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APPLICATION NUMBER:

761092Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader, Division Director, and Deputy Office Director Summary Review

Date	See signature page
From	Ozlem Belen, MD, MPH Renata Albrecht, MD John Farley, MD, MPH
Subject	Cross-Discipline Team Leader, Division Director, and Deputy Office Director Joint Summary Review
BLA #	761092
Applicant	Leadiant Biosciences, Inc.
Submit/Received Date	10/24/2017
PDUFA Goal Date	10/24/2018
Trade Name	Revcovi Injection
Established or Proper Name	elepegademase-lvlr
Dosage Form(s)	1.6 mg/mL injection
Applicant Proposed Dosing Regimen(s)	<u>Treatment-naïve patients</u> : 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.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	REVCovi (elapegademase-lvlr) Injection is indicated for the treatment of adenosine deaminase severe combined immune deficiency (ADA-SCID).

Material Reviewed/Consulted	Names of Discipline Reviewers and Dates
Medical Officer Review	Marc W. Cavaillé-Coll
Pharmacology Toxicology Review	María I. Rivera, Lori E. Kotch
OPQ Review	Steven Bowen, Maria Gutierrez Lugo
Microbiology/Immunology Review	Shukal Bala
Clinical Pharmacology Review	Abhay Joshi, Philip Colangelo, John A. Lazor
Associate Director for Labeling	Jane Filie
OPDP	Carrie Newcomer
OSE/DMEPA	Nasim Roosta
Memorandum to file Review Designation Change from Standard to Priority	John Farley

OND=Office of New Drugs

OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

CDTL=Cross-Discipline Team Leader

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Adenosine deaminase deficient severe combined immunodeficiency (ADA-SCID) is a rare (one in 10⁶ 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). In addition, ERT is used to treat patients awaiting bone marrow transplant as well as patients participating in gene therapy trials. To-date since 1990, ERT has been provided by Adagen[®] (pegademase bovine), which is a modified enzyme derived from bovine intestines. Production of the active ingredient derived from bovine intestines has ceased and the remaining supply will be exhausted before the end of 2018. REVCovi (elapegademase-lvlr) injection, which is a recombinant adenosine deaminase (rADA), based on the bovine 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/hr/L and sustained activity above 30 mmol/hr/L when administered at an equivalent dose of units of ADA in patients already stabilized on a therapeutic dose of Adagen. The clinical benefit of a stable plasma ADA activity > 15 mmol/hr/L (trough measurement) is well established, supporting a traditional rather than accelerated approval. The potential risks of REVCovi (elapegademase-lvlr), are the same as Adagen 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, thrombocytopenia, 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 far outweighs the risks of ERT with REVCovi[®].

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Adenosine deaminase deficient severe combined immunodeficiency (ADA-SCID) is a rare (one in 10⁶ births in the US) serious life-threatening inherited congenital condition. Without treatment death usually occurs within the first years of life. 	<ul style="list-style-type: none"> 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).
Current Treatment Options	<ul style="list-style-type: none"> To-date since 1990, adenosine deaminase (ADA) enzyme replacement therapy (ERT) has been provided by Adagen[®] (pegademase bovine) (b) (4) 	<ul style="list-style-type: none"> A new safe and effective drug to provide life-saving ERT is needed.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	<ul style="list-style-type: none"> • 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. • 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). • Achieving a stable plasma ADA activity > 15 mmol/hr/L (trough measurement) was identified during the Adagen clinical trial and in subsequent clinical experience as the clinically important threshold below which toxic metabolites return and immune function deteriorates. Managing patients on ERT using this plasma ADA activity threshold is associated with long term survival. 	<ul style="list-style-type: none"> • The clinical benefit of a stable plasma ADA activity > 15 mmol/hr/L (trough measurement) is well established. • REVCOVI (elapegademase-lvlr) Injection provides improvement in clinical benefit compared to Adagen® (pegademase bovine) with respect to the validated surrogate endpoint of plasma ADA activity > 15 mmol/hr/L.
Risk and Risk Management	<ul style="list-style-type: none"> • 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). • Delay in improvement of immune function in ERT- naïve patients • Hematologic adverse events such as anemia, thrombocytopenia, and thrombocytopenia would be expected. 	<ul style="list-style-type: none"> • Monitoring of ADA plasma levels and testing for antibodies to REVCOVI should be performed, if a persistent decline in trough plasma ADA activity occurs • 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. • Standard of care includes appropriate monitoring for hematologic adverse events.

2. Background

Revcovi (elapegademase-lvlr) Injection ([monomethoxypolyethylene glycol] recombinant adenosine deaminase; (also known as EZN-2279 and SC-PEG-rADA during development) 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). The currently available therapy for ADA-SCID is Adagen (NDA 19181), a pegylated bovine adenosine deaminase purified from bovine intestine. Adagen, also produced by Leadiant Biosciences Inc. (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. 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 (provided in the package insert)¹. 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.

In Adagen-naïve patients, the proposed recommended dosage involves a starting weekly IM dose of REVCovi of 0.4 mg/kg of ideal body weight (divided into twice a week doses) 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.

ADA-SCID is a rare (estimated incidence of 1 case per 10⁶ 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. 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.²

¹ Revcovi package insert, section 2.1 REVCovi dose in mg/kg = Adagen dose in U/kg divided by 150.

² Gaspar HB, Ajuti A, Porta F, et al. How I treat ADA deficiency. *Blood*, 2009; 114(17):3524-3532

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.² The highly successful outcome in matched sibling and family donor transplantations is most probably the result of the absence of any chemotherapeutic regimen.

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 US has been provided by the laboratory of Michael S. Hershfield in the Department 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.² 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.² Half of the deaths on ERT occurred within the first 6 months (40% in the first month), and the overall probability of surviving 20 years on ERT is estimated to be 78%. A patient alive 6 months after starting ERT had approximately 90% probability of surviving the next 12 years.²

3. Product Quality

Revcovi is a recombinant version of bovine ADA which has a favorable stability and impurity profile compared to Adagen. The succinimidyl carbonate (SC) PEG linker used for Revcovi is (b) (4) because Revcovi is recombinant, production is not dependent on the supply of primary bovine tissue as is the case with Adagen, and therefore is at a lower risk of drug shortage.

Manufacturing and Post-Marketing Commitments

Revcovi is based on the bovine adenosine deaminase amino acid sequence and manufacture using recombinant technology. The Revcovi manufacturing processes are well-controlled and yield product that is safe, pure and potent. Five post-marketing commitments (PMCs) were agreed upon with the applicant to improve the robustness of the (b) (4) DS manufacturing processes and the Post-Marketing Development Templates for these were completed by OPQ. Microbial stability (b) (4) is controlled through routine testing and validation studies with one batch. Two PMCs are to conduct hold time and method qualification studies with additional batches. The third PMC is to conduct a study to investigate whether (b) (4) can be removed from the product. (b) (4)

Stability of end of production cells (EPCs) was supported by small-scale studies whereas absence of adventitious agents is controlled through routine testing. The fourth PMC is to conduct a study to confirm that

EPCs (b) (4) are stable and free from adventitious agents. These four PMCs will further support the robustness of the (b) (4) DS manufacturing process from microbial and product quality perspectives. The risk of leachables from the manufacturing processes and container closure systems assessed by risk assessments and individual studies is low. The fifth PMC is to conduct leachable studies to confirm this assessment. Based on the Overall OPQ assessment, these five PMCs will result in improvement and increased robustness of the manufacturing processes of Revcovi. OPQ concluded that the data submitted in this application support the conclusion that the manufacture of Revcovi is well controlled and yields a product that is safe, pure and potent. From a product quality perspective, it was concluded that this product is approvable for human use. On October 2, 2018, Leadiant submitted a letter to the application committing to conduct these 5 PMCs within prespecified timelines (See Section 13 of this Review for details)

Facilities review/inspection:

(b) (4)
A pre-license inspection (PLI) (b) (4) was conducted (b) (4) A Form 483 was issued with a recommendation of Voluntary Action Indicated (VAI).

Elapegademase (b) (4) drug product (DP) manufacturing is performed at Exelead Inc., Indianapolis, Indiana, USA (FEIN:1000517970). A PLI was performed at Exelead Inc. May 7-15, 2018. A Form FDA 483 was issued with an initial recommendation of Withhold Approval. The Firm's responses to the FDA 483 observations were adequate and the status of the PLI was downgraded to Approve.

A surveillance inspection of Exelead Inc. was conducted by the Office of Regulatory Affairs (ORA) July 9- 30, 2018. A Form FDA 483 was issued with a preliminary recommendation of Official Action Indicated (pOAI). On August 17, 2018 the firm responded to the Form FDA 483 and the responses were reviewed by the Office of Pharmaceutical Quality Operations and Office of Regulatory Affairs. The responses were deemed adequate to reclassify the inspection to Voluntary Action Indicated (VAI).

Recommendations

The Office of Biotechnology Products (OBP, OPQ, CDER), the Division of Microbiology Assessment (DMA, OPF, OPQ, CDER), and the Division of Inspectional Assessment (DIA, OPF, OPQ, CDER) recommend approval of BLA 761092 for Revcovi manufactured by Leadiant Biosciences Inc. The manufacturing data and information provided in the submission were found to be sufficient to support a conclusion that the manufacturing process of Revcovi is well controlled and leads to a product that is pure and potent for the duration of the product shelf life. OPQ recommends that this product be approved for human use under conditions specified in the package insert. We concur with these conclusions.

4. Nonclinical Pharmacology/Toxicology

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

The nonclinical PK studies showed a longer terminal half-life ($t_{1/2}$) 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. Moreover, SC-PEG rADA was slightly more efficacious than Adagen® in the ADA-deficient mouse model, i.e., ADA-deficient mice treated with SC rPEG-ADA showed a longer life span than those treated with Adagen®. The Reviewer stated that these results likely reflect SC-PEG rADA's more favorable PK.

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. The NOAEL in both rats and dogs was the highest dose, 300 U/kg 2x/week (equivalent to 1.92 mg/kg) SC-PEG rADA. These doses resulted in exposure margins of 0.54-fold (rat) and 1.86-fold (dogs) the mean human AUC normalized to the dose of SC-PEG rADA administered per patient.

The to-be-marketed formulation given every 3 or 4 days for 4 weeks (eight doses total) at a dose of 500 U/kg to rats did not result in drug related adverse effects, other than a slight prolongation of APTT was observed as noted in earlier studies. This study also included an arm with SC-PEG rADA spiked with (b) (4)% (b) (4) impurity excess. A (b) (4)% (b) (4) excess of impurity was used to give an adequate exposure margin for establishing impurity specification limits (current specification limit for impurity is not more than (NMT) (b) (4)%). The presence of (b) (4)% impurities in the test article had no effects on safety profile, TK, or immunogenicity, compared to unspiked SC-PEG rADA. The results from this study show that the safety profile of the to-be-marketed product is the same as the safety profile from earlier lots of 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. Given the structural and pharmacological comparability and similar toxicity profile of Adagen® and SC-PEG rADA, additional nonclinical reproductive studies were not considered necessary for approval.

Long-term studies in animals to evaluate carcinogenic potential of elapegademase have not been performed. As noted in the Pharmacology/Toxicology review, per ICH S6 guidance, standard carcinogenicity studies are generally not appropriate for biotechnology-derived pharmaceuticals. Additionally:

- The mechanism by which SC-PEG rADA produces its pharmacologic effect is through replacement of naturally occurring ADA (deficient in target population), which is essential for the survival of lymphocytes and to the immunity of ADA-SCID patients.
- SC-PEG rADA is structurally and pharmacologically similar to Adagen®. As the nonclinical and clinical safety profile of Adagen® is well-established, specific carcinogenicity studies were not conducted for SC-PEG rADA.

The Pharmacology/Toxicology Reviewer concluded that the nonclinical studies conducted established comparable pharmacological and toxicological profile for SC-PEG rADA and Adagen® and that the 25-year clinical experience with Adagen® use provides additional support for the safety of chronic treatment with SC-PEG rADA. Overall, the Reviewer concluded that the nonclinical data presented in the application support the approval of the marketing application of SC-PEG rADA for the treatment of SCID due to ADA deficiency. We concur with the Reviewer's conclusions.

5. Clinical Pharmacology

From a Clinical Pharmacology perspective, the key review issues were the proposed starting dose of EZN-2279 and the proposed plasma trough ADA activity levels following weekly IM administration of EZN-2279 that are used to adjust doses for ADA-SCID patients. A summary of OCP's recommendations and comments on key review issues are provided below, derived from Table 1 of the Clinical Pharmacology Review.

Pivotal and supportive evidence of effectiveness

The pivotal evidence of effectiveness is derived from six patients enrolled in ongoing Study STP-2279-002. Additional supportive evidence is derived from four patients enrolled in ongoing Study STM-279-301. From the 10 patients enrolled in these two studies, PK evaluation of steady-state plasma ADA activity levels were conducted in six ADA-SCID patients. In these studies, patients' plasma trough ADA activity levels (desired marker) were maintained at 15 mmol/hr/L or greater, and deoxyadenosine nucleotide (dAXP; undesired marker) levels were maintained under 0.02 mmol/L.

General dosing instructions

Information on this topic is provided in Section 2 of this Review. In brief, patients converting from Adagen to EZN-2279 treatment are to receive 0.2 mg/kg weekly intramuscular (IM) dose for EZN-2279 and increased in increments of 0.033 mg/kg weekly to maintain plasma trough ADA activity at 30 mmol/hr/L or greater, deoxyadenosine nucleotide (dAXP) under 0.02 mmol/L, and/or to maintain adequate immune reconstitution as judged by the treating physician. Clinical Pharmacology found this dose to be acceptable and supported by the information in the current application. In addition, as noted in the Clinical Pharmacology Review and summary below, 4 of 6 patients from Study STP-2279-002 achieved levels of 30 mmol/hr/L.

For Adagen-naïve patients, the proposed starting total weekly dose for EZN-2279 is 0.4 mg/kg (i.e., 0.2mg/kg two times a week) for a minimum of 12 to 24 weeks (b) (4)

Once immune reconstitution is achieved, the total weekly dose may be gradually adjusted down to maintain plasma trough ADA activity level at 30 mmol/hr/L or greater, dAXP under 0.02 mmol/L, and/or to maintain adequate immune reconstitution as judged by the treating physician. Clinical Pharmacology noted that the data supporting the 0.4 mg/kg are limited. After discussion, it was noted that this starting dose was used in an Adagen-naïve patient in STM-279-301, and the patient was monitored for ADA levels. (b) (4)

Overall, EZN-2279 dosing is adjusted to maintain (1) plasma trough ADA activity, (2) total erythrocytes dAXP levels, and/or (3) to maintain adequate immune reconstitution as judged the treating physician.

Labeling and formulation information

Labeling in the Prescribing Information Section 2 was finalized to reflect the data submitted, including the formula for converting patients from Adagen to Revcov. The proposed dose conversion factor, 1 mg EZN-2279 = 150 U Adagen is considered acceptable by OCP.

$$EZN2279 \text{ dose (mg/kg)} = \frac{\text{Adagen dose (U/kg)}}{150}$$

The to-be-marketed IM formulation of EZN-2279 is being used in the clinical studies that are supporting this application.

Summary and Recommendations

The Clinical Pharmacology Reviewer recommends approval of this BLA. The Reviewer noted that the plasma trough ADA activity level based dose adjustment criterion of 15 mmol/hr/L or greater was used in the two ongoing pivotal clinical studies supporting this application. However, in four out of six PK evaluable patients enrolled in the US study, trough plasma ADA activity levels were maintained at or above 30 mmol/hr/L, which supports the dose increments and target ADA activity levels of 30 mmol/hr/L included in the Prescribing Information for Adagen-naïve patients. (b) (4)

We concur

with these recommendations and the conclusion that there are no Clinical Pharmacology issues precluding approval.

6. Mechanism of Action/Immunology

The Reviewer concluded that a genetically engineered ADA-deficient mouse model shows that SS-PEG-rADA is effective in improving survival, body weight, lymphoid organ weight, ADA activity, and lymphocyte cell number as well as reducing metabolite levels in blood and BALF. SS-PEG-rADA was more effective than SC-PEG-nADA in improving survival; this may be due to numerically higher enzyme activity levels after treatment with SS-PEG-rADA compared to SC-PEG-nADA. This model closely resembles the human disease, ADA-SCID. The Reviewer commented, the Applicant has proposed to include details of pathogenesis of the disease in patients with ADA-SCID in Section 12.1 of the labeling. Similar information has been added to other labeling for rare diseases including enzyme replacement therapies. Minor edits were recommended for clarity. The Reviewer did not identify any issues precluding approval and we concur with her findings.

7. Clinical/Statistical- Efficacy

Study STP-2279-002 (NCT 01420627) was reviewed for safety and efficacy by the Clinical Reviewer. Study STM-279-301 was also reviewed and provides additional evidence of efficacy in patients with a shorter duration of exposure to treatment with elepegademase-lv1r. The Clinical Reviewer concluded that substantial evidence of effectiveness has been provided and we concur with this conclusion.

Clinical Benefit of Study Endpoints

The goal of enzyme replacement therapy is to maintain sufficient plasma ADA activity to eliminate dAdo nucleotides (dAXP), toxic purine substrates, from erythrocytes, referred to as detoxification. The optimal dosage and administration schedule of Adagen was established for each individual patient, based on measurement of erythrocyte dAXP, plasma ADA activity, and parameters of immune function. Target laboratory measures on therapy include a decline in erythrocyte dAXP to ≤ 0.02 mmol/L packed erythrocytes (measured pre-injection) and maintenance of plasma ADA activity > 15 mmol/hr/L (trough measurement).^{3,4} Achieving a stable plasma ADA activity > 15 mmol/hr/L (trough measurement) was identified during the Adagen clinical trial and in subsequent clinical experience as the clinically important threshold below which toxic metabolites return and immune function deteriorates.⁵ The absence of stable plasma ADA activity > 15 mmol/hr/L (trough measurement) leads to frequent dosing regimen for patients with respect to both dose and frequency and prompts an evaluation for antibody to ADA.

Appropriate management of patients treated with Adagen utilizing these target laboratory measures is associated with long term survival. Data from a cohort of 98 ADA-SCID patients treated with enzyme replacement therapy has been published.⁶ Patients who discontinued enzyme replacement therapy to undergo stem cell transplantation or gene transfer therapy were censored at the time enzyme replacement therapy was

³ Hershfield MS. PEG-ADA: An alternative to haploidentical bone marrow transplantation and an adjunct to gene therapy for adenosine deaminase deficiency. *Human Mutation*. 1995;5:107-12.

⁴ Adagen (pegademase bovine) Injection Prescribing Information; Sigma-tau Pharmaceuticals Inc. 2013. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/019818s0531bl.pdf

⁵ Hershfield MS. PEG-ADA replacement therapy for adenosine deaminase deficiency: an update after 8.5 years. *Clinical Immunology and Immunopathology*. 1995;76:S228-32.

⁶ Gaspar HB, Aiuti A, Porta F, Condotti F, Hershfield MS, Notarangelo LD. How I treat ADA deficiency. *Blood*. 2009;114:3524-32.

stopped. The overall probability of surviving 20 years on enzyme replacement therapy was estimated to be 78%, with half of the deaths occurring in the first 6 months of treatment.

The review team concluded that the clinical benefit of these target laboratory measures on therapy (a decline in erythrocyte dAXP to ≤ 0.02 mmol/L packed erythrocytes (measured pre-injection) and maintenance of plasma ADA activity > 15 mmol/hr/L (trough measurement)) was well established and we concur with this conclusion. These laboratory measures were the pre-specified primary and key secondary endpoints in Study STP-2279-002 and the key endpoints of interest in the review of Study STM-279-301. We further conclude that the well-established clinical benefit of these endpoints supports traditional rather than accelerated approval.

Clinical Study STP-2279-002 (NCT 01420627)

Study Design and Patient Disposition

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

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) \times 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).

After 5 patients had been enrolled, an amended version (Version Number 2.0) of the original study protocol was implemented on March 7, 2016. Some of the major changes (not all) included:

- 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.

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). 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.

Study Endpoints and Efficacy Results

The primary endpoint was metabolic detoxification is defined as a trough dAXP concentration ≤ 0.02 mmol/L and maintenance of detoxification during the treatment phase. The key secondary endpoint was adequate trough ADA activity is defined as ADA activity ≥ 15 $\mu\text{mol/hr/mL}$ (≥ 15 mmol/hr/L) and maintenance of adequate trough levels during the treatment phase.

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). The third patient (ID 004-001) 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) Patient IDs (b) (6) and (b) (6) could not be evaluated for the primary endpoint because results through Week T-21 were not available for the interim analysis.

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 maintenance 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.

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)). 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) maintained a plasma ADA activity > 15 mmol/L/h, all but Patient (b) (6) reached and maintained ADA activity > 30 mmol/L/h 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 consistent 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.

Clinical Study STM-279-301

Study Design and Patient Disposition

This is a Multicenter, Open-Label, Uncontrolled Clinical Study of STM-279 in Patients with Adenosine Deaminase (ADA) Deficiency (Phase III Clinical Study) [Protocol No. STM-279-301];⁷ it is an open label clinical trial intended to evaluate the efficacy and safety of SC-PEG rADA injected IM in patients with ADA-

⁷ Study STM-279-301 was conducted in Japan by (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.

SCID. This study is still ongoing. An interim report containing 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.

The study consists of an evaluation phase (including a 5-week SC-PEG rADA dose adjustment period and a 16-week SC-PEG rADA dose maintenance period) and a continuous SC-PEG rADA administration (extension) phase.

Study Endpoints and Efficacy Results

Endpoints included trough erythrocyte dAXP concentration and trough serum ADA activity. Trough plasma ADA activity was not available for efficacy assessment. A serum ADA activity of 1100 U/L is equivalent to a plasma ADA activity of 15 mmol/L/h.

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 > 110 U/L after Day 8. The Clinical Reviewer concluded that all 4 patients achieved and maintained detoxification (dAXP <0.02 mmol/L) throughout the maintenance phase of the study.

8. Safety

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: one study was performed in the US and the second study was performed in Japan. Overall, 10 patients were treated for periods ranging from 3 weeks to 156 weeks. The patients ranged in age from 3.4 months to 37 years. Adverse reactions reported are summarized below.

Clinical Study STP-2279-002 (NCT 01420627)

In Study STP-2279-002, 6 male and female patients, 8 to 37 years of age enrolled in the study. Caucasian and Black patients were enrolled, including Hispanic patients. Patients' exposure to REVCovi ranged from 3 weeks to 156 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, when (b) (4) was removed from the formulation. Patients who reported injection site pain (one moderate, one severe, Patient (b) (6)), moderate migraine (Patient (b) (6)) and severe oral neoplasm and mouth cyst (Patient (b) (6)) required hospitalization for management of their conditions.

Based on the 120-day safety update, the longer durations of exposure were reported, including 49 weeks (patient (b) (6)), 61 weeks ((b) (6)), 148 weeks ((b) (6)), 154 weeks ((b) (6)), and 156 weeks ((b) (6) 1).

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.

Clinical Study STM-279-301

In Study STM-279-301, 4 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).

Immunogenicity

Immunogenicity was assessed from 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, and every 13 weeks during the SC-PEG rADA Maintenance phase. 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. Results were considered positive if results of both first and second assay tiers were positive, as described in the protocol.

As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity results from the two studies suggest that patients who previously received Adagen may present an immunologic response to REVCOVI. Therefore, monitoring for changes in ADA levels during REVCOVI treatment is recommended. The observed incidence of antibodies (including neutralizing antibodies) is dependent on assay sensitivity and specificity, assay methodology, and concomitant medications. Therefore, the comparison of the incidence of antibodies to REVCOVI with the incidence of antibodies to other products may be misleading.

Most of the immunogenicity tests in the patients in these studies were negative for anti-drug antibodies. The occasionally positive results of antidrug antibodies did not seem to affect the efficacy or safety outcomes, as summarized in Sections 7 Efficacy and Section 8 Safety, of this document. Immunogenicity tests conducted during the reporting phase for the 120-day safety update were negative.

Warnings/Precautions and Postmarketing Experience with ADAGEN

As noted previously, Adagen was approved in 1990, and there is over 25 years of experience with this product. While not specifically reported in the Revcovi trials, the following information was included in the Adagen package insert and is included in the Revcovi labeling since these are both adenosine deaminase products, used as enzyme replacement therapy in the treatment of ADA-SCID. Thus, these may be seen in patients treated with Revcovi.

Injection Site Bleeding in Patients with Thrombocytopenia

Since REVCOVI is administered by IM injection, it should be used with caution in patients with thrombocytopenia and should not be used if thrombocytopenia is severe.

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.

Postmarketing Experience

The adverse reactions reported for Adagen are:

- Hematologic: hemolytic anemia, auto-immune hemolytic anemia, thrombocythemia, thrombocytopenia and autoimmune thrombocytopenia

- Dermatological: injection site erythema, urticaria
- Lymphomas

Since these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Summary and Recommendations

Based on the information from these studies, the adverse event (AE) profile of Revcovi did not identify any new safety signals compared to Adagen. Most AEs reported during Revcovi treatment were mild or moderate in severity (37/41; 90.2%). The Clinical Reviewer recommends that the benefit of Revcovi outweigh the risk of adverse events and we concur with this recommendation.

9. Advisory Committee Meeting

This application was not referred to an advisory committee, as it is not the first adenosine deaminase enzyme replacement therapy for ADA-SCID and the application did not raise significant safety or efficacy concerns or controversial scientific issues that would benefit from outside expertise or advisory committee discussion.

10. Pediatrics

This application included data on pediatric patients. Additionally, since this drug product for this indication has orphan drug designation, PREA does not apply.

11. Other Relevant Regulatory Issues

The product was developed under BB IND 100687 for EZN-2279 which was preceded by Pre-IND discussions 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 Product designation. A new IND 100687 was submitted by 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 Pharmaceuticals, effective March 11, 2010.

On March 19, 2015, the Applicant's orphan-drug designation request of (monomethoxypolyethylene glycol) recombinant adenosine deaminase was granted for *treatment of adenosine deaminase deficiency in patients with severe combined immunodeficiency*.

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 Leadiant Biosciences, Inc.

On May 25, 2017 the Applicant was granted their request (request dated December 22, 2016) recombinant adenosine deaminase (rADA) for enzyme replacement therapy for adenosine deaminase (ADA) deficiency in

patients with severe combined immunodeficiency (SCID) as a drug for a "rare pediatric disease," as defined in section 529(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360ff(a)(3)).

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

On October 24, 2017 the Applicant submitted the fourth (and final) 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 December 15, 2017, a request for Breakthrough Therapy Designation (BTD) for the treatment of ADA, submitted on November 3, 2017 was denied (See letter dated November 3, 2017 in DARRTS).

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/hr/L. 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.⁸

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 08/24/2018.

Rare Pediatric Disease Priority Review Voucher (PRV) Eligibility Checklist was placed in DARRTS by Althea Cuff on September 19, 2018. OOPD, OPT, DPMH, Dr. Cavaille-Coll and the Rare Diseases Program met to review the PRV eligibility criteria for Revcovi and it was determined that the criteria has been met for Leadiant to receive a voucher if the product is approved. Language awarding a voucher and outlining the responsibility of the applicant will be included in the approval letter.

12. Labeling

The labeling (including package insert and carton/container labels) were reviewed, with input from clinical, clinical pharmacology, pharmacology/toxicology, OPQ, and consulting groups. The Associate Director for

⁸ The rationale for this decision is summarized in the memorandum regarding the Review Designation by Dr. John Farley (signatory authority) dated July 27, 2018. His conclusions in this memorandum were based on evidence of increased effectiveness of Revcovi compared with the currently available therapy Adagen. During the Adagen Lead-in phase of Study STP-2279-002, enrolling patients on a stable dose of Adagen during the prior 6 months, all of the patients had trough plasma ADA activity level measurements below the target of 15 mmol/hr/L (2-6 events/patient). A stable plasma ADA activity > 15 mmol/hr/L (trough measurement) is a clinically important threshold below which toxic metabolites return, immune function deteriorates and patients are at risk for morbidity/mortality. During the Revcovi Treatment and Revcovi Maintenance Phases of this study, there was a single measurement in a single patient below the target of 15 mmol/hr/L. Patients receiving Revcovi in the Maintenance Phase had sustained detoxification and lymphocyte counts improved compared with the Adagen Lead-in phase.

Labeling assessed the labeling to assure it is consistent with the PLR and PLLR and summarized major labeling issues in her review. A summary of labeling issues includes:

Established Pharmaceutical Class

It was noted that Adagen's EPC is "bovine intestinal adenosine deaminase" and initially the applicant proposed (b) (4) which was not considered an appropriate term to describe the pharmacological class. Potential EPC names included "recombinant bovine adenosine deaminase" or simply "adenosine deaminase". Discussion included the importance to distinguish the source of the enzyme, as well as what sequence it contained, instead of simply calling it "adenosine deaminase." Therefore, the EPC was designated as "recombinant adenosine deaminase" and in the Description section of labeling it was stated that "Elapegademase-lvlr is a recombinant adenosine deaminase (rADA) based on bovine amino acid sequence, conjugated to monomethoxypolyethylene glycol (mPEG)."

Indications and Usage

To be consistent with the latest guidance, the I&U specifically lists both the pediatric and adult patient populations that participated in the Revcovi studies as follows:

"REVCovi is indicated for the treatment of adenosine deaminase severe combined immune deficiency (ADA-SCID) in pediatric and adult patients."

Dosage and Administration

The Clinical and Clinical Pharmacology Reviewers discussed the starting doses and the target ADA levels for both patients converted from Adagen to Revcovi, and Adagen-naïve patients. Based on the availability data, it was possible to provide reasonable detail about patients converting from Adagen (as summarized in Sections 2, 5 and 7 of this document). On the other hand, data for Adagen naïve patients was limited and a starting dose was listed based on the Japanese study (b) (4)

Information on Administration Instructions, Preparation of Injection, Therapeutic Monitoring Schedule, and measurements of ADA activity, erythrocyte dAXP and immune function was described, to align with the data collected from the clinical studies.

Warnings

Two Warnings/Precautions from Adagen labeling were incorporated in the Revcovi labeling since the products are in the same class of enzymes and the events may be reported with Revcovi as well.

Adverse Reactions

Tabular presentation of data is not provided since there is no concurrent randomized control arm in these trials, as most of the patients were crossed over from Adagen to Revcovi.

Clinical Pharmacology/MOA

Section 12.1 Mechanism of Action includes a brief summary of pathogenesis of the disease in patients with ADA-SCID. Addition of this information was determined to be acceptable based on reviews of other labeling for products approved for use in rare diseases, including enzyme replacement therapies, where similar information was included.

Clinical Studies

It was determined that details about the patient duration of Revcovi treatment as well as target ADA and erythrocyte dAXP levels should be provided to help the prescriber understand the patient-level information to help guide treatment decisions.

13. Postmarketing Requirements and Commitments

Postmarketing Requirements

None

Postmarketing Commitments

Clinical

The Division communicated the proposed plan for a clinical postmarketing commitment that is intended to collect long term efficacy and safety data (in the postmarketing setting) on July 26, 2018 and discussed the PMC during the late cycle meeting with the Applicant, on July 30, 2018. Leadiant responded to this information request and submitted their Clinical PMC on August 10, 2018 in an amendment to the BLA. The Applicant committed to submit a new protocol for a registry study by the end of January 2019 and follow the timelines provided below.

- 3497-1 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 also be enrolled and contribute data to the analyses.

Draft Protocol Submission: 10/2018
Final Protocol Submission: 01/2019
Study/Trial Completion: 01/2023
Interim /Other: 01/2021
Final Report Submission: 07/2023

Product Quality

Leadiant submitted their five Product Quality PMCs on October 2, 2018 in an amendment to the BLA. The Applicant committed to complete the Product Quality PMCs and follow the timelines provided below.

- 3497-2 To provide data from two additional rADA studies to support the (b) (4) hold times of the (b) (4) from a microbial control perspective.

Final Report Submission: 02/2020

- 3497-3 To conduct the bioburden method qualification using one additional batch of the SC-PEG rADA (b) (4) bulk drug substance using the same sample volume used in routine testing.

Final Report Submission: 12/2018

3497-4 To perform a study to evaluate the impact of the removal of (b) (4) (b) (4) If the data support removal of (b) (4), a plan for the removal of (b) (4) manufacturing process will be provided. The plan should include an evaluation of consistency of the (b) (4) and comparability of elapegademase manufactured with and without (b) (4)

Final Report Submission: 07/2019

3497-5 To characterize the purity and stability of end of production cells at full commercial scale for the manufacturing of drug substance (b) (4) recombinant adenosine deaminase (rADA).

Final Report Submission: 05/2020

3497-6 To perform a leachable study to evaluate leachables from the manufacturing process and the container closure system in Revcovi (elapegademase-lvlr) Injection drug product and assess potential impact of leachables on product quality. The analysis will be performed using one drug product lot and/or a representative sample (e.g. (b) (4)) analyzed at the end of shelf life. Appropriate methods will be used to detect, identify, and quantify organic non-volatile, volatile and semi-volatile species, and metals. Characterization of potential impact on product quality will be assessed using adequate analytical methods. Complete data and the risk evaluation for potential impact of leachables on product safety and quality will be provided in the final study report.

Final Report Submission: 12/21

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.

/s/

RENATA ALBRECHT
10/05/2018
Ozlem Belen and

JOHN J FARLEY
10/05/2018