Chiesi Farmaceutici S.p.A.

Statistical Analysis Plan

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

Protocol / Study Number: CLI-06814AA1-01

Sponsor's Name: Chiesi Farmaceutici S.p.A.

Study Drug: Revcovi™

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LIST OF ABBREVIATIONS/ DEFINITION OF TERMS

Abbreviation	Term
ADA	adenosine deaminase
ADA-SCID	ADA-deficient SCID
AE	adverse event/experience
AT	As-Treated
BLA	Biologics License Application
BMI	Body Mass Index
dAXP	deoxyadenosine nucleotide
eCRF	Electronic Case Report Form
ERT	Enzyme Replacement Therapy
Ig	immunoglobulin
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
h	hour
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
PEG	polyethylene glycol
PEG-ADA	PEGylated ADA, Adagen®
PEG-rADA	PEGylated recombinant ADA, EZN-2279
rADA	recombinant ADA
SAE	serious adverse event/experience
SAP	Statistical Analysis Plan
SCID	severe combined immunodeficiency
SOC	System organ class
UBC	United BioSource Corporation
WHO Drug	World Health Organization dictionary of medical codes

1. INTRODUCTION

Leadiant Biosciences, Inc. (Leadiant Biosciences) has 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).

This Statistical Analysis Plan (SAP) is intended to provide a detailed description of the statistical analyses that will be performed for Study CLI-06814AA1-01. Analyses described in this SAP are based on protocol Version 4.0, dated 05Aug2021.

2. STUDY OBJECTIVES

2.1 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 and/or clinical assessment by the treating physician. The study will include Adagen-naïve patients started on de novo enzyme replacement therapy (ERT) with Revcovi or converted from Adagen to Revcovi, over the course of 2 years and continued to be followed until the last enrolled patient has 2 years of follow up. Patients who are expected to receive 3 to 4 months of ERT prior to proceeding to hematopoietic stem cell transplantation (HSCT) or gene therapy will also be included in the study.

2.2 Associated Endpoints

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

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 SF 36 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. Quality of life 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.

3. STUDY DESIGN

3.1 General Design and Study Procedures

Protocol CLI-06814AA1-01 is designed as a single arm, open-label, multicenter registry study. The study will include ADA-SCID subjects requiring Revcovi as Enzyme Replacement Therapy (ERT). This is inclusive of:

- adults currently receiving chronic ERT with Adagen®; and transitioned/transitioning to Revcovi
- infants diagnosed via new-born screening and/or definitive testing for ADA deficiency prescribed Revcovi;
- subjects 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.

Patients for whom written informed consent/assent is obtained will be assigned a number and undergo enrollment procedures. The date of ICF signature is considered the date of enrollment into the registry. Subjects enrolled in the registry study should have initial, trough erythrocyte dAXP levels and plasma ADA activity measurements collected prior to start of Revcovi. 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 (Table 1 and Table 2) and in conformity to local standard of care practice.

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), but quality of life will be assessed throughout the treatment period up to 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.

Full details are found in the protocol. Visit-specific study activities are outlined in Table 1 and Table 2. The schedule of assessments in both tables is the most rigorous suggested by the prescriber information – individual schedules for each subject are a matter of best practice and standard of care determined by the provider.

Table 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)**	**TM 12 (±3 wk)**	**TM 15 (±3 wk)**	**TM 18 (±3 wk)**	**TM 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 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
Additional visits may be added for some patients, depending on the duration of the enrollment period.
DC = Discontinuation

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			

Table 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

Table 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
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 ofinfection. 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.
Additional visits may be added for some patients, depending on the duration of the enrollment period.
DC = Discontinuation

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		

3.2 Sample Size and Power Considerations

No formal sample size is calculated for this study. This registry study will enroll all eligible subjects over a minimum of 2 years.

3.3 Randomization

This is an open-label, single-arm study with no randomization.

3.4 Changes to the Design and Study Procedures Proposed in Protocol

None.

4. ANALYSIS POPULATIONS

The analysis populations used to assess the results of this study are described.

4.1 All Patients Population

The All Patients population will include all patients who signed informed consent.

4.2 As-Treated (AT) Population

The as-treated population, defined as all subjects who fulfill all eligibility criteria, had an informed consent form signed either by the patient or a legal guardian, are enrolled and receive at least one dose of Revcovi, will be the primary analysis set in all analyses. For the derivation of the AT population, the eligibility criteria will be used as collected in the eCRF.

5. GENERAL ANALYSIS CONSIDERATIONS

All analysis will be descriptive and no statistical hypothesis will be tested. Descriptive statistics for continuous variables will include number of observations (n), mean, standard deviation (SD), median, minimum (min), and maximum (max); for categorial variables counts and percentages for each category. Ninety-five percent confidence intervals (CIs) will be calculated for the main outcome variables without adjustment for multiplicity to generalize the results to the general population. If not otherwise noted, confidence intervals for continuous variables will be based on normal distribution, for categorial variables on Clopper-Pearson (Clopper and Pearson 1934). Confidence intervals for Poisson distributions will be calculated by the method of Ulm (Ulm 1990).

Time to event analyses will be performed by the Kaplan-Meier method (Kaplan and Meier 1958). Confidence intervals for the median survival time will be calculated based on the method of Brookmeyer and Crowley (Brookmeyer and Crowley 1982) after log-log transformation.

All analyses will be performed by subject status (Adagen-Naïve subject, Adagen-Transitioning subject, or STP-2279-002 participant) and overall. Subject status is as collected on the Adagen/Revcovi Treatment page in the eCRF. There is a different recommended visit schema for the Adagen naïve subjects and the Adagen transitioning subjects (Table 1 and Table 2). However, a data review revealed that the timing of the assessments is not following the suggested visit schema. Therefore, the slotting schema within each subject status will be uniform for all assessments. All assessments will be slotted to the closest visit suggested for the Adagen transitioning or Adagen naïve subjects, respectively, regardless of whether or not the specific assessment is recommended for this visit, Participants of the STP 2279-002 study will be analyzed per the Suggested Schedule of Assessments for Adagen-Transitioning Subjects. Therefore, the visit windows will be specific for each type of subjects (see Section 13.3). All visits will be included in the overall column, regardless of whether or not the specific visit is analyzed for all type of subjects.

For the subjects transitioning from the STP-2279-002 study, the assessments during the STP-2279-002 study will be included in the data listings; however these assessments will not be included in the effectiveness or safety summary tables, because these results are already documented in the report of the STP-2279-002 study.

6. STUDY POPULATION SUMMARY AT SCREENING

The study population will be summarized based on the as-treated population. All summaries in this section describe the subjects at the time of enrollment. All summaries will be by subject status (Adagen-Naïve subject, Adagen transitioning subject or STP-2279-002 participant) and overall. All data of the as-treated population set will also be listed.

6.1 Changes to the Planned Population Summarization Proposed in Protocol

None.

6.2 Subject Disposition

Number of subjects who signed informed consent, number of subjects fulfilling all inclusion/exclusion questions (based on the criteria in the eCRF), subjects in the as-treated set, subjects who completed the study, subjects who underwent a transplantation, and subjects who discontinued from the study will be summarized using counts and percentages. Subjects who withdrew from the study will also be summarized using descriptive statistics by reason for withdrawal.

Subjects who do not fulfill the eligibility criteria will be listed with the reason for not fulfilling the eligibility criteria.

6.3 Demographics

The continuous variable of subject's age at study entry (reported start date of Revcovi in the CLI-06814AA1-01 study) will be summarized using descriptive statistics. The continuous variables of weight, height, and body mass index (BMI) will be summarized using descriptive statistics for the last available data prior to or on the date of reported start date of Revcovi in the CLI-06814AA1-01 study. The categorical variables of subject's gender, race, and ethnicity will be summarized using counts and percentages for each category. Missing categories will be presented if applicable.

6.4 Disease Background and History

Disease background will also be summarized at screening by subject status and overall. Missing categories will be presented if applicable. Disease background includes age at first diagnosis of ADA-SCID (years), time from first diagnosis of ADA-SCID to start of Revcovi treatment in the STP 2279-002 study, if applicable, (months), and availability of ADA-SCID mutations. All parameters will also be listed. Missing categories will be presented if applicable.

6.5 Medical History

Medical history at screening will be listed, but not summarized.

6.6 Prior ADA-SCID Treatment excluding ERT

The number and percentages of patients who received prior ADA-SCID treatment (excluding ERT) will be summarized by type of treatment and overall. Free text for other treatments will be listed but not summarized.

6.7 Prior ERT Treatments

Prior ERT medications (Adagen treatment) will be summarized for all subjects transitioning from Adagen to Revcovi and for the STP 2279-002 subjects. The following parameters will be summarized: duration of Adagen treatment (i.e. last dose – first dose +1 day), units per administration, administration frequency, total weekly dose (as reported on the eCRF) and calculated total weekly dose per kg body weight for the prescribed and actual dose. For subjects who were treated according to the prescription, actual dose will be derived from the prescribed dose. The number and percentages of subjects who stopped Adagen treatment prior to the first dose will also be reported together with summary statistics for the time from the last dose of Adagen until the first dose of Revcovi. For the STP 2279-002 subjects, the duration of treatment with Revcovi in the STP 2279-002 study (last dose – first dose of Revcovi in the STP 2279-002 study + 1 day) will be summarized. All prior treatments with Adagen will also be presented in a data listing.

6.8 Physical Examination

Physical examination results at screening will be reported as medical history and will be analyzed and presented as such.

6.9 Protocol Deviations

A full list of protocol deviations will be presented in the clinical study report. Because this is a registry with no scheduled assessments or planned treatments, on-study protocol violations are restricted to administrative and operational deviations (e.g. delayed reporting of an SAE or transmission of clear names together with SAE reports). Protocol deviations will be listed but not summarized.

7. EFFICACY ANALYSIS

The as-treated (AT) population will be used for all efficacy analyses. All efficacy data will also be listed.

All efficacy analyses will be descriptive (i.e., no statistical testing and no reported p-values), although 95% confidence intervals (CI) will be presented to show the variability of estimates as indicated below.

7.1 Changes to the Planned Efficacy Analysis Proposed in Protocol

None.

7.2 Efficacy Endpoint and Analysis

7.2.1 Biochemical assessments

Biochemical assessments to adjust Revcovi dosing throughout the study include trough plasma dAXP and ADA activity, which will be assessed from trough plasma samples obtained during the study. Summary statistics for the absolute value and the changes from baseline will be calculated for plasma dAXP and ADA activity for all time points. 95% CIs for the means will be calculated for each time point based on the normal distribution function for the actual values and the changes from baseline. For subjects transitioning from the STP 2279-002 study, baseline is defined as the last available value prior to the initiation of Revcovi in the STP 2279-002 Study. The mean and its standard error (SE) for the plasma dAXP and ADA activity for all suggested time points will be plotted by the subject status. The number and percentages of subjects (including 95% CIs) maintaining an erythrocyte dAXP concentration of $\leq 0.02\mu mol/ml$ will be calculated for each time point. Also, the number and percentages of subjects (including 95% CIs) maintaining a trough ADA activity of $\geq 30\mu mol/h/ml$ will be calculated for each time point.

7.2.2 Immune status assessments

Immune status will be assessed by the following end points:

- 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).

The absolute values and the changes from baseline for all endpoints for immune status will be summarized by descriptive statistics for all time points. 95% CIs for the means will be calculated for each time point based on the normal distribution function for the actual values and the changes from baseline. Baseline for the STP 2279-002 transitioning subjects will be handled the same as for the biochemical assessments.

It is recommended that Investigators consider a measurement of immune response (PHA stimulation or equivalent). These data will be listed but not summarized.

7.2.3 Clinical status

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

Infections will be extracted from the adverse event dataset as all reported adverse events where the question “Is this event an Infection?” is answered by “Yes” and the Classification is reported as “Clinically documented” or “Microbiologically documented”. Events classified as “Unknown” will not be included in the analysis of the infections. However, events classified as Unknown will be included in the analysis of the adverse events as part of the safety analysis (see section 8.2). The following time periods will be analyzed:

1. The year prior to treatment start with Revcovi (study day -365 to -1)

2. From Treatment initiation until 1 year after treatment initiation with Revcovi (Study day 1 to 365)
3. From one to 2 years after treatment initiation with Revcovi (Study day 366 to 730).
4. From 2 to 3 years after treatment initiation with REVCOVI (Study days 731 to 1095)
5. From 3 to 4 years after treatment initiation with REVCOVI (Study days 1096 to 1461).
6. From 4 to 5 years after treatment initiation with REVCOVI (Study days 1462 to 1826).
7. From 5 to 6 years after treatment initiation with REVCOVI (Study days 1827 to 2191).
8. From 6 to 7 years after treatment initiation with REVCOVI (Study days 2192 to 2556).
9. From 7 to 8 years after treatment initiation with REVCOVI (Study days 2557 to 2921).
10. From 8 to 9 years after treatment initiation with REVCOVI (Study days 2922 to 3286).
11. At any time after treatment initiation with REVCOVI (Study day 1 onwards)

For the STP-2270-002 subjects, the observational period for infections and hospitalizations after treatment initiation starts at the first dose of REVCOVI in the CLI-06814AA1-01 study. Infections and hospitalizations occurring during the STP-2279-002 study will not be included in the summary tables for the CLI-06814AA1-01 study.

The time periods will be defined as follows:

The year prior to treatment start with Revcovi will be defined as study day -365 to study day -1. For subjects younger than 1 year of age at the time of treatment initiation with Revcovi, it will be defined as the time period from the date of birth until study day -1 (time period calculated as date of first dose of Revcovi - date of birth + 1 day).

The end date of the time periods 1, 2, 3, 4, 5, 6, 7, 8, and 9 years after treatment initiation of Revcovi, respectively, will be defined as the earliest of the following events:

- End of time period (study day 365, 730, 1095, 1461, 1826, 2191, 2556, 2921, and 3286 respectively)
- Last date of treatment with Revcovi + 30 days
- Study completion date
- Study discontinuation date

- Date of death
- Date of transplantation

Infections occurring more than 30 days after the last dose of Revcovi will not be included in the calculation of the incidence rates, but will be included in the data listings and flagged.

The following analyses will be performed for the infections for each time period defined above:

- Number of events, number and percentages of affected subjects by SOC and PT. The denominator for the calculation of the percentages is the number of subjects with an observational period of 1 day or more in the respective analysis period, i.e. if the end date as defined above is not prior to the start date of the respective analysis period. .
- Incidence rate of infections (in number of infections per year). The incidence rate will be based on the number of events, not on the number of affected subjects. 95% CIs will be calculated for the incidence rates by the method of Ulm, assuming a Poisson distribution. The total observational period will be defined as the sum of the time periods for each subject from the start until the end date of the respective time period as defined above (end date - start date + 1 day).

For both analyses, the infections will be slotted to the analysis periods based on the onset date of the adverse event.

The number of hospitalizations will be analyzed similarly as the infections, i.e. number of hospitalizations, number and percentages of hospitalized subjects, incidence rates of hospitalizations for the time periods described above. The duration of hospitalizations will be described by descriptive statistics for continuous variables based on the number of hospitalizations. Subjects who are hospitalized in one analysis period and discharged from the hospital in the subsequent analysis period will be counted for the full hospitalization period (i.e. from admission to discharge) in the analysis period where they were hospitalized. All hospitalizations will also be presented in a data listing.

For subjects <18 years of age, height-for age and weight-for age and for patients between 24 months and 18 years of age, BMI-for age will be presented by z-scores at baseline and each intermediate collection time-point. Z-scores will be calculated programmatically based on reported age, gender, height and weight.[1] Z-scores and changes from baseline of z-scores to each visit (at which height and weight are assessed) will be summarized using descriptive statistics.

1 http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm

Overall survival will be analyzed by a Kaplan-Meier analysis. Kaplan-Meier survival curves will be plotted by subject status. Subjects who are alive at the end of the observational period will be counted as a censored observation. Observational period is the time from initiation of Revcovi until the date of study completion or study discontinuation (calculated as: date of study completion or study discontinuation – date of treatment initiation + 1 day) or from treatment initiation until the date of death, for subjects who die (calculated as date of death – date of treatment initiation + 1 day). Date of study completion or date of study discontinuation will be used as reported on the Patient Disposition page in the eCRF. For subjects transitioning from the STP-2279-002 study, overall survival will be calculated based on the date of the first dose of Revcovi in the STP-2279-002 study. If it is known that the subject died, but the date of death is unknown, it will be assumed that the subject died the day after their last assessment (whatever has been entered as last available date to the database, e.g. date of laboratory value, onset or resolution date of an AE, date of study discontinuation).

8. SAFETY ANALYSIS

The as-treated population will be used for all of the safety analyses. All safety data will be listed.

8.1 Changes to the Planned Safety Analysis Proposed in Protocol

None.

8.2 Adverse Events and Other Complications

As part of this registry, only infections, clinically meaningful laboratory abnormalities (except infections) and Revcovi related adverse events will be recorded in the eCRF. A treatment-emergent AE will be defined as an AE with an onset date at or after the reported start date of Revcovi in the CLI-06814AA1-01 study and no later than 30 days after the last dose of Revcovi. All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1 or the most recent version prior to database lock. Summaries will be presented for all treatment-emergent adverse events (overall and by severity), adverse events determined by the investigator to be treatment-related (overall and by severity), serious adverse events (SAEs), adverse events causing discontinuation from Revcovi, and non-serious AEs. In addition to being summarized as adverse events, infectious complications and hospitalizations are considered efficacy measures as summarized in Section 7.2.3.

The frequency of adverse events will be summarized using descriptive statistics by system organ class (SOC), preferred term and subject status. Subjects are counted only once in each SOC category, and only once in each preferred term category. Treatment-related adverse event summaries will include adverse events with missing relationship to study drug. For the summaries by severity, subjects with multiple events are counted only once at the greatest non-missing severity. If all are of missing severity grade, then the AE term (SOC or PT) will be included in “Missing” severity category. Adverse events missing the flag indicating serious will be excluded from the summary of serious adverse events but included in the summary of non-serious adverse events. The total number of adverse events and serious adverse events and the corresponding yearly rates will also be reported.

Listings for all adverse events, deaths, serious adverse events and adverse events leading to study drug discontinuation will be presented. AEs from STP-2279-002 subjects with an onset date prior to the first documented dose of Revcovi in the CLI-06814AA1-01 study and a resolution date after the reported start date of Revcovi in the CLI-06814AA1-01 study or an outcome of ongoing, will be included in the AE listings but not in the summary tables.

8.3 Clinical Laboratory Tests

Summary statistics for chemistry, hematology, and urinalysis laboratory tests will be presented at baseline, and for each visit. Laboratory tests results and changes from baseline to each visit will be summarized using descriptive statistics. For the STP 2279-002 subjects, changes will be calculated from the last non-missing value prior to the first dose of Revcovi in the STP 2279-002 Study.

Listings for laboratory data will be presented identifying clinically significant abnormal results and out-of-normal range values. Clinically significant abnormal results and results out of normal range will be identified by the status: Abnormal, NCS will be classified as 'Out of normal range result'; Abnormal, CS will be classified as 'Clinically significant abnormal results'; and normal status and missing status will be classified as normal result.

Results of pregnancy tests will be listed, but not summarized. The values of positive tests in the urine analysis will also be listed but not summarized.

8.4 Vital Signs

Summary statistics for vital signs will be presented for all suggested visits. Vital signs results and changes from baseline to each visit will be summarized using descriptive statistics. For the STP 2279-002 subjects, changes from baseline will be handled in the same way as for the laboratory values.

Listings for vital signs will be provided.

8.5 Physical Examination

Physical examination findings will be reported as medical history or adverse events and analyzed as such.

8.6 Procedures

Procedures performed after the first dose of Revcovi will be listed but not summarized.

8.7 Study Drug Administration

Study drug administration for Revcovi will be summarized by subject status based on the prescribing data for Adagen/Revcovi Treatment. For subjects transitioning from the STP-2279-002 study, study drug administration will be summarized from the first dose of Revcovi in the CLI-06814AA1-01 study until the end of the CLI-06814AA1-01 registry.

Duration of treatment (months treated) is the number of days on treatment based on the first and last days of treatment with the study drug (last day of study drug – first day of study drug + 1)/30.4375. For subjects who are still taking Revcovi at the end of the observational period,

the duration will be counted until the date of study completion or study discontinuation, respectively, as reported on the study disposition page. Duration of treatment will be summarized by descriptive statistics.

The number of doses administered will be summarized by descriptive statistics. The number of doses will be calculated by the number of weeks x number of times per week for each treatment period and summed for each subject.

Frequency statistics will be calculated for the number of subjects with dose modifications and for subjects with dose omissions/delays will be calculated. A dose omission/delay will be defined as a dose interruption of 8 days or more. The duration of the dose interruption will be calculated as start of the subsequent treatment period – end date of the previous treatment period + 1 day. The duration of dose interruptions will be summarized on subject level, i.e. multiple dose interruptions will be summed on subject level and summarized by descriptive statistics. Duration of dose interruptions will be calculated as an absolute value and as percentages of the duration of treatment.

The total weekly dose of Revcovi (in mg/kg) will be summarized for each suggested visit. This is defined as the dose on the targeted study day. If a new dose is started on the targeted study day, the new dose is used as weekly dose. The weekly dose is calculated as dose per administration (mg) x number of times per week.

Prescribing data of Revcovi will also be presented in a data listing. Revcovi administration data from the subject diary will be listed but not summarized.

8.8 Immunogenicity

The percentage of subjects positive for each type of antibody will be summarized for each visit. Denominator for the calculation is the number of subjects in the AT population. Subjects who were tested as positive will be counted as positive for all subsequent visits. All immunogenicty data will also presented in a comprehensive data listing.

Additionally, the number and percentages of subjects who are positive at any point in time and becomes negative later will be calculated. Subjects who resolve positivity with or without medication will be presented also in a separate data listing.

Data regarding blood sample collections for antibody titers, and antibody levels for any positive tests, will be listed but not summarized.

8.9 Concomitant Medication of Interest

Concomitant medications of interest are all anti-infectives which are administered after the reported start date of Revcovi in the CLI-06814AA1-01 Study, regardless of when they were started. All concomitant medications will be coded using the WHO Drug, Version 2020 Q1 or most recent version prior to database lock. The frequency of concomitant medications

will be summarized using descriptive statistics by therapeutic class (ATC level 2) and preferred term. Subjects are counted only once in each therapeutic class category, and only once in each preferred term category.

9. QUALITY OF LIFE ANALYSIS

The following quality of life (QoL) questionnaires will be administered prior and during the treatment with Revcovi: 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 questionnaire and the PADQoL-16 will be administered at the following time points:

Baseline (prior to first dose of Revcovi)

3-months

6 months

9 months

12 months

18 months

24 months

A data review revealed that only few QoL data has been captured during the study. Therefore, QoL data collected will only be listed but not summarized.

Changes for QoL data will only be summarized for Adagen naïve and Adagen transitioning patients.

PedsQL

The PedsQL will be scored[2] to the 4 scales physical functioning, emotional functioning, social functioning, and school functioning. For children 1-12 months and 13 to 24 months, the school functioning scale is replaced by the cognitive functioning scale. Two summary scores (total score and psychological health summary score) will also be calculated and analyzed. All scales will be transformed to a scale from 0 to 100 where 100 is the best possible value. The actual values and the changes from baseline will be listed for all analysis time points.

SF-36 Version 1.0

The SF 36-questionnaire is a 36-item questionnaire which will be condensed to 8 scores (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health). All scores will be normalized to a scale from 0 to 100.

PADQoL-16

The PADQoL-16 will be scored to 7 subscores (general health, vitality, physical functioning, role (physical), role (emotional), mental health, social functioning) and one total score. The exact scoring algorithm is summarized in Appendix B. All scales will be standardized to a range from 0 to 100. The actual values and their changes from baseline will be listed for all analysis time points.

10. INTERIM ANALYSES

An interim analysis was be performed 24 months after the first subject is enrolled. The following data has been presented in the interim analysis:

- Subject disposition
- Demography and other baseline characteristics
- Administration of Revcovi (until the data cut date)
- Biochemical assessments of trough plasma dAXP and ADA activity
- Prior ERT treatment
- Lymphocytes subsets
- Quantitative immunoglobulin
- Hospitalizations and infections
- Adverse events

11. PHARMACOKINETIC ANALYSIS

N/A.

12. STATISTICAL SOFTWARE

All data listings, summaries, and statistical analyses will be generated using SAS® Version 9.4 or higher.

13. RULES AND DEFINITIONS

13.1 Timing of Analyses

One interim analysis has been performed approximately 24 months after the first subject was enrolled in the registry. The final analysis will be performed after database lock.

13.2 Assignment of Study Days

For the purposes of data listings and summaries, "Study Day" will be calculated relative to the reported first dose of Revcovi, which is for the STP2270-002 patients, the reported date of the first dose of Revcovi in the STP-2279-002 study (i.e., date of interest – reported date of first dose of Revcovi). One day will be added if this difference is ≥ 0, so that the first dose of study medication is considered "Study Day 1." The day prior to the first dose of study medication is considered "Study Day -1". For analysis purposes, there will be no "Study Day 0".

13.3 Baseline and Assignment to Suggested Study Visits

For Adagen-naïve patients and Adagen-transitioning patients, baseline will be defined as the last measurement for a variable with a non-missing value prior or on the treatment start date with Revcovi in this study (CLI-06814AA1-01). For STP 2279-002 subjects, the baseline will be defined as the last measurement for a variable with a non-missing value prior or on the treatment start date with Revcovi in STP 2279-002. At Study Day 1, it is assumed that all assessments are performed prior to the application of the first dose of Revcovi. However, adverse events with the same onset date as the start date of Revcovi will be assumed to be post-treatment and counted as treatment-emergent AEs.
Assessments will be 'slotted' to the treatment visits as described below. Reference date for all visits will be the start date of Revcovi (Study Day 1). Study Day 1 for the subjects transitioning from the STP-2279-002 study will be the reported start date of Revcovi in the STP-2279-002 study. Depending on the subject status (Adagen-Naïve subject or Adagen transitioning subject), the suggested visit schedule is different for the first 9 treatment months. For the Adagen-Naïve subjects, there are more suggested visits compared to the Adagen transitioning subjects. Participants of the STP 2279-002 study will be analyzed according to the Schedule of Assessments for Adagen-Transitioning Subjects. The visit windows will be defined for all assessments as follows:

Adagen-Transitioning subjects

Suggested Visit	Targeted Study Day	Visit window (Study Day)
Enrollment/Baseline	Last available data prior or at Study Day 1	-∞ to 1
TW 4	30	2-45
TW 8	60	46-75

TW 12	91	76-136
TM 6	182	137-227
TM 9	273	228-319
TM 12	365	320-410
TM 15	456	411-501
TM 18	547	502-592
TM 21	638	593-684
TM 24	730	685-776
TM 27	822	777-867
TM 30	913	868-958
TM 33	1004	959-1049
TM 36	1095	1050-1141
TM 39	1187	1142-1232
TM 42	1278	1233-1324
TM 45	1370	1325-1415
TM 48	1461	1416-1506
TM 51	1552	1507-1597
TM 54	1643	1598-1689
TM 57	1735	1690-1780
TM 60	1826	1781-1871
TM 63	1917	1872- 1962
TM 66	2008	1963-2055
TM 69	2100	2056-2145
TM 72	2191	2146-2236
TM 75	2282	2237-2328
TM 78	2374	2329-2419
TM 81	2465	2420-2510
TM 84	2556	2511-2601
TM 87	2647	2602-2693
TM 90	2739	2694-2784
TM 93	2830	2785-2875
TM 96	2921	2876-2966
TM 99	3012	2967-3057
TM 102	3103	3058-3148
TM 105	3194	3149-3240
TM 108	3286	3241 or later
1-month post-transplantation*	30	1-60

6-month post-transplanation*	182	61 onwards

*Reference date for the 1- and 6-month post-transplantation visit is the date of the last dose of REVCOVI

Adagen-Naïve Subjects

Suggested Visit	Targeted Study day	Visit window
Enrollment/Baseline	Last available data prior or at Study Day 1	-∞ - 1
TW 2	15	1-22
TW 4	30	23-37
TW 6	45	38-52
TW 8	60	53-67
TW 10	75	68-83
TW 12	91	84-106
TM 4	121	107-136
TM 5	151	137-166
TM 6	182	167-197
TM 7	212	198-227
TM 8	242	228-257
TM 9	273	258-319
TM 12	365	320-410
TM 15	456	411-501
TM 18	547	502-592
TM 21	638	593-684
TM 24	730	685-776
TM 27	822	777-867
TM 30	913	868-958
TM 33	1004	959-1049
TM 36	1095	1050-1141
TM 39	1187	1142-1232
TM 42	1278	1233-1324
TM 45	1370	1325-1415
TM 48	1461	1416-1506
TM 51	1552	1507-1597
TM 54	1643	1598-1689
TM 57	1735	1690-1780
TM 60	1826	1781-1871
TM 63	1917	1872- 1962
TM 66	2008	1963-2055

TM 69	2100	2056-2145
TM 72	2191	2146-2236
TM 75	2282	2237-2328
TM 78	2374	2329-2419
TM 81	2465	2420-2510
TM 84	2556	2511-2601
TM 87	2647	2602-2693
TM 90	2739	2694 or later
TM 93	2830	2785-2875
TM 96	2921	2876-2966
TM 99	3012	2967-3057
TM 102	3103	3058-3148
TM 105	3194	3149-3240
TM 108	3286	3241 or later
1-month post-transplantation*	30	1-60
6-month post-transplanation*	182	61onwards

*Reference date for the 1- and 6-month post-transplantation visit is the date of the last dose of REVCOVI

For by-visit summaries, if there are multiple assessments in the specified time windows, the value most closely to the targeted time point will be used for the analysis. If 2 timepoints have the same distance from the targeted time point, the value after the targeted timepoint will be used for the analysis.

Missing data will not be imputed.

13.4 Efficacy Data Handling

Change from baseline to Week X in efficacy endpoints will be calculated from as:

- (Endpoint Value at Week X) – (Endpoint Value at Baseline), where baseline is defined as in Section 13.3.

13.5 Safety Data Handling

For the purposes of AE reporting, three time periods will be defined based upon the onset date of the AE:

- "Pre-treatment AEs" are AEs with onset dates < date of the reported start date of Revcovi in the CLI-06814AA1-01 study.

- "Treatment-emergent AEs" are AEs with onset dates ≥ date of the reported start date of Revcovi in the CLI-06814AA1-01 study and within 30 days following the date of the last dose of Revcovi.

- "Post-treatment AEs" are AEs with onset dates > 30 days after the date of the last dose of Revcovi within study CLI-06814AA1-01.

"Pre-treatment" and "Post-treatment" AEs are considered non-treatment-emergent AEs. For AEs with partially missing onset dates, an onset date is imputed as detailed in Section 14 (Programming Specifications). If an AE has a completely missing onset date, it is counted as a "treatment-emergent" event, unless the stop date is on or before the date of the first dose of study medication.

If relationship to study drug is missing, for analysis purposes it will be assumed to be related to study drug. For AEs which occur more than once within a time period (see above), the AE which is most related to study drug in that time period will be used in the summary of AEs by categories of relationship to study drug. Similarly, the AE with the maximum intensity in that time period will be used in the summary of AEs by categories of severity.

Concomitant medication of interest is any anti-infective medication applied on or after the reported start date of Revcovi in the CLI-06814AA1-01 study, including medication which was initiated prior to the reported start date of Revcovi in the CLI-06814AA1-01 study and continued until or after the reported start date of Revcovi in the CLI-06814AA1-01 study. Imputation rules for partially missing start/stop dates are described in Section 14 (Programming Specifications).

Change from baseline to Week X in safety endpoints will be calculated in the same way as for the efficacy end points.

14. PROGRAMMING SPECIFICATIONS

- The following algorithm should be used to estimate adverse event start dates for which only partial information is known. To conservatively assign start dates as early as possible, the first day on study drug is the reported start date of Revcovi in the CLI-06814AA1-01 study.

    - Missing day and month

        - If the year is the same as the year of first day on drug, then the day and month of the start date of drug will be assigned to the missing fields.
        - If the year is prior to the year of first day on drug, then December 31 will be assigned to the missing fields.
        - If the year is after the year of first day on drug, then January 01 will be assigned to the missing fields.

    - Missing month only

        - Treat day as missing and replace both month and day according to the above procedure.

    - Missing day only

        - If the month and year are the same as the year and month of first day on drug, then the start date of drug will be assigned to the missing day.
        - If the month and year are before the year and month of first day on drug, then the last day of the month will be assigned to the missing day.
        - If the month and year are after the year and month of first day on drug, then the first day of the month will be assigned to the missing day.

If the resultant imputed start date is after the AE stop date (and the AE stop date is complete), the imputed start date will be reset to the AE stop date.

- Adverse events with partially missing stop dates and the outcome is “Resolved” or “Resolved with sequelae” will have stop dates imputed as follows:

    - *year is missing* – date left missing.

    - *month is missing* – impute ‘December’.

    - *day is missing* – impute ‘last date of that month’.

- It is assumed that for the start and stop date of Revcovi, at least month and year are known. If day is missing, it will be imputed by the first of the month, if necessary.
- Partially missing start dates for Adagen pre-treatment (Adagen transitioning patients) will be imputed as follows:
    - Day is missing – impute 01 of the month
    - Day and month is missing: impute 01July.
- It is assumed that at least month and year is known for the QoL questionnaires, physical examinations, vital signs, and other laboratory data. If the day is missing, day will be imputed by the 15th of the month. If month and/or year is missing, the records will be excluded from all analyses.
- Partially missing dates for the diagnosis of ADA-SCID will be imputed as follows:
    - Year is missing – impute with date of birth
    - Month is missing and year is available – impute by 01 January. If the imputed date is prior to the date of birth, impute date of birth.
    - Day is missing – impute first day of month. If this imputed date is prior to the date of birth, impute date of birth.
- Complete dates for concomitant medications with missing or partially missing start dates will be imputed, if necessary, using the same algorithm described for adverse event onset dates. If the stop date is missing or partially missing and the "ongoing" variable is indicated as 'no', the imputation rule is applied <u>in the following order</u>:

    - *year is missing* - the medication will be considered to have been received at all periods after that period determined by the start date. Date is left missing.

    - *month is missing* - impute 'December'.

    - *day is missing* - impute 'last date of that month'.

- The following algorithm should be used, when necessary, to calculate a start date that is partially missing for medical history:

    - *missing day and month* - January 01 will be assigned to the missing fields.

    - *missing month only* - treat day as missing and replace both month and day according to the above procedure.
    - *missing day only* - assign first of the month to the missing day.
- Partially missing stop dates will be imputed as:

    - *year is missing*, no imputation. Date left missing.

- *month is missing and year is prior to year of first dose of study medication*- impute 'December'.

- *month is missing and year the same as the year of the first dose of study medication* – impute same month as in start date.

- *day is missing:* impute 'last date of that month'. If this results in a date ≥ the date of the first dose of study medication, impute day as the day prior to the first dose of study medication.

- Partial missing death dates will be imputed in the same way as adverse event start dates.

- Date imputations will be applied to the process of assigning study day and should be retained in the analysis datasets, but the data listings should display the original, partially missing dates.

- Adverse event summary tables will only include treatment-emergent AEs. However, listings will include all AEs (i.e., treatment-emergent and non treatment-emergent AEs) with the non treatment-emergent AEs flagged.

15. REFERENCES

Ballow, M., Conaway, M.R., Sriaroon, P., Rachid, R.A., Seeborg, F.O., Duff, C.M., Bonilla, F. A., Younger, E. M., Shapiro, R., and Burns, T.M. (2017) “Construction and validation of a novel disease-specific quality-of life instrument for patients with primary antibody deficiency disease (PADQOL-16)” J Allergy Clin Immunol. 139(6):2007–2010

Brookmeyer, R. and Crowley, J. (1982), “A Confidence Interval for the Median Survival Time,” Biometrics, 38, 29–41.

Clopper, C.; Pearson, E. S. (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 26 (4): 404–413.

Kaplan, E. L.; Meier, P. (1958). "Nonparametric estimation from incomplete observations". J. Amer. Statist. Assoc. 53 (282): 457–481.

Ulm K. (1990) A simple method to calculate the confidence interval of a standardized mortality ratio. American Journal of Epidemiology131(2):373-375.

Ware JE, Kosinski M, Keller S. (1994) SF-36 physical and mental summary scales: A user’s manual. Boston, Massachusetts: The Health Institute, New England Medical Center.

APPENDIX A: SCORING THE SF-36V1

The SF-36v1 consists of 36 questions covering 8 health domains: physical functioning, bodily pain, role limitations due to physical problems, role limitations due to emotional problems, general health perceptions, mental health, social function, and vitality. The SF-36v1 will be scored for the 8 sub-domains according to the standard SF-36v1 scoring algorithms (0 to 100 scale) according to Table 1.

In the event that data is missing for an individual item from the domains of the SF-36v1 Health Status Survey, the average value of the completed items in the corresponding domain will be used as an estimate of the missing item. If more than 50 percent of the items from a domain are missing for an individual questionnaire, the corresponding deficient domain(s) will be excluded from analyses. For example, if only 3 of the 5 general health questions are answered, the mean of those 3 answers will be used to fill in the responses of the remaining 2 general health questions. However, if only 1 or 2 general health questions are answered, the general health score would be set to missing.

Table 1. Coding and Scoring for the 8 SF-36 (Version 1) Scales

Scale	Item	Coding	Range of Raw Score	Normalization*
Physical functioning	*Items 3a to 3j*	Yes, limited a lot = 1 Yes, limited a little = 2 No, not limited = 3	10-30	(S-10)/20 × 100
Role-physical	*Items 4a to 4d*	All of the time = 1 Most of the time = 2 Some of the time = 3 A little of the time = 4 None of the time = 5	4-20	(S-4)/16 × 100
Bodily pain	*Item 7*	None = 6 Very mild = 5.4 Mild = 4.2 Moderate = 3.1 Severe = 2.2 Very severe=1	2-12	(S-2)/10 × 100

Scale	Item	Coding	Range of Raw Score	Normalization*
	Item 8 if both items 7 and 8 are answered	Not at all and item7 equals 'None' = 6 Not at all and item7 not equal 'None' = 5 A little bit = 4 Moderately = 3 Quite a bit = 2 Extremely = 1		
	Item 8 if item 7 is not answered	Not at all = 6 A little bit = 4.75 Moderately =3.5 Quite a bit = 2.25 Extremely = 1		
General health	*Item 1*	Excellent = 5 Very good = 4.4 Good = 3.4 Fair = 2 Poor = 1	5-25	(S-5)/20 × 100
	Items 11a and 11c	Definitely true = 1 Mostly true = 2 Don't know = 3 Mostly false = 4 Definitely false = 5		
	Items 11b and 11d	Definitely true = 5 Mostly true = 4 Don't know = 3 Mostly false = 2 Definitely false = 1		
Vitality	*Items 9a and 9e*	All of the time = 5 Most of the time = 4 Some of the time = 3 A little of the time = 2 None of the time = 1	4-20	(S-4)/16×100

Scale	Item	Coding	Range of Raw Score	Normalization*
	Items 9g and 9i	All of the time = 1 Most of the time = 2 Some of the time = 3 A little of the time = 4 None of the time = 5		
Social functioning	*Item 6*	Not at all = 5 Slightly = 4 Moderately = 3 Quite a bit = 2 Extremely = 1	2-10	(S-2)/8 × 100
	Item 10	All of the time = 1 Most of the time = 2 Some of the time = 3 A little of the time = 4 None of the time = 5		
Role-emotional	*Items 5a to 5c*	All of the time = 1 Most of the time = 2 Some of the time = 3 A little of the time = 4 None of the time = 5	3-15	(S-3)/12 × 100
Mental health	*Items 9b, 9c and 9f*	All of the time = 1 Most of the time = 2 Some of the time = 3 A little of the time = 4 None of the time = 5	5-25	(S-5)/20 × 100
	Items 9d and 9h	All of the time = 5 Most of the time = 4 Some of the time = 3 A little of the time = 2 None of the time = 1		

*S = raw score = sum of item scores after coding

APPENDIX B: SCORING THE PADQOL-16 QUESTIONNAIRE

The questions will be combined to 7 scales and to a total score as follows (Ballow et al., 2017):

Abbreviation	Meaning	Question
GH	General health	(1) I get infections between infusions. (5) I have to seek unscheduled medical visits for my PIDD. (7) I have trouble with infections.
VT	Vitality	(2) I am more tired than normal. (10) I struggle to keep up with others.
PF	Physical functioning	(3) My cough has worsened. (4) I have flare-ups and symptoms of sinusitis. (8) The effects of my treatment wear off between infusions. (9) I have trouble with shortness of breath.
RP	Role (physical)	(6) I have nausea and bloating. (13) I have missed school or work due to my PIDD.
RE	Role (emotional)	(11) I have trouble sleeping. (14) I feel that I am a burden to others.
MH	Mental health	(12) I feel downhearted and depressed about my PIDD.
SF	Social functioning	(15) I require help from others frequently. (16) I avoid certain places and situations because of my PIDD.

Each question will be scored as follows and sumed for each of the scales above:

Rarely/Never = 0

Sometimes = 1

Often/always = 2.

Each scale will be standardized to a range of 0 to 100 by the following equation:

Standardized scale=raw scale*50/number of questions.

The total scale includes all questions and will be calculated in the same way as the sub-scales. The sub-scales will only be calculated if all questions of the sub-scale are available. The total scale will be calculated if 15 or more questions are answered. The total scale will be standardized as follows:

Standardized total scale=raw scale*50/number of questions answered.

APPENDIX C: STANDARDIZED UNITS FOR PRESENTING THE LABORATORY VALUES

For the statistical analysis and all tables and listings, the laboratory values will be converted to and reported by the following standardized units:

LBTESTCD	LBTEST	LBCAT	Unit
ALB	Albumin	CHEMISTRY	g/dL
ALP	Alkaline Phosphatase	CHEMISTRY	U/L
ALT	Alanine Aminotransferase	CHEMISTRY	U/L
AST	Aspartate Aminotransferase	CHEMISTRY	U/L
BICARB	Bicarbonate	CHEMISTRY	mEq/L
BILI	Bilirubin	CHEMISTRY	mg/dL
CA	Calcium	CHEMISTRY	mg/dL
CL	Chloride	CHEMISTRY	mEq/L
CREAT	Creatinine	CHEMISTRY	mg/dL
GLUC	Glucose	CHEMISTRY	mg/dL
K	Potassium	CHEMISTRY	mEq/L
MG	Magnesium	CHEMISTRY	mg/dL
PHOS	Phosphate	CHEMISTRY	mg/dL
PROT	Protein	CHEMISTRY	g/dL
SODIUM	Sodium	CHEMISTRY	mEq/L
UREAN	Urea Nitrogen	CHEMISTRY	mg/dL
BASO	Basophils	HEMATOLOGY	10^9/L
BASOLE	Basophils/Leukocytes	HEMATOLOGY	%
EOS	Eosinophils	HEMATOLOGY	10^9/L
EOSLE	Eosinophils/Leukocytes	HEMATOLOGY	%
HCT	Hematocrit	HEMATOLOGY	%
HGB	Hemoglobin	HEMATOLOGY	g/dL

LYM	Lymphocytes	HEMATOLOGY	10^9/L
LYMLE	Lymphocytes/Leukocytes	HEMATOLOGY	%
MONO	Monocytes	HEMATOLOGY	10^9/L
MONOLE	Monocytes/Leukocytes	HEMATOLOGY	%
NEUT	Neutrophils	HEMATOLOGY	10^9/L
NEUTLE	Neutrophils/Leukocytes	HEMATOLOGY	%
PLAT	Platelets	HEMATOLOGY	10^9/L
WBC	Leukocytes	HEMATOLOGY	10^9/L
IGA	Immunoglobulin A	IMMUNOLOGY	g/L
IGG	Immunoglobulin G	IMMUNOLOGY	g/L
IGM	Immunoglobulin M	IMMUNOLOGY	g/L
BACT	Bacteria	URINALYSIS	/HPF
GLUC	Glucose	URINALYSIS	mg/dL
KETONES	Ketones	URINALYSIS	mg/dL
PROT	Protein	URINALYSIS	mg/dL
RBC	Erythrocytes	URINALYSIS	/HPF
UROBIL	Urobilinogen	URINALYSIS	mg/dL
WBC	Leukocytes	URINALYSIS	/HPF

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