Statistical Analysis Plan for Study STP2279-002
April 04, 2019

A Study of EZN-2279 (Polyethylene Glycol Recombinant Adenosine Deaminase [PEG-rADA]) Administered as a Weekly Intramuscular Injection in Patients with Adenosine Deaminase (ADA)-Deficient Combined Immunodeficiency

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Statistical Analysis Plan

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Protocol / Study Number: STP-2279-002

Sponsor's Name: Leadiant Biosciences, Inc.

Study Drug: Polyethylene Glycol Recombinant Adenosine Deaminase [PEG-rADA]

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LIST OF ABBREVIATIONS/ DEFINITION OF TERMS

Abbreviation	Term
λ	half-life
µmol	micromole
ADA	adenosine deaminase
Adagen®	pegademase bovine, SS-PEG-ADA, PEG-ADA, PEGylated ADA
ADA-SCID	ADA-deficient SCID
AE	adverse event/experience
ALC	absolute lymphocyte count
AT	As-Treated
AUC	area under the drug concentration-time curve
AUC(0-t)	AUC from time zero to time t
BMI	Body Mass Index
Cmax	Maximum observed drug concentration.
Ct	last measurable concentration
Ctrough	concentration minimum before repeat dosing
dAXP	deoxyadenosine nucleotide
DNA	deoxyribonucleic acid
DSMC	Data and Safety Monitoring Committee
EZN-2279	PEG-rADA; SC-PEG-rbADA-C74S
Ig	immunoglobulin
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
h	hour
ln	natural logarithm
Kel	Terminal elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
PEG	polyethylene glycol
PEG-ADA	PEGylated ADA, Adagen®
PEG-rADA	PEGylated recombinant ADA, EZN-2279
PK	pharmacokinetic(s)
rADA	recombinant ADA
SAE	serious adverse event/experience
SAP	Statistical Analysis Plan
SCID	severe combined immunodeficiency
SOC	System organ class
$t_{1/2}$	time of elimination half-life calculated as ln(2)/Kel

Abbreviation	Term
tmax	time of the maximum drug concentration (obtained without interpolation)
UBC	United BioSource Corporation
WHO Drug	World Health Organization dictionary of medical codes
BLA	Biologics License Application

1. INTRODUCTION

The purpose of this clinical study is to evaluate the safety and efficacy of PEGylated rADA (EZN-2279) in patients with ADA-deficient combined immunodeficiency. The goal of this study is replacing PEGylated native bovine ADA (Adagen®) with EZN-2279. The EZN-2279 drug product is manufactured using deoxyribonucleic acid (DNA) recombinant technology, with a more stable linker, which may potentially reduce immunogenicity and which will replace bovine protein with recombinant protein in patients with ADA-deficient 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 STP-2279-002. Analyses described in this SAP are based on protocol Version 3.0, dated 23-Aug-2017.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to evaluate whether therapy with EZN- 2279 achieves metabolic detoxification, as demonstrated by total erythrocyte deoxyadenosine nucleotide (dAXP) concentration from a trough blood sample.

2.2 Secondary Objectives

- Evaluate the safety and tolerability of EZN-2279
- Assess the immunogenicity to EZN-2279 and Adagen®, including binding antibodies, neutralizing antibodies and anti-PEG antibodies
- Evaluate whether therapy with EZN-2279 maintains the trough plasma ADA activity ≥15 μmol/h/mL
- Determine the PK profile of EZN-2279
- Assess the effect of EZN-2279 on immune status as determined by absolute lymphocyte count (ALC), lymphocyte subset (B, T, and NK) analysis, and immunoglobulin (Ig) concentration (IgA, IgG, IgM)
- Compare the clinical status (infections and hospitalizations) of the patients during the EZN- 2279 treatment period compared to the prior six months
- Assess the clinical growth status of the patients during the EZN-2279 treatment and maintenance periods

2.3 Associated Endpoints

The endpoints that address the primary and secondary objectives are described in Section 6 (Efficacy) and Section 7 (Safety).

3. STUDY DESIGN

3.1 General Design and Study Procedures

Protocol STP-2279-002 is designed as an open-label, multicenter, single-arm, one way crossover study of EZN 2279 to determine the safety, efficacy, and pharmacokinetic (PK) of EZN-2279 in patients with ADA-SCID who are currently being treated with Adagen®. Each patient will serve as his or her own control with respect to assessment of study endpoints. The study will enroll enough patients to allow for up to six evaluable patients with ADA-deficient combined immunodeficiency and stable clinical status while currently receiving therapy with Adagen® who meet all eligibility criteria and written informed consent/assent is obtained.

Patient participation in the study will be defined by the four distinct study periods defined below:

- Screening (up to 28-days prior to start of Adagen® Lead- in dosing) – This period starts at the time of the initial screening procedure through administration of the first dose of Adagen® in the Lead- in period. Note: patients will continue to receive his/her prescribed dose of Adagen® during this period.
- Adagen® Lead-in – This period starts with the initial dose of study-required Adagen® dosing through the start of EZN-2279 study treatment. This period will be a minimum of 3 weeks.
- EZN-2279 Study Treatment – This period starts with the initial dose of EZN-2279 through completion of at least 21 weeks of EZN-2279 dosing.
- EZN-2279 Maintenance – This period begins after completion of the EZN-2279 study period and continues until the end of the study (commercial availability of EZN-2279 or early study termination).

The initial three patients will be enrolled and complete through full EZN-2279 pharmacokinetic sampling (Week T-9). An independent data and safety monitoring committee (DSMC) will review safety, PK (ADA activity), and erythrocyte dAXP data. If no concerns are noted, enrollment will continue for the remaining three patients. A similar DSMC review will occur for EZN-2279 dosing for the following:

- All six patients who complete through (Week T-9).
- All six patients who complete through (Week T-21).
- All six patients who complete one year (i.e. two maintenance cycles).

Throughout the duration of the study (i.e., Adagen® Lead-in, EZN-2279 treatment and EZN-2279 maintenance) patients will continually be assessed for adverse events, infectious complications, hospitalizations, concomitant medications changes and concomitant procedures.

Full details are found in the protocol. Visit-specific study activities are outline in Table 1 and Table 2.

Table 1: Study Activities

Procedure	Screening	Adagen® Lead-In Period										
						Adagen® Pharmacokinetics						
		Week 1	Week 2	Week 3	Weeks 4+	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Informed assent/consent	X											
Demographics	X											
Disease background/history (Prior Treatments, Adagen® Dose Adagen® AEs, Infectious complications, and Hospitalizations)	X					X						
Medical history	X					X						
Medication history	X											
Physical examination	X					X						
Vital signs	X					X						
Performance status	X					X						
Height, weight, growth curve	X					X						
Pregnancy test	X											
Serum chemistry	X					X						
Hematology	X					X						
Urinalysis	X					X						
Total trough erythrocyte dAXP	X[a]	X	X	X	X	X						
Trough ADA activity	X[a]	X	X	X	X	X						
Full PK profile[j]							X	X	X	X	X	X
B-/T-/NK-lymphocyte subset						X						
Quantitative immunoglobulins						X						
Antibody titers (binding, neutralizing), anti-PEG antibodies	X	X				X						
Clinical status Infectious complications Hospitalizations						X						
Adverse Events	←											→
Concomitant medications/procedures		X				X						
Adagen® administration (± 1 day)	X	X	X	X		X						
Adagen® dose/regimen adjustment	X	X[b]		X[c]	X[c]							
EZN-2279 administration (± 1 day)												

a – if necessary, only for patients maintained on a once weekly dose regimen; b – if necessary, only patients on a twice weekly or greater dose regimen; c – if necessary based upon meeting inclusion criteria for trough dAXP and ADA activity; patient requires trough dAXP ≤ 0.02 µmol/mL and trough ADA activity ≥15 µmol/h/mL on 2 consecutive weekly measurements to proceed to Adagen® pharmacokinetics; j- full PK profile conducted only on patients ≥ 10 years of age. Patients < 10 years of age will have limited PK sampling of trough and 48 hour post dosing only.

Procedure	EZN-2279 Treatment Period (Weeks 1 through 8)								
	Week T-1 (Day1)	Week T-2 (Day 8)	Week T-3 (Day 15)	Week T-4 (Day 22)	Week T-5 (Day 29)	Week T-6 (Day 36)	Week T-7 (Day 43)	Week T-8 (Day 50)	EZN-2279 Dose Adjustment[e]
Informed assent/consent									
Demographics									
Disease background/history Prior Treatments Adagen® Dose Adagen® AEs Infectious complications Hospitalizations									
Medical history									
Medication history									
Physical examination	X				X				
Vital signs	X				X				
Performance status	X				X				
Height, weight, growth curve	X				X				
Pregnancy test									
Serum chemistry	X				X				
Hematology	X				X				
Urinalysis	X								
Total trough erythrocyte dAXP	X		X		X		X	X	
Trough ADA activity	X[d]		X		X		X	X	
Full PK profile[j]									
B-/T-/NK-lymphocyte subset	X								
Quantitative immunoglobulins	X								
Antibody titers (binding, neutralizing), anti-PEG antibodies	X		X						
Clinical status Infectious complications Hospitalizations	X	X	X	X	X	X	X	X	
Adverse Events	←								→
Concomitant medications/procedures	X	X	X	X	X	X	X	X	
Adagen® administration (± 1 day)									
EZN-2279 administration (± 1 day)	X	X	X	X	X	X	X	X	X

d – trough sample for ADA activity is also the 168 hour full PK sample
e – prior to week T-9 if necessary based upon dAXP and ADA results from weeks T-7 and T-8; if adjustment made, patients return to week T-5

	EZN-2279 Treatment Period (Weeks 9 through 13)										
	Week T-9							Week T-10	Week T-11	Week T-12	Week T-13
Procedure	Day 57	Day 58	Day 59	Day 60	Day 61	Day 62	Day 63	Day 64	Day 71	Day 78	Day 85
Informed assent/consent											
Demographics											
Disease background/history Prior Treatments Adagen® Dose Adagen® AEs Infectious complications Hospitalizations											
Medical history											
Medication history											
Physical examination	X										X
Vital signs	X										X
Performance status	X										X
Height, weight, growth curve	X										X
Pregnancy test											
Serum chemistry	X										X
Hematology	X										X
Urinalysis											
Total trough erythrocyte dAXP	X							X	X		X
Trough ADA activity	X							X[f]	X		X
Full PK profile[j]	X	X	X	X	X	X	X				
B-/T-/NK-lymphocyte subset	X										
Quantitative immunoglobulins	X										
Antibody titers (binding, neutralizing), anti-PEG antibodies								X			
Clinical status Infectious complications Hospitalizations	X							X	X		X
Adverse Events	←										→
Concomitant medications/procedures	X							X	X		X
Adagen® administration (± 1 day)											
EZN-2279 administration (± 1 day)	X							X	X	X	X

f – trough sample for ADA activity is also the 168 hour full PK sample
j – Full PK profile conducted only on patients ≥ 10 years of age. Patients < 10 years of age will have limited PK sampling of trough and 48 hour post dosing only.

Procedure	EZN-2279 Treatment Period (Weeks 14 through 21)								EZN-2279 Maintenance[g]	End of Study/Early Discontinuation	30-Day Early Discontinuation Follow-up[i]
	Week T-14	Week T-15	Week T-16	Week T-17	Week T-18	Week T-19	Week T-20	Week T-21			
	Day 92	Day 99	Day 106	Day 113	Day 120	Day 127	Day 134	Day 141			
Informed assent/consent											
Demographics											
Disease background/history Prior Treatments Adagen® Dose Adagen® AEs Infectious complications Hospitalizations											
Medical history											
Medication history											
Physical examination				X				X	X	X	X
Vital signs				X				X	X	X	X
Performance status				X				X	X	X	X
Height, weight, growth curve				X				X	X	X	X
Pregnancy test											
Serum chemistry				X				X	X	X	X
Hematology				X				X	X	X	X
Urinalysis								X	X	X	X
Total trough erythrocyte dAXP		X		X		X		X	X	X	
Trough ADA activity		X		X		X		X	X	X	
Full PK profile[j]											
B-/T-/NK-lymphocyte subset								X	X	X	
Quantitative immunoglobulins								X	X	X	
Antibody titers (binding, neutralizing), anti-PEG antibodies								X	X	X	
Clinical status Infectious complications Hospitalizations		X		X		X		X	X	X	
Overall Survival								X	X	X	
Adverse Events	←----------										----------→
Concomitant medications/procedures		X		X		X		X	X	X	X
Adagen® administration (± 1 day)											
EZN-2279 administration (± 1 day)	X	X	X	X	X	X	X	X	X[h]		

g - assessments every 13 weeks ± 3 weeks; h – dosing of EZN -2279 continues once a week ± 1 day; i – only for patients who discontinue the study early

3.2 Sample Size and Power Considerations

The study will enroll a sufficient number of patients with ADA-SCID who meet all study entry criteria described to assure six (6) patients are evaluable, where evaluable is defined as completing the EZN-2279 treatment period (Week T-21) and providing primary study endpoint data.

More than 6 patients may be enrolled to achieve the required number of evaluable patients. It is expected that up to 12 study centers will participate in the study. There are no restrictions on the number of patients a single study center may enroll.

The sample size of six patients accounts for more than 5% of the entire eligible patient population worldwide and 10% of the entire eligible patient population in the United States.

The patients enrolled in this study all will have achieved metabolic detoxification with weekly Adagen® dosing prior to initiating EZN-2279 treatment. All patients are expected to maintain the target trough total erythrocyte dAXP concentration with EZN-2279. Therefore, the usual statistical sample size calculations using precision analysis, power analysis, or probability are not applicable due to zero variability.

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 As-Treated (AT) Population

The as-treated population, defined as all patients who are enrolled and receive at least one dose of either EZN-2279 or Adagen® Lead-in dosing, will be the primary analysis set in evaluating patient characteristics, treatment administration/compliance and safety.

If, during the Adagen® Lead in phase, a patient cannot have his/her Adagen® dose adjusted such that inclusion criteria for trough dAXP levels (≤0.02 μmol/mL) and trough ADA activity (≥15 μmol/h/mL) levels are met, then this patient will not be eligible to move into the EZN-2279 treatment period (i.e., this patient will have no EZN-2279 treatment and dosing data).

4.2 PK Population

The PK evaluable population, defined as all patients who have received EZN-2279 for at least 9 weeks (i.e. through at least Week T-9) and who have PK data at study week T-9 to indicate exposure, will be the analysis set for evaluating PK parameters.

Patient datasets with samples collected until at least 120hr following dosing of EZN-2279 in Week T-9 will be considered sufficient for PK analysis. Data will be considered insufficient for extrapolation of the terminal phase for determination of PK parameters if the following criteria are met: non-negative slope for the terminal phase; R^2 <0.80 for the determination of λ_z by log-linear regression; less than 3 data points after T_{max}; extrapolated area-under-the-curve >80%.

Patients < 10 years of age will not have full PK sampling done due to the blood volume requirements and will only have limited sampling done.

4.3 Completer Population

The completer population, defined as all patients who have received EZN-2279 through the primary endpoint visit (i.e., through Week T-21) will be the analysis set for evaluating efficacy endpoints because the complete EZN-2279 treatment period is required to establish maintenance of the target trough levels, immune function status and other efficacy endpoints.

5. STUDY POPULATION SUMMARY AT SCREENING

The study population will be summarized based on the as-treated population. All summaries in this section describe the patients at the end of the screening period. All study population data will be listed.

5.1 Changes to the Planned Population Summarization Proposed in Protocol

None.

5.2 Patient Disposition

Patients screened, patients enrolled, patients in the as-treated, PK, and completer populations, patients who completed the study, and patients who withdrew from the study will be summarized using descriptive statistics. Patients who withdrew from the study will also be summarized using descriptive statistics by reason for withdrawal.

5.3 Demographics

Demographics will be examined at the end of the screening period. The continuous variables of patient's age, weight, height, and body mass index (BMI) will be summarized using descriptive statistics. The categorical variables of patient's gender, race, and ethnicity will be summarized using descriptive statistics for each category. Growth curve percentiles for height, weight and BMI will also be calculated and summarized while patients are 18 years of age and younger. Missing categories will be presented if applicable.

5.4 Disease Background and History

Disease background will also be summarized at screening. Missing categories will be presented if applicable. Disease background includes ADA-SCID diagnosis and current dose of Adagen®, prior treatments for SCID including Adagen®, prior Adagen® toxicities in the past year, infectious complications, and hospitalizations.

5.5 Medical History

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

5.6 Prior Medications

All prior medications will be coded using the World Health Organization dictionary of medical codes (WHO Drug), Version 2013 Q1, or most recent version prior to database lock. The frequency of prior medications will be summarized using descriptive statistics by therapeutic class and preferred term. Patients are counted only once in each

therapeutic class category, and only once in each preferred term category. Prior medications will include all medications taken prior to the first day of Adagen® study drug, in addition to prior to lead in Adagen® drug.

5.7 Physical Examination

Physical examination data, including that collected at screening will be listed, but not summarized, as described in Section 7.6.

5.8 Protocol Deviations

A full list of protocol deviations will be compiled and reviewed by the clinical team to identify major versus minor violations/deviations. For violations at study entry, patients will be assessed against the inclusion and exclusion criteria of the protocol. For on-study deviations, compliance with the protocol will be examined using review of the database with regard to prohibited therapies, and timing and availability of planned assessments. Protocol deviations will be listed but not summarized.

6. EFFICACY ANALYSIS

The completer population will be used for the primary efficacy analysis, because the endpoint cannot be evaluated until T-21, and the as-treated population will be used for a sensitivity analysis of the primary efficacy endpoint. The as-treated population will be used for all other efficacy analyses, unless otherwise noted. Summaries will only be presented for the EZN-2279 group. Efficacy is evaluated in comparison to the Adagen® Lead in period ('baseline'). All efficacy data will be listed.

Given the sample size, all efficacy analyses will be descriptive (i.e., no statistical testing and no reported p-values), although 95% confidence intervals (CI) may be presented to show the variability of estimates.

6.1 Changes to the Planned Efficacy Analysis Proposed in Protocol

The protocol called for interim analyses when three patients will be enrolled and complete through full EZN-2279 pharmacokinetic sampling (Week T-9) and again when six patients complete through 9-weeks of EZN-2279 dosing. There will be a third look that will be used for a Biologics License Application (BLA). In addition, there will be a final analysis (fourth look) to be completed on all patients on EZN-2279 after one year (i.e. two maintenance cycles).

6.2 Primary Endpoint and Analysis

The primary endpoint is the proportion of patients achieving metabolic detoxification, assessed from trough dAXP samples obtained at Weeks T-15, T-17, T-19, and T-21. Metabolic detoxification is defined as a trough dAXP concentration equal to or below 0.02 μmol/mL.

Trough dAXP level will be summarized at each above time point. Maintenance of detoxification is defined as meeting the target trough levels for each of the 4 weeks listed above in the EZN-2279 treatment period. The proportion of patients meeting this definition of maintenance will be summarized.

Trough dAXP level will be summarized at last observed value as a sensitivity analysis using the as-treated population.

6.3 Secondary Endpoints and Analysis

Data regarding blood sample collections for trough samples, lymphocyte subset, and quantitative immunoglobulins will be listed but not summarized.

6.3.1 Trough Plasma ADA Activity

Trough plasma ADA Activity will be assessed from trough plasma ADA samples obtained at Weeks T-15, T-17, T 19, and T-21. Adequate trough ADA activity will be defined as ADA activity ~~≥30~~ 15 µmol/h/mL. Trough ADA activity level will be summarized at each above time point. Maintenance of adequate trough levels is defined as meeting the target trough levels for each of the 4 weeks listed above in the EZN-2279 treatment period. The proportion of patients meeting this definition of maintenance will be summarized.

6.3.2 Maintenance Phase Trough Plasma dAXP and ADA Activity

Maintenance phase trough plasma dAXP and ADA activity will be assessed from trough plasma dAXP and ADA samples obtained during the maintenance phase of the study (every 3 months following T-21) through completion of EZN-2279 maintenance treatment period. Trough dAXP and ADA levels will be summarized at each time point during the maintenance period. Maintenance of adequate trough dAXP and ADA levels is defined as meeting the target trough levels for both dAXP and ADA at each visit during the maintenance period. The proportion of patients meeting this definition of maintenance will be summarized.

6.3.3 Immune Status

Immune Status will be assessed through completion of the EZN-2279 maintenance period, through assessment of:

- Absolute lymphocyte count
- B-, T-, and NK-lymphocyte subset analysis: The number of cells for each subset will be determined by FACS using the following panel:
    - Percent and Absolute 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)
    - Absolute Lymphocytes (CD45+)
    - %CD4 (Helper Cells) / %CD8 (Suppressor T Cells)
- Quantitative immunoglobulin concentration (IgG, IgA, IgM)

Summary statistics for immune status variables will be presented at baseline, each intermediate collection time-point, and endpoint. Immune status values and changes from baseline to each visit and endpoint will be summarized using descriptive statistics. The frequency of clinically significant abnormal values will be summarized for selected immune status variables using descriptive statistics.

6.3.4 Clinical Status

Clinical status will be assessed through the conclusion of the EZN-2279 maintenance treatment period, through assessment of:

- Infections determined and defined as either:
    - Clinically documented – patients with documented signs and symptoms of infection without positive microbiologic cultures
    - Microbiologically documented - patients with documented signs and symptoms of infection and with positive viral or bacterial cultures
- Hospitalizations - incidence and duration of hospitalizations
- Change in growth – height, weight and growth curve determinations while patients are 18 years of age and younger
- Overall survival – through the EZN-2279 maintenance phase

The total number of infections and the incidence and duration of hospitalizations during the EZN-2279 treatment period will be summarized. Summary statistics for height, weight and BMI percentiles will be presented at baseline, each intermediate collection time-point, and endpoint. Percentiles will be calculated programmatically based on reported age, gender, height and weight.[1] Percentile scores and changes from baseline of percentile scores to each visit (at which height and weight are assessed) and endpoint will be summarized using descriptive statistics.

The proportion of patients surviving through the EZN-2279 maintenance phase will be summarized.

6.4 Interim Analyses

As noted in Section 3.1, the initial three patients will be enrolled and complete through full EZN-2279 pharmacokinetic sampling (Week T-9). An independent data and safety monitoring committee (DSMC) will review safety, PK (ADA activity), and erythrocyte dAXP data.

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

If no concerns are noted, enrollment will continue for the remaining three patients. A similar DSMC review will occur after all six patients complete through 9-weeks of EZN-2279 dosing.

Interim data will be used for a BLA when three subjects have complete data through week T-21. The BLA will include all patients enrolled at that time. Details of this analysis will be described in the BLA Statistical Analysis Plan.

7. SAFETY ANALYSIS

The as-treated population will be used for all of the safety analyses. Summaries will be presented by study drug group (EZN-2279 or Adagen®), if appropriate, through completion of the EZN-2279 maintenance period. All safety data will be listed.

7.1 Changes to the Planned Safety Analysis Proposed in Protocol

The protocol called for interim analyses when three patients will be enrolled and complete through full EZN-2279 pharmacokinetic sampling (Week T-9) and again when six patients complete through 9-weeks of EZN-2279 dosing. There will be a third look that will be used for a BLA. In addition, there will be a final analysis (fourth analysis) on subjects who complete one year (two maintenance cycles).

7.2 Study Drug Administration

Study drug administration for both Adagen® and EZN-2279 will be summarized. Duration of treatment (days treated) is the number of days on each treatment based on the first and last days of treatment with each study drug (last day of study drug – first day of study drug + 1). The number and percent of patients and the number of doses within categories for weeks on treatment will be summarized for Adagen®. The percent of patients and the number of doses within categories for months of treatment for EZN-2279 during the EZN-2279 treatment period, and months of treatment combining the EZN-2279 treatment and maintenance periods will be summarized with categories. Duration of treatment (days) will also be summarized as a continuous variable for Adagen®, EZN-2279 treatment, and overall EZN-2279 (treatment plus maintenance) using descriptive statistics.

Administration of both Adagen® and EZN-2279 will be listed.

7.3 Adverse Events and Other Complications

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 16.0 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 study, adverse events causing discontinuation from study drug, and non-serious adverse events. In addition to being summarized as adverse events, infectious complications and hospitalizations are considered efficacy measures as are summarized in Section 6.3.

The frequency of adverse events will be summarized using descriptive statistics by system organ class (SOC), preferred term and study drug group. Patients 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, patients are counted at the greatest severity. 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.

There will be two treatment emergent adverse event summaries provided: all treatment emergent adverse events while the patient takes Adagen® study drug and all treatment emergent adverse events while the patient takes EZN-2279, where treatment emergent are new or worsening adverse events that occur while on the respective therapies.

Listings for all adverse events, deaths, serious adverse events, adverse events leading to discontinuation, MedDRA dictionary terms for adverse event descriptions, and adverse event preferred terms by patient number will be presented.

7.4 Clinical Laboratory Tests

Summary statistics for chemistry, hematology, and urinalysis laboratory tests will be presented at baseline, each intermediate collection time-point, and endpoint. Laboratory tests results and changes from screening (for Adagen® drug group) or from the end of the Adagen® Lead-in period (for EZN-2279 drug group) to each visit and endpoint will be summarized using descriptive statistics.

Listings for laboratory data will be presented identifying clinically significant abnormal results. Results of pregnancy tests will be listed, but not summarized.

7.5 Vital Signs

Summary statistics for vital signs will be presented at baseline. Abnormal vital sign values will be reported and summarized as adverse events.

Actual vital sign values will be listed, but not summarized.

7.6 Physical Examination

Physical examination data will be listed, but not summarized.

7.7 Performance Status

Performance status data (Karnofsky and Lansky) will be listed, but not summarized. Patients that are < 16 years when first assessed then are 16 or older at subsequent visits will have their scores reported appropriate to the age at the time of the assessment (Lansky for < 16 years, Karnofsky ≥16 years).

7.8 Concomitant Medications

All concomitant medications will be coded using the WHO Drug, Version 2013Q1 or most recent version prior to database lock. The frequency of concomitant medications will be summarized using descriptive statistics by therapeutic class and preferred term. Patients are counted only once in each therapeutic class category, and only once in each preferred term category.

There will be two concomitant medication summaries provided: all medications taken while the patient takes Adagen® study drug and all medications taken while the patient takes EZN-2279.

7.9 Immunogenicity

The percentage of patients positive for each type of antibody will be summarized at baseline, each intermediate collection time-point, and endpoint.

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

8. PHARMACOKINETIC ANALYSIS

A full description of planned analyses are detailed in the PK analysis plan, Appendix A

9. STATISTICAL SOFTWARE

All data listings, summaries, and statistical analyses will be generated using SAS® Version 9.1 or higher.[2]

Phoenix® WinNonlin® Version 6.1 or higher[3] will be used for the calculation of pharmacokinetic parameters and the statistical analysis of steady-state data.

[2] SAS Institute Inc. 2004. SAS/STAT® 9.1 *User's Guide*. Cary, NC: SAS Institute Inc.

[3] Pharsight®, a Certara™ company

10. RULES AND DEFINITIONS

10.1 Timing of Analyses

The initial three patients will be enrolled and complete through full EZN-2279 pharmacokinetic sampling (Week T-9). An independent data and safety monitoring committee (DSMC) will review safety, PK (ADA activity), and erythrocyte dAXP data. If no concerns are noted, enrollment will continue for the remaining three patients. A similar DSMC review will occur for EZN-2279 dosing for the following:

- All six patients who complete through (Week T-9).
- All six patients who complete through (Week T-21).
- All six patients who complete one year (i.e. two maintenance cycles).

Listings will be produced for the BLA when three subjects have complete data through final analysis (one year/two maintenance cycles). The BLA will include all patients enrolled at that time.

10.2 Association with Study Drug

Assessments collected at EZN-2279 Day 1 (Week T-1) are associated with Adagen® treatment because EZN-2279 is not administered until all procedures are complete. All endpoints are measured in comparison to screening or the Adagen® Lead -in phase (baseline), as appropriate, within each patient.

10.3 Assignment of Study Days

For the purposes of data listings and summaries, "Study Day" will be calculated relative to the first dose of study medication (i.e., date of interest – date of first dose of Adagen®). 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".

10.4 Screening, Baseline and Study Weeks

No windowing schemes will be applied to the data. For by-visit summaries, if there are multiple assessments at a post baseline visit then the last non-missing assessment at that visit will be used for the summary. This includes assessments at the scheduled and unscheduled visits. For Patients who withdraw from the study, data at the early termination visit will be excluded from the by-visit summaries but will be included in the endpoint summaries.

Screening is defined as the last measurement for a variable before the initial dose of Adagen® study drug. With the exception of adverse events and medications, assessments collected at the screening visit are associated with the screening period because Adagen®

is not administered until all procedures are complete. Adverse events and medications starting on the day of the first dose of Adagen® are associated with Adagen® treatment.

Baseline is defined as the last measurement for a variable before the initial dose of EZN-2279 study drug, and is only used as the starting point for efficacy endpoints. With the exception of adverse events and concomitant medications, assessments collected at EZN-2279 Day-1 (Week T-1) are associated with Adagen® treatment because EZN-2279 is not administered until all procedures are complete. Adverse events and concomitant medications starting on the day of the first dose of EZN-2279 are associated with EZN-2279 treatment.

With regard to screening and baseline determination, assessments falling exactly on the date of the first dose of each study medication will be considered pre-dosing for that medication with the exception of adverse events and concomitant medications, which will be associated with the respective study drug.

Missing data will not be imputed.

10.5 Efficacy Data Handling

Change from baseline to Week X in efficacy endpoints will be calculated from the end of the Adagen® Lead-in period as:

- (Endpoint Value at Week X) – (Endpoint Value at Baseline), where baseline is defined as in Section 11.4.

10.6 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 first dose of Adagen® study medication.

- "Treatment-emergent AEs" are AEs with onset dates ≥ date of the first dose of study medication and within 30 days following the date of the last dose of study medication.

- "Post-treatment AEs" are AEs with onset dates > 30 days after the date of the last dose of study medication, within study STP-2279-002.

"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 12 (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.

For each study drug (EZN-2279 or Adagen®) medications will be assigned to a time period as follows:

- Medications taken any time < date of the first dose of Adagen® during the Lead-in phase will be considered prior medications.

- Medications can be concomitant with either Adagen®, EZN-2279, or both. Medications taken any time ≥ date of the first dose of respective study medication and within 30 days following the date of the last dose of respective study medication will be considered concomitant medications for that study drug.

- Medications taken > 30 days after the date of the last dose of respective study medication will be considered "post treatment" medications for that study drug.

Note that medications can be counted in more than one category (i.e., prior/concomitant) and can have different assignments for different study drugs. Imputation rules for partially missing start/stop dates are described in Section 12 (Programming Specifications).

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

- Adagen® Drug Group: (Endpoint Value at Week X) – (Endpoint Value at Screening), where screening is defined as in Section 11.4.

- EZN-2279 Drug Group: (Endpoint Value at Week X) – (Endpoint Value at End of Adagen® Lead-in phase).

11. PROGRAMMING SPECIFICATIONS

- All output should have the following header at the upper left margin:

  Leadiant Biosciences, Inc.
  Study STP-2279-002

  And the following header (right-justified) at the upper right margin:

  Page X of Y
  Report Date: DDMMMYYYY

- Tables and listings should be internally paginated (i.e., page numbers should appear sequentially within each table). All output should have the SAS program name as xxxx.sas in the lower right, and the data source(s) as ADxx used to generate the output in the lower left.

- In general, data listings should be sorted by Patient ID, study drug, and visit/assessment/collection/start dates, unless specific instructions to do otherwise.

- 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 is possible first day on study drug is first day of Adagen® study medication.

  - 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 "continuing" variable indicated as 'no' 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'.

- 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 in the following order:
  - *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.

- 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.

- Unless otherwise noted (see below), the mean and median (standard deviation and standard error) of a set of values should be printed out to one (two) more decimal place(s) than the raw value.

e.g.,	if raw:	xx
	mean and median:	xx.x
	standard deviation and standard error:	xx.xx
	range (minimum and maximum):	xx, xx

In those cases where the raw data are reported to 2 or 3 decimal places, the mean, median, standard deviation, and standard error will all be displayed to 1 more decimal place than the raw data (e.g., tables summarizing changes from baseline in laboratory parameters).

- All table percentages should be reported to the precision of tenths (i.e., 0.1) unless otherwise noted.

- The following specifications apply to tables that summarize categorical data unless otherwise noted:

  - Percent of events should be left blank (including the parentheses) if the number of events is zero.

  - If the categories of a parameter are ordered, then all categories between the maximum possible category and the minimum category should be included, even if n=0 for a given category between the minimum and maximum level for that parameter.

  - If the categories are not ordered, then only those categories for which there is at least one Patient represented should be included.

  - A 'Missing' category should be added to any parameter for which information is not available for any patients.

- Missing data should be represented on listings as 1) dashes "-", and properly footnoted: " - = data not available" or 2) "N/A", with footnote "N/A" = Not Applicable", whichever is appropriate.

- Times should be printed in the format "HH:MM". "HH" represents the 2-digit hour portion of the time. "MM" represents the 2-digit minute portion of the time. Both hour and minute portions of time are zero-filled on the left if they have only one digit. Missing time portions should be represented on patient listings as dashes ("10:--" and "--:--"). Times that are missing because they are not applicable for the patient should be printed as "N/A" unless otherwise specified.

- 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.

APPENDIX A: PK ANALYSIS PLAN

(Please see separate companion document containing the mock displays.)

APPENDIX B: STATISTICAL ANALYSIS PLAN MOCK DISPLAYS

(Please see separate companion document containing the mock displays.)

APPENDIX C: MOCK DISPLAYS OF PATIENT PROFILES

(Please see separate companion document containing the mock displays.)