repeat-dose studies were 1.7- to 2.0-fold higher in rats and 3.2-fold higher in dogs than the corresponding Day 1 values.

5.3.1.4 Conclusions

The nonclinical data demonstrate that Revcovi was highly efficacious in a mouse knockout model that mimics human ADA-SCID. In such ADA-deficient mice, compared with Adagen, Revcovi was at least as effective in its ability to:

- Increase ADA plasma levels to clinically relevant levels.
- Decrease abnormally high adenosine levels found in the lung, spleen or thymus to a similar extent.
- Maintain thymus and spleen cellularity, including total cell numbers and T- and B-cell populations.
- Promote the survival of mice.

Revcovi was well tolerated in rats and dogs at doses that are physiologically relevant.

5.3.2 Clinical Experience

Revcovi was administered intramuscularly in two prospective, open-label, single-arm, multicenter studies to evaluate efficacy, safety, tolerability, and PK in patients with ADA-SCID: STP-2279-002 (Study 1) was conducted in the United States and STM-279-301 (Study 2) was conducted in Japan under Teijin Ltd., a Leadiant Biosciences partner.

5.3.2.1 Study 1

Study 1, conducted in the US (NCT 01420627), is a Phase III, open-label multicenter, single-arm, one-way crossover study of Revcovi, which has been completed. The purpose of this clinical study is to evaluate the safety, efficacy, and PK of Revcovi in 6 subjects with ADA-SCID, 4 males and 2 females, who are receiving therapy with Adagen. The study treatment consists of three phases: Adagen Lead-in phase (minimum of 3 weeks), the Revcovi Treatment Phase (weeks 1 through 21), and a Revcovi Maintenance Phase. Six subjects treated in the study were 8 to 37 years of age at the start of the study. The starting weekly dose of Revcovi is calculated based on the last Adagen dose received in the study. Revcovi doses range from 0.188 mg/kg to 0.292 mg/kg. The initial treatment for the 8 yr old was with a product that contained EDTA and resulted in significant pain at the injection site. That subject withdrew from the study and the product was reformulated without EDTA. Subsequently a total of 6 subjects aged 16-37 were evaluated for efficacy and safety.

The efficacy endpoints assessed are: 1) trough dAXP Level (metabolic detoxification was defined as a trough erythrocyte dAXP concentration equal to or below 0.02 mmol/L), 2) trough plasma ADA activity (adequate trough plasma ADA activity is defined as trough plasma ADA activity equal to or above 15 mmol/hr/L), and 3) immune status (lymphocyte and B-, T-, and natural killer (NK)-lymphocyte subset counts as well as quantitative immunoglobulin [Ig] concentration [IgG, IgA, IgM]). A PK assessment was performed during Week 9 of the Revcovi Treatment phase.

All six subjects reached the 21-week endpoint of the treatment phase, and 5 out of 6 subjects received treatment with Revcovi for over 135 weeks. These subjects (except for one value in a subject at treatment week 47) had erythrocyte dAXP concentration equal to or below 0.02 mmol/L. These subjects had trough plasma ADA activity equal to or above 15 mmol/hr/L at

88/89 timepoints and maintained metabolic detoxification for at least 2 years under Revcovi treatment. Subjects achieved trough plasma ADA activity above 30 mmol/hr/L by week 5, except for one subject who achieved this level at week 1.

Lymphocyte and subset counts during Revcovi treatment increased above levels observed during the Adagen Lead-in phase (i.e., PK day 1 or before the start of Revcovi treatment): maximum increases of approximately 3-fold at Weeks 60-73 for one subject, maximum increases of approximately 2- to 3-fold at Weeks 73-99 for one subject and approximately 1.5- to 3-fold for the third subject at several timepoints. For the five subjects who completed the primary endpoint (21 weeks of treatment) and received Revcovi for over 135 weeks, a positive trend between high trough plasma ADA activity and increased total lymphocyte counts was observed.

Observations for the other subject in the study, indicate that this subject also achieved complete detoxification based on trough dAXP and trough plasma ADA activity level, and showed stable or slightly increased lymphocyte counts during Revcovi treatment relative to values recorded during the Adagen lead-in phase.

The most common adverse reactions were cough (3/6 subjects) and vomiting (2/6 subjects). Other adverse reactions that were reported in one subject each were: abdominal pain upper, arthralgia, asthenia, cerumen impaction, conjunctivitis, convulsion, dental caries, diarrhea, ear canal irritation, ear lobe infection, epistaxis, fatigue, fungal skin infection, gait disturbance, gastrointestinal infection, groin abscess, hematochezia, haemophilus infection (pulmonary), hemoptysis, influenza, injection site discomfort, laceration, lymphadenopathy, migraine, nasal edema, nausea, nephrolithiasis, oral candidiasis, oropharyngeal pain, otitis externa, productive cough, rash, stoma site infection, swelling face, tooth abscess, tooth extraction and upper respiratory tract infection, regardless of Investigator causality assessment.

5.3.2.2 Study 2

Study 2, conducted in Japan, is a single-arm clinical study that assessed the safety, efficacy and PK of Revcovi in subjects with ADA-SCID. The study includes two phases: 1) Evaluation, consisting of a Dose Adjustment Period (5 weeks) and a Dose Maintenance Period (16 weeks); and 2) Continuous Administration (Extension) Phase, to be continued until the end of the study.

A total of four subjects were enrolled in the study: two males (age 25 years and 3.4 months) and two females (age 16 years and 4.3 months). Two subjects who were on Adagen treatment within four weeks before entering the study received a first dose of Revcovi that was calculated to be equivalent to the last Adagen dose received. One subject who did not receive Adagen within four weeks prior to entering the study was given the first dose of Revcovi at 0.1 mg/kg body weight, followed by second and third doses at 0.133 mg/kg body weight and weekly thereafter. Over the dose adjustment phase of the study, the dose was titrated to meet criteria for dAXP level (equal to or below 0.02 mmol/L) and adequate trough ADA activity (equal to or above 15 mmol/ hr/L). These 3 subjects received Revcovi for at least 21 weeks (having completed the 5-week Dosage Adjustment Period and the 16-week Dose Maintenance Period) before entering the Extension Period. The fourth subject (newly diagnosed Adagen-naïve subject with cytomegalovirus (CMV) pneumonia was dosed at a 0.4 mg/kg weekly (divided into twice a week administration) for 16 weeks.

All 4 of the subjects in Study 2 achieved and maintained detoxification (trough dAXP [erythrocyte or blood] ≤ 0.02 mmol/L throughout their participation in the Treatment Phase of 21 weeks (Evaluation Phase for Study 2). Serum ADA activity increased after administering Revcovi for all four subjects, with three subjects achieving level over 15 mmol/hr/L during the Dose Maintenance period. Total lymphocyte counts and B-/T-/NK-lymphocyte subset counts for three subjects increased from Screening to Day 15 during dose adjustment and were stable or increasing during the Dose Maintenance Period.

There were 22 reported adverse events (AEs) for four subjects. The most common AEs were respiratory infections (2/4 subjects).

5.4 Target Population and Study Rationale

Study CLI-06814AA1-01 is being performed as a post-marketing commitment following the approval of Revcovi by the FDA for the treatment of ADA-SCID in pediatric and adult patients. The introduction of Revcovi is the first new product as an ERT in ADA-SCID patients since Adagen approval in 1990. Revcovi is a PEGylated rADA that has been developed to replace the bovine-derived components in PEG-ADA (Adagen). Similar to Adagen, Revcovi provides a specific and direct replacement of the ADA enzyme. As for Adagen, the mechanism of action of Revcovi is to correct the metabolic abnormalities associated with adenosine accumulation due to the absence of ADA and to detoxify cells. The purpose of the study is to bolster the established safety and efficacy data on Revcovi in patients with ADA-SCID and collect safety and efficacy data on patients started de novo ERT with Revcovi.

There are four types of patients with ADA-SCID who may be eligible for treatment with Revcovi, including:

- Patients currently receiving chronic ERT with Adagen
- Infants diagnosed via newborn screening and/or definitive testing for ADA deficiency
- Patients preparing for HSCT or HSC-GT
- Patients who decline, are ineligible or do not respond to HSCT or HSC-GT

5.5 Potential Risks and Benefits

Revcovi (elapegademase-lvlr) is approved by the FDA for the treatment of ADA-SCID in pediatric and adult patients. Its safety and efficacy were established on the basis of two prospective studies. Revcovi provides an exogenous source of ADA enzyme that is associated with a decrease in toxic adenosine and deoxyadenosine nucleotides levels as well as an improvement in lymphocyte number and function. Information gathered will supplement the safety, tolerability and efficacy of Revcovi in post-approval use in patients with ADA-SCID.

Refer to the Revcovi PI for additional information.

6 STUDY PURPOSE, OBJECTIVES AND ENDPOINTS

6.1 Purpose

The purpose of this clinical registry study is to bolster the established safety and efficacy data on Revcovi in patients with ADA-SCID and collect safety and efficacy data on patients started *de novo* ERT with Revcovi.

6.2 Objectives

To conduct a registry study on patients with ADA-SCID treated with Revcovi and have periodic clinical and biochemical assessments for safety and dose adjustment based on ADA activity, erythrocyte dAXP levels and/or clinical assessment by the treating physician.

6.3 Endpoints

The procedures used to collect study data for the assessment of study endpoints are described in Section 10.

Biochemical assessments to adjust Revcovi dosing throughout the study include trough plasma ADA activity and RBC dAXP, which will be assessed from trough plasma samples obtained during the study as outlined in the Suggested Schedule of Assessments in Appendix 1 and Appendix 2.

Immune status (optional) will be analyzed throughout the study by the following (if assessed):

- absolute lymphocyte count
- lymphocyte subset (B, T, and NK) analysis: the number of cells for each subset will be determined by fluorescence-activated cell sorter (FACS) using the following panel:
- CD3+ (Mature T cells) - Percent and Absolute
- CD3+ CD8+ (Suppressor T Cells) - Percent and Absolute
- CD3+ CD4+ (Helper Cells) - Percent and Absolute
- CD (16+56) + (NK Cells) - Percent and Absolute
- CD19+ (B Cells) - Percent and Absolute
- Absolute Lymphocytes (CD45+)
- %CD4 (Helper Cells)/%CD8 (Suppressor T Cells)
- Quantitative immunoglobulin (Ig) concentration (IgG, IgA, IgM).
- It is recommended that Investigators consider a measurement of immune response (PHA stimulation or equivalent)

Clinical status will be assessed through determination of the following:

- Infections will be determined and defined as either:

- Clinically documented – subjects with documented signs and symptoms of infection without positive microbiologic cultures
- Microbiologically documented – subjects with documented signs and symptoms of infection and with positive viral or bacterial cultures
- Hospitalizations – incidence and duration of hospitalizations through completion of the study
- Growth – height, weight and growth curve determinations through completion of the study (Note: this assessment should be done for subjects < 18 years of age)
- Overall survival through the end of the study
- Quality of life will be assessed using the PedsQL Infant Scales (ages 1 to 12 months), PedsQL Infant Scales (ages 13 to 24 months), PedsQL 4.0 Toddler (2 to 4 years), PedsQL 4.0 Young Child Report (5 to 7 years), PedsQL 4.0 Child Report (8 to 12 years), PedsQL 4.0 Teen Report (13 to 18 years), and for subjects older than 18 years, the SF36 and the PADQOL. Assessments for those under age 5 will be completed by the parent. For children 5 to 18 years, the parent or health care provider will determine the ability of the subject to self-report. QOL assessment data will be collected from study participants via scripted phone calls by the study call center and QOL responses will be entered directly into the electronic data capture (EDC) system. QOL assessments will be collected prospectively for 24 months after starting Revcovi.

Safety will be assessed by determination of AEs, SAEs, clinical signs and symptoms from physical examination, and laboratory evaluations.

A decrease of ADA activity below 30 mmol/hr/L from a previous acceptable level suggests an increase in weight requiring a dose increase adjustment, noncompliance to treatment or a development of antibodies (anti-drug, anti-PEG, and neutralizing antibodies). Antibodies to Revcovi should be suspected if a persistent fall in pre-injection levels of trough plasma ADA activity below 15 mmol/hr/L occurs. In such subjects, testing for antibodies to Revcovi should be performed as is recommended in the Revcovi PI.

7 STUDY DESIGN

7.1 Overview of Study Design

Protocol CLI-06814AA1-01 is designed as a single-arm, open-label, multicenter registry study in patients with ADA-SCID requiring Revcovi as ERT. The eligible study population includes adult subjects who are currently receiving chronic ERT with Adagen, infants diagnosed via newborn screening and definitive testing for ADA deficiency, patients preparing for HSCT or HSC-GT, and patients who decline, are ineligible or do not respond to HSCT or HSC-GT.

Subjects for whom written informed consent/assent is obtained will be assigned a number and undergo enrollment procedures. The date of ICF signature is the date of enrollment into the registry. Subjects should have initial, trough erythrocyte dAXP levels and plasma ADA activity measurements collected prior to start of Revcovi as part of standard of care. Additionally, at enrollment, physical examination, vital signs, and laboratory values for total

lymphocytes and subset analysis, as well as quantitative immunoglobulins, should be collected. Subjects who started treatment with Revcovi before enrollment into the CLI-06814AA1-01 study, should have data collected retrospectively in accordance with the Suggested Schedule of Assessments (Appendix 1 and Appendix 2) and in conformity to local standard of care practice.

Subjects should receive weekly IM dose(s) of Revcovi and will be followed throughout a period of at least 24-months according to the Suggested Schedule of Assessments (Appendix 1 and Appendix 2). Trough dAXP and ADA activity should be monitored throughout this treatment period, and AEs, immunogenicity, laboratory assessments, physical examination, and vital signs will also be assessed.

All Phase III STP-2279-002 participants are permitted to enroll into the CLI-06814AA1-01 registry at the time they discontinue from the Phase III STP-2279-002 study. Their first post-baseline visit in the CLI-06814AA1-01registry will be Treatment Month 6. See the Suggested Schedule of Assessments (Appendix 1).

Enrolled subjects will be followed until the last enrolled patient has reached a minimum of 24 months of Revcovi treatment or until undergoing HSCT or HSC-GT, whichever occurs first. Subjects undergoing HSCT or HSC-GT will be followed one month after the last Revcovi dose and again at six months to assess AEs and survival.

Throughout the duration of the study, subjects will continually be assessed for AEs. Immune status (lymphocyte subsets and quantitative immunoglobulins), clinical status (infections, hospitalization, growth, and overall survival) should also be assessed throughout the treatment period. QOL assessments will be prospectively collected for a maximum of 24 months after starting Revcovi.

A yearly review of AEs will be conducted by a Data Safety Monitoring Committee to identify any safety signals or trends.

7.2 Study Treatments

All subjects, including Adagen-naïve subjects and those previously treated with Adagen, should receive Revcovi according to dosing recommendations in the Revcovi PI. Subjects who started Revcovi treatment prior to study enrollment should continue to be dosed in accordance with provider or Revcovi PI recommendations. Study medication administration details are presented in Section 10.10.1.

7.3 Assignment of Subjects to Treatment

This is a non-randomized study. Each patient who is on treatment with Revcovi under commercial setting, meets all eligibility criteria and is accepted for study participation, will be assigned a unique subject number (see Section 10.2) and will have Adagen/Revcovi treatment information collected

7.4 Study Duration

Enrolled subjects will be followed until the last enrolled patient has reached 24 months of Revcovi treatment or until undergoing HSCT or HSCGT, whichever occurs first. Subjects

undergoing HSCT or HSCGT will be followed one month and again at six months after final Revcovi dose to assess for AEs and survival.

7.5 Methods to Minimize Bias

Due to the single-arm, open-label study design, blinding is not necessary in this study.

Laboratory assessments performed for clinical and dose adjustments are objective data provided by certified clinical laboratories and are not subject to bias.

7.6 Appropriateness of Study Measurements

In this study, data on Revcovi treatment should be monitored by measuring trough plasma ADA activity, trough dAXP levels, and total lymphocyte counts as recommended in the Revcovi PI. Monitoring should be more frequent if therapy is interrupted or if an enhanced rate of clearance of plasma ADA activity develops.

Safety in this study will be assessed by monitoring AEs, laboratory parameters (serum chemistry, hematology, and urinalysis), physical examination changes and vital signs. These are standard assessments for monitoring safety in clinical trials. In addition, monitoring of binding and neutralizing antibodies is commonly used to monitor patients treated with therapeutic biological products such as Adagen and Revcovi.

Other measurements include additional immune status markers (see Section 10.7), assessments of clinical status (incidence of infections, growth assessment, hospitalization incidence and duration, and survival) (see Section 10.8), and assessments of quality of life (see Section 10.9). These assessments are commonly used to monitor patients treated with Adagen.

7.7 Study Monitoring Committees

An independent Data and Safety Monitoring Committee (DSMC) will be set up to monitor the conduct of the study. At minimum, the DSMC will review safety, ADA activity, and erythrocyte dAXP data on an annual basis. Chiesi PV will send notice via email to DSMC members regarding deaths, regardless of relatedness to Revcovi, along with associated MedWatch and any corresponding documentation. A Charter for the DSMC will be written as an independent document.

8 Revcovi

8.1 Description of Revcovi

Revcovi (elapegademase-lvlr) is rADA based on bovine amino acid sequence, conjugated to mPEG. rADA is manufactured in *E.coli* and is covalently conjugated to mPEG with a succinimidyl carbamate linker to produce methoxypolyethylene glycol recombinant adenosine deaminase (SC-PEG rADA). The approximate molecular weight of elapegademase-lvlr (SC-PEG rADA) is 113 KDa.

Revcovi (elapegademase-lvlr) injection is a sterile, preservative free, clear, colorless solution for IM use supplied in single-dose vials. Each vial provides 1.5 mL of solution containing 2.4 mg elapegademase-lvlr (1.6 mg/mL), sodium chloride (12.75 mg), sodium phosphate

dibasic heptahydrate (12.7 mg), sodium phosphate monobasic monohydrate (3.81 mg), and Water for Injection, USP. The pH is 6.9.

Revcovi is manufactured by Leadiant Biosciences, however, Chiesi is reported on the commercial labels.

8.2 Supply and Labeling

Commercially available Revcovi will be used for this study and obtained by patients directly from a specialty pharmacy. Revcovi will not be provided to patients by the site staff or pharmacy. Vials of commercially available Revcovi will be boxed individually and labeled in accordance with FDA requirements.

8.3 Storage Conditions (See Revcovi PI)

Revcovi should be stored refrigerated at +2°C to +8ºC (36°F to 46°F). **Do not freeze**. Refer to the Revcovi PI

8.4 Preparation for Administration (See Revcovi PI)

Revcovi is to be administered in accordance with instructions in the Revcovi PI.

8.5 Procedure for Unblinding

Not applicable

8.6 Revcovi Accountability

As this is a registry study, drug accountability procedures are not applicable because subjects will be obtaining drug directly from a pharmacy or healthcare provider.

9 STUDY POPULATION

9.1 Number of Subjects

The study will enroll all patients who meet all study entry criteria described in Sections 9.2 and 9.3. There are no restrictions on the number of subjects a single study center may enroll.

9.2 Inclusion Criteria

- Patients currently receiving chronic ERT with Adagen® and transitioned/transitioning to Revcovi;
- Infants diagnosed via newborn screening and definitive testing for ADA deficiency prescribed Revcovi;
- Patients receiving Revcovi while preparing for Hematopoietic Stem Cell Transplant (HSCT) or Hematopoietic Stem Cell Gene Therapy (HSCGT);
- Patients who decline, are ineligible or do not respond to HSCT or HSC-GT and resume/start Revcovi.

9.3 Exclusion Criteria

- Any condition that, in the opinion of the Investigator, makes the patient unsuitable for the study.

9.4 Post-enrollment Restrictions

9.4.1 Concomitant Medications

There are no known drug interactions with Revcovi.

9.4.2 Dietary Restrictions

There are no dietary restrictions for subjects enrolled in the study.

9.5 Withdrawal of Enrolled Subjects

In the absence of a significant protocol violation, every effort will be made by the Investigator to keep subjects in the study. The primary reason for a subject withdrawing prematurely should be selected from the following standard categories:

- AE – clinical or laboratory events that in the judgment of the Investigator require discontinuation of Revcovi in the best interests of subject.
- Death – death of the subject, whether study related or not.
- Withdrawal of Consent – subject desires to withdraw from further participation in the study in the absence of a medical need to withdraw determined by the Investigator.
- Lost to follow-up – the subject did not return for one or more follow-up visit(s) following the start of Revcovi treatment.
- Subject meets withdrawal criteria – the subject's condition meets the criteria for withdrawal from the study (Section 9.5.1).
- Other – causes of premature termination from the study other than the above (e.g., termination of study by Chiesi Farmaceutici S.p.A., subject relocated).

9.5.1 Withdrawal Criteria

There is not mandated criteria for withdrawal other than treatment discontinuation. Reasons for subject withdrawal or completion of the maintenance period may include the following:

- AE requiring the discontinuation of Revcovi treatment
- Death
- Loss to follow-up
- Withdrawal of consent
- Investigator's decision, e.g., Investigator believes it is no longer in the subject's best interest to remain in the study
- Study completion

- Other reason - causes of premature termination from the study other than the above (e.g., subject relocated)

The reason for study discontinuation should be documented in the subject's source documents and in the electronic case report form (eCRF).

Subjects are free to withdraw from the study at any time for any reason.

The reasons for subject withdrawal or study completion, as well as details relevant to the subject withdrawal or study completion, shall be recorded in the eCRF. Subjects withdrawn before their completion of the study will undergo all procedures scheduled for study completion as outlined in Section 11.3.

Any subject withdrawn due to any AE (whether serious or non-serious) or clinically significant abnormal laboratory test values will be evaluated by the Investigator or his/her designee, or a monitoring physician, and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator.

9.5.2 Withdrawal Procedures

Under any circumstance, a final physical examination of each subject must be performed at the time of study discontinuation. See Section 11.3 for procedures related to the discontinuation or the end of the study.

Should a subject be withdrawn from the study, all efforts will be made to complete and report the observations as thoroughly as possible, including a complete final evaluation at the time of the subject's withdrawal with an explanation of the reason subject was withdrawn from the study.

9.5.3 Replacement of Discontinued Subjects

Subjects who do not complete the study will not be replaced.

10 DESCRIPTION OF STUDY PROCEDURES AND VARIABLES

10.1 Informed Consent

Patients or the legally authorized representative of eligible patients who express interest in participating in the study must sign an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved Informed Consent Form that conforms to the Elements of the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule Authorization (see Sections 14.3.2 and 14.3.3) before initiation of any study activities. Documentation of consent must be completed by the Investigator or his/her designee.

The Investigator and other members of the study site's treating team will review the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits, and alternative therapies including best supportive care. Patients must be informed that participation in the study is voluntary, he/she may withdraw from the study at any time, and withdrawal from the study will not affect his/her subsequent medical treatment or relationship with the treating physician. Patients will also be informed of any financial costs that the patient will or may incur as a result of participation in the study, and that their study record and medical records/documents that pertain directly to the study will be reviewed and

possibly copied by Chiesi or its designee, or a governmental agency (such as the FDA), and that every effort will be made to maintain patient confidentiality.

The Informed Consent must be witnessed and dated by the Investigator or his/her designee, and the original retained by the Investigator/Study Site as part of the subject's study record.

For subjects under 18 years of age, Assent of the minor child must be obtained in accordance with Good Clinical Practices (GCP) and the requirements of the reviewing IRB/IEC.

A copy of the fully executed/signed Informed Consent Form and Assent Form (if applicable) must be given to the subject. In the event the subject is re-screened, the subject is not required to sign another Informed Consent form unless the subject is re-screened more than 30 days from the previous Informed Consent form's signature date.

10.2 Screening and Enrollment

The Investigator or his/her designee will obtain a signed Informed Consent and Assent (if required) before initiating any study-specific procedures. Each subject that is consented will be given a 3-digit sequential subject number, beginning with 001 at each study site. The date of ICF signature is considered the date of enrollment into the registry.

10.3 History and Baseline Characteristics

The following history and demographic data will be collected:

- Demographics – age, gender, race, and ethnicity
- Disease background and history:
    - Date of diagnosis
    - Prior treatments for severe combined immunodeficiency, including dates and results
    - History of hospitalizations and infectious complications over the past year
    - Other significant disease-related medical history
- Medical History – in addition to the disease background and history, a complete evaluation of history of disorders of the following systems – cardiovascular, pulmonary, gastrointestinal, urologic, hematologic, neurologic, ophthalmologic, otolaryngeal, musculoskeletal, endocrine, and psychosocial. Note: any medications being taken for active conditions should be included in the medication history, while prior surgical procedures and allergies to medications, including medication and reaction should be included in the medical history.
- Medication History – all prescription and non-prescription medications (including blood products, use of vitamins, supplements and herbal remedies) taken since the first dose of Revcovi will be recorded. Information recorded includes the medication name, dose, dose regimen, route of administration, start and stop (if applicable) dates, and indication for use. Note: if a product is being taken for the prevention of a condition, "prophylaxis for" or "prevention of" should be included in the description of indication.

10.4 Maximum Total Blood Collection Volume

During the study participation, the maximum amounts of venous blood that will be collected are listed in Sections 10.5.3 and 10.5.4. Whenever possible, microtainers should be used for pediatric subjects.

10.5 Safety Procedures

10.5.1 Physical Examination

Physical examination will be performed in accordance with the Investigator's standard of care, including an examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and nervous system.

Height and weight (must be in kg) should be collected as part of the physical examination.

A physical examination should be performed as indicated in the Suggested Schedules of Assessments as shown in Appendix 1 and Appendix 2.

Changes in physical examination findings (e.g., new findings, changes in status of previous findings) should be documented. Findings made after the start of Revcovi administration that meet the definition of an AE (see Section 12.2.1) should be recorded on the Adverse Event CRF.

10.5.2 Vital Signs

Vital signs should include sitting systolic and diastolic blood pressure, pulse rate, respirations, and temperature. Clinically meaningful changes in vital signs made after the start of Revcovi, which meet the definition of an AE, should be recorded on the Adverse Event CRF.

10.5.3 Safety Laboratory Assessments

The following safety laboratory evaluations are not required per protocol but may be performed by the site's local laboratory in accordance with the Investigator's standard of care.

- Hematology: Hemoglobin, hematocrit, white blood count, differential (includes at least: neutrophils [include bands], lymphocytes, monocytes, eosinophils, and basophils), and platelet count.
- Serum chemistry: Bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, magnesium, phosphate, potassium, sodium, and total protein, albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and total bilirubin.
- Urinalysis: Macroscopic (bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, and urobilinogen). Microscopic examination will include red blood cells, white blood cells, bacteria, and casts.

The safety laboratory assessment results, if available, will be included in the eCRF for the study.

Following the start of study treatment clinically meaningful laboratory abnormalities will be reported as AEs.

10.5.4 Immunogenicity

Immunogenicity should be assessed in accordance with the Revcovi PI. If testing is necessary, venous blood samples for determination of anti-Revcovi binding and neutralizing antibodies, and anti-PEG antibodies will be collected in 2-mL ethylenediaminetetraacetic acid (EDTA) tubes.

Once treatment with Revcovi has been initiated, a target trough plasma ADA activity level should be at least 30 mmol/hr/L. A decrease of ADA activity below this level suggests inadequate weight-based dosing, administration noncompliance or a development of antibodies (anti-drug, anti-PEG, and neutralizing antibodies). Antibody development to Revcovi should be suspected if a persistent fall in pre-injection levels of trough plasma ADA activity to below 15 mmol/hr/L occurs, and testing for antibodies to Revcovi should be performed.

10.5.5 Adverse Event Assessment

All AEs whether observed by the Investigator or his/her designee, elicited by the Investigator or his/her designee (e.g., via physical examination findings or review of laboratory results), or spontaneously reported by the subject will be documented in the subject's medical record/chart.

Subjects should be assessed for any change in interval health status including any AEs. For each AE the following information will be recorded in the medical record/chart:

- Onset date
- Resolution date
- Serious or non-serious (see Section 12.2.3)
- Relationship to Revcovi (see Section 12.2.4)
- Severity/intensity (see Section 12.2.5)
- Actions taken to manage/treat the event
- Outcome of the event—resolved, resolved with sequalae, ongoing, death

All AEs should be followed until they are resolved or until a stable clinical endpoint is reached. Any SAEs assessed by the investigator as ***causally related*** (i.e. "possibly", "probably" or "definitely" related) to the administration of Revcovi should be reported to Chiesi US PV (please see ***Section 12*** for complete information on SAE reporting).

Any subject withdrawn due to any AE (whether serious or non-serious) or clinically significant abnormal laboratory test value will be evaluated by the Investigator or his/her designee, or a monitoring physician, and will be treated and/or followed up until the symptom(s) or value(s) return to normal/Baseline or acceptable levels, as judged by the Investigator.

10.6 Biochemical Variables for Dose Adjustments and Efficacy

10.6.1 Trough Plasma ADA Activity

Venous blood samples for the determination of ADA activity should be collected in a 2-mL EDTA collection tube (or as otherwise specified by the testing laboratory) in accordance with recommendations in the Revcovi PI.

10.6.2 Erythrocyte dAXP

Venous blood samples for the determination of total erythrocyte dAXP (EDTA tube, 2 mL per timepoint) should be collected in accordance with recommendations in the Revcovi PI. Samples will be collected, processed, and shipped to the laboratory for analysis. Samples for dAXP can be assessed in the same 2-ml sample for ADA (Note: this should be confirmed with the laboratory).

10.7 Immune Status

10.7.1 Lymphocyte Subset Analysis

Blood samples for lymphocyte subset analysis should be done in accordance with provider-based standards and consistent with the PI recommendations as described below.

Samples will be collected, processed, and shipped to the laboratory for analysis according to each sites' standards of care.

- CD3+ (Mature T cells): Percent and Absolute
- CD3+ CD8+ (Suppressor T Cells): Percent and Absolute
- CD3+ CD4+ (Helper Cells): Percent and Absolute
- CD (16+56) + (Natural Killer Cells): Percent and Absolute
- CD19+ (B Cells): Percent and Absolute
- Absolute Lymphocytes (CD45+)
- %CD4 (Helper Cells) / %CD8 (Suppressor T Cells)
- Quantitative Immunoglobulins (IgG, IgA, IgM)

10.7.2 Immune Function analysis

Blood for assessments of Immune function according to provider standards (PHA stimulation, pneumococcal vaccine response, flow cytometry, etc.) should be done as deemed clinically necessary by the provider and recorded in the CRF

10.8 Clinical Status

10.8.1 Infections

Subjects suspected of having an infection should have signs and symptoms of the suspected infection evaluated. Appropriate cultures should be obtained based upon clinical presentation.

All infections will be classified by the Investigator as clinically or microbiologically documented as described below:

- Clinically documented – subjects with documented signs and symptoms of infection without positive cultures
- Microbiologically documented – subjects with documented signs and symptoms of infection and with positive cultures

10.8.2 Hospitalizations

All hospitalizations assessed by the investigator as ***causally related*** (i.e. "possibly", "probably" or "definitely" related) to the administration of Revcovi should be reported to Chiesi US PV (please see ***Section 12*** for complete information on SAE reporting).

10.8.3 Growth

For subjects younger than 18 years, height (in cm) and weight (in kg) should be obtained for determination of height-for-age and weight- for-age Z-scores.

10.8.4 Overall Survival

Subject survival will be recorded throughout the subject's participation in the study. If death is reported during the study, the date of death and reason for the subject death should be documented and recorded.

All subject deaths should be reported immediately (see Section 12.4) to Chiesi US PV.

10.9 Quality of Life

Age-based health-related quality of life assessments will be made using PedsQL scales for subjects aged 1 to 12 months (infants), 13 to 24 months (infants), 2 to 4 years (toddlers), 5 to 7 years (young children), 8 to 12 years (children), and 13 to 18 years (teens); for subjects over 18 years, the SF-36 and PADQOL will be administered. Assessments for subjects under age 5 will be completed by the parent. For subjects from 5 to 18 years old, parents and heath care providers will determine the ability of the subject to self-report. However, parental consent and attendance is required during the call. QOL assessment data will be collected prospectively for a maximum of 24 months after starting Revcovi from study participants via scripted phone calls by the study call center and QOL responses will be entered directly into the electronic data capture (EDC) system. These assessments will be conducted utilizing the schedule outlined in section 11.2 below, independent of clinic evaluations to minimize data collection requirements of the study sites.

10.10 Revcovi Administration and Compliance

10.10.1 Dosage and Administration

Beginning at the Enrollment Visit, subjects transitioning from Adagen to Revcovi and Adagen-naïve subjects (newborn) should be dosed in accordance with the Revcovi PI recommendation. Subjects who started Revcovi treatment prior to study enrollment should continue to be dosed in accordance with provider or Revcovi PI recommendation.

Subjects transitioning from Adagen to Revcovi: Trough ADA activity and dAXP levels should be assessed prior to transition.

For subjects currently receiving Adagen at ≤ 30 U/kg/wk or an unknown Adagen dose, the starting weekly IM dose with Revcovi is 0.2 mg/kg. The weekly dose may be increased by increments of 0.033 mg/kg weekly if trough ADA activity is under 30 mmol/hr/L, dAXP is above 0.02 mmol/L, and/or the immune reconstitution is inadequate based on the clinical assessment of the subject.

For subjects currently receiving Adagen at > 30 U/kg/wk, an equivalent Revcovi dose (mg/kg) can be calculated using the following equation:

$$\text{Revcovi dose in mg/kg} = \frac{\text{Adagen dose in U/kg}}{150}$$

The total weekly dose may be divided and administered in multiple IM injections per week. The weekly Revcovi dose may be increased by increments of 0.033 mg/kg weekly if trough ADA activity is under 30 mmol/hr/L, dAXP is above 0.02 mmol/L, and/or the immune reconstitution is inadequate based on the clinical assessment of the subject.

Adagen-naïve subjects: The starting weekly IM dose with Revcovi is 0.4 mg/kg of ideal body weight, divided into two weekly doses, for a minimum of 12 to 24 weeks until immune reconstitution is achieved based on clinical assessment by the treating physician. The dose may be gradually adjusted down to maintain trough ADA activity over 30 mmol/hr/L, dAXP under 0.02 mmol/L, and to maintain adequate immune reconstitution based on clinical assessment of the subject by the treating physician.

10.10.2 Dose Adjustments

Adjustments of the dose and/or schedule of Revcovi may be required if a subject's trough plasma ADA activity is less than 30 µmol/h/mL, trough dAXP level is greater than 0.02 µmol/mL, or immune reconstitution is inadequate based on clinical assessment of the subject by Investigator's determination.

The optimal long-term dose and schedule of administration should be established by a physician for each subject individually and may be adjusted based on the laboratory values for trough ADA activity, trough erythrocyte dAXP level, and on the treating physician's medical assessment of the subject's clinical status (see Revcovi PI).

10.10.3 Treatment Delays

Revcovi should be administered in accordance with the Suggested Schedules of Assessments for Adagen-transitioning and Adagen-naïve subjects (Appendix 1 and Appendix 2, respectively). The Investigator, upon consultation with Chiesi Farmaceutici S.p.A. and the Investigator, may elect to delay or withhold a dose if the clinical condition of the subject warrants such action.

10.10.4 Assessment of Revcovi Compliance

Subjects will often be self-administering drug from commercially available inventories. Dosing dates, times and volumes will be captured via subject-reported diaries/medication administration forms. Diaries/medication administration forms will be monitored as part of medication compliance.

10.11 Assessment of Concomitant Medications of Interest

The use of concomitant medications of interest, including ADA inhibitors and Ig replacement therapy, should be recorded at each visit. Concomitant medications of interest are all anti-infectives that are administered after the first dose of Revcovi, regardless of when they were started. If applicable, the name of the medication, total daily dose, route of administration, and start and stop dates should be documented.

10.12 Protocol Adherence

This study is conducted in accordance the principles of the Declaration of Helsinki, the International Council for Harmonisation Guidance on GCP and the requirements of federal and local regulatory authorities regarding the conduct of clinical trials and the protection of human subjects.

The Investigator and the study personnel will recommend subject adherence with the study requirements, procedures and suggested schedule of events. The Investigator or a licensed physician Sub-Investigator listed on Form FDA 1572 or equivalent, is present for initial dose administration of Revcovi at the Enrollment Visit and for the post-dose monitoring and evaluation for all subjects. The Investigator or physician sub-Investigator will be available by phone/pager at all other times throughout the study for the management of the subjects enrolled in this clinical trial. Deviations from any study evaluations/procedures is documented in the subject's source documents and CRFs and reported to the Sponsor and IRB/IEC as required.

11 SCHEDULE OF STUDY PROCEDURES

A schedule of suggested study procedures for subjects transitioning from Adagen to Revcovi is shown in Appendix 1 and for Adagen-naïve subjects in Appendix 2.

11.1 Enrollment

Subjects who fulfill all of the inclusion criteria and none of the exclusion criteria may be enrolled into the study. The date of ICF signature is the date of enrollment into the registry.

The following evaluations should be performed or collected retrospectively (if available) before starting Revcovi unless otherwise indicated.

- Informed assent/consent
- Demographics
- Medical history and baseline characteristics (including ADA-mutation results, if available)

- Assessment of infectious complications and hospitalizations within the past 12 months
- Concomitant medications/procedures
- Physical examination (including height and weight) from 1 year prior to start of Revcovi treatment
- Vital signs
- Safety laboratory assessments: hematology, serum chemistry, urinalysis (if available)
- Immune Function (if available)
- B-/T-/NK-lymphocyte subset
- Trough plasma ADA activity and erythrocyte dAXP
- Quantitative immunoglobulins
- Immune Function analyses (response to PHA, pneumococcal vaccine or equivalent)
- Immunogenicity – Revcovi antibody titers (i.e., neutralizing and binding antibodies) and anti-PEG antibodies (only if indicated)
- Quality of Life assessments

11.2 Revcovi Treatment Period

The assessments and schedule described in the following subsections are suggested based on recommendations described in the Revcovi PI.

Monitoring for trough plasma ADA activity and trough erythrocyte dAXP levels is essential to establish therapeutic levels of Revcovi and to maintain detoxification. The schedule of monitoring listed in the PI and in this protocol are recommended and not required. Clinicians should individualize the schedule of monitoring to assess the effect of Revcovi on trough plasma activity of ADA, erythrocyte dAXP, and immune function (lymphocyte counts, lymphocyte subsets and immune response) while balancing the risk of phlebotomy and subject visit burden. The listing for the schedule of assessments (Appendix 1 and Appendix 2) provides a template for reporting of monitoring and is not a rigid requirement.

Safety laboratory assessments should be collected, if available, but these assessments are not required (Section 10.5.3). Immunogenicity testing should also be performed, if indicated, in accordance with the Revcovi PI (see Section 10.5.4).

With the exception of ADA and dAXP assessments, a microtainer should be used for blood collection for subjects younger than 10 years of age whenever possible.

11.2.1 Adagen-transitioning subjects

Visit frequency is determined by Provider/Subject as needed for clinical standard of care with recommendations in the Prescribing information.

11.2.1.1 Treatment Week 4

At Treatment Week 4 (± 1 week), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Safety Laboratory assessments (if available)
- Immunogenicity

Blood samples should be obtained prior to administration of Revcovi for:

- Trough plasma ADA activity

11.2.1.2 Treatment Week 8

At Treatment Week 8 (± 1 week), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Safety Laboratory assessments (if available)
- Immunogenicity

Blood samples should be obtained prior to administration of Revcovi for:

- Trough erythrocyte dAXP

  Trough plasma ADA activity

11.2.1.3 Treatment Week 12

At Treatment Week 12 (±1 week), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments, if needed:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Safety Laboratory assessments (if available)
- Immunogenicity
- QOL will be assessed using the PedsQL Infant Scales (ages 1 to 12 months), PedsQL Infant Scales (ages 13 to 24 months), PedsQL 4.0 Toddler (2 to 4 years), PedsQL 4.0 Young Child Report (5 to 7 years), PedsQL 4.0 Child Report (8 to 12 years), PedsQL 4.0 Teen Report (13 to 18 years), and for subjects older than 18 years, the SF36 and the PADQOL. Assessments for those under age 5 will be completed by the parent. For children 5 to 18 years, the parent or health care provider will determine the ability of the subject to selfreport. QOL assessment data will be collected from study participants via scripted phone calls by the study call center and QOL responses will be entered directly into the EDC system. QOL assessments will be collected prospectively for 24 months after starting Revcovi.

Blood samples should be obtained prior to administration of Revcovi for:

- Trough plasma ADA activity
- B-/T-/NK-lymphocyte subset

11.2.1.4 Treatment Month 6

At Treatment Month 6 (± 3 weeks), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations

- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Safety Laboratory assessments (if available)
- Immunogenicity
- Quality of life will be assessed using the PedsQL Infant Scales (ages 1 to 12 months), PedsQL Infant Scales (ages 13 to 24 months), PedsQL 4.0 Toddler (2 to 4 years), PedsQL 4.0 Young Child Report (5 to 7 years), PedsQL 4.0 Child Report (8 to 12 years), PedsQL 4.0 Teen Report (13 to 18 years), and for subjects older than 18 years, the SF36 and the PADQOL. Assessments for those under age 5 will be completed by the parent. For children 5 to 18 years, the parent or health care provider will determine the ability of the subject to selfreport. QOL assessment data will be collected from study participants via scripted phone calls by the study call center and QOL responses will be entered directly into the EDC system. QOL assessments will be collected prospectively for 24 months after starting Revcovi.

Blood samples should be obtained prior to administration of Revcovi for:

- Trough plasma ADA activity
- B-/T-/NK-lymphocyte subset
- Quantitative immunoglobulins

11.2.1.5 Treatment Month 9

At Treatment Month 9 (± 3 weeks), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Safety Laboratory assessments (if available)
- Immunogenicity

- Quality of life will be assessed using the PedsQL Infant Scales (ages 1 to 12 months), PedsQL Infant Scales (ages 13 to 24 months), PedsQL 4.0 Toddler (2 to 4 years), PedsQL 4.0 Young Child Report (5 to 7 years), PedsQL 4.0 Child Report (8 to 12 years), PedsQL 4.0 Teen Report (13 to 18 years), and for subjects older than 18 years, the SF36 and the PADQOL. Assessments for those under age 5 will be completed by the parent. For children 5 to 18 years, the parent or health care provider will determine the ability of the subject to selfreport. QOL assessment data will be collected from study participants via scripted phone calls by the study call center and QOL responses will be entered directly into the EDC system

Blood samples should be obtained prior to administration of Revcovi for:

- Trough plasma ADA activity
- B-/T-/NK-lymphocyte subset

11.2.1.6 Treatment Month 12

At Treatment Month 12 (± 3 weeks), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Safety Laboratory assessments (if available)
- Immunogenicity
- Quality of life will be assessed using the PedsQL Infant Scales (ages 1 to 12 months), PedsQL Infant Scales (ages 13 to 24 months), PedsQL 4.0 Toddler (2 to 4 years), PedsQL 4.0 Young Child Report (5 to 7 years), PedsQL 4.0 Child Report (8 to 12 years), PedsQL 4.0 Teen Report (13 to 18 years), and for subjects older than 18 years, the SF36 and the PADQOL. Assessments for those under age 5 will be completed by the parent. For children 5 to 18 years, the parent or health care provider will determine the ability of the subject to selfreport. QOL assessment data will be collected from study participants via scripted phone calls by the study call center and QOL responses will be entered directly into the EDC system. QOL assessments will be collected prospectively for 24 months after starting Revcovi.

Blood samples should be obtained prior to administration of Revcovi for:

- Trough plasma ADA activity
- B-/T-/NK-lymphocyte subset
- Quantitative immunoglobulins

11.2.1.7 Treatment Month 15

At Treatment Month 15 (± 3 weeks), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Safety Laboratory assessments (if available)
- Immunogenicity

Blood samples should be obtained prior to administration of Revcovi for:

- Trough plasma ADA activity
- B-/T-/NK-lymphocyte subset

11.2.1.8 Treatment Month 18

At Treatment Month 18 (± 3 weeks), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)

- Quality of life will be assessed using the PedsQL Infant Scales (ages 1 to 12 months), PedsQL Infant Scales (ages 13 to 24 months), PedsQL 4.0 Toddler (2 to 4 years), PedsQL 4.0 Young Child Report (5 to 7 years), PedsQL 4.0 Child Report (8 to 12 years), PedsQL 4.0 Teen Report (13 to 18 years), and for subjects older than 18 years, the SF36 and the PADQOL. Assessments for those under age 5 will be completed by the parent. For children 5 to 18 years, the parent or health care provider will determine the ability of the subject to selfreport. QOL assessment data will be collected from study participants via scripted phone calls by the study call center and QOL responses will be entered directly into the EDC system. QOL assessments will be collected prospectively for 24 months after starting Revcovi.
- Safety Laboratory assessments (if available)
- Immunogenicity

Blood samples should be obtained prior to administration of Revcovi for:

- Trough erythrocyte dAXP
- Trough plasma ADA activity
- B-/T-/NK-lymphocyte subset
- Quantitative immunoglobulins

11.2.1.9 Treatment Month 21

At Treatment Month 21 (± 3 weeks), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Safety Laboratory assessments (if available)
- Immunogenicity

Blood samples should be obtained prior to administration of Revcovi for:

- Trough plasma ADA activity
- B-/T-/NK-lymphocyte subset

11.2.1.10 Treatment Month 24

At Treatment Month 24 (± 3 weeks), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Quality of life will be assessed using the PedsQL Infant Scales (ages 1 to 12 months), PedsQL Infant Scales (ages 13 to 24 months), PedsQL 4.0 Toddler (2 to 4 years), PedsQL 4.0 Young Child Report (5 to 7 years), PedsQL 4.0 Child Report (8 to 12 years), PedsQL 4.0 Teen Report (13 to 18 years), and for subjects older than 18 years, the SF36 and the PADQOL. Assessments for those under age 5 will be completed by the parent. For children 5 to 18 years, the parent or health care provider will determine the ability of the subject to selfreport. QOL assessment data will be collected from study participants via scripted phone calls by the study call center and QOL responses will be entered directly into the EDC system. QOL assessments will be collected prospectively for 24 months after starting Revcovi.
- Safety Laboratory assessments (if available)
- Immunogenicity

Blood samples should be obtained prior to administration of Revcovi for:

- Trough plasma ADA activity
- B-/T-/NK-lymphocyte subset
- Trough erythrocyte dAXP levels
- Quantitative immunoglobulins (IgA, IgG, IgM)

11.2.1.11 Treatment Month 27+

Subjects should continue to return to study site every 3 months ± 3 weeks until the last enrolled patient has reached 24 months of treatment. The following procedures should be performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications

- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Safety Laboratory assessments (if available)
- Immunogenicity
- Trough plasma ADA activity
- B-/T-/NK-lymphocyte subset
- Trough erythrocyte dAXP levels*
- Quantitative immunoglobulins (IgA, IgG, IgM)*

Blood samples should be obtained prior to administration of Revcovi. Please refer to schedule of assessments for applicable blood draws per treatment visit.

* to be performed at every other visit (M30, 36, 42...), please refer to appendix 1 schedule of assessments

11.2.2 Adagen-naïve subjects

Visit frequency is determined by Provider/Subject as needed for clinical standard of care with recommendations in the Prescribing information

11.2.2.1 Treatment Week 2

At Treatment Week 2 (± 3 days), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Safety Laboratory assessments (if available)

- Immunogenicity

Blood samples should be obtained prior to administration of Revcovi for:

- Trough erythrocyte dAXP
- Trough plasma ADA activity

11.2.2.2 Treatment Week 4

At Treatment Week 4 (± 3 days), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Safety Laboratory assessments (if available)
- Immunogenicity

Blood samples should be obtained prior to administration of Revcovi for:

- Trough erythrocyte dAXP
- Trough plasma ADA activity
- B-/T-/NK-lymphocyte subset
- Quantitative immunoglobulins

11.2.2.3 Treatment Week 6

At Treatment Week 6 (± 3 days), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations

- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Safety Laboratory assessments (if available)
- Immunogenicity

Blood samples should be obtained prior to administration of Revcovi for:

- Trough erythrocyte dAXP
- Trough plasma ADA activity

11.2.2.4 Treatment Week 8

At Treatment Week 8 (± 3 days), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Safety Laboratory assessments (if available)
- Immunogenicity

Blood samples should be obtained prior to administration of Revcovi for:

- Trough erythrocyte dAXP
- Trough plasma ADA activity
- B-/T-/NK-lymphocyte subset
- Quantitative immunoglobulins

11.2.2.5 Treatment Week 10

At Treatment Week 10 (± 3 days), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Safety Laboratory assessments (if available)
- Immunogenicity

Blood samples should be obtained prior to administration of Revcovi for:

- Trough erythrocyte dAXP
- Trough plasma ADA activity

11.2.2.6 Treatment Week 12

At Treatment Week 12 (± 3 days), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Safety Laboratory assessments (if available)
- Immunogenicity
- Quality of life will be assessed using the PedsQL Infant Scales (ages 1 to 12 months), PedsQL Infant Scales (ages 13 to 24 months), PedsQL 4.0 Toddler (2 to 4 years), PedsQL 4.0 Young Child Report (5 to 7 years), PedsQL 4.0 Child Report (8 to 12 years), PedsQL 4.0 Teen Report (13 to 18 years), and for subjects older than 18 years, the SF36 and the PADQOL. Assessments for those under age 5 will be completed by the parent. For children 5 to 18 years, the parent or health care provider will determine the ability of the subject to selfreport. QOL assessment data will be

collected from study participants via scripted phone calls by the study call center and QOL responses will be entered directly into the EDC system. QOL assessments will be collected prospectively for 24 months after starting Revcovi.

Blood samples should be obtained prior to administration of Revcovi for:

- Trough erythrocyte dAXP
- Trough plasma ADA activity
- B-/T-/NK-lymphocyte subset
- Quantitative immunoglobulins

11.2.2.7 Treatment Month 4

At Treatment Month 4 (± 1 week), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Safety Laboratory assessments (if available)
- Immunogenicity

Blood samples should be obtained prior to administration of Revcovi for:

- B-/T-/NK-lymphocyte subset

11.2.2.8 Treatment Month 5

At Treatment Month 5 (± 1 week), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations

- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Safety Laboratory assessments (if available)
- Immunogenicity

Blood samples should be obtained prior to administration of Revcovi for:

- B-/T-/NK-lymphocyte subset

11.2.2.9 Treatment Month 6

At Treatment Month 6 (± 1 week), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Quality of life will be assessed using the PedsQL Infant Scales (ages 1 to 12 months), PedsQL Infant Scales (ages 13 to 24 months), PedsQL 4.0 Toddler (2 to 4 years), PedsQL 4.0 Young Child Report (5 to 7 years), PedsQL 4.0 Child Report (8 to 12 years), PedsQL 4.0 Teen Report (13 to 18 years), and for subjects older than 18 years, the SF36 and the PADQOL. Assessments for those under age 5 will be completed by the parent. For children 5 to 18 years, the parent or health care provider will determine the ability of the subject to selfreport. QOL assessment data will be collected from study participants via scripted phone calls by the study call center and QOL responses will be entered directly into the EDC system. QOL assessments will be collected prospectively for 24 months after starting Revcovi.
- Safety Laboratory assessments (if available)
- Immunogenicity

Blood samples should be obtained prior to administration of Revcovi for:

- Trough plasma ADA activity
- B-/T-/NK-lymphocyte subset

- Quantitative immunoglobulins

11.2.2.10 Treatment Month 7

At Treatment Month 7 (± 1 week), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Safety Laboratory assessments (if available)
- Immunogenicity

Blood samples should be obtained prior to administration of Revcovi for:

- B-/T-/NK-lymphocyte subset

11.2.2.11 Treatment Month 8

At Treatment Month 8 (± 1 week), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Safety Laboratory assessments (if available)
- Immunogenicity

Blood samples should be obtained prior to administration of Revcovi for:

- Trough dAXP
- B-/T-/NK-lymphocyte subset

11.2.2.12 Treatment Month 9

At Treatment Month 9 (± 1 week), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Safety Laboratory assessments (if available)
- Immunogenicity
- Quality of life will be assessed using the PedsQL Infant Scales (ages 1 to 12 months), PedsQL Infant Scales (ages 13 to 24 months), PedsQL 4.0 Toddler (2 to 4 years), PedsQL 4.0 Young Child Report (5 to 7 years), PedsQL 4.0 Child Report (8 to 12 years), PedsQL 4.0 Teen Report (13 to 18 years), and for subjects older than 18 years, the SF36 and the PADQOL. Assessments for those under age 5 will be completed by the parent. For children 5 to 18 years, the parent or health care provider will determine the ability of the subject to self-report. QOL assessment data will be collected from study participants via scripted phone calls by the study call center and QOL responses will be entered directly into the EDC system. QOL assessments will be collected prospectively for 24 months after starting Revcovi.

Blood samples should be obtained prior to administration of Revcovi for:

- Trough plasma ADA activity
- B-/T-/NK-lymphocyte subset

11.2.2.13 Treatment Month 12

At Treatment Month 12 (± 3 weeks), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications

- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Quality of life will be assessed using the PedsQL Infant Scales (ages 1 to 12 months), PedsQL Infant Scales (ages 13 to 24 months), PedsQL 4.0 Toddler (2 to 4 years), PedsQL 4.0 Young Child Report (5 to 7 years), PedsQL 4.0 Child Report (8 to 12 years), PedsQL 4.0 Teen Report (13 to 18 years), and for subjects older than 18 years, the SF36 and the PADQOL. Assessments for those under age 5 will be completed by the parent. For children 5 to 18 years, the parent or health care provider will determine the ability of the subject to selfreport. QOL assessment data will be collected from study participants via scripted phone calls by the study call center and QOL responses will be entered directly into the EDC system. QOL assessments will be collected prospectively for 24 months after starting Revcovi.
- Safety Laboratory assessments (if available)
- Immunogenicity

Blood samples should be obtained prior to administration of Revcovi for:

- Trough erythrocyte dAXP
- Trough plasma ADA activity
- B-/T-/NK-lymphocyte subset
- Quantitative immunoglobulins

11.2.2.14 Treatment Month 15

At Treatment Month 15 (± 3 weeks), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)

- Safety Laboratory assessments (if available)
- Immunogenicity

Blood samples should be obtained prior to administration of Revcovi for:

- Trough plasma ADA activity
- B-/T-/NK-lymphocyte subset

11.2.2.15 Treatment Month 18

At Treatment Month 18 (± 3 weeks), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Assessment of Quality of Life (All subjects up to 18 years old will be assessed using the age specific PedsQL. Parents or health care providers will determine the ability of subjects from 5 to 18 years to self-report. Subjects over 18 years will be assessed using the SF 36 and PADQOL.) QOL assessment data will be collected from study participants via scripted phone calls by the study call center and QOL responses will be entered directly into the EDC system. QOL assessments will be collected prospectively for 24 months after starting Revcovi.
- Safety Laboratory assessments (if available)
- Immunogenicity

Blood samples should be obtained prior to administration of Revcovi for:

- Trough erythrocyte dAXP
- Trough plasma ADA activity
- B-/T-/NK-lymphocyte subset
- Quantitative immunoglobulins

11.2.2.16 Treatment Month 21

At Treatment Month 21 (± 3 weeks), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Safety Laboratory assessments (if available)
- Immunogenicity

Blood samples should be obtained prior to administration of Revcovi for:

- Trough plasma ADA activity
- B-/T-/NK-lymphocyte subset

11.2.2.17 Treatment Month 24

At Treatment Month 24 (± 3 weeks), the subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Assessment of Quality of Life (All subjects up to 18 years old will be assessed using the age specific PedsQL. Parents or health care providers will determine the ability of subjects from 5 to 18 years to self-report. Subjects over 18 years will be assessed using the SF 36 and PADQOL.) QOL assessment data will be collected from study participants via scripted phone calls by the study call center and QOL responses will

be entered directly into the EDC system. QOL assessments will be collected prospectively for 24 months after starting Revcovi.

- Safety Laboratory assessments (if available)
- Immunogenicity

Blood samples should be obtained prior to administration of Revcovi for:

- Trough erythrocyte dAXP
- Trough plasma ADA activity
- B-/T-/NK-lymphocyte subset
- Quantitative immunoglobulins

11.2.2.18 Treatment Month 27+

Subjects should continue to return to study site every 3 months ± 3 weeks until the last enrolled patient has reached 24 months of treatment. The following procedures should be performed as per suggested schedule of assessments:

- AE assessment
- Concomitant medications
- Revcovi dosing and compliance
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Vital signs
- Physical examination (including height and weight)
- Safety Laboratory assessments (if available)
- Immunogenicity
- Trough erythrocyte dAXP*
- Trough plasma ADA activity
- B-/T-/NK-lymphocyte subset
- Quantitative immunoglobulins*

Blood samples should be obtained prior to administration of Revcovi. Please refer to schedule of assessments for applicable blood draws per treatment visit.

* to be performed at every other visit (M30, 36, 42...), please refer to appendix 2 schedule of assessments

11.3 Study Completion

Study completion will be once the last patient enrolled has reached 24 months of Revcovi treatment or until undergoing HSCT or HSCGT, whichever occurs first. The subject should return to the study site and have the following procedures performed as per suggested schedule of assessments:

- AE assessment
- Assessment of infectious complications and hospitalizations
- Assessment of concomitant use of ADA inhibitors and Ig replacement therapy and any procedures performed since last study visit
- Assessment of Quality of Life (only performed during the first 24 months of starting on Revcovi)
- Vital signs
- Physical examination (including height and weight)

Blood samples should be obtained for:

- Trough erythrocyte dAXP
- Trough plasma ADA activity
- B-/T-/NK-lymphocyte subset
- Quantitative immunoglobulins
- Safety laboratory assessments: hematology, serum chemistry, urinalysis (if available)

All subjects, regardless of the reason for study withdrawal (see Section 9.5.1), subjects should have the above evaluations performed, whenever possible. All reasons for discontinuation of treatment must be documented.

12 ADVERSE EVENTS

12.1 Assessment Period

AEs are assessed from the time the subject receives their initial dose of Revcovi during the CLI-06814AA1-01 registry through 4 weeks following the last dose. Subjects undergoing HSCT or HSCGT will be followed one month and again at 6 months after last Revcovi dose to assess AEs and survival.

12.2 Definitions

12.2.1 Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality.

An untoward medical event which occurs outside the period of follow-up as defined in the protocol is not considered an AE. Worsening of a medical condition for which the efficacy of the drug is being evaluated is not considered an AE.

12.2.2 Unexpected Adverse Event

An adverse reaction is unexpected if the nature or severity of the event is not consistent with the applicable product information. An unexpected AE is one that is not listed in the PI or is not listed at the specificity or severity that has been observed.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the PI referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the package insert listed only cerebral vascular accidents.

"Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the PI as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

12.2.3 Serious Adverse Event

A *serious adverse event* (SAE) is an AE that in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- Is life-threatening (an event that in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death; it does not include an event that had it occurred in a more severe form, might have caused death.)
- Requires in-subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly or birth defect
- Is another important medical event that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The term "severe" is often used to describe the intensity (severity) of an event; the event itself may be of relatively minor medical significance (such as a severe headache). This is not the same as "serious", which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning.

12.2.4 Relationship to Revcovi

The Investigator must attempt to determine if an AE is in some way related to the use of the Revcovi. This relationship should be described based upon the following definitions:

- ***Unrelated:*** The AE is clearly due to causes distinct from the use of the Revcovi, such as a documented pre-existing condition, the subject's clinical state, environmental factors, or the effect of other concomitant medications or treatments administered.
- ***Unlikely:*** The AE does not follow a reasonable temporal sequence from administration of Revcovi, does not follow a known response pattern to Revcovi, and could readily have been due to other causes such as the subject's clinical state, environmental factors, or the effect of other concomitant medications or treatments administered.
- ***Possible:*** The AE follows a reasonable temporal sequence from administration of Revcovi and follows a known response pattern to Revcovi, *BUT,* the AE could readily have been produced by the subject's clinical state, environmental factors, or the effect of other concomitant medications or treatments administered.
- ***Probable:*** The AE follows a reasonable temporal sequence from administration of Revcovi and follows a known response pattern to Revcovi, *AND* cannot be reasonably explained by the subject's clinical state, environmental factors, or the effect of other concomitant medications or treatments administered. The event improves upon discontinuation of Revcovi.
- ***Definite:*** The AE follows a reasonable temporal sequence from administration of Revcovi and follows a known response pattern to Revcovi. Based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug. The AE improves upon discontinuation of Revcovi and reappears upon repeat exposure. Please use Definite if the causal association is considered "Certain".

12.2.5 Severity (Intensity)

The Investigator assesses the severity (intensity) of all AEs according to the following grading system:

- Grade 1 – (Mild AE) awareness of the event but is easily tolerated
- Grade 2 – (Moderate AE) interferes with activities of daily living
- Grade 3 – (Severe AE) incapacitating and causes inability to perform activities of daily living

12.3 Reporting of Adverse Events

All new events related to Revcovi, as well as those that worsen in intensity or frequency relative to baseline, which occur must be captured. The Investigator or his/her staff should elicit information regarding the occurrence of AEs through information volunteered by the subject, open-ended questioning of the subject, physical examination results and review of laboratory results.

Information recorded for each AE includes:

- A medical diagnosis of the event (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event should be recorded)
- The date and time of onset of the event

- The date and time of resolution of the event
- Assessments of seriousness, causal relationship, and severity of the AE (see definitions in Sections 12.2.3, 12.2.4, 12.2.5, respectively)
    - For the purposes of SAE Reporting, adverse events assigned one of the following causality assessments by the investigator are considered causally related to the administration of Revcovi:
        - Possible
        - Probable
        - Definite – (Please use Definite if the causal association is considered "Certain")
- Action(s) taken (if any) for management of the AE, including but not limited to change in Revcovi administration (e.g., temporary interruption in dosing, dose reduction); drug treatment; non-drug treatment; diagnostic procedures performed
- Outcome of the AE: recovered; recovering; recovered with sequelae; event ongoing or not recovered; death

All AEs are followed as medically appropriate until an outcome is determined as stated above.

12.4 Reporting of Serious Adverse Events

All AEs and SAEs assessed by the investigator as ***causally related*** (i.e. "possibly", "probably" or "definitely" related) to the administration of Revcovi should be reported by sending AE/SAE report form to Chiesi US Pharmacovigilance (PV) at **us.medical@chiesi.com.**

12.5 Reporting of Pregnancy

Adequate and well-controlled studies with Revcovi have not been conducted in pregnant women to inform a drug-associated risk. Animal reproduction studies have not been conducted with Revcovi. No pregnancy was reported for any subjects receiving Revcovi. It is not known whether Revcovi can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

If a female subject becomes pregnant or is found to be pregnant while on the study or a female partner of a male subject becomes pregnant during the study, the Chiesi Pharmacovigilance should be contacted immediately. Although pregnancy is not a SAE, all pregnancies occurring during this study should be reported to Chiesi within 24 hours of becoming aware of the pregnancy and complete and submit a pregnancy report form.

All pregnancies will be followed until delivery or pregnancy termination for maternal outcomes and at 1 month, 2 months, and 1 year for fetal outcomes.

13 STATISTICS

13.1 Sample Size Determination

No formal sample size is calculated. The study will be open to enroll all eligible patients over a minimum of 2 years.

13.2 Statistical Methodology

13.2.1 Level of Significance

No hypothesis test will be done.

13.2.2 Analysis Populations

The as-treated population, defined as all subjects who are enrolled and receive at least one dose of Revcovi, will be the primary analysis set in all analyses.

13.2.3 Data Analysis

Statistical analysis will be conducted by Chiesi, or its designee. Analysis of study data will be performed after the last subject has completed assessments for the Treatment Month 24 Visit or, in the case of subject undergoing HSCT or HSC-GT, the 6 -month follow-up visit.

Statistical analyses will be performed using Statistical Analysis Systems® (SAS®) Version 9.4 or later (SAS Institute, Cary, NC), or comparable software.

A complete description of data handling rules and planned statistical analyses is detailed in a separate Statistical Analysis Plan. Unless otherwise specified in this document or in the Statistical Analysis Plan, baseline is defined as the last measurement for a variable before the initial dose of Revcovi, and missing data will generally not be imputed. Baseline for the patients transitioning from the Phase III STP-2279-002 study is the last available non-missing value prior to the initiation of Revcovi in the STP-2279-002 study.

Analyses will be descriptive, with data listings, graphical presentations, frequency tabulations, and summary statistics as appropriate.

Each subject will serve as his/her own control based on the baseline assessment of each endpoint as appropriate, including changes in body weight as percentile on the growth curve, antibody formation, etc.

Exposure and safety summaries will be presented by whether or not they previously participated in study STP-2279-002.

Additional statistical analyses, other than those described in this section, may be performed if deemed appropriate to further explore the study data.

13.2.3.1 Study Conduct and Subject Disposition

The number of subjects treated will be tabulated. Subjects not meeting the eligibility criteria will be documented. Protocol violations will be reviewed. Subjects who withdraw from the study will also be summarized using descriptive statistics by reason for withdrawal.

13.2.3.2 Demographics and Baseline Characteristics

Subject demographic data, baseline characteristics, and disease background at study entry will be summarized. Continuous variables will be summarized using descriptive statistics, including mean, standard deviation, median, and range. Categorical variables will be summarized in frequency tables. Missing categories will be presented if applicable.

For subjects younger than 18 years, growth curve percentiles for height, weight, and BMI will also be calculated and summarized. Missing categories will be presented if applicable.

Medical history at study entry will be listed but not summarized.

13.2.3.3 Revcovi Administration

Revcovi administration will be summarized starting from the enrollment in the CLI-06814AA1-01 registry. The total number of doses administered; the median (range) of doses administered; the median (range) treatment duration; dose modifications, dose delays, and dose omissions; and reasons for deviations from planned therapy will be described.

Exposure summaries will be presented by whether or not they previously participated in study STP-2279-002.

13.2.3.4 Biochemical Endpoint and Immune Status Analysis

Analyses of the following biochemical endpoints used for adjusting Revcovi dosing will be primarily descriptive, with data listings, graphical presentations, frequency tabulations, and summary statistics at each time point, as appropriate.

- Total erythrocyte dAXP from a trough blood sample
- Trough plasma ADA activity
- Immune function status, including:

- Absolute Lymphocyte count
- B-, T-, and NK-lymphocyte subset analysis: the number of cells for each subset will be determined by FACS. The following subsets will be assessed:
- CD3+ (Mature T cells) - Percent and Absolute
- CD3+ CD8+ (Suppressor T Cells) - Percent and Absolute
- CD3+ CD4+ (Helper Cells) - Percent and Absolute

- CD (16+56) + (Natural Killer Cells) - Percent and Absolute
- CD19+ (B Cells) - Percent and Absolute
- Absolute Lymphocytes (CD45+)
- %CD4 (Helper Cells) / %CD8 (Suppressor T Cells)
- Quantitative immunoglobulin concentration (IgA, IgG, IgM)
- Immune function measurement, if indicated (PHA stimulation or equivalent)

13.2.3.5 Safety Data Analysis

Safety summaries will be presented by whether or not they previously participated in study STP-2279-002.

Adverse Events and Serious Adverse Events – AEs will be categorized using Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1 or later. Summaries will be presented for all treatment-emergent AEs, AEs determined by the Investigator to be treatment-related, serious adverse events (SAEs), AEs causing withdrawal from study, AEs causing discontinuation of Revcovi, and non-serious AEs. The intensity of toxicities will be graded by the Investigator as mild, moderate, or severe as described in Section 12.2.5. In addition to being summarized as AEs, infectious complications and hospitalizations are considered efficacy measures as described in Section 10.8.

AE incidence will be calculated based on the number of subjects per AE category. For each subject who has multiple AEs classified to the same category, that subject will be tabulated under the maximum toxicity intensity for that AE category. The incidence of AEs will be tabulated by MedDRA system organ class and preferred term.

An AE onset between the date of the first dose of Revcovi and 30 days after the last dose of Revcovi is considered as a treatment-emergent AE.

Laboratory Safety Data – Hematology, chemistry, and urinalysis data will be summarized by timepoint of collection and by treatment group. In addition, listings for laboratory data will be presented identifying clinically significant abnormal results and out-of-normal range values will be listed.

Other Safety Data – The results of antibodies against Revcovi and antibodies against PEG will be summarized. The relationships between immunogenicity, biochemical endpoints, and the clinical toxicities will be examined as appropriate. Concomitant medications and findings in physical examinations will be listed and described textually as recorded in the CRF. Descriptive statistics of vital signs measurements as well as changes from baseline will be tabulated; abnormal vital sign values will be reported and summarized as AEs.

13.2.3.6 Clinical Status Analysis

Analyses of the following clinical status endpoints will be primarily descriptive, with data listings, graphical presentations, frequency tabulations, and summary statistics as appropriate.

- Infections: The number of clinically documented and microbiologically documented events
- Incidence and duration (length of stay) of hospitalizations
- Growth: Height-for-age and weight-for-age Z-scores (for subjects > 18 years of age)
- Overall survival

13.2.3.7 Quality of Life Analysis

Quality of life will be assessed for subjects up to 18 years old using the age-specific Pediatric Quality of Life Inventory (PedsQL). Subjects over 18 years old will be assessed using the SF-36 and Primary Antibody Deficiency Quality of Life Questionnaire (PADQOL).

For PedsQL, the four scales (Physical Functioning, Emotional Functioning, Social Functioning, School Functioning) and 3 summary scores (Psychosocial Health, Physical health and Total Scale) will be calculated and presented with summary statistics at each time point.

Data will be summarized by age and stratified by previous participation in study STP-2279-002.

Subjects that age out of PedsQL into PADQOL will be summarized only in the PedsQL while their PADQOL will be listed.

13.2.4 Handling Missing, Repeated, Unused and Spurious Data

The handling of missing, repeated, unused and spurious data will be described in the statistical analysis plan for the study.

13.2.5 Reporting of Deviations to Statistical Methodology

The methods for documenting deviations to the statistical methodology will be described in the statistical analysis plan for the study. These deviations will be described in the clinical study report.

13.3 Interim Analyses

An interim analysis will be performed approximately 2 years after the first subject is enrolled.

13.4 Statistical Criteria for Termination of the Study

There are no statistical criteria for the termination of the study.

14 ADMINISTRATIVE

14.1 Changes to Study Protocol

14.1.1 Protocol Amendments

Protocol changes must be in the form of a written amendment approved by Chiesi.

Protocol amendments and necessary revisions to the informed consent form must be submitted by the Investigator to the local IRB/IEC and such amendments are implemented after written approval of the requisite IRB/IEC. Protocol changes to eliminate an immediate hazard to a study subject may, at the direction of Chiesi, be implemented immediately by the Investigator. The Investigator must then immediately inform the IRB/IEC and obtain required approvals.

If a protocol amendment requires revision to the informed consent form, the revised IRB/IEC approved form must be used to re-consent subjects currently enrolled in the study and the new form must be used to obtain consent from new patients prior to enrollment.

All amendments are submitted to local regulatory authorities by Chiesi as required by local regulation.

14.1.2 Protocol Deviations

It is recommended that the Investigator and study staff adhere to the Suggested Schedule of Assessments and guidelines for therapeutic monitoring as described in the Revcovi PI. Deviations from the Suggested Schedule of Assessments and the Revcovi PI should be documented but do not need to be reported as protocol deviations, due to the nature of this registry study.

Departures from the protocol involving informed consent, eligibility criteria, and Revcovi administration are reported to the reviewing IRB/IEC by the Investigator in accordance with the IRB's/IEC's requirements.

14.2 Study Termination

Chiesi reserves the right to temporarily or permanently discontinue the study at any site and at any time. Reasons for study discontinuation may include, but are not limited to, the following:

- Investigator non-compliance with the protocol, GCP guidelines or regulatory requirements
- Safety concerns
- Discontinuation of the study protocol and/or all studies with Revcovi
- Request to discontinue the study by a regulatory or health authority

Chiesi will promptly inform all Investigators and the requisite regulatory authorities if the study is suspended or terminated for safety reasons. In the case of such suspension or termination, Chiesi will provide the Investigator with instructions regarding the disposition of subjects (e.g., termination of treatment, subject follow-up) currently on the study. The Investigator promptly notifies the IRB/IEC and implement subject disposition instructions.

Should the study be terminated prematurely, unused study material may be returned to the Sponsor or designee

14.3 Ethics Compliance Statement

This study is conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation Guidance on GCP and the requirements of federal regulatory authorities regarding the conduct of clinical trials and the protection of human subjects.

14.3.1 Institutional Review Board/Ethics Committee

The Investigator submits the protocol and subsequent amendments, the informed consent and any other material used to inform patients about the study to the local IRB/IEC for approval prior to enrolling any patient into the study. The IRB/IEC should be duly constituted according to applicable regulatory requirements. Approval must be in the form of a letter signed by the Chairperson of the IRB/IEC or the Chairperson's designee, must be on IRB/IEC stationery and must include the protocol by name and/or designated number. IRB/IEC approval of the informed consent form must be clearly indicated in the IRB/IEC approval letter (indicating version/date of the version approved) or by other means utilized by the IRB/IEC (e.g., IRB approval stamp on the approved version of the form). If an Investigator is a member of the IRB/IEC, the approval letter must stipulate that the Investigator did not participate in the final vote, although the Investigator may participate in the discussion of the study.

The Investigator also reports the progress of the study to the IRB/IEC on an annual basis or more frequently as required by the IRB/IEC. The Investigator also promptly informs the IRB/IEC of:

- SAEs that the Sponsor reports to regulatory authorities in an expedited manner,
- All changes in research activity
- Protocol deviations, as required by Chiesi or the IRB/IEC
- Other reports as required by the IRB/IEC
- The completion, termination, or discontinuation of the study, and
- A final summary of the final results at the conclusion of the study as required by the IRB/IEC

Copies of all correspondence between the Investigator and the IRB/IEC is provided to Chiesi.

14.3.2 Informed Consent

The Investigator obtains written informed consent from each patient or the patient's legal representative using the current IRB/IEC-approved version of the informed consent form prior to performing any study-related procedures. The consent form used to document informed consent from study participants must contain the elements of informed consent as described in 21 CFR, Part 50/ICH E6 Section 4.8.10, as applicable to this registry study..

The study records (i.e., patient source documents and applicable study logs) documents that informed consent was obtained prior to patient's participation in the study.

14.3.3 Health Insurance Portability and Accountability Act for studies conducted in the US

The Investigator must obtain authorization from the patient to use and/or disclose protected heath information (PHI) in compliance with the HIPAA of 1996.

HIPAA authorization may be obtained as part of the informed consent form or in a separate document and includes:

- Identification of the parties that can use and disclose PHI
- Identification of the parties to whom PHI may be disclosed
- A description of the PHI
- A description of the purpose for use and disclosure
- Information pertaining to the patient's rights related to authorization
- Information about the expiration of the authorization and how to revoke authorization
- A statement about what may happen if authorization is not provided
- A statement that once information has been disclosed, it may be disclosed again without further authorization.

For studies conducted outside the US, compliance with applicable local regulations must be followed.

14.3.4 Confidentiality of Subject Records

It is the responsibility of the Investigator to ensure that the confidentiality of all subjects participating in the study and all of their medical information is maintained. eCRFs and other documents submitted to Chiesi must not contain the name of a study participant. Each subject in the study is identified by a unique identifier that is used within the eCRF and any other material submitted to Chiesi. Any identifying information must be kept in a secure location with access limited to the study staff directly participating in the study.

Personal medical information may be reviewed by representatives of Chiesi/designee, of the IRB or of regulatory authorities in the course of monitoring the progress of the study. Every reasonable effort should be made to maintain such information as confidential.

The results of the study may be presented in reports, published in scientific journals or presented at medical meetings; however, subject names are never to be used in any reports about the study.

14.4 Conflict of Interest

The Investigator shall acknowledge, by signing the Investigator's Statement/ Signature Page (Section 15) that the participation in this clinical study by the Investigator and his/her Sub-Investigators discloses any conflicts of interest or confirms no conflicts of interest with the study.

14.4.1 Monitoring and Audits

During the course of the study, a clinical monitor assigned by Chiesi or their designee makes regularly scheduled visits to the investigational site to review the progress of the study. The frequency of monitoring visits will depend on the enrollment rate and performance at each site. During each visit, the monitor reviews various aspects of the study including, but not limited to:

- Compliance with the protocol
- Compliance with the principles of GCP and regulatory requirements
- Review of written informed consent forms for subjects enrolled
- Comparison of source documentation to data recorded on CRFs to assure the completeness and accuracy of data collected
- Continued acceptability of facilities and staff
- Review of essential documentation for the study

During scheduled monitoring visits, the Investigator and the investigational site staff must be available to meet with the study monitor in order to discuss the progress of the study, make necessary corrections to eCRF entries, respond to data clarification requests, and respond to any other study-related inquiries of the monitor.

In addition to the above, representatives of Chiesi's auditing staff or government inspectors may review the conduct/results of the study at the investigational site. The Investigator must promptly notify Chiesi of any audit requests by regulatory authorities. The Investigator cooperates with the auditor(s), makes available to the auditor all requested documentation, and ensures that issues detected during the course of these audits are satisfactorily resolved. The Investigator supplies Chiesi with copies of all documentation and correspondence related to regulatory agency audits as outlined in the Clinical Study Agreement between Chiesi/designee and the Investigator and/or Institution. If the results of the audit result in a Form FDA-483 (or similar document from another regulatory agency), the Investigator promptly provides a copy to Chiesi and provides a copy of the draft response to Chiesi prior to submission to the regulatory agency.

14.5 Investigator Obligations

The Investigator is responsible to meet the obligations of clinical investigators as described in ICH GCP guidelines, the Declaration of Helsinki and U.S. federal regulations as defined in 21 CFR Parts 50, 54, 56, and 312.

These obligations include, but are not limited to:

1. Protect the rights, safety and welfare of subjects under the Investigator's care
2. Conduct the study in accordance with the approved study protocol
3. Conduct the study in accordance with GCP guidelines and applicable federal, state and local regulations and laws
4. Ensure that the staff involved with the conduct of the study is knowledgeable on the study agents used, the study protocol, study procedures, and reporting requirements
5. Properly obtain informed consent and HIPAA authorization from all subjects enrolled using the current IRB-approved forms
6. Prepare and maintain accurate and complete case histories for all subjects participating in this trial that document all study procedures performed and record all data required for this study protocol
7. Report all SAEs to the Sponsor and IRB/IEC (as necessary) within the timeframes described in this protocol
8. Report any changes in research activity and unanticipated problems involving risk to study participants promptly to the IRB/IEC.
9. Report all protocol deviations promptly to Chiesi/designee. Significant deviations require prompt notification to the IRB/IEC.
10. Provide the IRB/IEC with copies of reports of SAEs submitted by Chiesi to regulatory authorities in an expedited manner (e.g., Investigational New Drug [IND] Safety Reports)
11. Provide Chiesi with complete and accurate financial information to allow submission of complete and accurate certification and disclosure statements to FDA as required.

The Investigator, or a licensed physician Sub-Investigator to which the Investigator has delegated responsibility, is required to administer or oversee the care of study subjects and review study data (e.g., AEs, laboratory data, treatment response data) in a timely manner.

14.6 Financial Disclosure

All Investigators and Sub-Investigators listed on any Form FDA 1572 supplied by the Investigator disclose the following information as required by 21 CFR, Part 54:

1. Any financial arrangement entered into between Chiesi/designee and the Investigator/Sub-Investigator whereby the value of the compensation to the Investigator/Sub-Investigator for conducting the study could be influenced by the outcome of the study.
2. Any significant payments totaling more than $25,000 USD, exclusive of the costs of conducting this or other clinical studies, from Chiesi, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria.
3. Any proprietary interest in the test product.
4. Any significant equity interest in Chiesi in excess of $50,000 USD.

The Investigator/Sub-Investigator shall promptly update financial disclosure information if any changes occur during the course of the study and for 1 year following completion of this study. This financial disclosure requirement includes the spouse and the dependent children of the Investigator/Sub-Investigator.

14.7 Quality Control and Quality Assurance of Study Data

14.7.1 Data Processing and Data Quality Assurance

All site-generated study data are entered into an eCRF via an EDC system. Site personnel enters data from assessments performed as part of the standard of care for their patients who are taking Revcovi. These assessments include height and weight measurements, vital signs, and safety and specialty laboratory test results. The data are entered into specific time periods (e.g., Baseline, month 3, month 6, etc) that are defined relative to the Revcovi start date. Patients are also assessed throughout the duration of the registry for any concomitant medications, hospitalizations, procedures, and AEs, and that information is also entered into the EDC system. There are automatic system queries based on programmed edit checks, and there are manual queries that result from review of the data by the data manager, CRA, or other project team members. System queries include future dates, out of window dates, and out of range vital signs. Manual queries include cross-form checks, duplicate dates, and discrepant information.

14.8 Study Records

The Investigator is responsible for preparing and maintaining adequate records to enable the conduct of the study to be documented. Study records include, but are not limited to, regulatory documentation (Section 14.8.1) and subject records (Sections 14.8.2 and 14.8.3).

14.8.1 Regulatory Documentation

Prior to initiating the study, the Investigator provides the CRO or Chiesi the following documents:

- A signed Form FDA 1572 or equivalent
- A current curriculum vitae for the Investigator and each sub-Investigator listed on the Form FDA 1572
- Copy of the current medical licenses for the Investigator and Sub-Investigators, as applicable
- Written IRB/IEC approval of the protocol, informed consent form and any other material provided to potential study participants with information about the study (e.g., advertisements)
- A copy of the IRB/IEC-approved informed consent document and HIPAA/privacy authorization

- Current IRB/IEC membership list for the reviewing IRB/IEC and/or multiple project assurance number or an IRB organization number under the Federal Wide Assurance program
- A signed Investigator Protocol Agreement (Section 15 of study protocol)
- Completed financial disclosure form for the Investigator and all Sub-Investigators
- Local reference laboratory documentation, including current laboratory certification, current laboratory normal values, and director's CV

During the course of the study, the Investigator maintains current records to document regulatory compliance with the study including: the study protocol and amendments, all versions of the PI in effect during study conduct, signed Investigator Agreement protocol page(s), Form FDA 1572 or equivalent , curricula vitae of the Investigator and sub-Investigators, medical licenses of the Investigator and sub-Investigators, financial disclosure of the Investigator and sub-Investigators, IRB/IEC approvals of the protocol, protocol amendment(s), informed consent form(s), IRB/IEC membership list, IRB/IEC approved informed consent form(s), IRB/IEC correspondence, protocol deviations, study logs (as provided by Chiesi), drug dispensing and accountability records, safety reports, and all correspondence pertaining to the conduct of the study. Regulatory documentation is reviewed by Chiesi during monitoring visits to assure regulatory compliance.

14.8.2 Source Documents

The Investigator maintains records in the form of clinical charts, medical records, original laboratory, radiology and pathology reports, pharmacy records, subject diary cards, etc. The Investigator documents in the clinic chart or medical record the name and number of the study and the date on which the patient signed informed consent prior to the patient's participation in the study. Source documents must completely reflect the nature and extent of the subject's medical care and must be available, with direct access, for verification against CRF entries when Chiesi or its representatives visit the investigational site. All information obtained from source documents is to be kept in strict confidence.

14.8.3 Case Report Forms

All site-generated study data is entered into an electronic Case Report Form (eCRF) via an electronic data capture (EDC) system. The eCRFs are not used as the primary method for collection of study data and eCRF entries must be supported by source documents maintained by the Investigator. Only those site staff so authorized at the initiation of the study may enter data into an EDC system.

The Investigator is responsible for the completeness and accuracy of all eCRF data as certified by the Investigator's dated electronic signature within the EDC at the completion of the study.

14.8.4 Access to Study Records

The Investigator makes available, via direct access, all records pertaining to the conduct of this study to Chiesi and its representatives, and auditors from domestic and foreign regulatory authorities to facilitate monitoring visits and study audits.

14.8.5 Records Retention

The Investigator retains the records of the study for 15 years, or for 2 years following the closure of the study. Chiesi will notify Investigators when retention of study records is no longer required. All study records must be maintained in a safe and secure location that allows for timely retrieval, if needed.

Study records that must be retained include storage media containing eCRF data, signed informed consents, regulatory documentation, source documents, clinic charts, medical records, laboratory results, radiographic reports, and other study-specific documentation.

Should the Investigator relocate or retire or should there be any changes in the archival arrangements for the study records, Chiesi must be notified. The responsibility for maintaining the study records may be transferred to another suitable individual, but Chiesi must be notified of the identity of the individual assuming responsibility for maintaining the study records and the location of their storage. If no other individual at the investigational site is willing to assume this responsibility, Chiesi assumes responsibility for maintaining the study records.

14.9 Publication Policy

Publication of study data is addressed in the Clinical Study Agreement between Chiesi and Investigator(s) and/or Institution(s).

14.10 Financing and Insurance

Financing and Insurance are addressed in the Clinical Study Agreement between Chiesi/designee and the Investigator and/or Institution.

15 INVESTIGATOR AGREEMENT

I have reviewed Chiesi Farmaceutici's Protocol CLI-06814AA1-01 entitled "Single Arm, Open-Label, Multicenter, Registry Study of Revcovi (Polyethylene Glycol Recombinant Adenosine Deaminase [PEG-rADA]) Treatment in ADA-SCID Subjects Requiring Enzyme Replacement Therapy" and agree that it contains all the information necessary to conduct the study as required. I will conduct the trial in accordance with the principles of ICH Good Clinical Practice and the Declaration of Helsinki.

I will maintain as confidential all written and verbal information provided to me by Chiesi, including but not limited to, the protocol, case report forms, material supplied at investigator meetings, minutes of teleconferences, etc. Such material will only be provided as necessary to site personnel involved in the conduct of the trial, the IRB or IEC, or local regulatory authorities.

I will obtain written informed consent from each prospective trial subject or each prospective trial subject's legal representative prior to conducting any protocol-specified procedures. The consent form used will have the approval of the local IRB or IEC.

I will maintain adequate source documents and record all observations, treatments, and procedures pertinent to registry subjects in their medical records. I will accurately complete the electronic case report forms in a timely manner. I will ensure that my facilities and records are available for inspection by representatives of Chiesi, the local IRB or IEC or local regulatory authorities. I will ensure that my staff and I are available to meet with representatives of Chiesi during regularly scheduled monitoring visits.

My signature below indicates that my participation in this clinical study affirms the disclosure of any conflicts of interest for me or my sub-investigators with the study.

Investigator's Name (Print)

Investigator's Signature **Date**

16 REFERENCES

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Appendix 1: Suggested Schedule of Assessments for Adagen-Transitioning Subjects

	Enrollment	TW = Treatment Week			TM = Treatment Month						
Procedure	**ENR**	**TW 4 (±1 wk)**	**TW 8 (±1 wk)**	**TW 12 (±1 wk)**	**TM 6 (±3 wk)**	**TM 9 (±3 wk)**	**M 12 (±3 wk)**	**TM 15 (±3 wk)**	**M 18 (±3 wk)**	**M 21 (±3 wk)**	**TM 24/ DC (±3 wk)**
Informed assent/consent	X										
Demographics	X										
Medical history (including ADA-Mutation results if available)	X										
Inclusion/exclusion criteria	X										
Physical examination (including height and weight)	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Safety Laboratory Assessments (if available)	X	X	X	X	X	X	X	X	X	X	X
Total trough erythrocyte dAXP	X		X						X		X
Trough Plasma ADA activity[1]	X	X	X	X	X	X	X	X	X	X	X
B-/T-/NK-lymphocyte subset	X			X	X	X	X	X	X	X	X
Quantitative immunoglobulins	X				X		X		X		X
Immunogenicity[2]	X	X	X	X	X	X	X	X	X	X	X
Quality of Life	X			X[3]	X	X[3]	X		X		X
Adverse events		X	X	X	X	X	X	X	X	X	X
Potential ADA inhibitors and Ig replacement therapy	X	X	X	X	X	X	X	X	X	X	X
Revcovi Dosing and Compliance	X	X	X	X	X	X	X	X	X	X	X

[1] If a decline in ADA activity levels persists, immune function and clinical status will be monitored more closely, and precautions will be taken to minimize the risk of infection. Evaluation of immune function includes B-/T-/NK-lymphocyte subsets, quantitative immunoglobulins, and adequate immune reconstitution in accordance with the Revcovi Package insert and per Investigator discretion.

[2] Immunogenicity should be assessed in accordance with the Revcovi Package Insert.

Survival will be monitored throughout the study; for subjects undergoing gene therapy or stem cell transplant, survival will be assessed at 1 month and 6 months post final dose.

[3] The Pediatric Quality of Life Inventory (PedsQL) will be performed for infants aged 1 to 12 months only. All subjects up to age 18 years will be assessed at all other indicated visits using the age specific PedsQL. Subjects over 18 years will be assessed using the SF36 and Primary Antibody Deficiency Quality of Life Questionnaire (PADQOL). Quality of life assessment data will be collected prospectively for 24 months after starting Revcovi from study participants via scripted phone calls by the study call center and QoL responses will be entered directly into the EDC system. **Note -** The listing for the schedule of assessments provides a template for reporting of monitoring and is not a rigid

requirement. Clinicians should individualize the schedule of monitoring to assess the effect of Revcovi on trough plasma activity of ADA, erythrocyte dAXP, and immune function (lymphocyte counts, lymphocyte subsets and immune response) while balancing the risk of phlebotomy and subject visit burden.

Appendix 1: Suggested Schedule of Assessments for Adagen-Transitioning Subjects (cont.)

		TM = Treatment Month							HSCT or HSC-GT	
Procedure	**TM 27 (±3 wk)**	**TM 30 (±3 wk)**	**TM 33 (±3 wk)**	**TM 36 (±3 wk)**	**TM 39 (±3 wk)**	**TM 42 (±3 wk)**	**TM 45 (±3 wk)**	**TM 48/ DC (±3 wk)**	**Month 1**	**Month 6**
Informed assent/consent										
Demographics										
Medical history (including ADA-Mutation results if available)										
Inclusion/exclusion criteria										
Physical examination (including height and weight)	X	X	X	X	X	X	X	X		
Vital signs	X	X	X	X	X	X	X	X		
Concomitant medications	X	X	X	X	X	X	X	X		
Safety Laboratory Assessments (if available)	X	X	X	X	X	X	X	X	X	X
Total trough erythrocyte dAXP		X		X		X		X		
Trough Plasma ADA activity[1]	X	X	X	X	X	X	X	X		
B-/T-/NK-lymphocyte subset	X	X	X	X	X	X	X	X		
Quantitative immunoglobulins		X		X		X		X		
Immunogenicity[2]	X	X	X	X	X	X	X	X		
Quality of Life										
Adverse events	X	X	X	X	X	X	X	X	X	X
Potential ADA inhibitors and Ig replacement therapy	X	X	X	X	X	X	X	X		
Revcovi Dosing and Compliance	X	X	X	X	X	X	X	X		

Subjects undergoing HSCT or HSC-GT will be followed one month and again at six months after final Revcovi dose to assess for AEs and survival.

Appendix 2: Suggested Schedule of Assessment for Adagen-Naïve Subjects

	Enrollment	TW = Treatment Week					
Procedure	**ENR**	**TW 2 (±3 d)**	**TW 4 (±3 d)**	**TW 6 (±3 d)**	**TW 8 (±3 d)**	**TW 10 (±3 d)**	**TW 12 (±3 d)**
Informed Assent / Consent	X						
Demographics	X						
Medical History	X						
Inclusion / Exclusion Criteria	X						
Physical Examination (including height and weight)	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
Safety Laboratory Assessments (if available)	X	X	X	X	X	X	X
Total Trough Erythrocyte dAXP	X	X	X	X	X	X	X
Trough Plasma ADA activity[1]	X	X	X	X	X	X	X
B-/T-/NK-lymphocyte subset	X		X		X		X
Quantitative immunoglobulins	X		X		X		X
ADA-Mutation analysis (if available)	X						
Immunogenicity[2]	X	X	X	X	X	X	X
Quality of Life	X						X[3]
Adverse events		X	X	X	X	X	X
Potential ADA inhibitors and Ig replacement therapy	X	X	X	X	X	X	X
Revcovi Dosing and Compliance	X	X	X	X	X	X	X

Appendix 2: Suggested Schedule of Assessment for Adagen-Naïve Subjects (continued)

	TM = Treatment Month										
Procedure	**TM 4 (±1 wk)**	**TM 5 (±1 wk)**	**TM 6 (±1 wk)**	**TM 7 (±1 wk)**	**TM 8 (±1 wk)**	**TM 9 (±1 wk)**	**TM 12 (±3 wk)**	**TM 15 (±3 wk)**	**TM 18 (±3 wk)**	**TM 21 (±3 wk)**	**TM 24 /DC (±3 wk)**
Physical Examination (including height and weight)	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Safety Laboratory Assessment (if available)	X	X	X			X	X	X	X	X	X
Total Trough Erythrocyte dAXP					X		X		X		X
Trough Plasma ADA activity[1]			X			X	X	X	X	X	X
B-/T-/NK-lymphocyte subset	X	X	X	X	X	X	X	X	X	X	X
Quantitative immunoglobulins			X				X		X		X
Immunogenicity[2]	X	X	X			X	X	X	X	X	X
Quality of Life			X			X[3]	X		X		X
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Potential ADA inhibitors and Ig replacement therapy	X	X	X	X	X	X	X	X	X	X	X
Revcovi Dosing and Compliance	X	X	X	X	X	X	X	X	X	X	X

[1] If a decline in ADA activity levels persists, immune function and clinical status should be monitored more closely, and precaution will be taken to minimize the risk of infection. Evaluation of immune function includes B-/T-/NK-lymphocyte subsets, quantitative immunoglobulins, and adequate immune reconstitution in accordance with the Revcovi Package insert and per Investigator discretion.

[2] Immunogenicity should be assessed in accordance with the Revcovi Package Insert.

Survival will be monitored for the duration of the study; for subjects undergoing gene therapy or stem cell transplant, survival will be assessed at 1 month and 6 months post final dose.

[3] The Pediatric Quality of Life Inventory (PedsQL) will be performed for infants aged 1 to 24 months and for toddlers aged 2 to 4 years only using the age-specific inventory. All subjects up to age 18 years will be assessed at all other indicated visits using the age-specific PedsQL. Subjects over 18 years will be assessed using the SF-36 and Primary Antibody Deficiency Quality of Life Questionnaire (PADQOL). Quality of life assessment data will be collected prospectively for 24 months after starting Revcovi from study participants via scripted phone calls by the study call center and QoL responses will be entered directly into the EDC system.
Note - The listing for the schedule of assessments provides a template for reporting of monitoring and is not a rigid requirement. .Clinicians should individualize the schedule of monitoring to assess the effect of Revcovi on trough plasma activity of ADA, erythrocyte dAXP, and immune function (lymphocyte counts, lymphocyte subsets and immune response) while balancing the risk of phlebotomy and subject visit burden.

Appendix 2: Suggested Schedule of Assessment for Adagen-Naïve Subjects (continued)

		TM = Treatment Month							HSCT or HSC-GT	
Procedure	**TM 27 (±3 wk)**	**TM 30 (±3 wk)**	**TM 33 (±3 wk)**	**TM 36 (±3 wk)**	**TM 39 (±3 wk)**	**TM 42 (±3 wk)**	**TM 45 (±3 wk)**	**TM 48/ DC (±3 wk)**	**Month 1**	**Month 6**
Informed assent/consent										
Demographics										
Medical history (including ADA-Mutation results if available)										
Inclusion/exclusion criteria										
Physical examination (including height and weight)	X	X	X	X	X	X	X	X		
Vital signs	X	X	X	X	X	X	X	X		
Concomitant medications	X	X	X	X	X	X	X	X		
Safety Laboratory Assessments (if available)	X	X	X	X	X	X	X	X	X	X
Total trough erythrocyte dAXP		X		X		X		X		
Trough Plasma ADA activity[1]	X	X	X	X	X	X	X	X		
B-/T-/NK-lymphocyte subset	X	X	X	X	X	X	X	X		
Quantitative immunoglobulins		X		X		X		X		
Immunogenicity[2]	X	X	X	X	X	X	X	X		
Quality of Life										
Adverse events	X	X	X	X	X	X	X	X	X	X
Potential ADA inhibitors and Ig replacement therapy	X	X	X	X	X	X	X	X		
Revcovi Dosing and Compliance	X	X	X	X	X	X	X	X		