# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761092Orig1s000

# CLINICAL REVIEW(S)

# CLINICAL REVIEW

| | |
|---|---|
| Application Type | BLA – New Molecular Entity |
| Application Number(s) | 761092 |
| Priority or Standard | Priority |
| Submit Date(s) | 10/24/2017 |
| Received Date(s) | 10/24/2017 |
| PDUFA Goal Date | 10/24/2018 |
| Division/Office | DTOP/OAP |
| Reviewer Name(s) | Marc W. Cavaillé-Coll |
| Review Completion Date | 10/04/2018 |
| Established/Proper Name | elepegademase-lvlr |
| (Proposed) Trade Name | Revcovi Injection |
| Applicant | Lediant Biosciences, Inc. |
| Dosage Form(s) | 1.6 mg/mL injection |
| Applicant Proposed Dosing Regimen(s) | Treatment-naïve patients: Starting weekly dose of 0.4 mg/kg based on ideal body weight, divided in two weekly doses intramuscularly, for a minimum of 12 weeks until immune reconstitution is achieved. After that, the dose may be gradually adjusted down to maintain trough plasma adenosine deaminase activity over 30 mmol/hr/L, trough dAXP level under 0.02 mmol/L, and/or to maintain adequate immune reconstitution based on clinical assessment of the patient. |
| Applicant Proposed Indication(s)/Population(s) | Treatment of Adenosine Deaminase-Severe Combined Immunodeficiency (ADA-SCID) |
| Recommendation on Regulatory Action | Approval |
| Recommended Indication(s)/Population(s) (if applicable) | REVCOVI (elapegademase-lvlr) Injection is indicated for the treatment of adenosine deaminase severe combined immune deficiency (ADA-SCID) in pediatric and adult patients. |

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## Glossary

| | |
|---|---|
| AC | advisory committee |
| AE | adverse event |
| AR | adverse reaction |
| BLA | biologics license application |
| BPCA | Best Pharmaceuticals for Children Act |
| BRF | Benefit Risk Framework |
| CBER | Center for Biologics Evaluation and Research |
| CDER | Center for Drug Evaluation and Research |
| CDRH | Center for Devices and Radiological Health |
| CDTL | Cross-Discipline Team Leader |
| CFR | Code of Federal Regulations |
| CMC | chemistry, manufacturing, and controls |
| COSTART | Coding Symbols for Thesaurus of Adverse Reaction Terms |
| CRF | case report form |
| CRO | contract research organization |
| CRT | clinical review template |
| CSR | clinical study report |
| CSS | Controlled Substance Staff |
| DMC | data monitoring committee |
| ECG | electrocardiogram |
| eCTD | electronic common technical document |
| ETASU | elements to assure safe use |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FDASIA | Food and Drug Administration Safety and Innovation Act |
| GCP | good clinical practice |
| GRMP | good review management practice |
| ICH | International Council for Harmonization |
| IND | Investigational New Drug Application |
| ISE | integrated summary of effectiveness |
| ISS | integrated summary of safety |
| ITT | intent to treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified intent to treat |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Event |
| NDA | new drug application |
| NME | new molecular entity |

| | |
|---|---|
| OCS | Office of Computational Science |
| OPQ | Office of Pharmaceutical Quality |
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigation |
| PBRER | Periodic Benefit-Risk Evaluation Report |
| PD | pharmacodynamics |
| PI | prescribing information or package insert |
| PK | pharmacokinetics |
| PMC | postmarketing commitment |
| PMR | postmarketing requirement |
| PP | per protocol |
| PPI | patient package insert |
| PREA | Pediatric Research Equity Act |
| PRO | patient reported outcome |
| PSUR | Periodic Safety Update report |
| REMS | risk evaluation and mitigation strategy |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SGE | special government employee |
| SOC | standard of care |
| TEAE | treatment emergent adverse event |

# 1. Executive Summary

## 1.1. Product Introduction

SC-PEG-rADA (elapegademase) Injection ([monomethoxypolyethylene glycol] recombinant adenosine deaminase; EZN-2279) is a new biologic product intended to provide adenosine deaminase (ADA) enzyme-replacement therapy (ERT) to patients with adenosine deaminase severe combined immunodeficiency (ADA-SCID). (b) (4)

The proposed recommended dosage in patients currently receiving treatment with Adagen involves starting weekly intramuscular (IM) doses with REVCOVI at 0.2 mg/kg. The dose may be increased by increments of 0.033 mg/kg weekly if trough ADA activity is under 30 mmol/hr/L, deoxyadenosine nucleotides (dAXP) is above 0.02 mmol/L, and/or the immune reconstitution is judged as inadequate by the treating physician's medical assessment of the patients clinical status. Total weekly dose administration may be divided in multiple IM administrations.

If a patient's weekly Adagen dose is above 30 U/kg, an equivalent weekly REVCOVI dose (mg/kg) should be calculated using the following conversion formula:

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

Subsequent doses may be increased by increments of 0.033 mg/kg weekly if trough ADA activity is under 30 mmol/hr/L, trough deoxyadenosine nucleotides (dAXP) are above 0.02 mmol/L, and/or the immune reconstitution is inadequate based on the clinical assessment of the patient. The total weekly dose may be divided into multiple intramuscular (IM) administrations during a week.

In Adagen-naïve patients, the proposed recommended dosage involves a starting weekly dose of REVCOVI is 0.4 mg/kg based on ideal body weight, divided into two doses (0.2 mg/kg twice a week), intramuscularly, for a minimum of 12 to 24 weeks until immune reconstitution is achieved. After that, the dose may be gradually adjusted down to maintain trough ADA activity over 30 mmol/hr/L, trough dAXP level under 0.02 mmol/L, and/or to maintain adequate immune reconstitution based on clinical assessment of the patient.

The optimal long-term dose and schedule of administration should be established by the treating physician for each patient individually and may be adjusted based on the laboratory

values for trough ADA activity, trough dAXP level, and/or on the treating physician's medical assessment of the patient's clinical status.

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness, as demonstrated by the prolonged successful maintenance of plasma adenosine deaminase levels above 15 mmol/L/h (1100 U/L), a validated surrogate marker of efficacy, in patients with Adenosine Deaminase Severe Combined Immunodeficiency (ADA-SCID), receiving REVCOVI administered by intramuscular injection, in two clinical trials.

## 1.3. Benefit-Risk Assessment

## Benefit-Risk Integrated Assessment

Adenosine deaminase deficient severe combined immunodeficiency (ADA-SCID) is a rare (one in $10^6$ births in the US) serious life-threatening inherited congenital condition. Patients with ADA-SCID who are not suitable candidates for, or have failed hematopoietic stem cell transplantation, must receive life-long enzyme-replacement therapy (ERT). To-date since 1990, ERT has been provided by Adagen® (pegademase bovine), which is a modified enzyme derived from bovine intestines. (b) (4) REVCOVI® (elapegademase-lvlr) injection, which is a recombinant adenosine deaminase (rADA), based on the bovinr amino acid sequence, conjugated to monomethoxypolyethylene glycol (mPEG), is an acceptable substitute, that will assure continuation of life-saving ERT in patients with ADA-SCID. In clinical studies REVCOVI® has provided more consistent plasma ADA activity above the therapeutic threshold of 15 mmol/L/hr, and sustained activity above 30 mmol/L/hr when administered at an equivalent dose of units of ADA in patients already stabilized on a therapeutic dose of Adagen. The potential risks of REVCOVI® (elapegademase-lvlr) injection, are the same as Adagen®, minus the theoretical risk of transmission of Bovine Spongiform Encephalopathy (BSE), and include but are not limited to site bleeding in patients with thrombocytopenia, and immunogenicity, which could lead to changes in ADA levels and decreased effectiveness. Post marketing adverse events observed with Adagen® could also be expected to occur with REVCOVI® and include hemolytic anemia auto-immune hemolytic anemia, thrombocythemia, thrombocytopenia and autoimmune thrombocytopenia, injection site erythema, urticaria and lymphomas. Overall, the benefit of life-saving potential to improve immune function in patients with ADA-SCID are far superior to the potential risk of ERT with REVCOVI® (b) (4)

Benefit-Risk Dimensions

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • Adenosine deaminase deficient severe combined immunodeficiency (ADA-SCID) is a rare (one in $10^6$ births in the US) serious life-threatening inherited congenital condition. Without treatment death will occure within the first years of life. | • Patients with ADA-SCID who are not suitable candidates for, or have failed hematopoietic stem cell transplantation, must receive life-long enzyme-replacement therapy (ERT). |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Current Treatment Options | • To-date since 1990, adenosine deaminase (ADA) enzyme replacement therapy (ERT) has been provided by Adagen® (pegademase bovine) (b) (4) | • A new source of life-saving ERT is needed. |
| Benefit | • REVCOVI (elapegademase-lvlr) injection provides more stable plasma ADA activity, more consistently above the therapeutic threshold of 15 mmol/hr/L compared to Adagen® (pegademase bovine), a threshold associated with clinical benefit.<br>• At equivalent dose (Units to Units) in patients converted from Adagen to REVCOVI, achieve higher (> 30 mmol/hr/L) and more consistent ADA plasma activity (few drop below 30 mmol/hr/L, and virtually none below 15 mmol/hr/L). | • REVCOVI (elapegademase-lvlr) injection provides superior clinical benefit compared to Adagen® (pegademase bovine) with respect to the validated surrogate endpoint of plasma ADA activity > 15 mmol/hr/Lr. |
| Risk and Risk Management | • As with all recombinant non-human therapeutic proteins, there exists a potential risk of immunogenicity and development of antibodies (anti-drug, anti-PEG, and neutralizing antibodies).<br>• Delay in improvement of immune function in ERT- naïve patients<br>• Hematologic adverse events such as anemia, thrombocythemia, and thrombocytopenia would be expected. | • Monitoring of ADA plasma levels and testing for antibodies to REVCOVI should be performed, if a persistent decline in trough plasma ADA activity occurs<br>• Maintain precautions to protect immune deficient patients from infections until improvement in immune function has been achieved. The timing and degree of improvement in immune function may vary from patient to patient.<br>• Standard of care includes appropriate monitoring for hematologic adverse events. |

### 1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

| | | |
|---|---|---|
| □ | The patient experience data that was submitted as part of the application include: | Section where discussed, if applicable |
| | □ Clinical outcome assessment (COA) data, such as | [e.g., Sec 6.1 Study endpoints] |
| | □ Patient reported outcome (PRO) | |
| | □ Observer reported outcome (ObsRO) | |
| | □ Clinician reported outcome (ClinRO) | |
| | □ Performance outcome (PerfO) | |
| | □ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | |
| | □ Patient-focused drug development or other stakeholder meeting summary reports | [e.g., Sec 2.1 Analysis of Condition] |
| | □ Observational survey studies designed to capture patient experience data | |
| | □ Natural history studies | |
| | □ Patient preference studies (e.g., submitted studies or scientific publications) | |
| | □ Other: (Please specify) | |
| □ | Patient experience data that were not submitted in the application, but were considered in this review: | |
| | □ Input informed from participation in meetings with patient stakeholders | |
| | □ Patient-focused drug development or other stakeholder meeting summary reports | [e.g., Current Treatment Options] |
| | □ Observational survey studies designed to capture patient experience data | |
| | □ Other: (Please specify) | |
| X | Patient experience data was not submitted as part of this application. | |

## 2. Therapeutic Context

## 2.1. Analysis of Condition

ADA-SCID is a rare (estimated incidence of 1 case per $10^6$ births in the US), inherited, and often fatal disease if untreated. The disease is characterized by severe and recurrent opportunistic infection, failure to thrive, profound lymphopenia with absent or severely impaired cellular and humoral immune function, and metabolic abnormalities. ADA-SCID patients are lymphopenic at birth and predisposed to recurrent illnesses caused by pathogens and opportunistic organisms that often begin within a few weeks of age.

Patients with ADA-SCID are unable to produce the adenosine deaminase (ADA) enzyme in their cells because of mutations in the ADA gene on chromosome 20q. ADA is a purine salvage enzyme expressed in all tissues of the body and catalyzes the deamination of deoxyadenosine (dAdo) and adenosine (Ado) to deoxyinosine and inosine, respectively. The absence of ADA results in accumulation of dAdo in both intracellular and extracellular compartments. Within cells, conversion of dAdo by deoxycytidine kinase (dCydK) to deoxyadenosine-trisphosphate (dATP) leads to intracellular expansion of the dATP pool. The buildup of toxic metabolites have an effect on different organ systems, most notably the immune system. The buildup of both dATP and dAdo has deleterious effects on lymphocyte development and function and is the major cause of the immunologic defects. Accumulation of toxic metabolites may interfere with thymic stroma development, maturation, and function, resulting in impaired ability to support T-cell development. ADA-SCID is manifested with complete or partial deficiency of both cell-mediated and humoral immunity. Without treatment, ADA-SCID is fatal in the first years of life, and therefore, early intervention is required.[1] Long-term serious conditions, including lymphoid and possibly hepatic malignancies, as well as progression of chronic pulmonary insufficiency have emerged in patients who were treated with enzyme replacement therapy, and must all be considered part of this condition.

## 2.2. Analysis of Current Treatment Options

In the United States, current treatment options for patients with ADA-SCID include hematopoietic stem cell transplantation (HSCT), enzyme replacement therapy (ERT), as well as enrollment in investigational gene-therapy studies. HSCT is the treatment choice that is most widely available to most physicians and transplantation centers. Overall 1-year survival of 87% and 88% have been reported after matched sibling and matched family donor transplantations (often available because of the high incidence of consanguineous pedigrees) respectively. The highly successful outcome in matched sibling and family donor transplantations is most probably the result of the absence of any chemotherapeutic regimen. Lower 1-year survivals, about 67%, have been observed after fully matched unrelated donor transplantations. Even lower 1-year survival has been observed after mismatched unrelated or mismatched family

[1] Gaspar HB, Ajuti A, Porta F, et al. How I treat ADA deficiency. BLOOD, 2009; 114(17);3524-3532

donors (mainly parental haploidentical donors), 29% and 43% respectively.[2] The poor outcome in mismatched donor transplantations may be attributable to the vulnerability of patients to the toxicities associated with cytoreductive chemotherapy. The great majority (>90%) of patients surviving HSCT are able to discontinue immunoglobulin replacement therapy, suggesting a relatively complete immune recovery. In addition, surviving HSCT patients appear well detoxified after transplantation with marked reduction of dATP levels to a mean of approximately 100 µM, which, although not normal, represents an approximately 1-$\log_{10}$ reduction from levels at diagnosis.[3]

Enzyme replacement therapy (ERT) has been available in the US since the approval of Adagen® (PEG-ADA) in 1990. ERT requires appropriate biochemical (as well as immunologic) monitoring. Efficacy is associated with maintaining sufficient plasma ADA activity (> 15mmol/hr/L or 1100 U/L) to eliminate dAdo nucleotides (dAXP) from erythrocytes. While ERT has been performed by local physicians, biochemical monitoring for patients treated in the Uinted States has been provided by the laboratory of Michael S. Hershfield in the Depatment of Medicine and Biochemistry, Duke Medical Center, Durham, NC. Observation of a decline in plasma ADA with reaccumulation of dAXP in erythrocytes may indicate any of the following or combination of the following: inadequate dosing; development of neutralizing anti-ADA antibody; improper storage of PEG-ADA (unstable if frozen), or nonadherence.[4]

PEG-ADA has been used as initial therapy for patients who lacked a related HLA-identical marrow/stem cell donor, when assessment of risk and benefit by physicians and parents favored ERT over other options. Treatment with PEG-ADA is needed for patients who are considered too unstable to undergo conditioning for an immediate HLA-mismatched HSCT, or who cannot tolerate the delay while searching for matched unrelated donor.[5] Fewer than 10% of patients have received PEG-ADA as secondary therapy after failing HSCT (mainly haploidentical performed without conditioning) or investigational gene therapy.[6]

The figure below depicts the estimated probability of survival versus length of treatment with PEG-ADA in a cohort of 98 ADA-SCID patients treated with ERT. Half of the deaths on ERT occurred within the first 6 months (40% in the first month), resulting from conditions present at diagnosis. The overall probability of surviving 20 years on ERT is estimated to be 78%. A patient

[2] Booth C, Hershfield M, Notarangelo L, et al. Management options for adenosine deaminase deficiency: proceedings of the EBMT satellite workshop (Hamburg, March 2006). *Clin Immunol*. 2007;123(2):139-147.
[3] Gaspar. Id.
[4] Gaspar. Id.
[5] Booth. Id.
[6] Gaspar. Id.

alive 6 months after starting ERT had approximately 90% probability of surviving the next 12 years.[7]

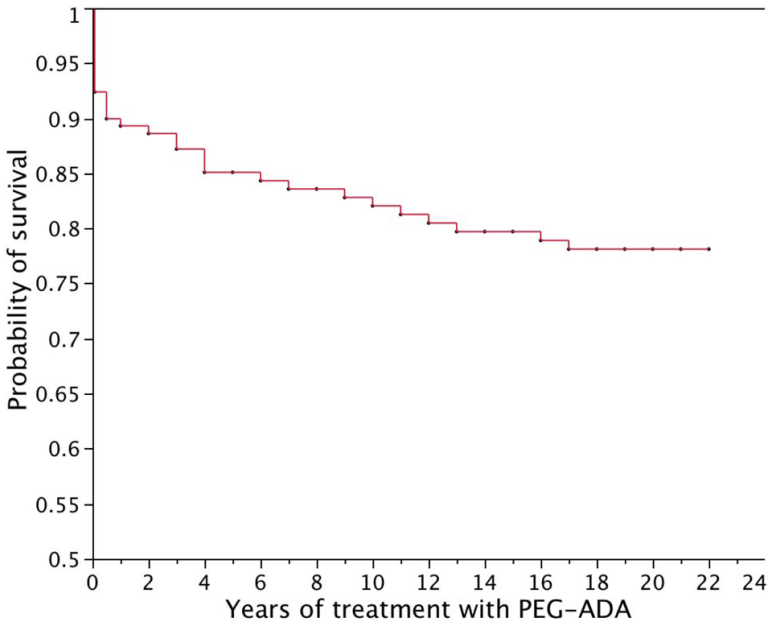



Figure 1: Estimated probability of survival while receiving ERT. Patients who discontinued ERT to undergo stem cell transplantation or GT were censored at the time ERT was stopped, except for 5 patients who developed refractory hemolytic anemia and subsequently died after attempted stem cell transplantation. In these latter 5 cases, death was attributed to ERT at the time PEG-ADA was discontinued.[8]

Whether treatment with PEG-ADA or SC-PEG-rADA to stabilize patients before they undergo HSCT has any clinical benefit has not been established; however, enzyme delivery is needed for successful detoxification of metabolic substrates and promotion of immune recovery in ADA-SCID patients, a condition diagnosed at birth in the US by universal gene testing, especially those who have failed or are not candidates for HSCT. Leadiant's Adagen® (NDA 019818) is currently the only available Enzyme Replacement Therapy for ADA-SCID and is cross-referenced in this BLA (Module 1.4.4). (b) (4)

[redacted]

[7] Gaspar. Id.
[8] Gaspar. Id. Figure 3

No gene-therapy product has been approved in the US for treatment of ADA-SCID.

# 3. Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

The product represents a new molecular entity, and is not currently marketed in the U.S.

## 3.2. Summary of Presubmission/Submission Regulatory Activity

The product was developed under BB IND 100687 for EZN-2279 which was preceded by substantial Pre-IND consultations beginning with a meeting with Enzon Pharmaceuticals, Inc, the original Sponsor of the IND, on July 10, 2007, to reach an agreement on appropriate Chemistry, Manufacturing and Control strategy, to discuss Pharmacology-Toxicology research plans, to review the proposed clinical development plan and to gain understanding in obtaining Orphan Products designation. A new IND 100687 was submitted bu ENZON Pharmaceuticals on November 2, 2009 for EZN-2279 (SC-PEG rADA) for the treatment of SCID-ADA and was allowed to proceed on November 23, 2009, and included a protocol for Study STP-2279-002.

Sponsorship of the IND was transferred to Sigma-Tau Pharmacueticals, effective March 11, 2010.

Orphan Drug Designation (DD;ODA 14-4675) was granted on March 19, 2015, based on the rarety of the proposed indication, and that the pegulated human recombinant product was a new molecular entity, distinct from the marketed ADAGEN product.

A type A meeting was held on December 16, 2015 at the Sponsor's request to discuss the clinical development plan and regulatory approach for an accelerated approval of EZN-2279. In particular the Sponsor proposed to submit a BLA for accelerated approval using efficacy and safety data from the first cohort of three patients enrolled in the Study STP-2279-002, which would be followed by a submission of information on all of the patients enrolled in the completed study. While the proposal appeared acceptable, FDA encouraged the Sponsor to collect information on all patients who have received the product at the time of the submission for proposed accelerated approval, as well as at the time of the submission for full approval.

> *Reviewer's Comment: While in 2015 one was considering maintenance of trough plasma ADA concentrations and erythrocyte dAXP levels as potential surrogate end points for an accelerated approval application under Subpart E, our thinking has changed to accept them as validated surrogate efficacy endpoint for a standard approval application, all the more these are the measurements used to guide and document successful therapy.*

> *Thus, the need for an accelerated approach has changed over time to accept an application for full approval, with the expectation of a post-marketing requirement for additional long-term follow-up of safety, efficacy and immunogenicity (See Memorandum to the File, John Farley, MD, MPH, Deputy Office Director, Office of Antimicrobial Producst, dated July 27, 2018, in DARRTS).*

A pre-BLA meeting was held on October 19, 2016 to discuss the non-clinical development plan as well as the content and format of a BLA for EZN-2279.

On February 17, 2017 the corporate name was changed from Sigma-Tau Pharmaceuticals to Lediant Biosciences, Inc.

On May 25, 2017 Rare Pediatric Disease Designation (RPD-2016-102) was granted by the Agency.

On June 7, 2017, Fast Track development program designation was granted for the investigation of EZN-2279 for the treatment of adenosine deaminase svere combined immunodeficiency (ADA SCID). The proposed plan for submission of portions for review of the planned marketing application was found acceptable.

On December 15, 2017, a request for Breakthrough Therapy Designation (BTD) for the treatment of ADA., submitted on November 3, 207 was denied (See letter dated November 3, 2017 in DARRTS).

*Reviewer's Comment:* (b) (4) [redacted]

On July 14, 2017 the Applicant submitted the first part of the BLA, containing Non-clinical information.

On August 15, 2017 the Applicant submitted the second part of the BLA, containing Chemistry Manufacturing and Controls (CMC) information.

On September 15, 2017 the Applicant submitted the third part of the BLA, containing additonal

CMC information.

On October 24, 2017 the Applicant submitted the fourth part of the BLA, containing the Clinical information, which completed the submission of the BLA. The Applicant requested Priority Review designation, (b) (4) At the filing meeting the application was designated Standard Review.

On March 2, 2018, the Applicant submitted a request to the Agency for reconsideration of the review designation, including new information on intra-patient variability of plasma ADA levels from a historical control group, and the ability to maintain levels > 15 mmol/L/h. The issue of a change in the review classification for BLA 761092 from Standard to Priority was discussed with the Medical Policy and Program Review Council (MPPRC) on June 27, 2018. Based on discussion of the data presented, the Council supported the Division recommendation to change the review classification from Standard to Priority.

On July 27, 2018, a letter was issued to the Applicant, notifying that the review classification is changed to from Standard to Priority; however, the regulatory decision goal date would not be changed, meaning the PDUFA goal date would remain 10/24/2018.

### 3.3. Foreign Regulatory Actions and Marketing History

The product is not marketed in any country. There are no pending foreign applications.

## 4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

### 4.1. Office of Scientific Investigations (OSI)

No OSI audit was requested for this application, given the small number of human subjects; however, inspection of the site where ADA levels and erythrocyte dAXP were measured was requested. No significant deficiencies that would preclude approval were identified.

### 4.2. Product Quality

Elapegademase-lvlr is a recombinant adenosine deaminase (rADA) based on bovine amino acid sequence, conjugated to monomethoxypolyethylene glycol (mPEG).

The Applicant [redacted] is using a [redacted] SC-PEG linker [redacted]

Factors that contribute to greater stability of SC-PEG rADA compared to Adagen include: [redacted]

The product used in the clinical trials development program is the same as the "to-be-marketed" product, with the exception that experience of pain at the site of study drug administration has led to the removal of [redacted] from the formulation used early in Study STP-2279-002. Most of the clinical data involves the use of the [redacted] to-be-marketed formulation.

> *Reviewer's Comment: Clinical correlates potentially related to product quality include greater and more stable levels of plasma ADA levels observed in patients converted from Adagen® to SC-PEG rADA (See Tables 5,6,7 and 8, as well as Figure 9 of this review and adjacent discussion of plasma ADA activity and variabilty).*

## 4.3. Clinical Microbiology

Not applicable.

## 4.4. Nonclinical Pharmacology/Toxicology

The following is derived from the nonclinical pharmacology/toxicology review.

A PK and PD bridging toxicology strategy was used in the nonclinical evaluations given (1) the 25-year successful clinical history with Adagen®, (2) the structural and pharmacological comparability of Adagen® and SC-PEG rADA and (3) the safe use of the stable PEG SC linker in other FDA approved biologics.

Early nonclinical studies were not conducted with the to-be-marketed formulation. These early lots of SC-PEG rADA were well-tolerated in repeat-dose toxicity studies in rats and dogs when given every 3 to 4 days for 4 weeks (nine doses total). Drug-related findings in rats and dogs were limited to a slight increase in APTT that was reversible or partially reversible during a 4-week recovery period. A slight prolongation of APTT was also observed in additonal studies concudted with the to-be-marketed formulation. Otherwise, the safety profile of the to-be-marketed product is the same as the safety profile from earlier lots of SC-PEG rADA.

The nonclinical PK studies showed a longer terminal half-life and systemic exposure (AUC), as

measured by ADA enzymatic activity, for SC-PEG rADA compared to Adagen®. These PK differences did not result in increased toxicity in the 4-week general toxicology studies.

The nonclinical studies conducted by the Applicant established comparable pharmacological and toxicological profile for SC-PEG rADA and Adagen®. Therefore, the 25-year clinical experience with Adagen® use provides additional support for the safety of chronic treatment with SC-PEG rADA.

Anti-drug antibodies were observed in the plasma of rats, as well as in most dogs that received repeated doses of SC-PEG rADA.

Long-term studies in animals to evaluate carcinogenic potential or studies to evaluate mutagenic potential have not been performed with SC-PEG rADA.

The Applicant conducted a dose-ranging embryo-fetal development study. No adverse maternal or embryofetal findings were observed. The study was not sufficiently powered to establish a reliable NOAEL, based on the low number of animals evaluated per group. Given study limitations, the dose-ranging embryofetal development study was not considered adequate for risk assessment, and the information was not included in the labeling.

Adequate pharmacovigilance is recommended for clinical effects on fertility and embryofetal toxicity.

## 4.5. Clinical Pharmacology

Mechanism of Action

SC-PEG rADA provides an exogenous source of ADA enzyme involved in purine metabolism, catalyzing the irreversible hydrolytic deamination of adenosine or deoxyadenosine to inosine or deoxyinosine, respectively, as well as several naturally occurring methylated adenosine compounds. Maintaining a low level of 2'-deoxyadenosine and adenosine is crucial for proper number and function of immune cells as well as decreasing the frequency of opportunistic infections. Elevated adenosine levels, as occurring in ADA deficiency, contribute to apoptosis and a block in the differentiation of thymocytes, causing severe T lymphopenia.

Elapegademase provides an exogenous source of ADA enzyme that is associated with a decrease in toxic adenosine and deoxyadenosine nucleotide levels as well as an improvement in lymphocyte number.

Pharmacokinetics

The pharmacokinetics (PK) of SC-PEG rADA was characterized based on plasma ADA activity levels in 6 patients with ADA-SCID (five adults and one pediatric) (See Clinical Study STP-2279-002 in Section 6.1 of this review). The results are summarized in the Table below from the Clinical Pharmacology Review.

Table 1. Individual Estimates from Non-Compartmental Analysis of Steady State Plasma ADA Activity Levels

| Study | Patient's Age (yrs), Gender, Race | Dose/Week (mg) [mg/kg] | $T_{max}$ (hr) | DN $AUC_{0\text{-}168hr}$ (hr*mmol/hr/L) /(mg/kg)[a] | DN $C_{max}$ (mmol/hr/L) /(mg/kg)[a] | DN $C_{trough}$ (mmol/hr/L)[a] |
|---|---|---|---|---|---|---|
| Study 1 | 19, Male, Hispanic/Latino | 10.0 [0.188] | 47.7 | 32710 | 237 | 29.0 |
| | 21, Male, Hispanic/Latino | 10.2 [0.224] | 71.9 | 31343 | 219 | 37.7 |
| | 37, Male, Black/African American | 19.6 [0.2] | 48.2 | 42400 | 292 | 46.2 |
| | 30, Female, White/Caucasian | 10.0 [0.209] | 72.0 | 24564 | 166 | 23.5 |
| Study 2 | 25, Male, Asian | 10.0 [0.167] | 48.0 | 37605 | 251 | 33.45 |
| | 16, Female, Asian | 4.99 [0.233] | 27.2 | 19013 | 150 | 20.2 |

DN=Dose-normalized to a mg/kg/week dose of REVCOVI;
[a]Individual absolute and dose-normalized (mg/kg/week) PK data calculated over the dosing interval after administration of REVCOVI by weekly IM injection at a stable dose for at least five consecutive weeks.

Plasma ADA Activity

Plasma ADA activity is the pharmacodynamic (PD) endpoint of interest used to assess response to treatment with REVCOVI. Maintenance of plasma ADA activity above ≥15 mmol/hr/L, is accepted as a surrogate marker of clinical efficacy.

## 4.6. Devices and Companion Diagnostic Issues

Not applicable.

## 4.7. Consumer Study Reviews

Not applicable

# 5. Sources of Clinical Data and Review Strategy

## 5.1. Table of Clinical Studies

Table 2. Clinical Studies Supporting Efficacy, Safety and Pharmacoknetics

| Trial Identity | Trial Design | Regimen/ schedule/ route | Study Endpoints | Treatment Duration/ Follow Up | No. of patients enrolled Study Population |
|---|---|---|---|---|---|
| STP-2279-002<br>NCT 01420627<br>5 Sites in US | Open-label, multicenter, one-way crossover | Adagen: Weekly IM injection at a starting dose equivalent to that received at enrollment; patients on 2 or more weekly doses had their dose regimen consolidated into one weekly dose. SC-PEG rADA: Weekly IM. injections at a starting dose equivalent to the Adagen dose received at the end of the Adagen Lead-in Period. | Trough ADA plasma activity ≥ 15 mmol/L/h<br>Detoxification (trough erythrocyte dAXP levels)<br>Safety, tolerability and PK profile.<br>Immunogenicity<br>Immune status as determined by: absolute lymphocyte count, lymphocyte subset (B, T, and NK) analysis, and immunoglobulin (Ig) concentration (IgG, IgA, IgM).<br>Clinical status (infections and hospitalizations) during the treatment period compared to the prior 6 months. | Adagen Lead-in Phase: at least 3 weeks. SC-PEG rADA Treatment Phase: 21 Weeks SC-PEG rADA Maintenance Phase: continuing for at least 1 year | N=7<br>Withdrew consent: 1<br>Received SC-PEG rADA: 6<br>DC due to AE: 1<br>Ongoing: 5<br>Completed 106.4-115.4 weeks of treatment: 3 |
| STM-279-301 | Open-label, multicenter, uncomtrolled | SC-PEG rADA: Weekly IM injections at a starting dose of 0.067 to 0.2 mg/kg body weight. Dose could be increased or decreased by 0.033 mg/kg body weight at protocolspecified times | Trough ADA plasma activity<br>Detoxification (trough erythrocyte dAXP levels)<br>Safety<br>Immune status (B-T-NK /lymphocyte subset and quantitative immunoglobulin | Dose Adjustment Period: 5 weeks<br>Dose Maintenance Period: 16 weeks<br>Continuous Administration Extension Phase: planned until marketing approval in Japan. | N=4<br>Completed study through dose Maintenance (Week 21 [Day 148]): 3<br>DC due to fatal event that was not related to study treatment (Week 15 [Day 107]): 1 |

### 5.2. Review Strategy

Study STP-2279-002 (NCT 01420627) will be reviewed for safety and efficacy (See Sections 6 and 7 of this review, as well as Section 8). Maintenance of plasma ADA activity > 15 mmol/hr/L is the validated surrogate endpoint that will be used to assess efficacy. Study STM-279-301 povides additional supportive information in patients with a shorter duration of exposure to treatment with elepegadesmase-lvlr.

The numbers provided by the Applicant have been verified by the FDA Clinical Pharmacology Reviewer, and will be used in the presentation of efficacy and safety analyses.

## 6. Review of Relevant Individual Trials Used to Support Efficacy

### 6.1. Clinical Study STP-2279-002 (NCT 01420627)

#### 6.1.1. Study Design

Overview and Objective

Study STP-2279-002 is a first in human Phase 3, open-label, multicenter, single-arm, one way crossover study of SC-PEG rADA.

Trial Design

The clinical study was constituted by three phases: the Adagen Lead-in phase (minimum of 3 weeks), the SC-PEG rADA Treatment phase (Weeks T-1 through T-21), and the SC-PEG rADA Maintenance phase (continuing until the end of the study [full approval of SC-PEG rADA or early study termination]).

Patients enrolled in the study entered the Adagen Lead-in phase and received a once weekly IM dose of Adagen weekly and were assessed weekly for dAXP levels and ADA activity. Patients receiving Adagen more frequently than once a week had the doses consolidated to a once-weekly dose regimen.

Adagen dose adjustments were made if the patient did not meet protocolspecified criteria for detoxification (dAXP ≤0.02 mmol/L) and adequate ADA activity (trough level ≥15 mmol/hr/L).

At the end of the Adagen Lead-In Phase, once the patient met the protocol-specified criteria for detoxification (trough dAXP ≤0.02 mmol/L), adequate ADA activity (trough

level ≥15 mmol/hr/L) and was at least 10 years old, he/she had a full Adagen PK assessment performed. For patients < 10 years of age, full PK sampling was not performed in an effort to minimize blood collection volumes to ensure the safety of pediatric subjects (as per amended protocol Version 2.0, dated March 7, 2016).

Following the Adagen PK assessment, treatment with SC-PEG rADA was initiated at an equivalent starting dose calculated based on the Adagen dose received during the Adagen Lead-in Phase as follows:

SC-PEG rADA dose (mg/kg) = Adagen dose (U/kg) × 1 mg SC-PEG rADA/150 U Adagen

Patients were evaluated during treatment for trough dAXP levels, ADA activity, SC-PEG rADA PK, immune function (lymphocyte and lymphocyte subset counts and quantitative immunoglobulins), clinical status (hospitalizations, infections, growth, and overall survival), AEs, SAEs, safety laboratory and physical assessments, and immunogenicity to SC-PEG rADA. A PK assessment was performed during the SC-PEG rADA Treatment phase (Week T-9).

Compliance was assured by having the study drug administered under the supervision of the PI and/or designated site staff members while the patient was at the clinic/study site during visits.

After 21 weeks, patients were given the opportunity to remain on SC-PEG rADA treatment (SC-PEG rADA Maintenance Phase) until full approval of SC-PEG rADA or early study termination.

For SC-PEG rADA Treatment Weeks 12, 14, 16, 18, and 20 and during the SC-PEG rADA maintenance period, the patient was permitted to self-dose at home.

Study Endpoints

The primary and secondary efficacy objectives of the study were measured according to the following endpoint assessments:

- Trough dAXP Level (Primary Endpoint): Metabolic detoxification is defined as a trough dAXP concentration ≤0.02 mmol/L. Maintenance of detoxification in the SC-PEG rADA Treatment Phase is defined as meeting the target trough levels foreach of Weeks T-15, T-17, T-19, and T-21.
- Trough Plasma ADA Activity: Adequate trough ADA activity is defined as ADA activity ≥15 µmol/hr/mL (≥15 mmol/hr/L). Maintenance of adequate trough levels in the SC-PEG rADA Treatment Phase is defined as meeting the target trough levels for each of Weeks T-15, T-17, T 19, and T-21.

- Maintenance Phase Trough Plasma dAXP and ADA Activity: 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 Phase.
- Immune Status: Absolute lymphocyte count; B-, T-, and NK-lymphocyte subset analysis; and quantitative immunoglobulin concentration (IgG, IgA, IgM)
- Clinical Status:
    - Infections determined and defined as either clinically documented (patients with documented signs and symptoms of infection without positive microbiologic cultures) or microbiologically documented (patients with documented signs and symptoms of infection and with positive viral or bacterial cultures)
    - Hospitalizations
    - Survival through the SC-PEG rADA Maintenance Phase
    - Growth curve determinations (patients 18 years of age and younger)
    - Performance Status: Patients had scores reported appropriate to their age at the time of the assessment (Lansky for <16 years, Karnofsky Performance Scale [KPS] for ≥16 years). Performance status was collected during the physical examination as a safety procedure (Interim CSR STP-2279-002.

*Reviewer's Comment: For the purpose of this Review, the Agency has accepted and recognized the maintenance of plasma ADA activity greater than 15 mmol/hr/L as a validated surrogate endpoint for clinical efficacy, in the treatement of ADA-SCID.*

Statistical Analysis Plan

The statistical analyses performed for this study are described in a Statistical Analysis Plan (SAP), which is provided in Appendix 16.1.9 (Documentation of Statistical Methods) of the Interim Clinical Study Report for Protocol STP-2279-002.

All study data were presented only as patient profiles and by-patient listings for the interim analysis summarized in the present report. Due to the very small sample size, the Applicant did not calculate Descriptive or inferential statistics.

Protocol Amendments

After 5 patients had been enrolled, an amended version (Version Number 2.0) of the original study protocol was implemented on March 7, 2016. Substantive changes included in the amendment (excluding administrative and typographical changes) were as follows:

- The enrollment target was revised to specify that enough patients were to be

enrolled to ensure inclusion of 6 evaluable patients.

- Criteria for entering PK assessment in the Adagen® lead-in phase and the EZN-2279 treatment phase (trough dAXP levels ≤0.02 mmol/L and trough plasma ADA activity ≥15 mmol/hr/L [following dose adjustment if needed]) were clarified by additionally specifying that the patient was considered to be fully detoxified.
- Additional DSMC reviews of study data were specified: after all patients completed the SC-PEG rADA Treatment Phase (i.e., Week T-21) and when all patients completed 1 year (i.e, 2 maintenance cycles) of treatment with SC-PEG rADA.
- A provision was added specifying that any patient not completing the SC-PEG rADA treatment phase (i.e., completion of Week T-21) was considered unevaluable and could be replaced to achieve 6 evaluable patients.
- An additional immunogenicity assessment was mandated if results of ADA activity indicated an unexpected reduction in activity from previous sampling timepoints and if there was an adequate amount of sample remaining for analysis.
- Requirements for PK assessments were revised to specify that all patients <10 years of age were to have only limited PK sampling done (trough samples along with 48 hours post-dose samples during Adagen® Lead-in Week T-5 and SC-PEG rADA Week T-9).
- Definitions of AEs, unexpected AEs, and SAEs were clarified.

Changes in Planned Analyses

Summary data tables planned in the SAP were not produced for the interim analysis. All study data were presented only as patient profiles and by-patient listings.

Given the very small number of patients, the Applicant believes the creation of summary tables is not likely to be useful and is potentially misleading because the lack of precision of the summary statistics with such a small sample size.

*Reviewer's Comment: This was agreed to with the Sponsor before the submission of the Interim Clinical Study Report to the Application.*

### 6.1.2. Study Results

Compliance with Good Clinical Practices

Study STP-2279-002 was conducted in the US under IND 100687 in accordance with the CFR governing the protection of human subjects (21 CFR part 50), and Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in

accordance with good clinical practice (GCP).

Financial Disclosure

The Applicant has submitted a signed Form FDA 3454, dated 10/04/2017, located in Module 1 of the Application in Section 1.3.4. The Applicant has no financial disclosures to report for the Principle Investigators involved in Study STP-2279-002 (See Appendix 13.2 of this review).

Patient Disposition

A total of 7 patients were enrolled in the study as of the data cutoff for this report; one was initially enrolled as ID (b) (6), was withdrawn due to not meeting inclusion criteria for ADA/dAXP levels during Adagen® lead-in, and later re-enrolled as ID (b) (6) (Table 3.). Six patients received EZN-2279: 1 patient discontinued EZN-2279 treatment after 1.1 weeks due to an AE, and the remaining 5 patients completed 8-115 weeks of EZN-2279 treatment, with 3 of these completing ≥106 weeks. One patient withdrew consent before starting study treatment.

Table 3. Patient Disposition (All Patients)

| Patient ID | Gender/Age/Race | Population[a] | Adagen Exposure Duration (weeks) | EZN-2279 Exposure Duration (weeks) | Completed Study | Discontinued Date/Day | Reason for Withdrawal |
|---|---|---|---|---|---|---|---|
| (b) (6) | Male/8/White | A | 2.1 | 1.1 | No | 2014-04-12 /43 | Adverse Event |
| | Male/19/Other | A/P/C | 3.1 | 115.4 | Ongoing | -- | -- |
| | Male/21/Other | A/P/C | 12.0 | 106.4 | Ongoing | -- | -- |
| | Male/37/Black or African American | A/P/C | 8.0 | 110.4 | Ongoing | -- | -- |
| | Female/30/White | A | 4.1 | -- | No | 2016-03-08/- | Patient Did Not Meet Inclusion #3 [screen failure] |
| | Female/30/White | A/P | 8.1 | 15.4 | Ongoing | -- | -- |
| | Female/16/White | A | 4.0 | 8.1 | Ongoing | -- | -- |
| | Female/8/White | -- | -- | -- | No | 2017-02-03/- | Subject Did Not Want Blood Drawn For Study Visits. [screen failure] |

-- = not applicable
a A=As-treated; P=PK; C=Completer
b Patient initially enrolled as ID (b) (6) was withdrawn and later re-enrolled as ID 006-002
Source: Applicant's Table 4 and Listings 16.2.1.1, 16.2.2.1

Protocol Violations/Deviations

Protocol deviations are summarized and are listed by deviation type in Section 10.2 of theApplicant's Interime Clinical Study Report (Source Applicant's Listing 16.2.4.1).

*Did not meet inclusion/exclusion criteria but entered in the study*

Patient ID (b) (6): [Adagen® PK Day 1 visit] Waiver granted for inclusion criteria #3 [Have both of the following during the Adagen® Lead-in phase of the study prior to SC-PEG rADA transition: (a) Trough plasma ADA activity □15 mmol/L/h while receiving Adagen®; (b) Total erythrocyte dAXP ≤0.02 mmol/L from a trough blood sample]
Applicant's Rationale: Patient did not achieve trough plasma ADA activity ≥15 mmol/L/h while receiving Adagen®. ADA activity (in mmol/L/h) was 15.3 at Week 10 but decreased to 9.7 at Week 11 and 10.4 at Week 12 (the final week of lead-in). Patient waived to continue to PK since dAXP levels were ≤0.02 mmol/L and the Medical Monitor, Lead PI, Scientific Consultant, and PI considered patient was stable and detoxified.

Patient ID (b) (6): [Screening visit] Patient was not stable on Adagen dosing for 6 months. Sponsor provided a waiver for this criteria to allow screening for the study.
Applicant's Rationale: Patient was not receiving Adagen® as her insurance would not cover Adagen® treatment.

Patient ID (b) (6): [PK Day 1 visit] Patient received inclusion criteria #3 [Have both of the following during the Adagen® Lead-in phase of the study prior to SC-PEG rADA transition: (a) Trough plasma ADA activity ≥15 mmol/L/h while receiving Adagen®; (b) Total erythrocyte dAXP ≤0.02 mmol/L from a trough blood sample] waiver to enter study.
Rationale: The patient had been clinically stable and detoxified for 2 consecutive weeks. Additionally, the ADA activity values in the last 2 weeks were 10.0 and 9.03 mmol/L/h. Patient did not have health insurance and was not routinely taking Adagen®. Patient enrolled in a compassionate use program and was receiving Adagen® for 1 month.

Patient ID (b) (6): [Screening visit] Subject wants to use abstinence as a form of birth control.
Rationale: The patient was 16 years old at the time of screening; subsequently, the patient is required to undergo pregnancy testing before visits.

*Study drug dosing deviations*

> Patient ID (b) (6): [Week T-1 and Week T-2 visits] Patient was dosed lot 3073a which was an old formulation which caused a repeat of Week T-1/Week T-2. [The formulation referred to was the initial formulation containing (b) (4), as described in Section 9.8.1.4.] This was captured as a deviation since, at the time, the formulation (b) (4) was to be used.

*Missed procedures*: Four patients had 1-3 missed visits or delays in laboratory sample processing.

*Other*: Five patients had 1-4 deviations each relating to errors in laboratory sample processing or insurance issues.

> *Reviewer's Comment: The Applicant's rationales for the protocol deviations, including missed procedures, are acceptable. Overall, the nature and frequency of such protocol deviations is not unexpected and should not significantly affect the review and interpretation of the data.*

Table of Demographic Characteristics

Table 4 Demographics and Diagnosis (As-treated Population)

| Patient ID | Gender/ Age (y) | Height (cm) Weight (kg) | Race | Ethnicity | ADA-SCID Diagnosis Date | First Adagen Dose Date | Dose (U/kg) | Current Regimen |
|---|---|---|---|---|---|---|---|---|
| (b) (6) | Male/ 8 | 112.1 / 17.1 | White | Not Hispanic or Latino | 2005-11 | (b) (4) | 43.9 | 2 times per week |
| | Male/ 19 | 157.8 / 53.2 | Other: Mexican-American | Hispanic or Latino | 1995-08 | | 28 | 2 times per week |
| | Male/ 21 | 163 / 45.6 | Other: Hispanic | Hispanic or Latino | 1994 | | 30 | 1 time per week |
| | Male/ 37 | 166 / 98 | Black or African American | Not Hispanic or Latino | 1977-09 | | 30 | 2 times per week |
| | Female/ 30 | 150 / 47.2 | White | Hispanic or Latino | 1991 | | 30 | 2 times per week |
| | Female/ 30 | 150 / 47.9 | White | Hispanic or Latino | 1991 | | 30 | 1 time per week |
| | Female/ 16 | 145 / 46.6 | White | Not Hispanic or Latino | 2003-12-03 | | 42.4 | 2 times per week |

a Patient initially enrolled as ID 006-001, was withdrawn, and later re-enrolled as ID 006-002.
Source: Listings 16.2.5.1, 16.2.6.1

Four male patients and 2 female patients were enrolled and treated (Table 4. Source: Applicant's Table 5, Listings 16.2.5.1, 16.2.6.1). These included 2 pediatric patients aged 8 and 16 years and 4 adults aged 19-37 years. All but 2 patients had a diagnosis of ADA-SCID within 1 year of birth. Weekly Adagen® dosages at enrollment ranged 28-88 U/kg/week.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)
The most frequently reported types of clinically significant medical history conditions reported were respiratory (5 patients) and immunological (4 patients) (Applicant's Table 6. Source: Applicant's Listing 16.2.8.1). Most conditions were ongoing at screening.

The Applicant's Table 7 in the Interim Clinical Study Report presents specific conditions reported by patient and system.

> *Reviewer's Comment: All patients had a history of, or ongoing multiple clinically significant conditions, many of which were considered disease-related. Examination and review of the Applicant's Table 7, of Clinically Significant Medical History by Patient and System, as well as the Source Listing 16.2.8.1 revealed a broad spectrum of multiple clinically significant medical events, commensurate with the severity of the consequences of living with ADA-SCID despite current management with available therapies, and reflecting an underlying dysimmune status, as manifested by atopy, celiac disease, psoriasis, and infections. No other clear pattern could be indentified.*

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

*Treatment Compliance*

For this interim analysis, self-dosing only occurred at one site (Site 004; 1 patient [ID (b) (6)]). SC-PEG rADA dosing records for this patient indicated full compliance with a once-weekly dosing schedule through Day 701 except for a single missed dose (See Applicants ICSR: Listing 16.2.13.1). The Applicant specifies that SC-PEG rADA was provided to this patient for home dosing via (b) (4) Site pharmacists would schedule a pick-up from (b) (4) in which a specific amount of SC-PEG rADA would be packaged, with shipping storage conditions maintained (b) (4) would deliver directly to the patient's home that same day and take back the temperature recording device and container. Patients were expected to store the SC-PEG rADA in their refrigerator. TempTale data were downloaded by (b) (4) and provided to Leadiant. All of these logistics were done to maintain chain of custody and ensure adequate temperature conditions.

> *Reviewer's Comment: The method used to account for study drug, appears acceptable, although no further detail is provided as to how the study drug was self-administered. Nevertheless, the level of plasma ADA activity achieved in this patient, support good*

*compliance with study drug administration. (See plasma ADA activity data for Patient 004-001 in Tables 5, 6, and 7 of this review).*

The Applicant further comments in Section 11.3 of the ICSR that other patients (IDs (b) (6), (b) (4), (b) (6)) were dosed in the clinic. Patient ID (b) (6) did not achieve Week T-12, and Patient ID (b) (6) did not do home dosing at the time of the interim analysis. Site 005/Rubinstein opted not to do home dosing so as to better assess patient treatment compliance. Additionally, Patient ID (b) (6) has left hemiparesis, making it difficult for the patient to dose himself.

*Concomitant Medications*

All patients had received numerous medications prior to enrollment in the study, and were receiving ongoing medications at enrollment to manage the numerous concomitant conditions.

Medications received concomitant to study treatment (standardized terms, in alphabetical order) are summarized below (based on the Applicant's Listings 16.2.26.1.1, 16.2.26.1.2). Medications were received concomitant to both Adagen® and SC-PEG rADA treatment, with the following exceptions: an asterisk (*) denotes medications received concomitant to SC-PEG rADA treatment only, and a double asterisk (**) denotes medications received concomitant to Adagen® treatment only.

- Patient ID (b) (6): amoxicillin, Bactrim, immunoglobulin human normal, paracetamol
- Patient ID (b) (6): antifungals for topical use*, azelastine hydrochloride*, Bactrim, carbamazepine, cetirizine hydrochloride, ciprofloxacin w/hydrocortisone*, docusate sodium*, ergocalciferol, fluticasone propionate, ibuprofen*, immunoglobulin human normal, lamotrigine, levofloxacin*, lidocaine*, macrogol, Maxitrol*, melatonin**, montelukast*, oseltamivir phosphate, pantoprazole sodium sesquihydrate, paracetamol, Polysporin sterile ophthalmic, risperidone, salbutamol, sodium chloride*, tolterodine l-tartrate*, xylocaine-epinephrine*
- Patient ID (b) (6): Augmentin**, azithromycin*, Bactrim, guaifenesin, mometasone furoate*, moxifloxacin hydrochloride*, Oxycocet**, salbutamol sulfate
- Patient ID (b) (6): alprazolam*, Augmentin*, azithromycin*, enoxaparin*, immunoglobulin G human, Laryton*, oxycodone*, paracetamol*, vancomycin*
- Patient ID (b) (6): Bactrim**, budesonide w/formoterol fumarate**, calcium w/magnesium**, cefpodoxime**, Cheracol**, doxycycline**, ergocalciferol**, fluconazole**, ibuprofen**, immunoglobulin human normal**, Lactobacillus rhamnosus**, levofloxacin**, lidocaine**, multivitamins**, nystatin**, oxycodone**, protein supplements**, salbutamol sulfate**, Tums**, Tussin DM**

- Patient ID (b) (6): amlodipine besilate, azithromycin**, Bactrim, budesonide w/formoterol fumarate, colecalciferol, immunoglobulin human normal, omeprazole, salbutamol sulfate
- Patient ID (b) (6): aciclovir, EMLA, epinephrine, immunoglobulin G human, levothyroxine, salbutamol sulfate, triamcinolone acetonide

*Reviewer's Comment: Polypharmacy commensurate with the degree of concomitant medical conditions, not uncommon in patients with ADA-SCID, was the rule among the participants in this study.*

Efficacy Results – Primary Endpoint – Metabolic Detoxification

Of the 3 patients who received SC-PEG rADA through Week T-21, 2 met the predefined criterion for maintenance of detoxification (dAXP <0.02 mmol/L at all timepoints from Week T-15 to T-21) (Table 5). The third patient (ID (b) (6)) had dAXP 0.047 mmol/L at Week T-17 but levels below 0.02 mmol/L at all other timepoints during SC-PEG rADA treatment and maintenance (through Week 99) (Source: Applicant's Interim Clinical Study Report Listing 16.2.16.1). Patient IDs (b) (6) could not be evaluated for the primary endpoint because results through Week T-21 were not available for the interim analysis.

Table 5. Metabolic Detoxification

| Patient ID | Week T-15 | Week T-17 | Week T-19 | Week T-21 | Maintained Detoxification?[a] |
|---|---|---|---|---|---|
| (b) (6) | < 0.002 | 0.047 | < 0.002 | < 0.002 | No |
| | < 0.002 | < 0.002 | < 0.002 | < 0.002 | Yes |
| | < 0.002 | < 0.002 | < 0.002 | < 0.002 | Yes |

NOTE: The LLQ for dAXP was 0.002 mmol/L.
a dAXP <0.02 mmol/L at all timepoints from Week T-15 to T-21
Source: Listing 16.2.16.1

*Reviewer's Comment: While the Applicant's primary efficacy endpoint, of maintained detoxification is evidence of clinical benefit, our opinion has evolved to consider maintenance of plasma ADA activity consistently above 15 mmol/L/h as a validated surrogate marker of the efficacy of enzyme replacement therapy in the treatment of ADA-SCID, in so far as prolonged detoxification cannot be maintained without maintaining such levels of plasma ADA activity. Moreover, the first sign of treatment failure, due to non-adherence or development of neutralizing antibodies, is a decrease of plasma ADA activity to sub-therapeutic levels less than 15 mmol/hr/L, which should be addressed before trough dAXP levels rise above 0.02 mmol/L.*

Data Quality and Integrity

No OSI inspections were performed or requested for this clinical study. No anomalies or inconsistencies have been identified during the conduct of this clinical review.

Efficacy Results – Secondary and other relevant endpoints

*Plasma ADA activity in Adagen® Lead-In Phase*

At PK Day 1 (end of Adagen® lead-in), all patients met the criterion for detoxification (erythrocyte dAXP <0.02 mmol/L). All but 2 patients met the criterion for adequate trough plasma ADA activity (≥15 mmol/hr/L). Activity for Patient ID (b) (6) was slightly under this level (14.5 mmol/hr/L). Activity for Patient ID (b) (6) was 9.02 mmol/hr/L; a waiver was granted for this patient to enter the SC-PEG rADA treatment phase.

Trough dAXP levels and ADA activity for the Adagen lead-in phase are summarized for the as-treated population in the Applicant's Table 9 copied in Table 6 below.

Table 6. Trough dAXP Levels and ADA Activity in Adagen® Lead-In Phase (As-treated Population)

| Patient ID/ Assessment (Units) | Screening | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 9 | Week 10 | Week 11 | Week 12 | PK Day 1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (b) (6) | | | | | | | | | | | | | | |
| dAXP (mmol/L) | <0.002 | -- | <0.002 | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | <0.002 |
| ADA activity (mmol/hr/L) [a] | 19.632 | -- | 15.156 | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | 18.084 |
| (b) (6) | | | | | | | | | | | | | | |
| dAXP (mmol/L) | <0.002 | <0.002 | <0.002 | <0.002 | -- | -- | -- | -- | -- | -- | -- | -- | -- | <0.002 |
| ADA activity (mmol/hr/L) [a] | 17.3 | 20.9 | 10.9 | 14.2 | -- | -- | -- | -- | -- | -- | -- | -- | -- | 14.5 |
| (b) (6) | | | | | | | | | | | | | | |
| dAXP (mmol/L) | 0.020 | 0.016 | <0.002 | -- | -- | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 |
| ADA activity (mmol/hr/L) [a] | <1.8 | <1.8 | 6.1 | -- | -- | 3.2 | <1.8 | 10.6 | 14.9 | 10.9 | 15.3 | 9.7 | 10.4 | 17.6 |
| (b) (6) | | | | | | | | | | | | | | |
| dAXP (mmol/L) | 0.014 | 0.015 | <0.002 | -- | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | -- | -- | -- | -- | <0.002 |
| ADA activity (mmol/hr/L) [a] | <1.8 | <1.8 | <1.8 | -- | <1.8 | 10.7 | 10.7 | 17.0 | 20.1 | -- | -- | -- | -- | 22.4 |
| (b) (6) | | | | | | | | | | | | | | |
| dAXP (mmol/L) | 0.012 | 0.008 | 0.016 | 0.010 | <0.002 | <0.002 | -- | -- | -- | -- | -- | -- | -- | -- |
| ADA activity (mmol/hr/L) [a] | 5.9 | <1.8 | <1.8 | 4.8 | <1.8 | 4.1 | -- | -- | -- | -- | -- | -- | -- | -- |
| (b) (6) | | | | | | | | | | | | | | |
| dAXP (mmol/L) | 0.008 | -- | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | -- | -- | -- | -- | <0.002 |
| ADA activity (mmol/hr/L) [a] | <lloq | -- | <lloq | 9.60 | 9.07 | 12.07 | 7.21 | 10.66 | 9.47 | -- | -- | -- | -- | 9.02 |
| (b) (6) | | | | | | | | | | | | | | |
| dAXP (mmol/L) | 0.002 | 0.006 | <0.002 | <0.002 | <0.002 | -- | -- | -- | -- | -- | -- | -- | -- | <0.002 |
| ADA activity (mmol/hr/L) [a] | 25.15 | 11.74 | 11.49 | 14.49 | 12.36 | -- | -- | -- | -- | -- | -- | -- | -- | 16.10 |

NOTE: The LLQ for dAXP was 0.002 mmol/L.

a Adagen® specificity

--: Data not available (patient discontinued prior to visit or visit not done or data not available as of data cutoff date);
lloq=lower limit of quantitation Source: Listings 16.2.16.1, 16.2.17.1

*Plasma ADA activity in SC-PEG rADA Treatment Phase*

Trough dAXP levels and ADA Activity from the SC-PEG rADA treatment phase are presented for the as-treated population in the Applicant's Table 10 copied in Table 7 below.

All patients met the predefined criterion for maintaining detoxification (erythrocyte dAXP <0.02 mmol/L) throughout the SC-PEG rADA treatment phase except for Patient ID (b) (6) at Week T-17 and ID (b) (6) at Week T-13.

All patients achieved adequate ADA activity by Weeks T-3 to T-7 and maintained adequate activity at subsequent visits. All 3 patients who received SC-PEG rADA through Week T-21 met the predefined criterion for maintenance of adequate ADA activity (≥15 mmol/hr/L at all timepoints from Week T-15 to T-21).

Table 7. Trough dAXP Levels and ADA Activity in SC-PEG rADA Treatment Phase (As-treated Population)

| Patient ID/ Assessment (Units) | PK Day 1 | Week T-1 | Week T-3 | Week T-5 | Week T-7 | Week T-8 | Week T-9 | Week T-10 | Week T-11 | Week T-13 | Week T-15 | Week T-17 | Week T-19 | Week T-21 | EOS/ Early D/C |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (b) (6) | | | | | | | | | | | | | | | |
| dAXP (mmol/L) | <0.002 | <0.002 | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | <0.002 |
| ADA activity (mmol/hr/L) [a] | 31.668 | 41.49 | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | 82.224 |
| (b) (6) | | | | | | | | | | | | | | | |
| dAXP (mmol/L) | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | 0.047 | <0.002 | <0.002 | -- |
| ADA activity (mmol/hr/L) [a] | 13.2 | 10.9 | 30.2 | 25.9 | 33.9 | 29.2 | 32.9 | 29.0 | 33.9 | 35.6 | 35.5 | 32.3 | 34.1 | 28.2 | -- |
| (b) (6) | | | | | | | | | | | | | | | |
| dAXP (mmol/L) | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | -- |
| ADA activity (mmol/hr/L) [a] | 12.2 | 10.2 | 21.2 | 28.4 | 35.7 | 33.8 | 36.4 | 37.7 | 37.7 | 36.6 | 33.1 | 27.6 | 32.0 | 31.4 | -- |
| (b) (6) | | | | | | | | | | | | | | | |
| dAXP (mmol/L) | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 | 0.032 | <0.002 | <0.002 | <0.002 | <0.002 | -- |
| ADA activity (mmol/hr/L) [a] | 18.0 | 17.4 | 28.2 | 30.1 | 40.3 | 48.7 | 44.4 | 46.2 | 42.0 | 46.6 | 43.3 | 29.9 | 26.1 | 28.9 | -- |
| (b) (6) [b] | | | | | | | | | | | | | | | |
| dAXP (mmol/L) | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| ADA activity (mmol/hr/L) [a] | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| (b) (6) | | | | | | | | | | | | | | | |
| dAXP (mmol/L) | <0.002 | <0.002 | <0.002 | -- | <0.002 | <0.002 | -- | <0.002 | <0.002 | -- | -- | -- | -- | -- | -- |
| ADA activity (mmol/hr/L) [a] | 11.38 | 11.33 | 11.86 | -- | 33.22 | 30.43 | 32.13 | 23.48 | 19.29 | -- | -- | -- | -- | -- | -- |
| (b) (6) | | | | | | | | | | | | | | | |
| dAXP (mmol/L) | <0.002 | <0.002 | <0.002 | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| ADA activity (mmol/hr/L) [a] | 17.78 | 14.26 | 25.00 | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |

NOTE: The LLQ for dAXP was 0.002 mmol/L.

a SC-PEG rADA specificity

b Patient discontinued before entering SC-PEG rADA treatment phase.

--: Data not available (patient discontinued prior to visit or visit not done or data not available as of data cutoff date); EOS/Early D/C= end of study/early discontinuation Source: Applicant's Table 10 and Listings 16.2.16.1, 16.2.17.1

*Maintenance Phase dAXP and ADA Activity*

All 3 patients who entered maintenance treatment maintained detoxification (dAXP <0.02 mmol/L) and adequate ADA activity (≥15 mmol/L/h) in the maintenance phase through Week 99, as summarized in the Table 8 below.

Table 8. Trough dAXP Levels and ADA Activity in SC-PEG rADA Maintenance Phase (As-treated Population)

| Patient ID | Assessment (Units) | Maint. Week 34 [a] | Maint. Week 47 [a] | Maint. Week 73 [a] | Maint. Week 86 [a] | Maint. Week 99 [a] |
|---|---|---|---|---|---|---|
| (b) (6) | dAXP (mmol/L) | < 0.002 | < 0.002 | 0.006 | < 0.002 | < 0.002 |
| | ADA (EZN-2279) (mmol/hr/L) | 31.1 | 23.7 | 39.96 | 34.96 | 27.33 |
| | dAXP (mmol/L) | < 0.002 | < 0.002 | < 0.002 | < 0.002 | < 0.002 |
| | ADA (EZN-2279) (mmol/hr/L) | 31.1 | 38.3 | 47.55 | 54.96 | 48.97 |
| | dAXP (mmol/L) | < 0.002 | < 0.002 | < 0.002 | < 0.002 | < 0.002 |
| | ADA (EZN-2279) (mmol/hr/L) | 29.77 | 37.5 | 42.19 | 45.47 | 57.09 |

NOTE: The LLQ for dAXP was 0.002 mmol/L. a Scheduled assessment time ±3 weeks
Source: Protocol STP-2279-002 Interim Clinical Study Report. Listings 16.2.16.1, 16.2.17.1

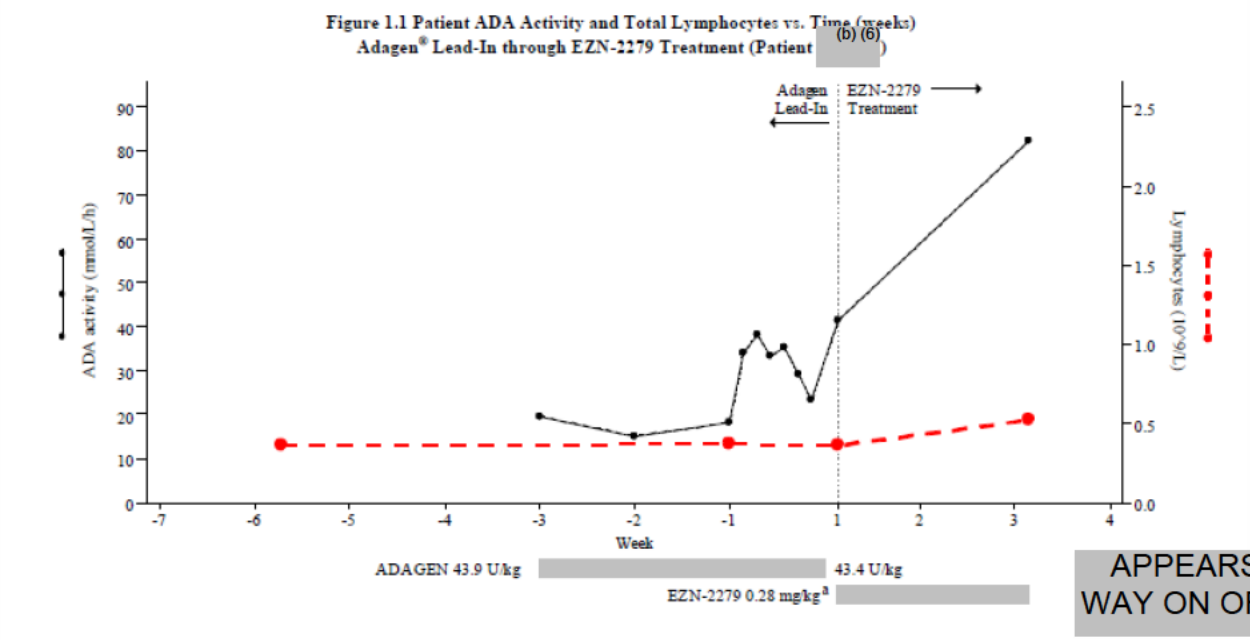
The figures below summarize plasma ADA activity, and lymphocyte counts over time for all patients enrolled in Study STP-2279-002, as provided in the Applicant's response, dated June 15, 2018, to the Agency's request, dated May 23, 2018, for updated figures showing ADA activity and total lymphocyte counts over time for patients enrolled in Study STP-2279-002 (BLA 761092/SN0016). These are based on updated listings for trough plasma ADA activity (Listing 16.2.17.1) and were generated by the Applicant using cumulative data from the beginning of the study to the the new cutoff date of March 28, 2018. Each figure summarizes the the Adagen dose during the Adagen Lead-In Period in unit per kilogram (U/kg) and the SC-PEG rADA dose in mg/kg during the SC-PEG rADA Treatment Period and Maintenance Phase. Plasma ADA activity is represented over time in mmol/hr/L. Peripheral blood lymphocyte counts are also presented over time in $10^9$/L.

Plasma ADA activity increased in all patients after conversion from Adagen Lead-In dose to SC-PEG rADA. All patients, with the exception the first 4 weeks in Patient (b) (6) (Figure 6), maintained a plasma ADA activity > 15 mmol/hr/L, all but Patient (b) (6) reached and maintained ADA activity > 30 mmol/hr/L during the SC-PEG rADA Treatment Period and Maintenance Period.

After crossover from Adagen to an equivalent dose of SC-PEG rADA, there was also a trend in increased peripheral blood lymphocyte counts, which was consisitent with increased ADA-

plasma activity; however, no reliable comparison between the study products could be made, since there were insufficient observation of lymphocyte counts under Adagen treatment, prior to conversion. Nevertheless, a trend in the opposite direction would have been worrisome.

**Figure 2.**



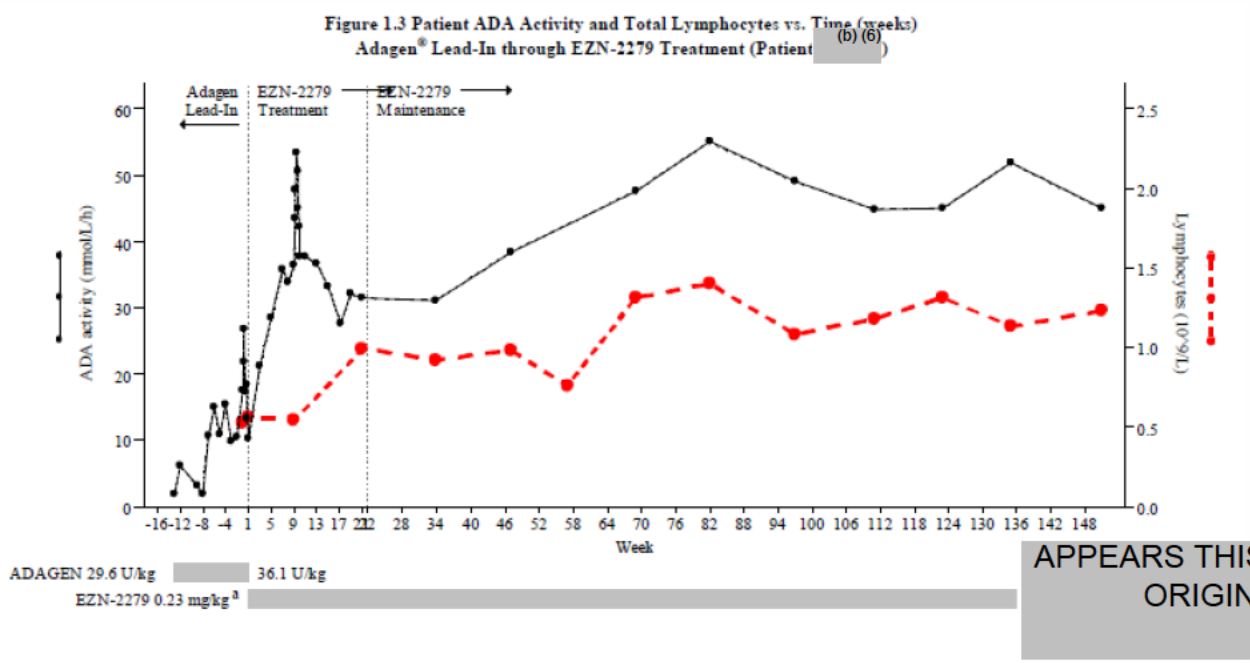

[a] EZN-2279 starting dose, 0.28 mg/kg, is equivalent to last Adagen dose of 43.4 U/kg.
Note: During Adagen Lead in at Week -1 and EZN-2279 phase at Week 9, multiple and more frequent sampling were collected to measure ADA activity to carry out PK analysis. For all other assessment time points, trough levels for ADA activity were measured and are displayed.
Note: Values for dAXP were below target levels of 0.02 µmol/mL for all assessment time points.
Please note that negative week refers to Adagen Lead in phase and positive week to EZN-2279 phase.

**Figure 3.**


APPEARS THIS WAY ON ORIGINAL

[a] EZN-2279 starting dose, 0.19 mg/kg, is equivalent to last Adagen dose of 27.9 U/kg.
Note: During Adagen Lead in at Week -1 and EZN-2279 phase at Week 9, multiple and more frequent sampling were collected to measure ADA activity to carry out PK analysis. For all other assessment time points, trough levels for ADA activity were measured and are displayed.
Note: Values for dAXP were below target levels of 0.02 µmol/mL for all assessment time points.
Please note that negative week refers to Adagen Lead in phase and positive week to EZN-2279 phase.

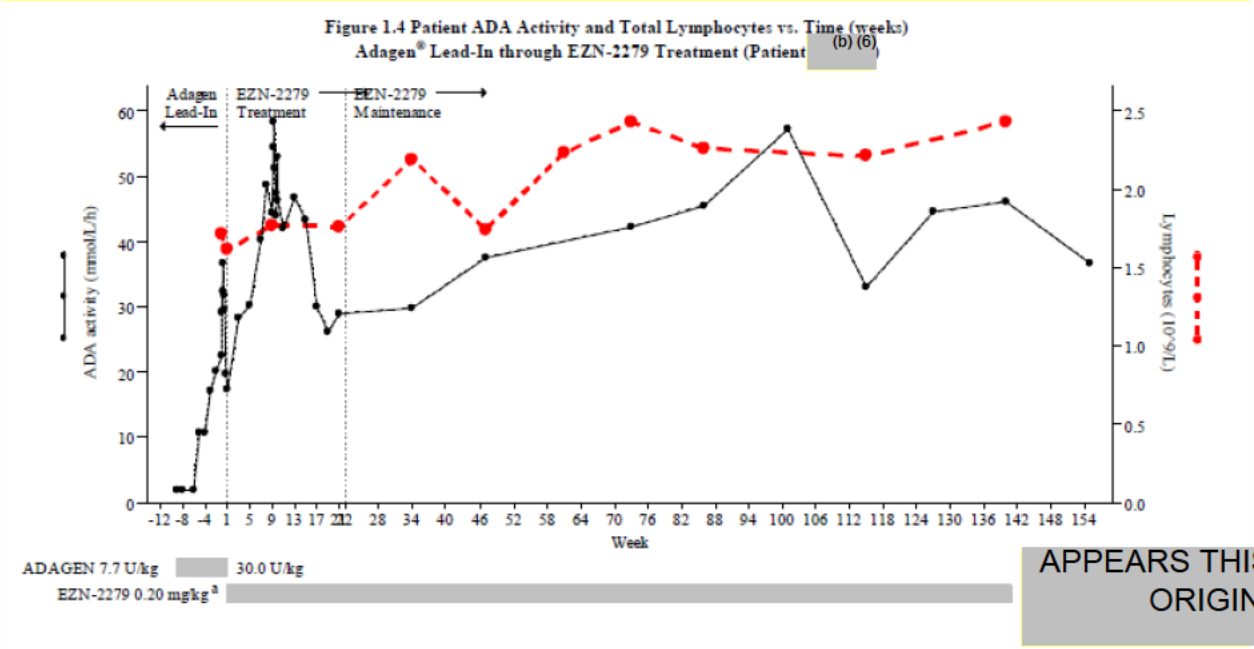
**Figure 4.**




APPEARS THIS WAY ON ORIGINAL

[a] EZN-2279 starting dose, 0.23 mg/kg, is equivalent to last Adagen dose of 36.1 U/kg.
Note: During Adagen Lead in at Week -1 and EZN-2279 phase at Week 9, multiple and more frequent sampling were collected to measure ADA activity to carry out PK analysis. For all other assessment time points, trough levels for ADA activity were measured and are displayed.
Note: Values for dAXP were below target levels of 0.02 µmol/mL for all assessment time points.
Please note that negative week refers to Adagen Lead in phase and positive week to EZN-2279 phase.

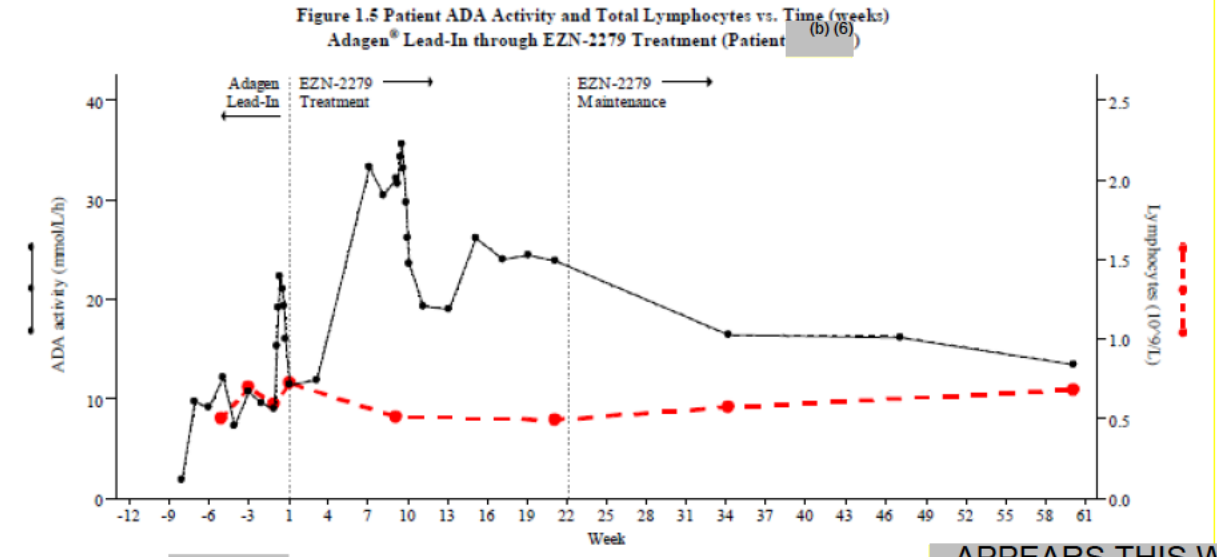
**Figure 5.**




APPEARS THIS WAY ON ORIGINAL

[a] EZN-2279 starting dose, 0.20 mg/kg, is equivalent to last Adagen dose of 30.0 U/kg.
Note: During Adagen Lead in at Week -1 and EZN-2279 phase at Week 9, multiple and more frequent sampling were collected to measure ADA activity to carry out PK analysis. For all other assessment time points, trough levels for ADA activity were measured and are displayed.
Note: Values for dAXP were below target levels of 0.02 µmol/mL for all assessment time points.
Please note that negative week refers to Adagen Lead in phase and positive week to EZN-2279 phase.

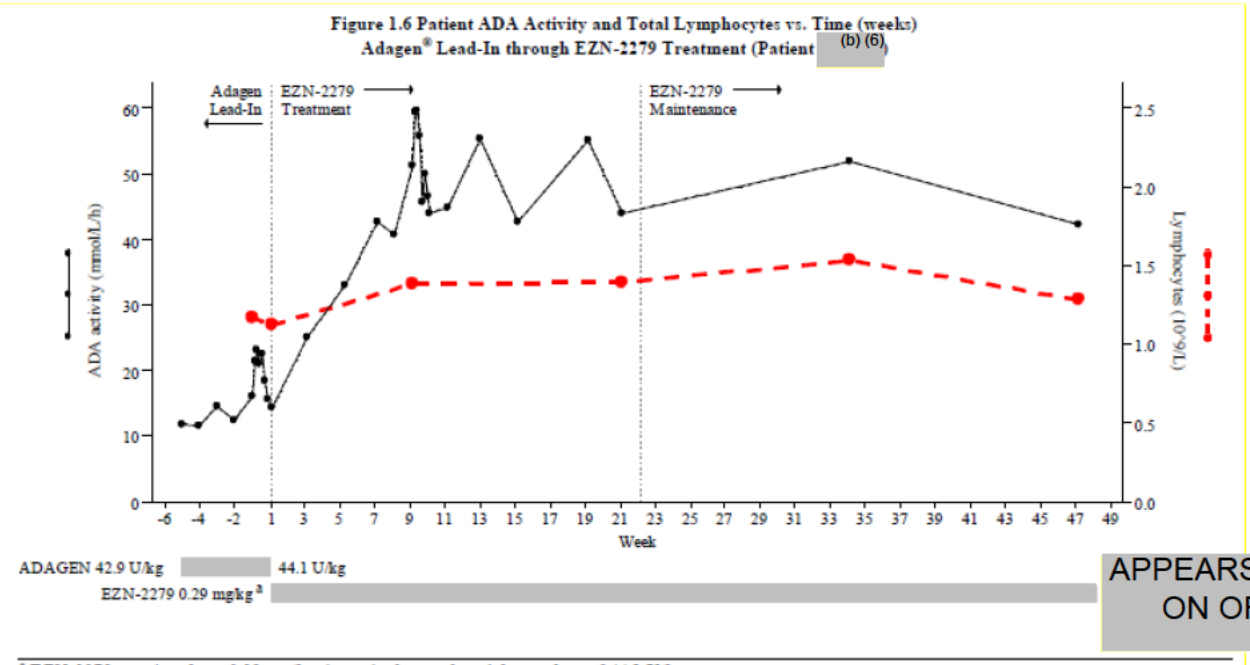
**Figure 6.**




APPEARS THIS WAY ON ORIGINAL

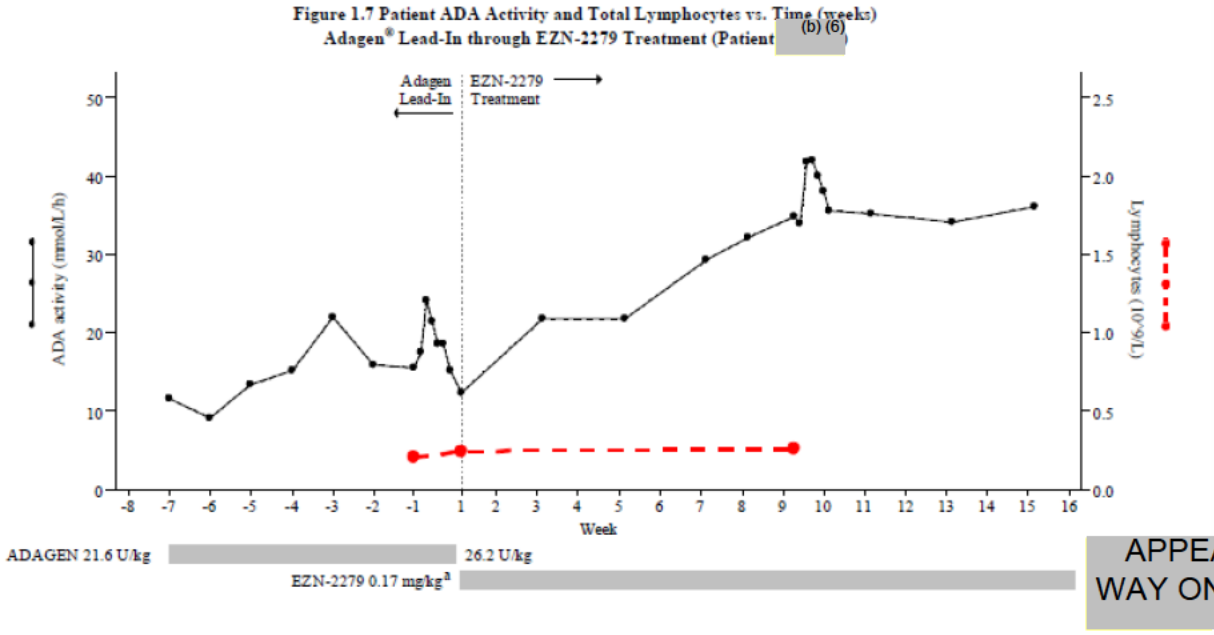
[a] EZN-2279 starting dose, 0.21 mg/kg, is equivalent to last Adagen dose of 32.2 U/kg.
Note: During Adagen Lead in at Week -1 and EZN-2279 phase at Week 9, multiple and more frequent sampling were collected to measure ADA activity to carry out PK analysis. For all other assessment time points, trough levels for ADA activity were measured and are displayed.
Note: Values for dAXP were below target levels of 0.02 µmol/mL for all assessment time points.
Please note that negative week refers to Adagen Lead in phase and positive week to EZN-2279 phase.

**Figure 7.**




APPEARS THIS WAY ON ORIGINAL

**Figure 8.**




APPEARS THIS WAY ON ORIGINAL

[a] EZN-2279 starting dose, 0.17 mg/kg, is equivalent to last Adagen dose of 26.2 U/kg.
Note: During Adagen Lead in at Week -1 and EZN-2279 phase at Week 9, multiple and more frequent sampling were collected to measure ADA activity to carry out PK analysis. For all other assessment time points, trough levels for ADA activity were measured and are displayed.
Note: Values for dAXP were below target levels of 0.02 µmol/mL for all assessment time points.
Please note that negative week refers to Adagen Lead in phase and positive week to EZN-2279 phase.

**Dose/Dose Response**

Doses of Adagen and subsequently of EZN-2279 were individualized for each Patient, and no dose response analyses were performed.

**Durability of Response**

Among the three patients who completed the SC-PEG rADA Treatment Phase of the study by the time of the submission of the clinical portion of the BLA, Patient (b) (6), Patient (b) (6) and Patient (b) (6), durability of the response to treatment in terms of maintence of detoxification and of plasma ADA activity > 15 mmol/hr/L (or even > 30 mmol/hr/L) was demonstrated for up to 156, 148, and 154 weeks, respectively. Information available in the 120 Day Safety Update on two additional Patients ((b) (6) and (b) (6)) who had completed the SC-PEG rADA Treatment Phase and entered the Maintenance Phase, show durability of the response for up to 61 weeks and 49 weeks respectively.

Persistence of Effect

All Patients, who achieved Plasma ADA activity ≥ 15 mmol/hr/L after conversion from Adagen to SC-PEG rADA, maintained Plasma ADA activity ≥ 15 mmol/hr/L for up to the last observation, ranging from 4 weeks (Patient (b) (6)) to 156 weeks (Patient (b) (6)).

Additional Analyses Conducted on the Individual Trial

On June 26, 2018, as requested by the Agency on March 20, 2018, the Applicant provided historical information on the intrapatient variability over time of ADA activity in plasma (trough levels before maintenance injection in patients with ADA-SCID treated with Adagen® (pegademase bovine) (See BLA 761092 SN0013, 1.11.2 Clinical Information Amendment) . Additonal information was provided on the intrapatient variability over time of ADA activity in patients administered Adagen during the lead-in phase of Study STP-2279-002. Finally, information was also provided on the intrasubject variability of plasma ADA activity in patients receiving SC-PEG rADA during the treatment and maintenance phase of Study STP-2279-002, and from Study STM-279-301. For the purpose of analysis of intrapatient variabilty, trough plasma ADA activity was normalized to the dose of 0.2 mg/Kg (equivalent to 30 U/Kg Adagen).

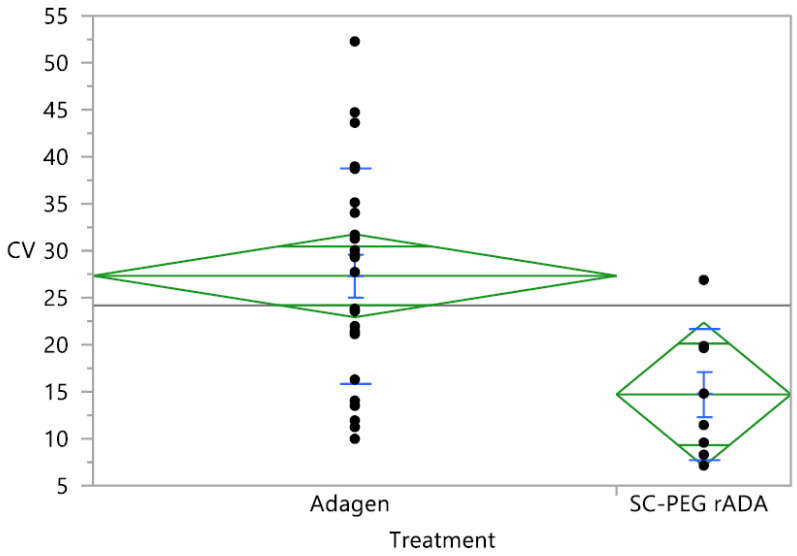
Information on ADA activity was available for analysis from Adagen pre-approval and post-approval data (NDA 19-818) in a total of 18 patients. Additional informations was available from 6 patients on Adagen during the lead-in phase of study STP-2279-002.

The relative intrapatient variability in trough ADA activity was assessed using the coeficients of variation (CV, or relative standard deviation) for each patient in the Adagen or SC-PEG rADA-treated group obtained from the distribution analysis. Distributions of the overall mean CVs were examined for the Adagen- and SC-PEG rADA-treated groups to obtain a measure of the average variability in trough ADA levels of patients treated with either drug.

The analysis showed that Adagen-treated patients (N= 24) had a mean CV of 27.3% (CI=22-32%), and SC-PEG rADA-treated patients (N=8) had a mean CV of 14.7% (CI=9-20%). By the Applicant's analysis, Student's T-test indicated that the mean CV of the Adagen-treated group was significantly higher than that of the SC-PEG rADA-treated group (p = 0.0066). These data suggest that patients treated with SC-PEG rADA are able to maintain more stable (less variable) trough levels of ADA activity and thus they may achieve more consistent metabolic detoxification compared to patients receiving Adagen treatment. This analysis is summarized in the Applicant's Figure 3, reproduced below as Figure 9:

Figure 9.

Analysis of Intrapatient Variability – Adagen and SC-PEG rADA




Means and Std Deviations

| Level | Number | Mean | Std Dev | Std Err Mean | Lower 95% | Upper 95% |
|---|---|---|---|---|---|---|
| Adagen | 24 | 27.3374 | 11.4711 | 2.3415 | 22.494 | 32.181 |
| SC-PEG rADA | 8 | 14.7124 | 6.9129 | 2.4441 | 8.933 | 20.492 |

Additional analyses of trough ADA plasma activity were performed by the Clinical Pharmacology Reviewer. The percent of of plasma samples with ADA activity above 15 mmol/L/h and 30 mmol/L/h among the 6 patients from Study STP-2279-002, while on EZ SC-PEG rADA are summarized in the table below.

Table 9. Summary of Plasma Samples with ADA Activity above 15 and 30 mmol/hr/L

| Patient Number | (b) (6) | | | | | |
|---|---|---|---|---|---|---|
| Percent Samples > 15 mmol/L/h | 100% | 96% | 96% | 100% | 90% | 100% |
| Percent Samples > 30 mmol/L/h | 100% | 75% | 85% | 85% | 40% | 90% |

*Reviewer's Comment: The information and analyses on intrapatient variability, provided by the Applicant, were examined and reproduced by FDA reviewers. This reviewer agrees*

*that the analyses support that REVCOVI provides superior clinical benefit compared to Adagen, with respect to stability of what we have come to agree is a validated surrogate endpoint for clinical efficacy in ERT for ADA-SCID, namely maintenance of trough plasma ADA activity above 15 mmol/hr/L.*

*In addition, although patients were converted from their dose of Adagen, adjusted during the lead-in period to achieve trough plasma ADA activity > 15 nmol/L/h, to an equivalent dose of* SC-PEG rADA*, their trough plasma ADA increased and remained mainly above 30 mmol/hr/L. This is the level of exposure that should be kept in mind when assessing safety in Section 8.*

## 6.2. Clinical Study STM-279-301

### 6.2.1. Study Design

Overview and Objective

Study Title: A Multicenter, Open-Label, Uncontrolled Clinical Study of STM-279[9] in Patients with Adenosine Deaminase (ADA) Deficiency (Phase III Clinical Study) [Protocol No. STM-279-301]

Study STM-279-301 is an open label clinical trial intended to evaluate the efficacy and safety of SC-PEG rADA injected IM in patients with ADA-SCID.

*Reviewer's Comment: This study is still ongoing. An interim report containg data from the first 4 patients enrolled (data cutoff March 8, 2017) in the study was submitted on October 24, 2017 with the Clinical Section of the BLA, to provide supportive information.*

Trial Design

Study STM-279-301 is a multicenter, open-label, uncontrolled Phase III clinical study of STM-279 in patients with ADA-SCID. The study consists of an evaluation phase (including a 5-week STM-279 dose adjustment period and a 16-week STM-279 dose maintenance period) and a continuous STM-279 administration (extension) phase planned to continue until marketing approval.

Key Inclusion Criteria

[9] STM-279 is the code name used to identify SC-PEG-rADA a.k.a EZN-2279 in this study and study report, and will be used in the description of the study design and study results.

Patients diagnosed with ADA-SCID by genetic diagnosis in the past, or patients diagnosed with ADA-SCID by investigators based on clinical symptoms and ADA activity, for whom the principal investigator judged enzyme replacement therapy was necessary.

Key Exclusion Criteria

- Patients with severe thrombocytopenia (platelet count <50 x $10^9$/L)
- Female patients who were pregnant or lactating
- Female patients of childbearing potential who were unwilling to practice adequate contraception by use of a condom from the time of obtaining informed consent to the completion of the continuous administration (extension) phase
- Patients other than the above whom investigators or subinvestigators judged not eligible
- *Prohibited medications*: Use of vidarabine or pentostatin was prohibited from the time of obtaining informed consent to the completion of the continuous administration (extension) phase. The following drugs and therapies were prohibited from the time of obtaining informed consent to the completion of the evaluation phase: Adagen®, hematopoietic stem cell transplant, gene therapy, and other investigational products.

Study Drug, Dose and Mode of Administration

SC-PEG rADA was supplied by Leadiant Biosciences, Inc. (previously Sigma-Tau Pharmaceuticals, Inc. - Gaithersburg, MD, United States [US]) as an aqueous solution containing 1.6 mg/mL polyethylene glycol-mutated recombinant bovine adenosine aminohydrolase analogue (SC-PEG rADA) with sodium chloride, dibasic sodium phosphate heptahydrate, and monobasic sodium phosphate monohydrate. (The product is also referred to as EZN-2279 and elapegademase [International Nonproprietary Names (INN) and United States Adopted Name (USAN) established name] in the US.)

SC-PEG rADA was administered once weekly via intramuscular injection at a starting dose of 0.067- 0.2 mg/kg body weight. The starting dose and dose titration were based on the Adagen package insert converted to an equivalent dose of STM-279. Patients who had not been treated with Adagen within 4 weeks before informed consent were administered their 1st dose of SC-PEG rADA at 0.1 mg/kg body weight and the 2nd and 3rd doses at 0.133 mg/kg body weight.

For patients who had been treated with Adagen within 4 weeks before informed consent, weekly SC-PEG rADA dose levels at the 1st dose to 3rd dose were determined according to the most recent Adagen dose (consolidated to a single weekly dose if necessary) using the following dose conversion equation:

Dose of SC-PEG rADA (mg/kg) = Dose of Adagen (U/kg) × 1 mg SC-PEG rADA / 150 U Adagen

The starting dose of 0.067-0.2 mg/kg body weight (determined as described below) could be increased or decreased by 0.033 mg/kg body weight at specified times defined as follows.Assessments for dose modification were performed after the 3rd or 5th dose during the dose adjustment period. The dose to be given as the 4th dose or for the dose maintenance period was adjusted if any of the following was observed:

- erythrocyte deoxyadenosine nucleotide (dAXP) level >0.02 mmol/L (blood dAXP could be used if erythrocyte result was unavailable); or
- serum ADA activity <1100 U/L (equivalent to <15 mmol/hr/L in plasma[10]); or
- onset, no change, or exacerbation of clinical symptoms (e.g., pneumonia, diarrhea); or
- change/abnormality in laboratory data such as immune function and liver function; or safety concerns.

Duration of Treatment

Dose adjustment period: approximately 5 weeks
Dose maintenance period: approximately 16 weeks
Continuous administration (extension) phase: Planned to continue until marketing approval in Japan.

Study Endpoints

[10] As specified by the Applicant, in this report, dAXP concentration is shown in mmol/L, which is numerically equivalent to the units used in the study protocol (μmol/mL). Serum ADA activity is shown in U/L; the protocol-specified threshold for adequate serum ADA activity (1100 U/L) is equivalent to plasma ADA activity of 15 mmol/hr/L. The equivalence of ADA activity of 1100 U/L (as measured by the laboratory in Japan used for the study) to 15 mmol/L/hr is based on results of a cross-validation study (Study Report A1502).

Efficacy

The protocol prespectively defined the following parameters, which would form the basis for evaluation of efficacy, without specifying which would be primary or secondary efficacy endpoints:

1) Trough erythrocyte dAXP concentration (not available for this interim report)
2) Trough blood dAXP concentration
3) Trough plasma ADA activity (available for PK assessment; not available for efficacy assessment for this interim report)
4) Trough serum ADA activity
5) Immune status
    i) Absolute lymphocyte count
    ii) Lymphocyte subset
        -CD3+ (Mature T cells) - Percent and Absolute
        -CD3+ CD8+ (Suppressor T Cells) - Percent and Absolute
        -CD3+ CD4+ (Helper Cells) - Percent and Absolute
        -CD (16+56)+ (Natural Killer Cells) - Percent and Absolute
        -CD19+ (B Cells) - Percent and Absolute
        -Absolute Lymphocytes (CD45+)
        -%CD4 (Helper Cells) / %CD8 (Suppressor T Cells)
    iii) Quantitative immunoglobulin concentration
6) Body height, body weight (components of vital signs; evaluated to assess general clinical condition)

Reviewer's Comment: While these assessments are representative of laboratory assessments used to guide dosing of treatment of ADA-SCID patients with Adagen, and/or the immune status of ADA-SCID patients, this study did not identify a specific hypothesis to be tested using prespecified primary endpoint.

Statistical Analysis Plan

(b) (4) the Japanese Sponsor conducting Study STM-279-301, had not planned an d interim analysis of efficacy and safety data for submission to the US BLA. The analyses presented in the summary report were conducted by the Applicant (Lediant) using raw data transferred (b) (4)

The interim statistical analysis outlined in Section 10 STATISTICAL METHODS of the interim report is also the one described in the Statistical Analysis Plan (SAP) for Lediant's Study STP-2279-002 described in Section 6.1 of this review.

No summary data tabulation or formal statistical analysis was performed. All study data were presented within listings and patient profiles for the current interim analysis.

Three analysis populations were defined:

- The As-Treated Population (the population used for all listings, except as noted) is equivalent to the protocol-defined "Safety Analysis Set," consisting of enrolled patients for whom safety evaluations exist following at least 1 dose of SC-PEG rADA. For this report, this population included all patients enrolled as of the data cutoff date.
- The PK Population consists of those patients from the As-Treated Population who had at least one PK measurement.
- The Completer Population consists of those patients from the As-Treated Population who completed the 16 weeks of dose maintenance and also completed the evaluationsof the maintenance phase. This population was not used for data displays in this report.

Displays were produced for the following data:

- Study population: disposition, inclusion/exclusion criteria, and protocol deviations (listed for all study patients); demographics; prior treatments and medications; medical history; study drug administration
- Efficacy: trough blood dAXP levels, trough serum ADA activity, immune status (B-/T-/NK-lymphocyte subset counts and quantitative evaluation of immunoglobulin)
- Safety: all AEs, treatment-emergent AEs (new or worsening AEs during SC-PEG rADA treatment), concomitant medications, immunogenicity (antibody titers), clinical laboratory tests, vital signs, ECG

All AEs were coded using the Japanese translation of the Medical Dictionary for Regulatory Activities (MedDRA/J) Version 19.1. Prior and concomitant medications were coded using the World Health Organization dictionary of medical codes (WHO Drug) Version 2014.

Protocol Amendments

N/A

### 6.2.2. Study Results

Compliance with Good Clinical Practices

Study STM-279-301 was conducted in Japan [redacted] (b) (4) not under the US IND, in compliance with the requirements of 21CFR312,120 and in accordance with GCPs as it applies to foreign clinical studies not conducted under an IND.

Financial Disclosure

Information on financial dsiclosures is provided for this study in Section 1.4.3 of Module 1 of the BLA Submission. No potential concerns have been identified by this reviewer. (See also Appendix 13.2 of this review)

Patient Disposition

Four patients were enrolled in the study as of the data cutoff date of 08 March 2017, defined as the last date of available data transfer from (b) (4) to Leadiant with the last data point of 20 October 2016.

Three patients completed the study through dose maintenance (study Day 148), with an exposure to SC-PEG rADA of 20.1 weeks: Patient (b) (6) (male; age 25 years), Patient (b) (6) (female, age 16 years), and Patient (b) (6) (female, age 4.3 months).

One patient ( (b) (6); male age 3.4 months) discontinued the study on study Day 107 during the maintenance period (due to death resulting from worsening of respiratory failure on the discontinuation date [See Section 15.1.2 of the CSR]) and received an exposure of 15 weeks of treatment.

Protocol Violations/Deviations

For Patient (b) (6) (male age 3.4 months), who was newly diagnosed and had not been administered Adagen within 60 Days prior to obtaining consent, a dose of 0.4 mg/kg of body weight/week (0.2 mg/kg of body weight administered twice weekly) of SC-PEG rADA was administered which corresponds to the dose for newborns with ADA-SCID. This was based on the judgment of the investigator, who implemented a protocol deviation for this patient. The PMDA and ethics committee were informed about this deviation.

No other protocol violations or deviations were identified in the Interim Summary Report for STM-279-301.

Demographic Characteristics

All patients were of Asian Race:

Patient (b) (6) (male, age 25 years)
Patient (b) (6) (female, age 16 years)
Patient (b) (6) (female, age 4.3 months)
Patient (b) (6) (male, age 3.4)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

All patients had concomitant medications reported such as antibiotics, antifungal and antiviral meedications, and immunoglobulins as summarized in the Interim Study Report Listings 16.2.26.

Use of concomitant human immunoglobulin during treatment for each patient was as follows:

- Patient (b) (6): Gammagard, 15 g every 3 weeks (Day 1-ongoing)
- Patient (b) (6): Hizentra 20%, 4 g/week (Days 1-13), 6 g/week (Day 14-ongoing)
- Patient: (b) (6): Gammagard, 30 mL every 2 weeks (Days 1-14), 50 mL QM (Days 37-121); Hizentra 20%, 0.7 g/week (Day 142-ongoing)
- Patient (b) (6): Gammagard, 50 mL QD (Day 14); Venoglobulin IH, 0.5 g QD (Days 34-35, 41-43), 1.5 g QD (Day 56), 2.5 g QD (Days 66, 69, 93); Venoglobulin IH (high anti-CMV titer), 2.5 g QD (Days 100, 107)

All patients had medical history including one or more ongoing clinical symptoms related to ADA-SCID such as hearing loss, bilateral cataract, bacterial and viral infections, and developmental delay (as described Interim Study Report Listing 16.2.8.2).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All study medication was administered by study personel.

Efficacy Results – Primary Endpoint

Trough Blood dAXP

Trough blood dAXP levels were <0.02 mmol/L at screening and all assessments during treatment for all patients except (b) (6) (0.0952, 0.0477, and 0.0279 mmol/L at screening and Days 8 and 15, respectively) and (b) (6) (0.0293 mmol/L at screening) (Source: Interim Study Report, Listing 16.2.16).

Trough Serum ADA Activity

Results for trough serum ADA activity for each patient were as follows (Source: Interim Study Report:Listing 16.2.17; Adagen dosing information from Listing 16.2.9):

- Patient (b) (6): 20.7 U/L at screening and ≥1100 U/L at Day 29 and all later assessments during treatment. The weekly STM-279 dose for this patient was increased from 0.1 mg/kg at the start of treatment to 0.167 mg/kg at the end of the dose maintenance period.
- Patient (b) (6): <1100 U/L throughout study: 223.7 U/L at screening; 724.0 U/L at end of dose adjustment (Day 29); 622.5-1027.0 U/L during maintenance phase. At screening,

this patient was receiving 32 U/kg Adagen. The weekly SC-PEG rADA dose for this patient was increased from 0.2 mg/kg at the start of treatment to 0.267 mg/kg at the end of the dose maintenance period.

- Patient: (b) (6): <1100 U/L at screening (884 U/L), the end of dose adjustment (Day 29; 1036.0 U/L) and through Day 71 during maintenance (796.0-1086.8 U/L); increased at later assessments to ≥1281.2 U/L. At screening, this patient was receiving 28 U/kg Adagen. The weekly SC-PEG rADA dose for this patient was increased from 0.167 mg/kg at the start of treatment to 0.233 mg/kg at the end of the dose maintenance period.
- Patient: (b) (6): 846 U/L at Day 8 and >1100 U/L at all later assessments (screening value was not available).

The Applicant concludes that although the small study population precludes statistical analysis, all 4 patients achieved and maintained detoxification throughout the maintenance phase.

*Reviewer's Comment: A serum ADA activity of 1100 U/L is equivalent to a plasma ADA activity of 15 mmol/hr/L. The target of enzyme replacement therapy with exogenous adenosine deaminase is to maintain plasma ADA activity > 15 mmol/hr/L, as described in the Adagen package insert and the medical literature. Over time, maintaining plasma ADA activity > 15 mmol/hr/L has has come to be recognized and accepted as a validated surrogate marker of clinical effectiveness, to the extent that maintaining such a level of ADA activity is associated with long term survival of > 80%.*[11] *Two patients, Patient* (b) (6) *and Patient* (b) (6) *achieved and maintained the goal plasma ADA activity > 1100 U/L or 15 mmol/hr/L. One other patient, Patient* (b) (6) *remained below this target threshold throughout the study. And finally, Patient* (b) (6) *achieved ADA activity > 1100 U/L after Day 8. Nevertheless, this reviewer agrees with the Applicant's conclusion, that all 4 patients achieved and maintained detoxification (dAXP* <0.02 mmol/L) throughout the maintenance phase, which is also a goal of the treatment associated with long term clinical benefit.

Data Quality and Integrity

[11] Gaspar Id.

No OSI inspections were requested. Examination of the line listing and comparisons by this reviewer did not reveal any inconsistencies.

Efficacy Results – Secondary and other relevant endpoints

Relevant secondary endpoints, including assessments of each patient's immune status are summarized in the Applicant's Table 3 copied below.

Lymphocyte Counts

Total lymphocyte counts and B-/T-/NK-lymphocyte subset counts for Patients (b) (6) and (b) (6) generally increased from screening to Day 15 during dose adjustment and were stable or increasing during maintenance (Source Interim Study Report Listing 16.2.18). Screening values and minimum and maximum values during treatment are shown in in the Applicant's Table 3 copied below. For Patient (b) (6), counts for total lymphocytes and CD16+CD56 NK and CD19 subsets were below screening levels during treatment.

> *Reviewer's Comment: Given the small number of patients it is difficult to draw definitive conclusions with respect to a potential treatment effect on lymphocyte counts and subset distributions; however, a trend in the opposite direction would have been concerning.*

Immunoglobulins

Quantitative Immunoglobulin G levels for all patients showed no consistent trends during treatment but generally did not decrease substantially relative to values at screening. Most reported Immunoglobulin A and M values were below limits of measurement.

> *Reviewer's Comment: In light of the use of concomitant human immunoglobulin during treatment with study drug, the results of these secondary endpoints may be difficult to interpret.*

Table 10. Immune Status Assessments

Applicant's Table 3: Immune Status Assessments

| Patient ID | Assessment | Screening | Minimum During Treatment | | Maximum During Treatment | | Comment |
|---|---|---|---|---|---|---|---|
| | | | Value | Day(s) | Value | Day(s) | |
| (b) (6) (Data available through Day 148) | CD16+CD56 NK | 0.013 x $10^9$/L | 0.03 x $10^9$/L | 15 | 0.081 x $10^9$/L | 92 | <LLN through Day 36; later near or above LLN [RR 0.070-0.76] |
| | %CD16+CD56 NK/Lymphocytes | 1.6% | 3% | 15 | 7.6% | 92 | Beginning at Day 36, all values WNL [RR 4-25] |
| | CD19 | 0.001 x $10^9$/L | 0.006 x $10^9$/L | 15 | 0.07 x $10^9$/L | 64 | All values < LLN [RR 0.11-0.66] |
| | CD19/Lymphocytes | 0.1% | 0.6% | 15 | 7% | 64 | Except for Day 64, all values < LLN [RR 6-29] |
| | CD3 | 0.779 x $10^9$/L | 0.836 x $10^9$/L | 64 | 1.076 x $10^9$/L | 36 | All values WNL except for Screening and Day 64 [RR 0.840-3.06] |
| | CD3/Lymphocytes | 94.6% | 83.2% | 64 | 93.7% | 15 | Most values >ULN [RR 57-85] |
| | CD4 | 0.143 x $10^9$/L | 0.151 x $10^9$/L | 64 | 0.25 x $10^9$/L | 120 | All values < LLN [RR 0.490-1.74] |
| | CD4/Lymphocytes | 18.1% | 15.8% | 64 | 24.3% | 120 | All values < LLN [RR 30-61] |
| | CD8 | 0.552 x $10^9$/L | 0.557 x $10^9$/L | 120 | 0.759 x $10^9$/L | 36 | All values WNL [RR 0.18-1.17] |
| | CD8/Lymphocytes | 69.8% | 54.1% | 120 | 64.1% | 15 | All values > ULN [RR 12-42] |
| | Helper/Supp. Ratio | 0.3 | 0.3 | 15-92 | 0.4 | 120-148 | All values < LLN [RR 0.86-5] |
| | Lymphocytes | 0.651 x $10^9$/L | 0.97 x $10^9$/L | 15 | 1.18 x $10^9$/L | 36 | All values WNL except at screening [RR 0.85-4.1] |
| | Immunoglobulin A | <10 mg/dL | <10 mg/dL | All | NA | NA | All values < 10 mg/dL [RR 81-463] |
| | Immunoglobulin G | 924 mg/dL | 748 mg/dL | 92 | 1058 mg/dL | 120 | All values WNL [RR 694-1618] |
| | Immunoglobulin M | <5 mg/dL | <5 mg/dL | 15-36 | 8 mg/dL | 120 | All values < LLN [RR 48-271] |
| (b) (6) (Data available through Day 148) | CD16+CD56 NK | 0.029 x $10^9$/L | 0.037 x $10^9$/L | 148 | 0.088 x $10^9$/L | 64 | <LLN at screen and Days 15, 120, 148 [RR 0.060-0.43] |
| | %CD16+CD56 NK/Lymphocytes | 21.8% | 22% | 148 | 41.3% | 92 | All values > ULN [RR 3-18] |
| | CD19 | 0.013 x $10^9$/L | 0.015 x $10^9$/L | 15 | 0.045 x $10^9$/L | 148 | All values < LLN [RR 0.13-0.80] |
| | CD19/Lymphocytes | 10.2% | 9.4% | 15 | 26.1% | 148 | All values WNL [RR 9-30] |
| | CD3 | 0.084 x $10^9$/L | 0.062 x $10^9$/L | 120 | 0.122 x $10^9$/L | 36 | All values < LLN [RR 0.860-2.42] |
| | CD3/Lymphocytes | 63.3% | 41.4% | 92 | 53% | 15 | Except for Screen, all values < LLN [RR 61-82] |
| | CD4 | 0.054 x $10^9$/L | 0.027 x $10^9$/L | 92 | 0.06 x $10^9$/L | 36 | All values < LLN [RR 0.510-1.45] |
| | CD4/Lymphocytes | 40.5% | 15.8% | 92 | 28.9% | 15 | Except for Screen, all values < LLN [RR 33-53] |
| | CD8 | 0.028 x $10^9$/L | 0.028 x $10^9$/L | 15 | 0.039 x $10^9$/L | 36 | All values < LLN [RR 0.24-0.89] |
| | CD8/Lymphocytes | 21.4% | 15.6% | 36 | 21.2% | 120 | Most values WNL [RR 17-36] |
| | Helper/Supp. Ratio | 1.9 | 0.8 | 92 | 1.8 | 15 | Most values WNL [RR 1.0-2.9] |
| | Lymphocytes | 0.13 x $10^9$/L | 0.192 x $10^9$/L | 15 | 0.241 x $10^9$/L | 92 | All values < LLN [RR 1.2-5.2] |
| | Immunoglobulin A | <10 mg/dL | <10 mg/dL | All | NA | NA | All values < 10 mg/dL [RR 81-463] |
| | Immunoglobulin G | 727 mg/dL | 633 mg/dL | 15 | 933 mg/dL | 92 | <LLN from Screen to Day 36; WNL Days 64-148 [RR 842-2013] |
| | Immunoglobulin M | <5 mg/dL | <5 mg/dL | All | NA | NA | All values < LLN [RR 23-281] |

Continued on next page.

| Patient ID | Assessment | Screening | Minimum During Treatment | | Maximum During Treatment | | Comment |
|---|---|---|---|---|---|---|---|
| | | | Value | Day(s) | Value | Day(s) | |
| (b) (6) (Data available through Day 148) | CD16+CD56 NK | 0.178 x $10^9$/L | 0.074 x $10^9$/L | 92 | 0.134 x $10^9$/L | 120 | <LLN except at screening [RR 0.160-0.930] |
| | %CD16+CD56 NK/Lymphocytes | 29.7% | 16.8% | 148 | 26.5% | 15 | All values > ULN [RR 3-14] |
| | CD19 | 0.35 x $10^9$/L | 0.146 x $10^9$/L | 92 | 0.276 x $10^9$/L | 36 | All values < LLN [RR 0.740-2.560] |
| | CD19/Lymphocytes | 58.2% | 41.3% | 120 | 60.4% | 15 | All values > ULN [RR 17-36] |
| | CD3 | 0.021 x $10^9$/L | 0.015 x $10^9$/L | 15 | 0.169 x $10^9$/L | 120 | All values < LLN [RR 2.16-5.54] |
| | CD3/Lymphocytes | 3.5% | 4% | 15 | 32.7% | 148 | All values < LLN [RR 54-76] |
| | CD4 | 0.008 x $10^9$/L | 0.018 x $10^9$/L | 15 | 0.123 x $10^9$/L | 148 | All values < LLN [RR 1.39-4.08] |
| | CD4/Lymphocytes | 1.5% | 4% | 15 | 22.1% | 148 | All values < LLN [RR 36-55] |
| | CD8 | 0 x $10^9$/L | 0.002 x $10^9$/L | 15 | 0.054 x $10^9$/L | 148 | All values < LLN [RR 0.60-1.49] |
| | CD8/Lymphocytes | 0.1% | 0.5% | 15 | 9.7% | 148 | All values < LLN [RR 12-24] |
| | Helper/Supp. Ratio | -- | 2.3 | 92,148 | 9 | 15 | Most values WNL [RR 1.7-3.9] |
| | Lymphocytes | 1.087 x $10^9$/L | 0.384 x $10^9$/L | 92 | 0.726 x $10^9$/L | 64 | All values < LLN [RR 4.0-10.5] |
| | Immunoglobulin A | <10 mg/dL | <10 mg/dL | All | NA | NA | All values < 10 mg/dL [RR 24-121] |
| | Immunoglobulin G | 601 mg/dL | 540 mg/dL | 36 | 954 mg/dL | 64 | Values were WNL [RR 533-1078] |
| | Immunoglobulin M | 8 mg/dL | 13 mg/dL | 15 | 51 mg/dL | 92,120 | Values were < LLN at Screen and Day 15 [RR 26-218] |
| (b) (6) (Data available through Day 107) | CD16+CD56 NK | 0.038 x $10^9$/L | 0.051 x $10^9$/L | 14 | 0.25 x $10^9$/L | 63 | <LLN except at Day 63 [RR 0.160-0.930] |
| | %CD16+CD56 NK/Lymphocytes | 77.6% | 7.7% | 91 | 52.6% | 14 | All values > ULN [RR 3-14] |
| | CD19 | 0 x $10^9$/L | 0.028 x $10^9$/L | 14 | 0.557 x $10^9$/L | 91 | All values < LLN [RR 0.740-2.560] |
| | CD19/Lymphocytes | 1.8% | 29.3% | 14 | 71.8% | 35 | <LLN at screen, later values >ULN except WNL Days 14,63 [RR 17-36] |
| | CD3 | 0.003 x $10^9$/L | 0.003 x $10^9$/L | 14 | 0.38 x $10^9$/L | 63 | All values < LLN [RR 2.16-5.54] |
| | CD3/Lymphocytes | 7.9% | 1.8% | 35 | 33.7% | 63 | All values < LLN [RR 54-76] |
| | CD4 | 0.003 x $10^9$/L | 0.002 x $10^9$/L | 14 | 0.059 x $10^9$/L | 63 | All values < LLN [RR 1.39-4.08] |
| | CD4/Lymphocytes | 7.3% | 1.1% | 35 | 5.5% | 91 | All values < LLN [RR 36-55] |
| | CD8 | 0.002 x $10^9$/L | 0.001 x $10^9$/L | 14 | 0.308 x $10^9$/L | 63 | All values < LLN [RR 0.60-1.49] |
| | CD8/Lymphocytes | 6% | 0.5% | 35 | 28% | 63 | Values < LLN except Days 63 (>ULN), 91 (WNL) [RR 12-24] |
| | Helper/Supp. Ratio | 1.5 | 0.2 | 63,91 | 2.3 | 35 | <LLN, except WNL Days 14, 35 [RR 1.7-3.9] |
| | Lymphocytes | 0.1 x $10^9$/L | 0.2 x $10^9$/L | 14 | 0.9 x $10^9$/L | 63,91 | All values < LLN [RR 4.0-10.5] |
| | Immunoglobulin A | 41 mg/dL | <23 mg/dL | All | NA | NA | WNL at Screen. <23 mg/dL Days 14-91 [RR 24-121] |
| | Immunoglobulin G | 956 mg/dL | 756 mg/dL | 14 | 971 mg/dL | 91 | Values were WNL [RR 533-1078] |
| | Immunoglobulin M | 21 mg/dL | <17 mg/dL | 35 | 253 mg/dL | 91 | All values < LLN until Day 91 (>ULN) [RR 26-218] |

Source: Interim Report of Study STM-279-301; Listings 16.2.18, 16.2.19
-- = data not available for interim analysis; LLN=lower limit of normal; RR=reference range; ULN=upper limit of normal; WNL=within normal limits

Dose/Dose Response

Doses were individualized targeting trough plasma ADA activity > 1100 U/L. No dose response analyses were performed.

Durability of Response

All patients in the study maintained detoxification, defined by trough blood dAXP levels <0.02 mmol/L for up to 147 days (range 102-147), which represented the entire duration of study participation described in the interim report.

Persistence of Effect

No patient was discontinued from study treatment, and therefore persistence of effect is not relevant.

Additional Analyses Conducted on the Individual Trial

No additional analyses were perfomed.

# 7. Integrated Review of Effectiveness

## 7.1. Assessment of Efficacy Across Trials

This entire section 7.1 is not applicable to this review. Study STP-2279-002, presented in Section 6.1 of this review provides the bulk of evidence of efficacy, and the Interim Report from Study STM-270-301, presented in Section 6.2 of this review, provides additonal supportive information.

### 7.1.1. Primary Endpoints

N/A

### 7.1.2. Secondary and Other Endpoints

N/A

### 7.1.3. Subpopulations

N/A

### 7.1.4. Dose and Dose-Response

N/A

### 7.1.5. Onset, Duration, and Durability of Efficacy Effects

N/A

## 7.2. Additional Efficacy Considerations

### 7.2.1. Considerations on Benefit in the Postmarket Setting

The small number of subjects that have provided clinical data in this application is commensurate with the rarity of this condition. Although the observed effects on detoxification, and maintenance of plasma ADA activity above therapeutic levels sumitted in this application are persuasive of the efficacy of the product in the treatment of ADA-SCID in both *de novo* and patients who are converted from Adagen® to Revcovi®, there would be value in collecting post marketing information, that would consist of long term follow-up in patients

enrolled in Studies STP-2279-002 and STM-279-301, as well as in additonal information from ADA-SCID patients who will be transitioned from Adagen® to Revcovi® in the near future (See Section 12 Postmarketing Requirements and Commitments in this review).

#### 7.2.2. Other Relevant Benefits

It is anticipated that the remaining available supplies of Adagen® will be exhausted by the end of the year. The impending need for of a safe and effective product that would allow maintenance of life-saving enzyme replacement therapy, could be filled by Revcovi, which has also demonstrated the ability to achieve and sustain higher and less variable levels of ADA plasma activity, compared to Adagen®.

### 7.3. Integrated Assessment of Effectiveness

Substantial evidence of efficacy of Revcovi for providing enzyme replacement therapy in the treatment of ADA-SCID has been demsontrated in Study STP-2279-003, with respect to the validated surrogate efficacy endpoint of maintenance of plasma ADA activity above the therapeutic threshold of 1100 U/L or 15 mmol/hr/L. Moreover, when administered at an equivalent dose, Revcovi achieves higher plasma ADA activity, > 30 mmol/hr/L (2200 U/L), compared to Adagen®, and the plasma ADA activity appears less variable, when assessed by intrapatient coefficient of variability. These observations are consistent with differences in pharmaceutical properties of the two products (b) (4)

## 8. Review of Safety

### 8.1. Safety Review Approach

Safety information is available from two clinical studies, STP-2279-002 and STP 279-301 (See Table of Clinical Studies in Section 5.1). Prior to initiating these two studies there was no prior human experience with SC-PEG rADA; however, based on the chemical and the pharmacologic similarities of SC-PEG and Adagen®, it is anticipated that the safety profile would be similar to that of Adagen.

Clinical experience with Adagen is based on the patient population estimated to be approximately 150-200 worldwide. Postmarketing voluntary reporting during post-approval use has informed adverse event information included in the Adagen product label. The following AEs are reported and included in the Adagen product label: hemolytic anemia,

autoimmune hemolytic anemia, thrombocythemia, thrombocytopenia, autoimmune thrombocytopenia, injection site erythema, urticaria, and lymphomas.

In Studies STP-2279-002 and STM-279-301, the safety and tolerability of study medication was assessed as a secondary objective as follows:

- Safety of SC-PEG rADA (and Adagen in Study STP-2279-002) was assessed through determination of AEs, SAEs, physical examinations, and laboratory evaluations.
- Immunogenicity of SC-PEG rADA (and Adagen in Study STP-2279-002) was assessed by the evaluation of binding antibodies, neutralizing antibodies, and anti-PEG antibodies.

## 8.2. Review of the Safety Database

### 8.2.1. Overall Exposure

Study STP-2279-002

Adagen and SC-PEG rADA dosing for the six patients treated with SC-PEGrADA as of the interim analysis BLA data cutoff of April 27, 2017 in summarized in the Applicant's Table copied below in Table 11:

Table 11. Study STP-2279-002: Adagen and SC-PEG rADA Dosages Administered (in Chronological Order)

| Patient ID | Study Drug | Weekly Dose a | Duration (Weeks) |
|---|---|---|---|
| (b) (6) | Adagen | 750 U (43.9 U/kg) | 3 |
| | SC-PEG rADA | 5 mg (0.292 mg/kg; 43.9 U/kg) | 2 b |
| | Adagen | 1500 U (28.2 U/kg) | 4 |
| | SC-PEG rADA | 10 mg (0.188 mg/kg; 28.2 U/kg) | 115 |
| | Adagen | 1350 U (29.6 U/kg) | 10 |
| | | 1575 U (34.5 U/kg) | 3 |
| | SC-PEG rADA | 10.2 mg (0.224 mg/kg; 33.6 U/kg) | 106 |
| | Adagen | 750 U (7.7 U/kg) | 2 |
| | | 1470 U (15 U/kg) | 3 |
| | | 2940 U (30 U/kg) | 4 |
| | SC-PEG rADA | 19.6 mg (0.2 mg/kg; 30 U/kg) | 110 |

| | | | |
|---|---|---|---|
| (b) (6) | Adagen | 1500 U (31.8 U/kg) | 5 c |
| | | 1500 U (31.3 U/kg) | 9 d |
| | SC-PEG rADA | 10 mg (0.209 mg/kg; 31.3 U/kg) | 15d |
| | Adagen | 2000 U (42.9 U/kg) | 5 |
| | SC-PEG rADA | 13.3 mg (0.285 mg/kg; 42.8 U/kg) | 8 |

Source: Module 5.3.5.2, Interim CSR STP-2279-002, Appendix 16.2.5 Listings 16.2.12.1, 16.2.13.1, Appendix 16.2.1 Listing 16.2.1.1
a Dose per kg based on body weight at Screening. SC-PEG rADA dose in U/kg calculated using conversion factor of 150 U per mg SC-PEG rADA.
b Patient was discontinued from treatment as described in Section 5.4.1 after two doses of SC-PEG rADA.
c Doses administered when patient was first enrolled as ID (b) (6). Patient was discontinued during Adagen Lead-in phase and later re-enrolled as ID (b) (6).
d Doses administered when patient was enrolled as ID (b) (6).

Study STM-279-301

SC-PEG rADA dosing for the four patients included in the interim analysis is shown in the Applicant's Table copied below in Table 12.

Table 12. Study STM-279-301: SC-PEG rADA Dosages Administered (in Chronological Order)

| Patient ID | Weekly Dose Per kg Body Weight [a] | Duration (Weeks) |
|---|---|---|
| (b) (6) | 0.1 mg/kg (15 U/kg) | 1 |
| | 0.133 mg/kg (20 U/kg) | 2 |
| | 0.167 mg/kg (25.1 U/kg) | 18 |
| | 0.2 mg/kg (30 U/kg) | 9 |
| | 0.233 mg/kg (35 U/kg) | 8 |
| | 0.267 mg/kg (40.1 U/kg) | 4 |
| | 0.167 mg/kg (25.1 U/kg) | 3 |
| | 0.2 mg/kg (30 U/kg) | 6 |
| | 0.233 mg/kg (35 U/kg) | 12 |
| | 0.4 mg/kg (60 U/kg) [b] | 16 |

Source: Module 5.3.5.2, Summary CSR STM-279-301, Section 15.4 Listing 16.2.13
a Dose in U/kg calculated using conversion factor of 150 U per mg SC-PEG rADA.
b Based on the recommended dose for newborns (Adagen-Naïve patients) with ADA-SCID [Booth and Gaspar 2009] and the judgement of the Investigator, this patient was administered a dose of 0.2 mg/kg twice weekly. A protocol deviation was implemented and the PMDA and ethics committee were informed.

Patients (b) (6) and (b) (6), who had been receiving Adagen before enrollment in Study STM-279-301, started on a weekly dose of SC-PEG rADA calculated at the equivalent to their weekly Adagen dose, using a conversion factor of 150 U per mg of SC-PEG rADA.

Of the two other patients who had not received Adagen within 4 weeks prior to enrollment, one (Patient (b) (6)) started SC-PEG rADA treatment at the protocol-specified regimen of 0.1 mg/kg for Week 1, 0.133 mg/kg for Weeks 2 and 3. The remaining patient (Patient (b) (6)) was started at 0.2 mg/kg twice weekly, based on the recommended dose for newborns (Adagen-Naïve patients) with ADA-SCID. REFERENCE Booth and Gaspar 2009. (See above Protocol Violations/Deviations under Section 6.2.2 of this review)

#### 8.2.2. Relevant characteristics of the safety population:

The safety and efficacy populations are essentially the same. Please refer to Table 3 in section 6.1.2 of this review (patient population in Study STP-2279-002) and to the Patient Demographic Characteristics (Study STM-279-301) under section 6.2.2 of this review.

#### 8.2.3. Adequacy of the safety database:

The duration of exposure was more than one year for most of the patients from Studies STP-2279-002 and STM-279-301, and up to 148 weeks in the former. The total number of 10 subjects who contributed safety information is small but comparable to what was used to support the safety of Adagen® when it was approved. Although, the number of patients is adequate to support a regulatory decision, it is expected that a postmarketing commitment to continue collection of efficacy and immunogenicity information will be needed. Such was the case for Adagen® for the first few years after it was approved. In deed, much of the safety information in the Adagen® label is derived from post marketing reporting of adverse events.

### 8.3. Adequacy of Applicant's Clinical Safety Assessments

#### 8.3.1. Issues Regarding Data Integrity and Submission Quality

The overall quality of the data and submission is acceptable.

#### 8.3.2. Categorization of Adverse Events

The Applicant's process for recording, and categorizing AEs, as well as their approach to safety analyses (limted to listings, given the total number of subjects) is acceptable.

#### 8.3.3. Routine Clinical Tests

Routine clinical tests were part of the safety assessment in patients enrolled in the clinical trial. Ultimately, much of the safety of SC-PEG rADA is informed by the post-marketing safety

described in the Adagen labeling.

## 8.4. Safety Results

### 8.4.1. Deaths

One death was reported (Interim Summary Report STM-279-301, Appendix 15.4 Listings 16.2.21, 16.2.22):

Patient (b) (6), aged 3.4 months, started the study with ongoing cytomegaloviral infection, interstitial pneumonia, and respiratory failure related to ADA-SCID. While on treatment, the patient had two episodes of pulmonary hemorrhage and subsequent worsening of respiratory failure, which resulted in a fatal outcome. The patient was managed and treated in the pediatric intensive care unit (PICU) for the second episode of pulmonary hemorrhage. The cause of death in this patient was initially recognized as cytomegalovirus pneumonia; however, information received after the data cutoff date of 08 March 2017 indicated that the investigator judged that this event was caused by respiratory failure. The investigator considered the event as not related to study drug. There was no action taken with regard to SC-PEG rADA/study drug.

> *Reviewer's Comment: The individual case summary for this parient was examined, and this reviewer concludes that the outcome of death was due to the grave condition of the young patient at the time ot enrollment, including CVM pneumonitis, a condition that is extremely difficult to survive unless one can correct the immune deficiency. Respiratory failure was present at enrollment, and pulmonary hemorrhage is a well known complication of CMV pneumonitis in an immunocopromized host.*

### 8.4.2. Serious Adverse Events

Five SAEs were reported for three patients under SC-PEG rADA treatment in Study STP-2279-002 (See Table 13 below).

Table 13. Study STP-2279-002: Serious Adverse Events (As-treated Population)

| Patient ID | Start/ Stop Day | SOC / Preferred Term / Verbatim | Severity | Relationship | Action Taken | Outcome | SAE Criteria |
|---|---|---|---|---|---|---|---|
| (b) (6) | 1/1 | General disorders and administration site conditions/ Injection site pain/ PAIN WITH STUDY MEDICATION INJECTION | Moderate | Definite | Dose Not Changed | Recovered/ Resolved | Other Medically Important Serious Event |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 8/8 | General disorders and administration site conditions/ Injection site pain/ PAIN WITH STUDY MEDICATION INJECTION | Severe | Definite | Drug Withdrawn | Recovered/ Resolved | Other Medically Important Serious Event |
| (b) (6) | 592/593 | Nervous system disorders/ Migraine/ VESTIBULAR MIGRAINE | Moderate | Unlikely | Dose Not Changed | Recovered/ Resolved | Requires or Prolongs Hospitalization |
| (b) (6) | 667/673 | Neoplasms benign, malignant and unspecified (incl cysts and polyps)/ Oral neoplasm a/ HARD PALATE MASS R/T AE | Severe | Unrelated | Non-Drug Therapy | Recovered/ Resolved | Requires or Prolongs Hospitalization |
| | 667/673 | Gastrointestinal disorders/ Mouth cyst a/ LARGE PERIAPICAL CYST RT MAXILLARY CUSPID TOOTH, DENTAL CARIES | Severe | Unrelated | Non-Drug Therapy | Recovered/ Resolved With Sequelae | Requires or Prolongs Hospitalization |

a The SAE terms "oral neoplasm" and "mouth cyst" were updated to "tooth abscess" and "tooth extraction" after the data lock point for this interim analysis.
Source: Module 5.3.5.2, Interim CSR STP-2279-002, Appendix 16.2.7 Listing 16.2.22.1

The two AEs of injection site pain (one moderate, one severe) for Patient (b) (6) were not reported as serious by the investigator but, following an investigation by the sponsor of the cause of these AEs (described in Section 2), were judged to be serious by the sponsor on the basis of meeting the criterion for a medically important serious event, as described in the narrative summary (Interim CSR STP-2279-002, Section 12.3.2.1). These were the only SAEs assessed as related to study drug administration.

Moderate migraine (Patient (b) (6)) and severe oral neoplasm and mouth cyst (Patient (b) (6)) required hospitalization or prolonged existing hospitalization.

In addition to the death described above from the Interim Summary Summary Report of STM-29-301, SAEs were reported for another patient. As summarized by the Applicant, and verified by this reviewer in the individual case summary, Patient (b) (6) started the study with ongoing respiratory conditions and neutropenia related to ADA-SCID. The patient had worsening of neutropenia, acute upper respiratory tract infection, and a second episode of worsening of neutropenia while on treatment. All were considered moderate and not related to study drug. All these SAEs were considered resolved. There was no action taken with regard to SC-PEG rADA/study drug.

### 8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

The second occurrence of injection site pain reported for Patient (b) (6) was the only reported AE leading to discontinuation of study medication (Interim CSR STP-2279-002, Appendix 16.2.7 Listing 16.2.23.1). The investigation led to removal (b) (4) from the SC-PEG rADA formulation (See Table 13 above).

No AEs leading to discontinuation of study medication were reported in Study STM-279-301.

### 8.4.4. Significant Adverse Events

No particularly significant adverse events were identified in this limited cohort of sick children, other than pain at the site of study drug administration, which lead to the removal (b) (4) from the formulation, and is discussed else where in this review.

### 8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Study STP-2277-002

Only a limited number of AEs were reported during the Adagen lead-in phase of STP-2279-002. The following will address the AEs that occurred during the SC-PEG rADA treatment and maintenance phases of Study STP-2279-002.

In Study STP-2279-002 A total of 41 AEs were reported during SC-PEG rADA treatment, which were coded to 27 preferred terms, for five of the six (5/6) treated patients (See Table Table 14 below). The most commonly reported adverse reactions were injection site discomfort (seven events for one patient), productive cough (four events for one patient), cough (three events in three patients), vomiting (two events in two patients), and lymphadenopathy (two events in one patient). Most AEs reported during the SC-PEG rADA Treatment and Maintenance phases were mild or moderate in severity (37/41; 90.2%).

Table 14. Study STP-2279-002: SC-PEG rADA TEAEs (As-treated Population)

| Preferred Term | No. of Patients (No. of AEs) by AE Category | | | | | |
|---|---|---|---|---|---|---|
| | All | Severe | Related a | Unrelated | Led to Discontinuation b | Serious |
| Any adverse event | 5 (41) | 2 (4) | 2 (9) | 3 (32) | 1 (1) | 3 (5) |
| Cough | 3 (3) | 0 | 0 | 3 (3) | 0 | 0 |
| Vomiting | 2 (2) | 0 | 0 | 2 (2) | 0 | 0 |
| Injection site discomfort | 1 (7) | 0 | 1 (7) | 0 | 0 | 0 |
| Injection site pain | 1 (2) | 1 (1) | 1 (2) | 0 | 1 (1) | 1 (2) |
| Lymphadenopathy | 1 (2) | 0 | 0 | 1 (2) | 0 | 0 |
| Asthenia | 1 (1) | 0 | 0 | 1 (1) | 0 | 0 |
| Cerumen impaction | 1 (1) | 0 | 0 | 1 (1) | 0 | 0 |
| Conjunctivitis | 1 (1) | 0 | 0 | 1 (1) | 0 | 0 |
| Dental caries | 1 (1) | 0 | 0 | 1 (1) | 0 | 0 |
| Diarrhoea | 1 (1) | 0 | 0 | 1 (1) | 0 | 0 |
| Ear disorder | 1 (1) | 0 | 0 | 1 (1) | 0 | 0 |
| Epistaxis | 1 (1) | 0 | 0 | 1 (1) | 0 | 0 |
| Fatigue | 1 (1) | 0 | 0 | 1 (1) | 0 | 0 |
| Gastrointestinal infection | 1 (1) | 0 | 0 | 1 (1) | 0 | 0 |
| Haematochezia | 1 (1) | 0 | 0 | 1 (1) | 0 | 0 |
| Influenza | 1 (1) | 0 | 0 | 1 (1) | 0 | 0 |
| Laceration | 1 (1) | 0 | 0 | 1 (1) | 0 | 0 |
| Migraine | 1 (1) | 0 | 0 | 1 (1) | 0 | 1 (1) |
| Mouth cyst c | 1 (1) | 1 (1) | 0 | 1 (1) | 0 | 1 (1) |
| Nasal oedema | 1 (1) | 0 | 0 | 1 (1) | 0 | 0 |
| Nephrolithiasis | 1 (1) | 1 (1) | 0 | 1 (1) | 0 | 0 |
| Oral neoplasm c | 1 (1) | 1 (1) | 0 | 1 (1) | 0 | 1 (1) |
| Oropharyngeal pain | 1 (1) | 0 | 0 | 1 (1) | 0 | 0 |
| Otitis externa | 1 (1) | 0 | 0 | 1 (1) | 0 | 0 |
| Productive cough | 1 (4) | 0 | 0 | 1 (4) | 0 | 0 |
| Rash | 1 (1) | 0 | 0 | 1 (1) | 0 | 0 |
| Swelling face | 1 (1) | 0 | 0 | 1 (1) | 0 | 0 |

NOTE: For “No. of Patients,” each PT is counted once per patient. For “No. of AEs,” each occurrence of a PT is counted.
a Relationship reported as Possible, Probable, or Definite. b Action taken reported as Drug Withdrawn.
c The event terms “mouth cyst” and “oral neoplasm” were updated to “tooth abscess” and “tooth extraction” after the data lock point for this interim analysis.
Source: Module 5.3.5.2, Interim CSR STP-2279-002, Appendix 16.2.7 Listing 16.2.20.1.3

*Reviewer's Comment:* [redacted] *Thus, this reviewer concludes that a total of 39 adverse reactions, relevant to the proposed REVCOVI were reported in the study. See Section 10. Labeling Recomentdattions, 10.1 Presription Drug Labeling in this review. It was finally recommended to include a narrative paragraph* [redacted] *to summarize the adverse events in Section 6.1 of the Package Insert, since there was no concurrent control group to provide comparisons in a tabular format.*

*AEs Assessed as Severe*

Four AEs reported for two patients were assessed as severe: injection site pain in Patient [redacted]; and nephrolithiasis, oral neoplasm, and mouth cyst in Patient [redacted] All these AEs except injection site pain were unrelated to study medication, and all were resolved or resolved with sequelae.

*AEs Assessed as Related to Study Medication*

Nine AEs in two patients involving injection site pain or discomfort were the only AEs assessed as related to study medication. Two of these nine (2/9) AEs were occurrences of injection site pain in Patient [redacted] who received the initial clinical SC-PEG rADA formulation containing [redacted] were also assessed as severe and/or serious and led to discontinuation of study medication. Following an investigation of these AEs, the initial clinical SC-PEG rADA formulation was revised to remove [redacted] Seven of the nine (7/9) drug-related AEs were occurrences of injection-related AEs reported for Patient [redacted] described as "injection site discomfort" and coded as injection site sensitivity), who was treated with the revised [redacted] formulation; these AEs were assessed as mild and nonserious.

*AEs Assessed as Serious (See Section 8.4.2 of this review above).*

Study STM-279-301

Twenty-two (22) treatment emergent AEs were reported and are listed below (Source: Interim Summary Report STM-279-301, Appendix 15.4 Listing 16.2.20.2).

- Patient [redacted]: Upper respiratory tract inflammation, Procedural pain, Pneumonia [not resolved], Otitis media [not resolved]

- Patient (b) (6): Neutropenia [2 occurrences; serious], Anaemia, Upper respiratory tract infection [serious], Cholesteatoma [not resolved], Hepatic function abnormal [not resolved]
- Patient (b) (6): Catheter site dermatitis [not resolved]
- Patient (b) (6): Tracheal haemorrhage, Dermatitis contact (two occurrences), Glucose urine present, Protein urine present, Haematemesis, Device related infection, Pulmonary haemorrhage [2 occurrences, with outcome unknown as of the interim analysis for one occurrence; serious], Interstitial lung disease [outcome unknown as of the interim analysis], Respiratory failure [fatal; serious]. See also Section 8.4.1 Deaths, in this review for more information on Patient (b) (6).

  *Reviewer's Comment: To the extent that the study population from Study STM-279-301 differed from those in STP-2279-002, with only two having had prior treatment with Adagen (for a much shorter time than those in Study STP-2279-002, without a lead-in time to adjust Adagen dosing before conversion to fixed starting dose of SC-PEG rADA) while the two others were receiving de novo treatmen with SC-PEG rADA, it would not be appropriate or meaningful to merge these AEs into a common table or narrative with the observations from Study STP-2279-002 in Section 6.1 of the proposed Package Insert (See Section 10.1 of this Review).*

### 8.4.6. Laboratory Findings

Study STP-2279-002

*Hematology and Chemistry*

For the three patients who entered the SC-PEG rADA maintenance period (Patients (b) (6) (b) (6)) hematology and chemistry assessments were generallystable through Weeks 86-99.

- Most abnormal results observed during study treatment were also abnormal at screening.

- No clinically significant abnormal values were observed for these patients during SC-PEG rADA treatment.

- No abnormal laboratory values were reportable as AEs.

Based on the data available at the time of the BLA data cutoff for the interim analysis, similar results were observed for the other three patients (Patients (b) (6)) who did not yet reach the protocol-defined primary endpoint.

*Hematology and Chemistry*

Most abnormal hematology and chemistry laboratory values observed during treatment were either also abnormal at screening or represented small changes from screening values.

Abnormal hematology and chemistry laboratory values were reported as AEs for Patient (b) (6) includling abnormal low values for hematocrit, hemoglobin and neutrophils, reported as anemia and neutropenia. These AEs were moderate in severity, were not related to study medication, did not require changes in study medication dosing, and were resolved. The neutropenia was a worsening of ongoing neutropenia related to ADA-SCID that was assessed as an SAE.

Abnormal chemistry values were reported as AEs for Patient (b) (6): abnormal high values for liver function tests were reported as abnormal hepatic function. This AE was moderate in severity, was not related to study medication, did not require changes in study medication dosing, and had not resolved as of the data cutoff date of 08 March 2017.

Abnormal urinalysis results were sporadic based on limited availability of the data at the time of data cutoff. For Patient (b) (6), positive on-treatment results for glucose and protein were reported as AEs, which were mild in severity, were not related to study medication, and did not require changes in study medication dosing, and were resolved.

### 8.4.7. Vital Signs

In both studies, vital sign values (temperature, blood pressure, pulse/heart rate, weight, and height) were generally stable throughout SC-PEG rADA treatment relative to screening or pre-treatment values, with the exception of one patient (b) (6) in Study STM-279-301 with worsening results (increasing blood pressure and pulse rate and minimal weight and height gains) consistent with the patient's declining health and eventual death due to causes unrelated to study treatment. See Section 8.4.1 of this review.

### 8.4.8. Electrocardiograms (ECGs)

Not Applicable.

### 8.4.9. QT

Not Applicable.

### 8.4.10. Immunogenicity

Study STP-2279-002

Immunogenicity was assessed for trough samples collected at screening; Week 1 and PK Day 1 of the Adagen Lead-in phase; Weeks T-1, T-3, T-10, and T-21 during the SC-PEG rADA treatment phase; every 13 weeks during the SC-PEG rADA maintenance phase; and (if applicable) at an end of study (EOS)/early discontinuation visit.

The assessments included tests for anti-Adagen and anti-Adagen IgM antibodies, anti-SC-PEG rADA and anti-SC-PEG rADA IgM antibodies, and anti-PEG antibodies. All tests used a multi-tier protocol as described in Interim CSR STP-2279-002, Section 9.5.1.2.4.

Overall results for each sample were deemed positive only if results for both first and second assay tiers were positive; results were deemed negative if negative at the first tier or if positive first-tier results were not confirmed at the second tier (see Module 2.7.1 of the BLA Submission for more details).

Most immunogenicity tests were negative for anti-drug antibodies. The occasionally positive results for antidrug antibodies did not seem to affect efficacy or safety outcomes. In particular, the occasionally positive results were not associated with any detectible decrease in plasma ADA activity.

Results for immunogenicity tests by patient were as follows (Source: Interim CSR STP-2279-002, Appendix 16.2.8 Listing 16.2.15.1):

> Patient (b) (6): Positive test results were reported for anti-Adagen antibodies (all timepoints except Screening), Adagen IgM antibodies (all timepoints), and anti-PEG antibodies (Week T-1 and end of study). Results for anti-SC-PEG rADA and SC-PEG rADA IgM antibody tests were negative at all timepoints except for positive SC-PEG rADA IgM antibodies at Adagen PK Day 1.
>
> Patient (b) (6): Results for anti-Adagen and anti-SC-PEG rADA antibodies were negative at all timepoints except Week 47. The patient had positive results for both anti-Adagen IgM and anti-SC-PEG rADA IgM antibodies from Adagen PK Day 1 through Week 47 and negative results at all later timepoints, and positive results for the anti-PEG assay at Weeks T-21 and 47. Testing for neutralization antibodies at Week 47 was not conducted.
>
> Patient (b) (6): Anti-Adagen IgM and anti-SC-PEG rADA IgM assay results were negative at Screening but positive from Adagen PK Day 1 through Week T-3. Subsequent results for these assays and all results for other assays were negative except for the anti-SC-PEG rADA IgM assay at Week 34. Testing for immunogenicity at Week 47 and

neutralization antibodies at Week 34 were not conducted.

Patient [redacted]: All assay results were negative at all tested timepoints.

Patients [redacted]: All assay results were negative at all tested timepoints.

Study STM-279-301

Immunogenicity test results for anti-SC-PEG rADA antibodies were negative at screening and all on-treatment assessments for all patients. (Source: Interim Stummary Report STM-279-301, Section 15.4, Listing 16.2.15).

Since there were no positive test results for anti-SC-PEG rADA antibodies, testing for anti-SC-PEG rADA IgM, neutralizing antibodies, or anti-PEG antibodies were not performed.

*Reviwer's Comment: In the limited number of patients from Study STP-2279-002, some evidence of immunogenicity was detected early without associated effects on plasma ADA activity, among those who had been on Adagen for some time before enrollment in the study; however, these did not appear to have an effect on ADA plasma activity after the patients were converted to SC-PEG rADA. Additional information on immunogenicity should be collected postmarketing during long term followup of patients enrolled in Studies STM-2279-002 and STM-279-301, as well as additonal patients enrolled in a postmarkeing study.*

## 8.5. Analysis of Submission-Specific Safety Issues

No submission-specific safety issues were identified or analyzed.

## 8.6. Safety Analyses by Demographic Subgroups

No safety analyses by demographic subgroups were performed.

## 8.7. Specific Safety Studies/Clinical Trials

Not applicable.

## 8.8. Additional Safety Explorations

### 8.8.1. Human Carcinogenicity or Tumor Development

No tumors were identied in study subjects.

#### 8.8.2. Human Reproduction and Pregnancy

No human reproductive data was included in this submission.

#### 8.8.3. Pediatrics and Assessment of Effects on Growth

No specific assessment of effects on growth were perforemed.

#### 8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

### 8.9. Safety in the Postmarket Setting

#### 8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable, since the product is not yet marketed.

#### 8.9.2. Expectations on Safety in the Postmarket Setting

The safety and tolerability of this product in the postmarketing setting is anticipated to be as generally benign as that of Adagen which has been on the market and used to treat patients with ADA-SCID for more than 28 years in the US.

#### 8.9.3. Additional Safety Issues From Other Disciplines

None identified.

### 8.10. Integrated Assessment of Safety

The results of both clinical studies support that SC-PEG rADA was generally well tolerated. There were no new unexpected safety events reported as compared to the safety profile of Adagen. Aside from reports of injection site discomfort ad headaches, none of the volunteered spontaneous postmarketing AE reports that have been reported for Adagen were reported in the clinical studies of SC-PEG rADA; however, this may be due to the limited number of patients and duration of follow-up in these studies, an information gap which does not preclude approval, but should be addressed in the post-marketing setting.

## 9. Advisory Committee Meeting and Other External Consultations

No advisory commity meeting or other external consultations were required, other than the presentation/consultation of the Medical Policy and Program Review Council (MPPRC) in the

FDA's Center for Drug Evaluation's Office of New Drugs on June 27, 2018, regarding the reclassification of the BLA from Standard Review to Priority Review (See Section 3.2 of this Review).

# 10. Labeling Recommendations

## 10.1. Prescription Drug Labeling

Recommendations were communicated to the Applicant regarding Section 2 DOSAGE AND ADMINISTRATION. The following text was included in Final Proposed Labeling submitted on September 18, 2018, (and confirmed in SN 0049 submitted on September 28, 2018) by the Applicant, accepting our recommendations:

2.1 Recommended Dosage

Patients transitioning from Adagen to REVCOVI

If a patient's weekly Adagen dose is unknown, or a patient's weekly Adagen dose is at or lower than 30 U/kg, the recommended minimum starting dose of REVCOVI is 0.2 mg/kg, intramuscularly, once a week.

If a patient's weekly Adagen dose is above 30 U/kg, an equivalent weekly REVCOVI dose (mg/kg) should be calculated using the following conversion formula:

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

Subsequent doses may be increased by increments of 0.033 mg/kg weekly if trough ADA activity is under 30 mmol/hr/L, trough deoxyadenosine nucleotides (dAXP) are above 0.02 mmol/L, and/or the immune reconstitution is inadequate based on the clinical assessment of the patient. The total weekly dose may be divided into multiple intramuscular (IM) administrations during a week.

Adagen-naïve patients

The starting weekly dose of REVCOVI is 0.4 mg/kg based on ideal body weight, divided into two doses (0.2 mg/kg twice a week), intramuscularly, for a minimum of 12 to 24 weeks until immune reconstitution is achieved. After that, the dose may be gradually adjusted down to maintain trough ADA activity over 30 mmol/hr/L, trough dAXP level under 0.02 mmol/L, and/or to maintain adequate immune reconstitution based on clinical assessment of the patient.

> The optimal long-term dose and schedule of administration should be established by the treating physician for each patient individually and may be adjusted based on the laboratory values for trough ADA activity, trough dAXP level, and/or on the treating physician's medical assessment of the patient's clinical status.
>
> *Reviewer's Comment: The proposed wording for Section 2.1 Recommended dosage of the package insert is acceptable, and accurately reflects our recommendations.*

SEC-PEG rADA was administered by intramuscular injection, including self-administration by a few patients in Study STP-2279-002. Therefore it is reasonable to recommend the inclusion under WARNINGS AND PRECAUTIONS a section 5.1 Injection Site Bleeding in Patients wth Thrombocytopenia, which reads as follows:

> Since REVCOVI is administered by intramuscular injection, it should be used with caution in patients with thrombocytopenia and should not be used if thrombocytopenia is severe.
>
> *Reviewer's Comment: This wording was included in the Final Proposed Labeling submitted September 18, 2018.*

Since it is expected that normalization of immune function in patients with ADA-SCID may take time after initiation of enzyme replacement therapy the following should be included in section 5 WARNINGS AND PRECAUTIONS under 5.2 Delay in Improvement of Immune Function:

> Maintain precautions to protect immune deficient patients from infections until improvement in immune function has been achieved. The timing and degree of improvement in immune function may vary from patient to patient.
>
> *Reviewer's Comment: This wording was included in the Final Proposed Labeling submitted September 18, 2018.*

Recommendations were communicated to the Applicant regarding Section 6.1 Clinical Trials experience. The following text was included in Final Proposed Labeling submitted on September 18, 2018, by the Applicant, accepting our recommendations:

> 6.1 Clinical Trials Experience
>
> Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

REVCOVI was administered intramuscularly in two prospective, open-label, single-arm, multi-center studies to evaluate efficacy, safety, tolerability, and pharmacokinetics in patients with ADA-SCID: Study 1 was performed in the US and Study 2 was performed in Japan *[see Clinical Studies (14)]*. Overall, 10 patients were treated and adverse reactions reported are summarized below.

Study 1

Study 1 is a one-way crossover study, conducted in the US, to evaluate the safety, efficacy, and pharmacokinetics of REVCOVI in patients with ADA-SCID who were receiving therapy with Adagen. Six patients, 8 to 37 years of age enrolled in the study. Patients' exposure to REVCOVI ranged from 2 weeks to 146 weeks. No deaths were reported and one patient discontinued treatment due to injection site pain associated with an earlier drug product formulation that was consequently modified.

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

Study 2

Study 2 is a single-arm clinical study that was conducted to assess the safety, efficacy and pharmacokinetics of REVCOVI in patients with ADA-SCID. Four patients 3.4 months to 25 years of age, all Asian, were enrolled in the study and received REVCOVI. Three patients received REVCOVI for 21 weeks and one patient received REVCOVI for 15 weeks. One death due to CMV pneumonitis and respiratory failure was observed in an infant, who had also experienced pulmonary hemorrhage, respiratory failure and upper respiratory tract infection that represented serious adverse events. Neutropenia was a serious adverse reaction reported by one of the patients. There were 22 reported adverse events for four patients. Most common adverse events were respiratory infections (2/4 patients).

*Reviewer's Comment: The proposed wording for Section 6.1 of the package insert is acceptable.*

A Section 6.3 Postmarketing Experience with ADAGEN is recommended and should include safety information with Adagen according to the following recommended text:

> The following postmarketing adverse reactions were voluntarily reported for Adagen, the same class of enzyme replacement therapy used in the treatment of ADA-SCID, and may also be seen with REVCOVI treatment:
>
> - Hematologic: hemolytic anemia, auto-immune hemolytic anemia, thrombocythemia, thrombocytopenia and autoimmune thrombocytopenia.
> - Dermatological: injection site erythema, urticaria.
> - Lymphomas

Recommendations regarding Section 14 CLINICAL STUDIES of the package insert were communicated to the Applicant and the following text was included in Final Proposed Labeling submitted on September 18, 2018 to the Application to address our recommendattions:

> 14 CLINICAL STUDIES
>
> 14.1 Study 1
>
> Study 1, conducted in the US (NCT 01420627), is an ongoing Phase 3, open-label, multicenter, single-arm, one-way crossover study of REVCOVI. The purpose of this clinical study is to evaluate the safety, efficacy, and PK of REVCOVI in 6 patients with ADA-SCID, 4 males and 2 females, who are receiving therapy with Adagen. The study treatment consists of three phases: Adagen Lead-in Phase (minimum of 3 weeks), the REVCOVI Treatment Phase (weeks 1 through 21), and followed by the REVCOVI Maintenance Phase. Six patients treated in the study were 8 to 37 years of age at the start of the study. The starting weekly dose of REVCOVI was calculated based on the last Adagen dose received in the study. Weekly REVCOVI doses ranged from 0.188 mg/kg to 0.292 mg/kg *[see Dosage and Administration (2.1)].*
>
> The efficacy endpoints assessed were as follows:
> - Trough dAXP Level (metabolic detoxification was defined as a trough erythrocyte dAXP concentration equal to or below 0.02 mmol/L)
> - Trough plasma ADA activity (adequate trough plasma ADA activity is defined as trough plasma ADA activity equal to or above 15 mmol/hr/L)
> - Immune status (lymphocyte and B-, T-, and NK-lymphocyte subset counts as well as quantitative immunoglobulin [Ig] concentration [IgG, IgA, IgM])
>
> A PK assessment was performed during Week 9 of the REVCOVI Treatment phase *[see*

*Clinical Pharmacology (12.3)]*.

Five of six patients reached the 21-week endpoint of the Treatment Phase, and three of six patients received treatment with REVCOVI (elapegademase-lvlr) for over 135 weeks. These patients (except for one value in a patient at Treatment Week 47) had erythrocyte dAXP concentration equal to or below 0.02 mmol/L. These patients had trough plasma ADA activity equal to or above 15 mmol/hr/L at 88/89 timepoints and maintained metabolic detoxification for at least 2 years under REVCOVI treatment. Patients achieved trough plasma ADA activity above 30 mmol/hr/L by week 5, except for one patient who achieved this level at week 1. The mean trough plasma ADA activity for patients receiving REVCOVI at a normalized dose of 0.2 mg/kg/week were 34.3 ± 6.6 mmol/hr/L. The same patients had a mean trough plasma ADA activity of 14.2 ± 5.1 mmol/hr/L when treated with Adagen at a normalized dose of 30 U/kg/week during the Lead-in Phase of the study.

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

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

14.2 Study 2

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

A total of four patients were enrolled in the study: two males (age 25 years and 3.4 months) and two females (age 16 years and 4.3 months). Two patients, who were on Adagen treatment within 4 weeks before entering the study, received a first dose of REVCOVI that was calculated to be equivalent to the last Adagen dose received. One

patient, who did not receive Adagen within four weeks prior to entering the study, was given the first dose of REVCOVI at 0.1 mg/kg body weight, followed by second and third doses at 0.133 mg/kg body weight and weekly thereafter. Over the dose adjustment phase of the study, the dose was titrated to meet criteria for dAXP level (equal to or below 0.02 mmol/L) and adequate trough ADA activity (equal to or above 15 mmol/hr/L). These three patients received REVCOVI for at least 21 weeks (having completed the 5-week Dosage Adjustment Period and the 16-week Maintenance Period) before entering the Extension Phase. The fourth patient (newly diagnosed Adagen-naïve patient with CMV pneumonia *[see Adverse Reactions (6.1)]*) was dosed with REVCOVI at 0.4 mg/kg weekly (divided into two IM administrations) for 16 weeks.

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

*Reviewer's Comment: The final proposed text is acceptable and accurately reflects our comments and recommendations.*

### 10.2. Nonprescription Drug Labeling

Not applicable

## 11. Risk Evaluation and Mitigation Strategies (REMS)

Not applicable. No REMS is needed.

## 12. Postmarketing Requirements and Commitments

The following proposed clinical PMR/PMC (b) (4) was sent to the Applicant on July 26, 2018 and discussed during the late cycle meeting with the Applicant, July 30, 2018.

(b) (4)


On August 10, 2018 the Applicant submitted the following postmarketing commitment, subject to reporting requirements under Section 506b, with the timetable, which should be included in the Regultory Action Letter:

> To conduct a study to enroll ADA-SCID naïve patients started on de novo enzyme replacement therapy (ERT) with Revcovi or converted from Adagen to Revcovi including patient transitioned from the Study STP-2279-002, over the course of 2 years and continue to follow those patients 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 be included and contribute data to the analyses.
>
> Draft Protocol Submission: 10/2018
> Final Protocol Submission: 01/2019
> Study/Trial Completion: 01/2023
> Interim Report Submission: 01/2021

Final Report Submission: 07/2023

# 13. Appendices

## 13.1. References

N/A - See footnotes in the text.

## 13.2. Financial Disclosure

Information on financial certification and disclosure is submitted in Module 1.3.4 of the Application.

*Reviewer's Comment: Although signed Formes 3454 (Certication of Financial Interests) were submitted for both Study STP-2279-002 and Study STM-279-302, and box 3 was checked, the list of names of clinical invdestigators was not attached as required by the form, nor was there any attachment to the respective Forms 3454 providing the reason why the information required under 54.4 was not obtained. This information was requested from the Applicant on September 21, 2018, and was submitted by the Applicant to the BLA on September 28, 2018. The information provided is acceptable.*

*It is also noted, that Section 4 (Module 1.3.4) titled FINACIAL CERTIFICATION AND DISCLOSURE, includes the names, address, phone number, and site number for the principal investigators in Studies STP-2279-002 and STM-279-301.*

*Furthermore, Section 4.1 for Study STP-2270-002 states that Leadiant has no financial disclosures to report for the Principal Investigators. Regarding Study STM-279-301, the Applicant described in Section 4.2, that it tried to obtain financial information from their partner* (b) (4) *who conducted the study, and obtained a statement (Attachment 1.3.4-1 in Module 1) attesting that there is no financial agreement entered between* (b) (4) *and principal investigators whereby the value of the compensation could be influenced by the outcome of the study.*

*The information provided in Section 1.3.4 of Module 1 in acceptable.*

Covered Clinical Study (Name and/or Number): STP-2279-002

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 5 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: _____<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in S<br>Sponsor of covered study: _____ | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☐ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☐ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____ | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☒ (Request explanation from Applicant) |

Covered Clinical Study (Name and/or Number): STM-279-301

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 3 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |

| | | |
|---|---|---|
| | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: _____<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in S<br>Sponsor of covered study: _____ | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☐ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☐ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____ | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☐ (Request explanation from Applicant) |

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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MARC W CAVAILLE COLL
10/04/2018