CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761092Orig1s000

CLINICAL MICROBIOLOGY/VIROLOGY REVIEW(S)

MICROBIOLOGY/IMMUNOLOGY REVIEW
DIVISION OF TRANSPLANT AND OPTHALMOLOGY PRODUCTS

BLA 761092
(SDN-005; -017)

REVIEWER : Shukal Bala
CORRESPONDENCE DATE: 10/24/2017; 6/15/2018
CDER RECEIPT DATE : 10/24/2017; 6/18/2018
REVIEW ASSIGN DATE : 10/25/2017; 6/22/2018
REVIEW COMPLETE DATE: 08/14/2018

APPLICANT: Leadiant Biosciences, Inc.
9841 Washingtonian Blvd, Suite 500
Gaithersburg, Maryland 20878

DRUG CATEGORY: (b) (4)

INDICATION: Treatment of adenosine deaminase severe combined immune deficiency (ADA-SCID)

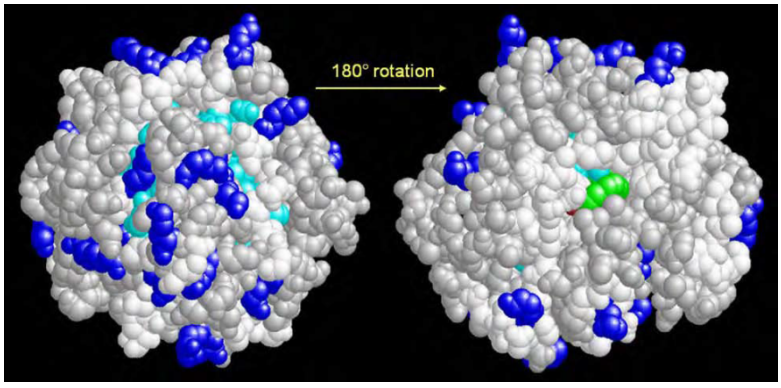
DOSAGE FORM: Solution for intramuscular administration

PRODUCT NAMES:

a. PROPRIETARY: REVCOVI

b. NONPROPRIETARY: Elapegademase-lvlr; SC-PEG-rADA; EZN-2279; STM-279

c. CHEMICAL: PEGylated (monomethoxypolytheylene glycol) recombinant form of modified bovine adenosine deaminase (ADA)



Structural model of bovine rADA indicating positions of active site (green) and lysine (blue) amino acid residues

Molecular Weight: 40 kDa
Molecular Formula: $C_{1797}H_{2795}N_{477}O_{544}S_{12}$ (peptide monomer)

SUPPORTING DOCUMENTS: NDA 19818 (Adagen) and IND 100687

Table of Contents

1. Executive Summary

The adenosine deaminase (ADA) enzyme in elapegademase-lvlr (Revcovi; SC-PEG-rADA) is the recombinant form of the bovine ADA pegademase (Adagen®; SS-PEG-nADA). The studies in ADA deficient ($ADA^{-/-}$) knockout mice show that treatment with elapegademase-lvlr, compared to untreated mice, is effective in improving ADA activity and general health of the animals as measured by body weight, lymphoid organ (thymus and spleen) weights and cellularity (lymphocyte cell numbers that include T-cells and B-cells in spleen and thymus). Also, metabolic disturbances are reduced and survival of $ADA^{-/-}$ mice improved compared to untreated mice. The metabolic disturbances are known to lead to the destruction of the immune system.

A single dose of SC-PEG-rADA was more effective than SS-PEG-nADA in improving survival of $ADA^{-/-}$ mice (Figure 4).

After administration of multiple doses of SC-PEG-rADA, compared to those treated with SS-PEG-nADA, a trend towards improved activity was observed in $ADA^{-/-}$ mice as measured by improvement in survival rate, restoration of cellularity of lymphoid organs, and reduction in metabolic disturbances. Also, numerically higher ADA enzyme activity levels were observed in $ADA^{-/-}$ mice treated with SC-PEG-rADA, compared to SS-PEG-nADA; this could be due to increased stability and longer half-life of SC-PEG-rADA compared to SS-PEG-nADA.

In patients with ADA deficiency, Revcovi treatment, like Adagen®, replaces the deficient ADA enzyme activity. A trend towards higher enzyme activity was reported after Revcovi (>30 mmol/hour/L) treatment compared to Adagen® (>15 mmol/hour/L). Like Adagen® treatment, Revcovi is effective in maintaining the number of total lymphocytes and subsets (T-cells, B-cells and natural killer-cells) in the peripheral blood as well as reducing the toxic adenosine and deoxyadenosine nucleotides levels in plasma. This should help in reducing apoptosis, improving the immune status of the host, frequency of opportunistic infections, and extending the life span of the ADA-SCID patients.

2. Introduction and Background

The subject of this BLA is REVCOVI (elapegademase-lvlr, EZN-2279, SC-PEG-rADA) for the treatment of adenosine deaminase (ADA) severe combined immune deficiency (SCID). Elapegademase-lvlr will be administered once a week, intramuscularly.

The current treatment options for patients include bone marrow transplantation, enrollment in the investigational gene-therapy studies or enzyme replacement therapy. Adagen® [pegademase, polyethylene glycol (PEG)-bovine ADA] is approved in the US for the treatment of SCID associated with a deficiency of ADA. The enzyme in Adagen® is purified from the bovine intestine and provides specific and direct replacement of the ADA enzyme. (b) (4)

2.1. Elapegademase-lvlr

Elapegademase-lvlr is a PEGylated recombinant (r) form of bovine ADA enzyme. The rADA is expressed in *Escherichia coli* and covalently conjugated to multiple strands of PEG with (b) (4) succinimidyl carbamate (SC) linker to produce elapegademase-lvlr. The PEG used for manufacturing REVCOVI and Adagen® are similar; however, the succinimidyl succinate (SS) linker used to link PEG to native bovine ADA in Adagen® was replaced by (b) (4) SC linker. (b) (4)

The pharmacokinetics (PK) profile of REVCOVI was evaluated in 6 patients with ADA-SCID (five adults and one pediatric) administered weekly intramuscular (IM) injections at a dose from 4.99 to 19.6 mg. The half-life of the product varied between 145 and 496 hours i.e., 6 to 21 days whereas that of Adagen® was 3 to >6 days (Table 1).

Table 1: REVCOVI pharmacokinetic parameters

Study	Patient's Age (yrs), Gender, Race	Dose (mg) [mg/kg]	T_{max} (hr)	$T_{1/2}$ (hr)	DN $AUC_{0\text{-}168hr}$ (hr*mmol/hr/L)*	DN C_{max} (mmol/hr/L)*	DN C_{trough} (mmol/hr/L)*
Study 1	19, Male, Hispanic/Latino	10.0 [0.188]	47.7	219	6160	44.6	29.0
	21, Male, Hispanic/Latino	10.2 [0.224]	71.9	177	7480	52.3	37.0
	37, Male, Black/African American	19.6 [0.2]	48.2	496	4330	29.7	23.6
	30, Female, White/Caucasian	10.0 [0.209]	72.0	145	5260	35.6	23.5
Study 2	25, Male, Asian	10.0 [0.167]	48.0	360	6270	41.8	33.4
	16, Female, Asian	4.99 [0.233]	27.2	227	8890	70.0	40.4

DN=Dose-normalized to a dose of 10 mg TRADE NAME;
*Individual absolute and dose-normalized (to a dose of 10 mg) PK data calculated over the dosing interval after administration of TRADE NAME by weekly IM injection at a stable dose for at least five consecutive weeks.

Source: Applicant (b) (4)

2.2. Adenosine deaminase severe combined immune deficiency

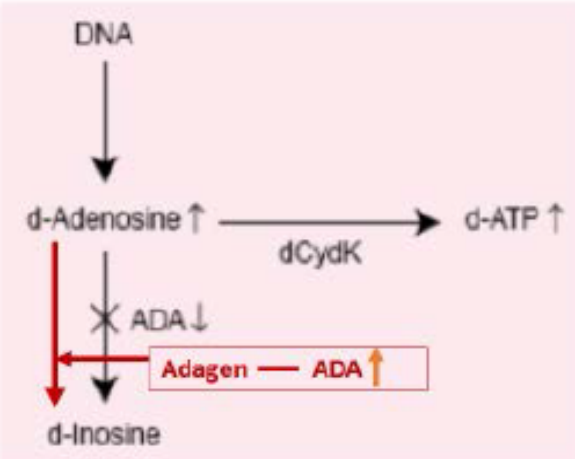
ADA-SCID is a genetic rare pediatric disease that is often fatal if the patients go untreated. The disease is characterized by severe and recurrent opportunistic infections, failure to thrive, lymphopenia [marked depletion of T-cells, B-cells, and natural killer (NK)-cells], impaired

cellular and humoral immune function, and metabolic abnormalities. The onset of disease may be early or late:

- *Early onset*: Most severe form of immunodeficiency, usually diagnosed by the age of 6 months to 1 year. In the absence of immune restoring treatment, the infants rarely live beyond the age of 2 years.
- *Delayed onset*: A less severe form ADA-SCID, usually diagnosed in children 1 - 10 years old. Delayed onset of ADA deficiency is thought to be related to the specific ADA mutation. In adults, ADA-SCID is usually diagnosed in the second to fourth decades of life.

The clinical manifestations of ADA-SCID are due to the toxic effects of purine metabolites e.g., 2'-deoxyadenosine 5'-triphosphate (dATP) on cells; dATP is a product of elevated 2′-deoxyadenosine in the absence of ADA (Figure 1). ADA enzyme therapy using Adagen® is effective in reducing metabolic disturbances by reducing ADA substrates (adenosine and deoxyadenosine) in the circulation and tissues (Figure 1), leading to improved immune function, ADA activity and life span of ADA-deficient patients.

Figure 1: Diagrammatic representation of biochemical defects in ADA deficiency



ADA is expressed in all tissues of the body. In normal cells, adenosine and deoxyadenosine are kept at low levels in the cells due to ADA activity; DNA turnover is mediated by ADA enzyme catalyzing the deamination of d-adenosine to d-inosine. The inosine and 2'-deoxyinosine are exported from the cells and converted in the extracellular fluid to hypoxanthine, xanthine, and uric acid.

In ADA-deficient cells, there is an accumulation of purine metabolites such as d-adenosine, which is then converted by dCydK to d-ATP. The build-up of these two metabolites has profound effects on lymphocyte development and function – through effects on DNA synthesis, impaired cell division, and apoptosis – causing immunological defects.
ADA = adenosine deaminase; d-adenosine = 2'-deoxyadenosine; d-ATP = 2'-deoxyadenosine 5'-triphosphate; dCydK = deoxycytidine kinase; d-inosine = 2'-deoxyinosine; DNA = deoxyribonucleic acid.

Source: Adapted from the Investigator Brochure

3. Nonclinical studies

3.1. Mechanism of action

The ADA enzyme in elapegademase-lvlr is the recombinant form of the bovine ADA pegademase (Adagen®; for details see Section 2.1 above). Elapegademase-lvlr, like pegademase, replaces the deficient ADA activity leading to reduced purine metabolism, and improved lymphoid cell number as well as life span of the ADA-SCID patients.

3.2. Activity in vitro

No studies were conducted *in vitro* to compare the activity of SC-PEG-rADA with the native ADA or Adagen®.

3.3. Activity in vivo

The activity of SC-PEG-rADA and/or SS-PEG-rADA was measured in ADA deficient ($ADA^{-/-}$) mice on a mixed 129Sev/C57BL/6J genetic background (Blackburn, 2007[1]; 2012[2]). The genetically engineered $ADA^{-/-}$ mice (homozygous for the null *Ada* allele) are known to develop pronounced adenosine accumulations in the lungs by postnatal Day 18 and are sick with outward signs of respiratory distress such as tachypnea. The thymus and spleen size as well as the lymphoid cell number of the $ADA^{-/-}$ mice are less than ADA producing ($ADA^{+/+}$) littermates. Also, adenosine and deoxyadenosine levels are elevated in the lymphoid organs. These metabolic disturbances, due to reduced purine metabolism, are associated with increased apoptosis such as the death of thymocytes and splenocytes. $ADA^{-/-}$ mice die by postnatal Day 25. Like ADA-SCID patients, the accumulation of adenosine and deoxyadenosine, substrates of the ADA enzyme reaction, are considered as useful markers of ADA deficiency in mice.

The genetically engineered $ADA^{-/-}$ mice were identified at birth by genotyping for *Ada* allele and screened for ADA enzymatic activity in the blood and used in the studies to support the activity of elapegademase-lvlr.

3.3.1. Effect of treatment with a single dose

The effect of treatment with a single dose of Adagen® or SC-PEG-rADA was measured in both $ADA^{-/-}$ and $ADA^{+/+}$ mice; the parameters measured include ADA levels in blood, adenosine in bronchoalveolar lavage fluid (BALF), and survival.

- *Effect on ADA levels and adenosine in bronchoalveolar lavage fluid*

On postnatal Day 18, $ADA^{-/-}$ and $ADA^{+/+}$ mice were administered, 5 units of either Adagen® or SC-PEG-rADA, intra-peritoneally (IP). Mice were necropsied 3 days after treatment; control untreated mice were necropsied on Day 18. Blood was collected for measuring ADA activity by zymogram analysis and BALF for measuring adenosine levels by HPLC. The results show the presence of ADA in the blood in both $ADA^{-/-}$ and $ADA^{+/+}$ mice treated with either Adagen® or PEG-rADA (Figure 2A). The adenosine levels in BALF, were the same in $ADA^{-/-}$ and $ADA^{+/+}$ mice treated with either Adagen® or SC-PEG-rADA; adenosine levels were ~7-fold higher in untreated control group of $ADA^{-/-}$ mice compared to $ADA^{+/+}$ mice (Figure 2B).

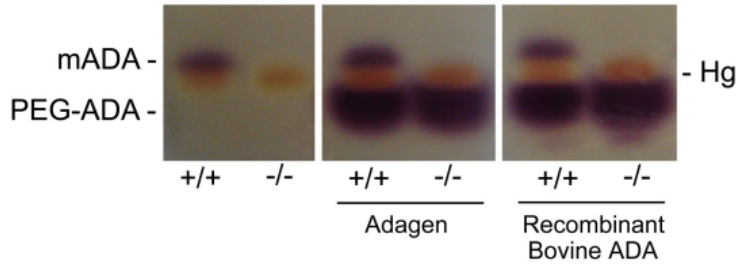
The authors state that all the treated mice showed an improvement in outward signs of respiratory distress and were alive on Day 21. Follow-up of a group of mice beyond Day 21 was not performed.

[1] Blackburn MR: Study report no. AD09005. Analysis of recombinant bovine PEG-ADA in adenosine deaminase deficient mice. October 12, 2009 (Includes 3 progress reports: April 2007, July 2007 and October 2007).

[2] Blackburn MR: Study report no. 0007330. Pharmacodynamics of SS NPEG-ADA, SS RPEG-ADA and SC RPEG-ADA in adenosine deaminase deficient mice. January 19, 2012.

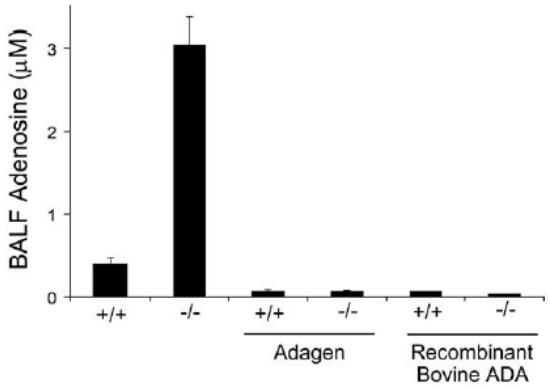
Figure 2: Effect of treatment of ADA$^{+/+}$ and ADA$^{-/-}$ mice with Adagen® or SC-PEG-rADA on ADA in blood and adenosine levels in BALF.

A: Zymogram analysis of ADA in the blood



Blood was lysed and run on agarose gels for zymogram analysis. Zymogram gels were loaded with 1 µL of whole blood from ADA$^{+/+}$ and ADA$^{-/-}$ mice at postnatal Day 18, or ADA$^{+/+}$ and ADA$^{-/-}$ mice 72 h following IP treatment with a single 5 Unit IP injection of either Adagen® or SC-PEG-rADA.
Hg, hemoglobin; mADA, mouse ADA.

B: Adenosine concentrations in BALF



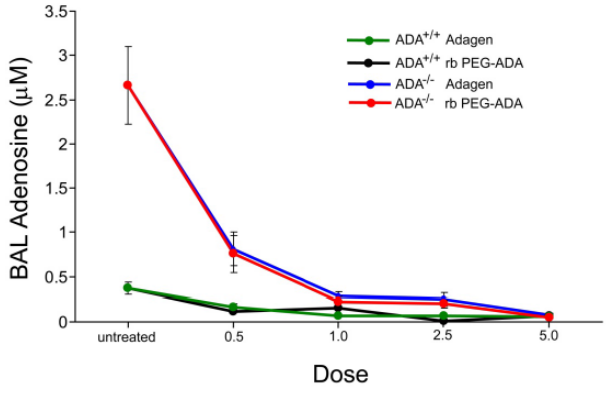
BALF fluid was obtained from ADA$^{+/+}$ and ADA$^{-/-}$ mice on postnatal Day 18 and from ADA$^{+/+}$ and ADA$^{-/-}$ mice 72 h following a single 5 Unit IP injection of Adagen® or SC-PEG-rADA. Adenosine levels were quantified using reversed phase HPLC and data are presented as mean adenosine concentrations (µM) ± S.E.M.
n = 6 for each group.

BALF, bronchial alveolar lavage fluid

Source: Study report no. AD09005, Progress report April 2007

In another experiment, the effect of a single IM dose (5, 2.5, 1 or 0.5 Units) of Adagen® or SC-PEG-rADA, on adenosine levels in BALF was measured. Mice were necropsied on Day 21 and BALF collected. The results show that treatment with either Adagen® or SC-PEG-rADA reduced adenosine levels in ADA$^{-/-}$ mice; such an effect was dose dependent (Figure 3).

Figure 3: Dose response analysis of BALF adenosine levels following ADA enzyme therapy.



18-day old ADA$^{+/+}$ or ADA$^{-/-}$ mice were either lavaged or treated with a single IM injection of increasing concentration of Adagen® or PEG-rADA. 72 h later mice were anesthetized and lavage performed. Adenosine levels were quantified using reverse phase HPLC and data are presented as mean µM adenosine concentrations + SEM, n = 6 per group per dose.

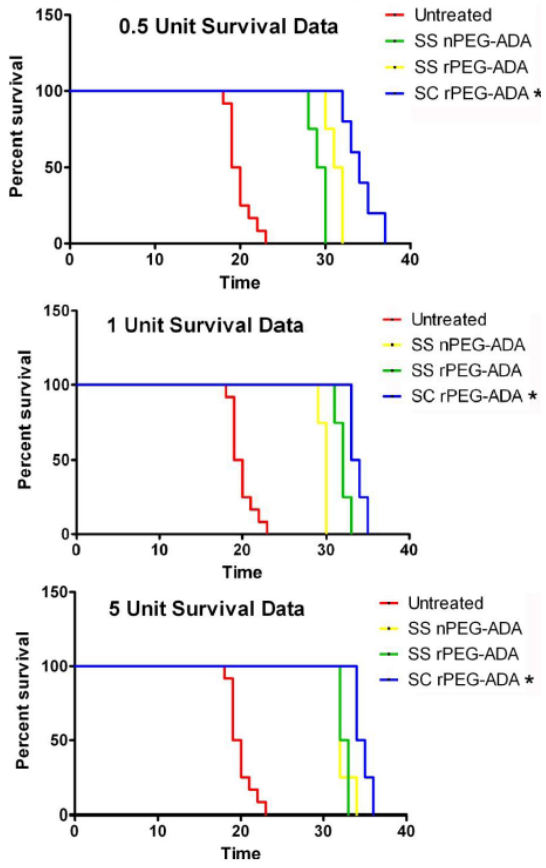
Source: Study report no. AD09005, Progress report October 2007

- *Effect on survival*

ADA$^{-/-}$ mice were administered IP, a single dose (0.5, 1.0 and 5 Units) of either Adagen® (SS-PEG-nADA) or the recombinant forms of bovine ADA preparations (SS-PEG-rADA and SC-PEG-rADA) on postnatal Day 18. Untreated mice died between Days 19 and 23 postnatally. At all the 3 doses tested, SC-PEG-rADA extended the survival of ADA$^{-/-}$ mice significantly longer

than Adagen® or SS-PEG-rADA; SC-PEG-rADA was most effective at all the doses tested (Figure 4).

Figure 4: Kaplan-Meier survival curves of $ADA^{-/-}$ mice treated with pegylated ADAs (Adagen®, SS-PEG-rADA or SC-PEG-rADA).



Red line, untreated ADA-deficient mice (n = 12),

Yellow line, SS-PEG-nADA (n = 4),

Green line, SS-PEG-rADA (n = 4),

Blue line, SC-PEG-rADA (n = 4).

* significantly different from SS-PEG-nADA and SS-PEG-rADA at a p value of 0.001.

nADA=native bovine ADA
rADA=recombinant bovine ADA

Source: Study report no. 0007330

Reviewer's Comments:
The studies show that a single IP or IM dose of SC-PEG-rADA (elapegademase-lvlr) extends the life span of ADA-deficient mice compared to SS-PEG-nADA or SS-PEG-rADA. Also, improved survival is associated with a decrease in adenosine levels in BALF and restoration of ADA activity in blood.

3.3.2. Effect of treatment with multiple doses

$ADA^{-/-}$ and $ADA^{+/+}$ mice were administered 5 Units of Adagen® or PEG-rADA, IM, every 4 days until Day 21. The Applicant states that this study was designed to deliver ADA specific enzyme activities in the plasma of between 20 and 150 µmol/h/mL; this range is comparable to that measured in ADA-deficient patients given twice weekly injections of 30 units/kg Adagen®. Treatment was initiated on postnatal Day 1 and mice necropsied on Day 21. Blood was collected 24 hours after the last dose to measure ADA enzyme activity in plasma. The effect of treatment on body weight, lymphoid organ (thymus and spleen) weight and cellularity, as well as adenosine and deoxyadenosine levels in spleen, by reverse phase HPLC, was measured.

- *Effect on ADA enzyme activity*

The results of two experiments, show increased ADA activity in $ADA^{-/-}$ mice treated with either Adagen® or SC-PEG-rADA compared to untreated mice (Table 2). The ADA enzyme activity levels were numerically higher in mice treated with SC-PEG-rADA compared to Adagen®. However, the difference in enzyme activity, between the two treatment groups, is not statistically significant; this may be due to a small number of mice tested.

Table 2: Plasma ADA specific activity. Plasma was collected and ADA enzymatic activity determined and presented as mean µMol adenosine converted to inosine/hour/mL ± SEM.

A: Plasma ADA specific activities approximately 24 hours after the last injection of Adagen® or SC-PEG-rADA

		µmol/h/ml
$ADA^{+/+}$	n = 6	1.22 ± 0.19
$ADA^{-/-}$	n = 5	0.02 ± 0.01
$ADA^{-/-}$ + Adagen®	n = 8	87.9 ± 27.3
$ADA^{-/-}$ + rbPEG-ADA	n = 7	120.3 ± 41.6

The ADA enzyme activity levels in rbPEG-ADA treated mice are numerically higher compared to Adagen® treated mice, the difference was not statistically significant.
Source: Study report no. AD09005, Progress report July 2007

B: Trough plasma ADA Activity

		µmol/h/ml
$ADA^{+/+}$	n = 8	1.17 ± 0.15
$ADA^{-/-}$	n = 7	0.02 ± 0.01
$ADA^{-/-}$ + Adagen®	n = 6	46.5 ± 8.21
$ADA^{-/-}$ + rbPEG-ADA	n = 6	64.3 ± 7.91

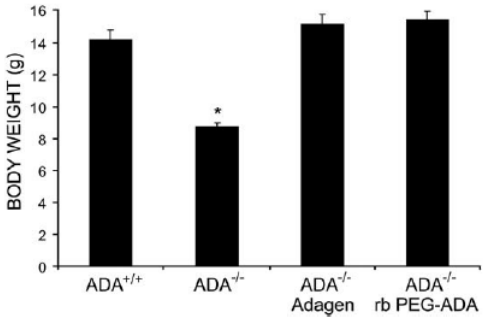
Trough values for rbPEG-ADA are numerically higher than those for Adagen®; however, the differences do not reach significance.
Source: Study report no. AD09005, Progress report October 2007

- *Effect on body weight, lymphoid organ weight and cell count*

Treatment with 5 Units of Adagen® or SC-PEG-rADA, IM, every 4 days until Day 21 was associated with increased body weight, spleen and thymus weights, as well as increase in cellularity in $ADA^{-/-}$ compared to the untreated mice; organ weights and cell numbers in $ADA^{-/-}$ treated mice were comparable to $ADA^{+/+}$ mice (Figure 5). The effect of treatment on cell count in blood was not measured.

Figure 5: The effect of treatment with Adagen® or SC-PEG-rADA on body weights, spleen and thymus weights as well as cell numbers on postnatal Day 20 and 21

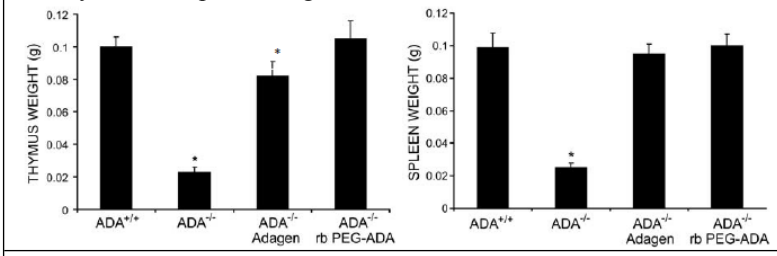
A: Body weight



Body weights of $ADA^{+/+}$ and $ADA^{-/-}$ mice were obtained on postnatal Day 20, while the body weights of $ADA^{-/-}$ mice treated with Adagen® or SC-PEG-rADA were obtained on postnatal Day 21.

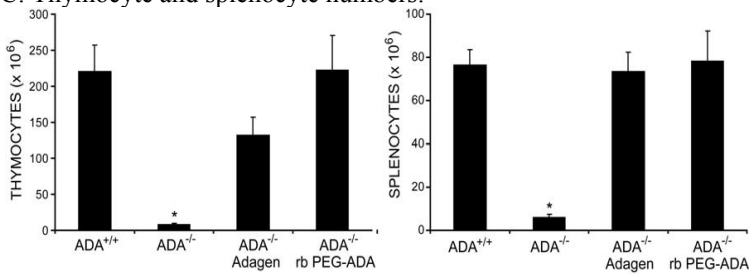
Data are presented as mean body weights in grams (g) ± SEM. N = 14 to 21.

B: Thymus and spleen weights



Thymus and spleen weights of $ADA^{+/+}$ and $ADA^{-/-}$ mice were obtained on postnatal Day 20, while the weights of the thymus and spleen of $ADA^{-/-}$ mice treated with Adagen® or SC-PEG-rADA were obtained on postnatal Day 21.
Data are presented as mean organ weights in grams (g) ± SEM.
N = 7 to 10.

C: Thymocyte and splenocyte numbers.



The thymus and spleen was removed from $ADA^{+/+}$ and $ADA^{-/-}$ mice on postnatal Day 20 and single cell suspensions were generated and counted. Thymocyte and splenocyte numbers from $ADA^{-/-}$ mice treated with Adagen® or SC-PEG-rADA were obtained on postnatal Day 21.
Data are presented as mean thymocytes or splenocytes X 10^6 ± SEM.
N = 5 to 8.

*Significantly different from $ADA^{+/+}$ at $p < 0.05$ using a Mann Whitney test.
Source: Study report no. AD09005, Progress report July 2007

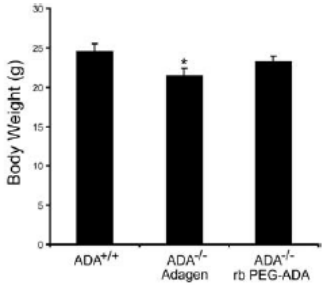
Similar observations (increased body weight, spleen and thymus weight) were made in another study; the experimental design was same as summarized above except that treatment (once weekly with 5 units) was continued beyond Day 20 until the mice were 6-week old. Splenocytes were processed for T-cell and B-cell phenotyping by flow cytometry. There was an increase in the number of splenocytes in treated mice at Week 6 compared to postnatal Day 18; the increase in splenocyte number was associated with an increase in the number of both T-cells and B-cells (Figure 6).

- *Effect on survival*

Five out of the 6 $ADA^{-/-}$ mice treated with Adagen® survived to six weeks; one mouse died during Week 4. All the 6 $ADA^{-/-}$ mice treated with SC-PEG-rADA and 6 of 6 untreated control $ADA^{+/+}$ mice survived until the end of the study i.e., six weeks. Overall, the study suggests that SC-PEG-rADA can improve survival of $ADA^{-/-}$ mice (Table 3).

Figure 6: The effect of treatment with Adagen® or PEG-rADA on body weights, spleen and thymus weights as well as cell numbers at Week 6. ADA$^{-/-}$ mice were injected with Adagen® or SC-PEG-rADA from birth until six weeks of age.

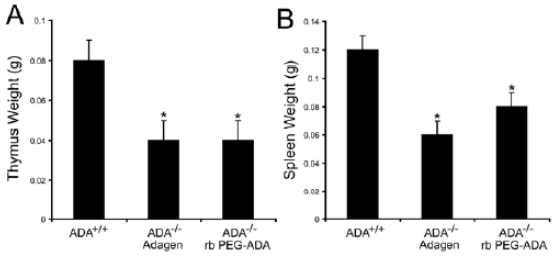
A: Body weights



Body weight at 6 weeks of ADA$^{+/+}$ and ADA$^{-/-}$ mice treated with either Adagen® or SC-PEG-rADA.

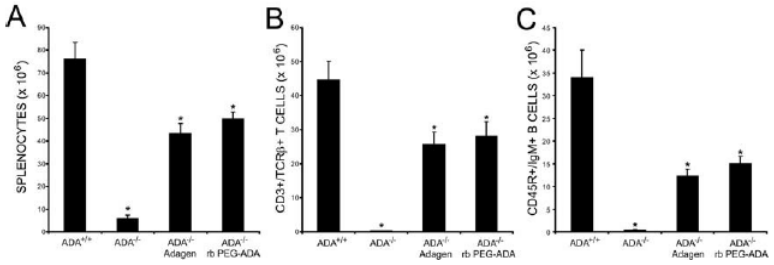
Data are presented as mean body weights (g) + SEM.
n = 5 to 6 mice per group.

B: Thymus and spleen weights

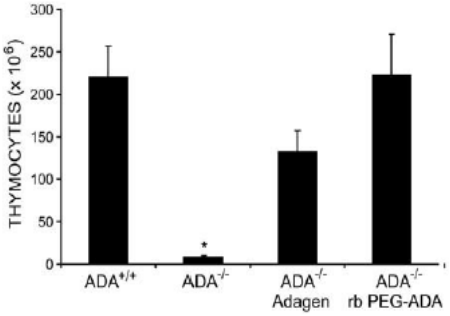


ADA$^{-/-}$ mice were injected with Adagen® or SC-PEG-rADA from birth until six weeks of age.
(A) Thymus weights. (B) Spleen weights.
Data are presented as mean weights in grams (g) + SEM.
n = 5 to 6 mice per group.

C: Splenocyte counts and composition at six weeks of age.



D: Thymocyte count



A: Single cell suspensions were made from spleens. Cells were counted using a hemocytometer and data are presented as mean splenocytes + SEM.
B: Cells were fixed and stained with cell surface markers for T cells (CD3 and TCR-β).
C: B cells (C, CD45R and IgM).
Stained cells were subjected to flow cytometry, and numbers quantified using FacScan software. All untreated ADA$^{-/-}$ data points were gathered at postnatal Day 18. Values are presented as mean T or B cells + SEM. n = 5 to 6 mice per group.

*Significant differences when different parameters compared between ADA$^{-/-}$ and ADA$^{+/+}$ mice using a Student's T-test ($P < 0.05$).
Source: Study report no. AD09005, Progress report October 2007

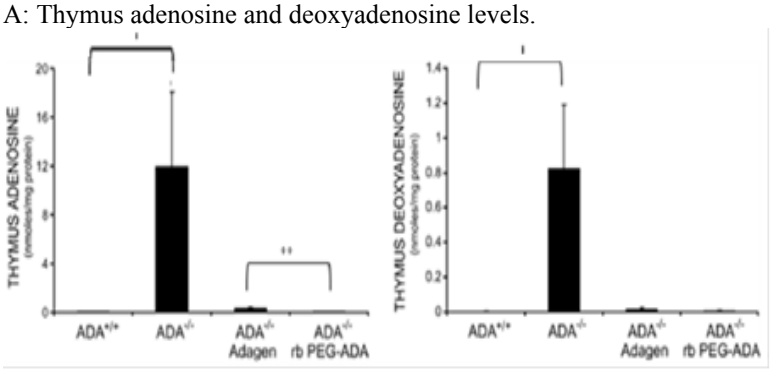
Table 3: Effect of treatment on survival at Week 6		
Treatment group	ADA$^{-/-}$	ADA$^{+/+}$
SC-PEG-rADA	6/6	ND
Adagen®	5/6	ND
Vehicle	ND	6/6

- *Effect on adenosine and deoxyadenosine levels in lymphoid organs*

Treatment with either Adagen® or SC-PEG-rADA prevented the metabolic disturbances as measured by adenosine and deoxyadenosine levels in lymphoid organs of $ADA^{-/-}$ mice on postnatal Day 21 (Figure 7).

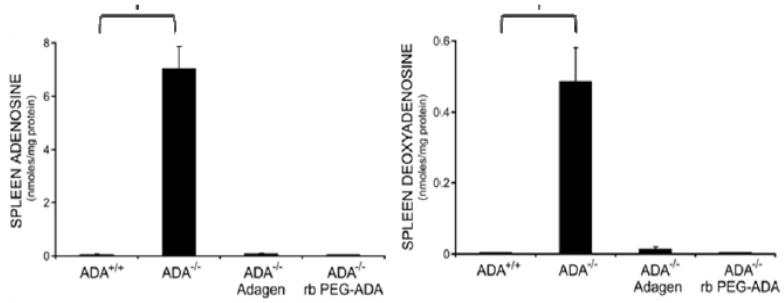
Figure 7: The effect of treatment with Adagen® or SC-PEG-rADA on adenosine and deoxyadenosine in thymus and spleen on postnatal Day 21.

A: Thymus adenosine and deoxyadenosine levels.



The thymus was removed from $ADA^{+/+}$ and $ADA^{-/-}$ mice on postnatal Day 20, while the thymuses of $ADA^{-/-}$ mice treated with Adagen® or SC-PEG-rADA were obtained on postnatal Day 21. Nucleosides were extracted and analyzed by reversed phase HPLC. Data are presented as mean adenosine or deoxyadenosine levels ± SEM.
N = 5 to 10 per group.
*Significantly different from $ADA^{+/+}$ at $p < 0.05$ using a Mann Whitney.
** $ADA^{-/-}$ SC-PEG-rADA significantly different from $ADA^{-/-}$ Adagen® at $p<0.05$ using a Mann Whitney test.

B: Spleen adenosine and deoxyadenosine levels.



The spleen was removed from $ADA^{+/+}$ and $ADA^{-/-}$ mice on postnatal Day 20, while the spleens of $ADA^{-/-}$ mice treated with Adagen® or SC-PEG-rADA were obtained on postnatal Day 21. Nucleosides were extracted and analyzed by reversed phase HPLC. Data are presented as mean adenosine or deoxyadenosine levels ± SEM. N = 5 to 10 per group.
*Significantly different from $ADA^{+/+}$ at $p < 0.05$ using a Mann Whitney test.

Source: Study report no. AD09005, Progress report July 2007

***Reviewer's Comments**:*
Studies show that PEG-rADA is effective in improving ADA activity; compared to Adagen® treatment, ADA enzyme activity levels are numerically higher in SC-PEG-rADA treated $ADA^{-/-}$ mice (Table 2). The improved ADA activity is associated with improvement in general health of the $ADA^{-/-}$ mice as measured by body weight, lymphoid organ (thymus and spleen) weights and cell numbers that includes T-cells and B-cells. Also, metabolic disturbances (Figures 2 and 7) are reduced and survival (Figure 4) of $ADA^{-/-}$ mice improved compared to untreated mice. The metabolic disturbances are thought to lead to the destruction of the immune system. Lymphocyte count in blood was not measured.

4. Clinical studies

The Applicant has included interim results for subjects enrolled in Study STP-2279-002 in the US as well as a Japanese Study STM-279-301.

4.1. Study STP-2279-002

The Applicant is conducting an open-label, multi-center, single-arm, one-way crossover study to determine safety, efficacy, and PK of SC-PEG-rADA in patients with ADA-SCID who are currently being treated with Adagen®.

Primary objective

To evaluate whether treatment with SC-PEG-rADA allows metabolic detoxification, as demonstrated by total erythrocyte deoxyadenosine nucleotide (dAXP; represents sum of dAMP+dADP+dATP) concentration from a trough blood sample.

Secondary objectives

- Evaluate safety and tolerability of SC-PEG-rADA, as assessed by the incidence of adverse events (AEs), serious adverse events (SAEs), physical examinations, and laboratory assessments.
- Assess immunogenicity of SC-PEG-rADA, including binding antibodies, neutralizing antibodies and anti-PEG antibodies.
- Evaluate whether therapy with SC-PEG-rADA maintains trough plasma ADA activity ≥15 µmol/hr/mL (15 mmol/hr/L).
- Determine the PK of SC-PEG-rADA, as assessed by plasma ADA activity.
- Assess the effects of SC-PEG-rADA on immune status as determined by absolute lymphocyte count, lymphocyte subset (B, T, and NK) analysis, and immunoglobulin (Ig) concentration (IgG, IgA, IgM).
- Assess clinical status (infections, hospitalizations, survival, and growth).

There were three phases in the study:

- Adagen® lead-in phase (minimum of 3 weeks).
- SC-PEG-rADA* treatment phase (Weeks 1 -21).
- SC-PEG-rADA* maintenance phase.

(*SC-PEG-rADA was administered as a weekly intramuscular injection.)

Study design

Inclusion criteria

- Diagnosis of ADA-deficient combined immunodeficiency.
- Stable clinical status while receiving therapy with Adagen®. Patients previously receiving gene therapy or undergoing hematopoietic stem cell transplantation who still require Adagen® treatment were eligible. The dose of Adagen® must be stable for at least 6 months prior to study entry.
- Have both of the following during the Adagen® lead-in phase of the study prior to EZN-2279 transition:
  - Trough plasma ADA activity ≥15 µmol/h/mL while receiving Adagen®, and
  - Total erythrocyte dAXP ≤0.02 µmol/mL from a trough blood sample.
- Patients or parent/guardian must be capable of understanding the protocol requirements and risks and providing written informed assent/consent.

Exclusion criteria

- Autoimmunity requiring immunosuppressive treatment.
- Patients with detectable neutralizing anti-Adagen® antibodies at screening evaluation.
- Severe thrombocytopenia (platelet count <50 $x10^9$/L).
- Current participation in other therapeutic protocols for ADA-deficient combined immunodeficiency.
- Current or prior participation in another clinical study with an investigational agent and/or use of an investigational drug in the 30 days before study entry.
- Known planned participation in a gene-therapy study for the planned duration of this study.
- Any condition that, in the opinion of the PI, makes the patient unsuitable for the study.
- Inability or unwillingness to administer Adagen® or EZN-2279 on a one time per week regimen.
- Inability to comply with the study protocol.
- Female patients who are pregnant or lactating.
- Female patients who are breast-feeding.
- Female patients of childbearing potential who are not using an FDA approved birth control method.

Each patient served as his or her own control with respect to assessment of study endpoints. The patients were followed for clinical response, laboratory parameters that included total erythrocyte dAXP concentration, and immunological measurements. Immunological measurements included enumeration of total lymphocytes and subsets.

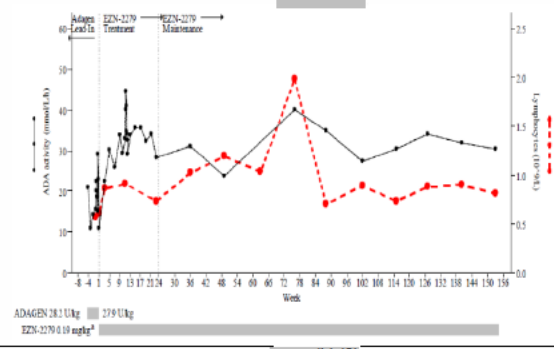
Results

The Applicant has submitted the results of 7 patients with ADA-SCID that were on Adagen® therapy. Of the 7 patients, 3 (Subject ID 004-001, 005-001, and 005-002) have completed at least 148 weeks of SC-PEG-rADA dosing, 3 patients (006-002, 011-001 and 012-001 and) have completed 15 – 58 weeks of treatment, and 1 patient (Subject ID 002-001) discontinued.

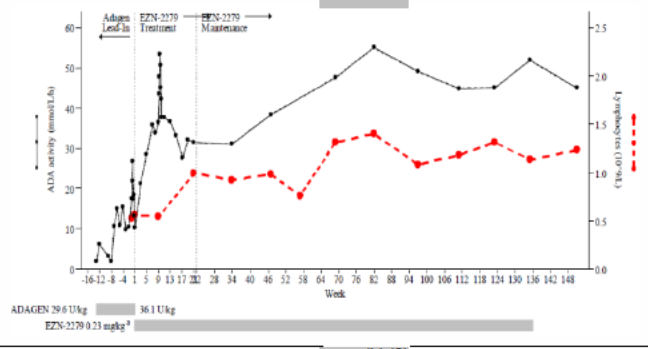
Approximately 2-fold higher enzyme activity levels (>30 mmol/hour/L) were reported after SC-PEG-rADA treatment compared to Adagen® (15 mmol/hour/L; for details see Clinical Pharmacology review). The lymphocyte count during the Adagen® lead-in phase, SC-PEG-rADA treatment and maintenance phase were maintained (Figure 8). Similarly, the T-cell, B-cell, and NK-cell counts were similar during the different phases of the study (Appendix-1). The trough dAXP level was <0.02 mmol/L through the 3 phases of the study in all subjects. For more details see Medical Officer review.

Figure 8: Study STP-2279-002 - ADA activity and total lymphocytes vs. time (weeks), Adagen® Lead-In through SC-PEG-rADA treatment and maintenance

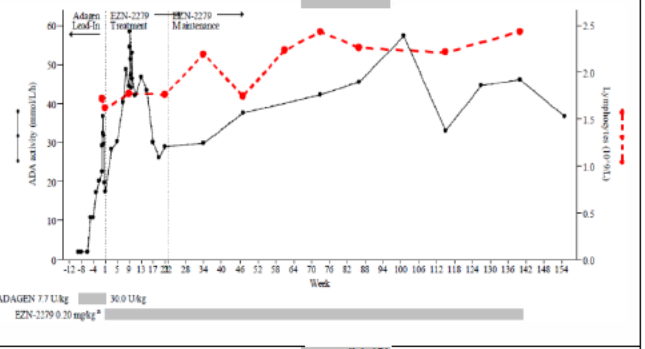
Patient (b) (6)



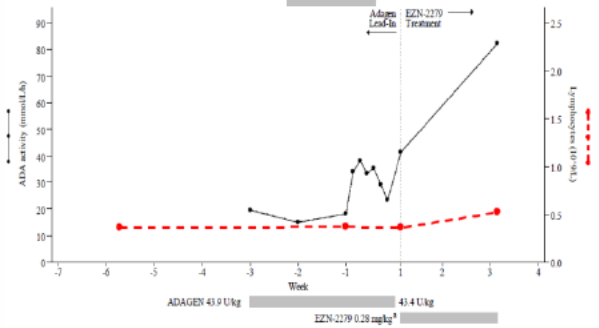
Patient (b) (6)



Patient (b) (6)

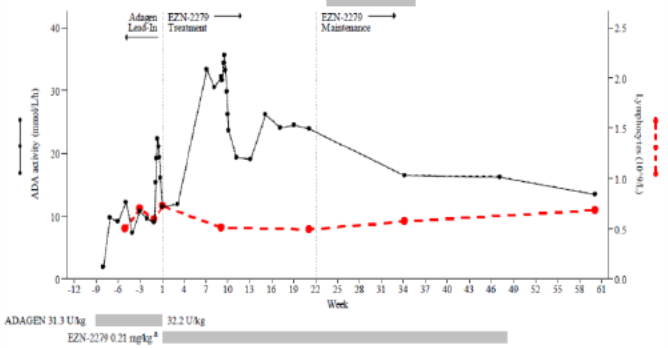


Patient (b) (6) *

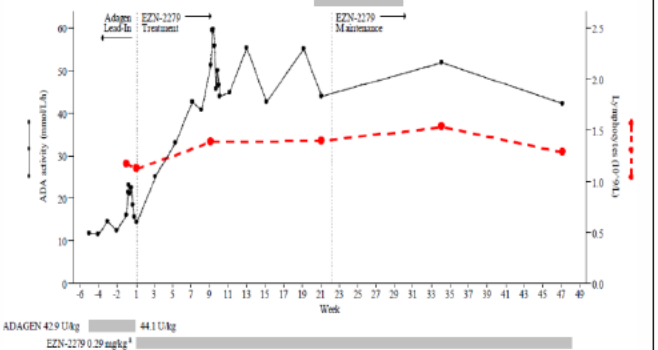


Patient 002-001* Patient discontinued after 2 doses of SC-PEG-rADA treatment

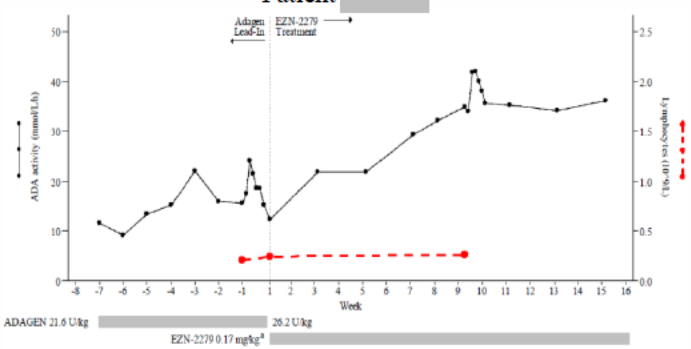
Patient (b) (6)



Patient (b) (6)



Patient (b) (6)



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.

Reviewer's Comments:
The study suggests that SC-PEG-rADA is effective in maintaining lymphocyte count, ADA activity as well as reducing dAXP levels (detoxification) in patients with ADA-SCID. Numerically higher enzyme activity levels were observed after SC-PEG-rADA treatment compared to Adagen® treatment; these observations in ADA deficient patients are similar to those in ADA deficient mice.

4.2. Study STM-279-301

This is a multicenter, open-label, single-arm clinical study, conducted by (b) (4) to assess the safety, efficacy and PK of SC-PEG-rADA in patients with ADA-SCID.

Primary objective
To evaluate efficacy and safety of SC-PEG-rADA injected IM once per week in patients with ADA-SCID.

Other objectives
Assess effect on clinical conditions and immune status of the patient.

Study design

Inclusion criteria
- 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.
- Patients for whom the principal investigator judged enzyme replacement therapy was necessary.

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 sub-investigators 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.

The study includes two phases:
- Evaluation Phase, consisted of a dose adjustment period (5 weeks) and a dose maintenance period (16 weeks).
- Continuous administration (extension) phase, which continued until the end of the study (commercial availability of SC-PEG-rADA in Japan or early study termination).

SC-PEG-rADA was administered once a week intramuscularly.

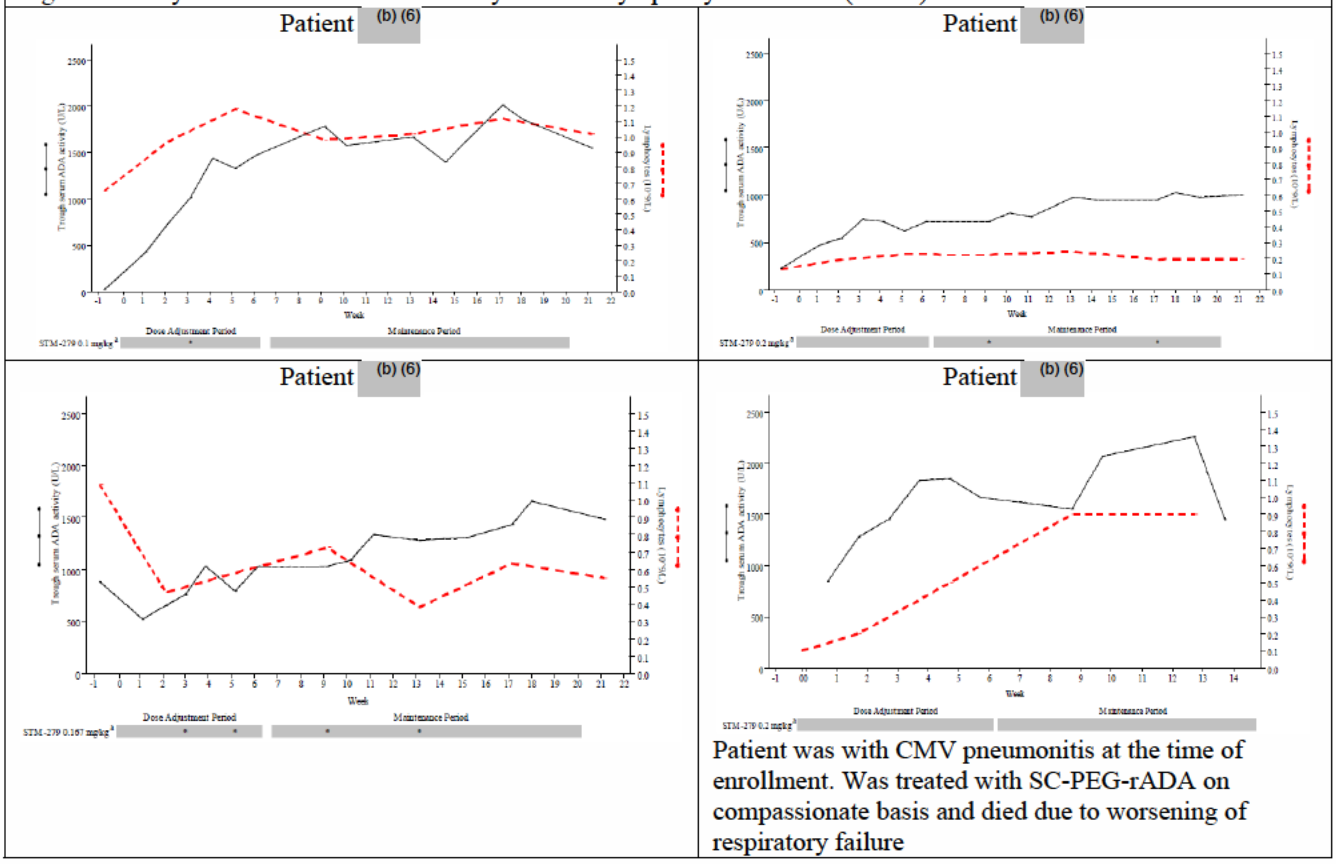
Patients were evaluated at different time intervals for clinical response and laboratory parameters that include trough dAXP levels, ADA activity, and immunological assessments. The immunological parameters measured were the same as for the Study STP-2279-002.

Results

The Applicant has included results from the interim data for 4 subjects. One patient (02-03) was seriously ill with CMV infection, interstitial pneumonia, and respiratory failure at the time of enrollment; the patient was treated with SC-PEG-rADA on compassionate basis. The patient died due to worsening of respiratory failure at Week 15. The death does not appear to be due to SC-PEG-rADA treatment (for details see Medical Officer Review).

Overall, the results show a trend towards an increase in ADA activity and lymphocyte numbers (Figure 9). Also, the target blood dAXP levels, for detoxification, were reached and maintained with treatment. The T-cell, B-cell, and NK-cell counts were similar during the different phases of the study (Appendix-2).

Figure 9: Study STM-279-301- ADA activity and total lymphocytes vs. time (weeks).



Patient was with CMV pneumonitis at the time of enrollment. Was treated with SC-PEG-rADA on compassionate basis and died due to worsening of respiratory failure

Reviewer's Comments:

Overall, the study suggests that SC-PEG-rADA, like Adagen®, provides replacement of the ADA enzyme. SC-PEG-rADA treatment is effective in maintaining lymphocyte count, as well as detoxification (measured by dAXP levels) in patients with ADA-SCID.

5. Conclusions

The studies in genetically engineered ADA-deficient mouse model show 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 studies in a small number of subjects with ADA deficiency show that SC-PEG-rADA, like Adagen®, provides replacement of the ADA enzyme that is associated alleviation of metabolic disturbances and maintaining lymphocyte cell number.

6. The Labeling

6.1. The Applicant's proposed labeling

12.1 Mechanism of Action

SCID associated with a deficiency of ADA is a rare, inherited, and often fatal disease. ADA is an 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 function of immune cells. Elevated adenosine levels, as occurring in ADA deficiency, contribute to apoptosis and a block in the differentiation of thymocytes, causing severe T lymphopenia (b) (4)

Reviewer's Comments

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 labelings for rare diseases including enzyme replacement therapies. Minor edits are recommended for clarity.

6.2. FDA's version of the labeling

(Additions are double-underlined and deletions striked out)

12.1 Mechanism of Action

SCID associated with a deficiency of ADA enzyme, is a rare, inherited, and often fatal disease. ADA (b) (4) -enzyme is 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 (b) (4)

Elapegademase-lvlr provides an exogenous source of ADA enzyme that is associated with a decrease in toxic (b) (4) adenosine and deoxyadenosine nucleotides levels as well as an increase in lymphocyte number (b) (4) [see *Clinical Studies (14)*].

7. Recommendations

This BLA is approvable with respect to Immunology/Microbiology pending an accepted version of the labeling. For changes to the labeling see Section 6.2 above.

Shukal Bala
Shukal Bala, Ph.D.
Microbiologist/Immunologist

CONCURRENCE:
Division Director/Renata Albrecht, M.D.

CC:
DTOP/BLA 761092
DTOP/PM/Jacquelyn Smith

Appendix-1: Study STP-2279-002: Immune status assessments

Patient Assessment	PK Day 1	Week T-1	Week T-9	Week T-21	Maint. Week 34 [a]	Maint. Week 47 [a]	Maint. Week 60 [a]	Maint. Week 73 [a]	Maint. Week 86 [a]	Maint. Week 99 [a]	EOS/ Early D/C
Patient (b) (6)											
CD16+CD56 NK, (x10^9/L)	0.117	0.107	--	--	--	--	--	--	--	--	0.123
CD19, (x10^9/L)	0.142	0.155	--	--	--	--	--	--	--	--	0.261
CD3, (x10^9/L)	0.09	0.09	--	--	--	--	--	--	--	--	0.11
CD4, (x10^9/L)	0.08	0.07	--	--	--	--	--	--	--	--	0.09
CD8, (x10^9/L)	0.02	<0.02	--	--	--	--	--	--	--	--	0.02
Helper/Supp. Ratio	3.58	3.65	--	--	--	--	--	--	--	--	3.58
Total lymphocytes	0.37	0.36	--	--	--	--	--	--	--	--	0.52
Immunoglobulin A, (g/L)	0.36	0.42	--	--	--	--	--	--	--	--	0.55
Immunoglobulin G, (g/L)	14.60	11.80	--	--	--	--	--	--	--	--	11.30
Immunoglobulin M, (g/L)	0.56	0.55	--	--	--	--	--	--	--	--	0.58
Patient (b) (6)											
CD16+CD56 NK, (x10^9/L)	0.114	0.113	0.157	0.122	0.218	0.19	0.142	0.362	0.14	0.11	--
CD19, (x10^9/L)	0.030	0.038	0.071	0.076	0.066	0.058	0.107	0.093	0.054	0.095	--
CD3, (x10^9/L)	0.42	0.44	0.67	0.53	0.73	0.94	0.78	1.40	0.50	0.67	--
CD4, (x10^9/L)	0.16	0.19	0.32	0.25	0.28	0.33	0.36	0.45	0.20	0.34	--
CD8, (x10^9/L)	0.23	0.21	0.35	0.26	0.43	0.57	0.40	0.89	0.28	0.34	--
Helper/Supp. Ratio	0.70	0.91	0.91	0.93	0.66	0.59	0.89	0.50	0.71	0.99	--
Total lymphocytes, (x10^9/L)	0.57	0.60	0.91	0.73	1.02	1.19	1.03	1.98	0.70	0.89	--
Immunoglobulin A, (g/L)	0.95	1.01	1.05	1.01	1.02	1.23	1.21	1.24	1.37	1.44	--
Immunoglobulin G, (g/L)	10.60	10.00	10.10	9.39	11.80	11.40	9.89	9.92	11.20	13.30	--
Immunoglobulin M, (g/L)	0.99	0.99	1.14	1.04	1.08	1.22	1.00	0.98	1.06	1.30	--
Patient (b) (6)											
CD16+CD56 NK, (x10^9/L)	0.054	0.15	0.066	0.141	0.075	0.133	0.082	0.096	0.165	0.175	--
CD19, (x10^9/L)	0.138	0.114	0.143	0.285	0.267	0.248	0.206	0.340	0.347	0.231	--
CD3, (x10^9/L)	0.29	0.28	0.30	0.56	0.55	0.57	0.46	0.83	0.84	0.64	--
CD4, (x10^9/L)	0.22	0.18	0.22	0.37	0.38	0.38	0.31	0.60	0.58	0.44	--
CD8, (x10^9/L)	0.11	0.10	0.10	0.18	0.18	0.20	0.15	0.27	0.28	0.20	--
Helper/Supp. Ratio	2.05	1.82	2.29	2.10	2.12	1.93	2.04	2.28	2.08	2.22	--
Total lymphocytes, (x10^9/L)	0.52	0.56	0.54	0.99	0.92	0.98	0.76	1.31	1.40	1.08	--
Immunoglobulin A, (g/L)	1.16	1.13	1.08	0.87	0.87	0.89	0.84	0.73	0.95	0.90	--
Immunoglobulin G, (g/L)	11.80	11.60	10.10	8.95	8.63	8.37	8.99	8.20	9.70	9.16	--
Immunoglobulin M, (g/L)	0.73	0.64	0.40	0.61	0.42	0.36	0.64	0.34	0.43	0.44	--
Patient (b) (6)											
CD16+CD56 NK, (x10^9/L)	0.171	0.157	0.153	0.17	0.297	0.232	0.215	0.291	0.212	--	--
CD19, (x10^9/L)	0.070	0.053	0.051	0.052	0.171	0.119	0.131	0.178	0.193	--	--
CD3, (x10^9/L)	1.43	1.37	1.54	1.52	1.73	1.37	1.82	1.94	1.82	--	--
CD4, (x10^9/L)	0.24	0.27	0.26	0.30	0.39	0.35	0.47	0.49	0.41	--	--
CD8, (x10^9/L)	1.14	1.12	1.27	1.22	1.32	1.06	1.45	1.43	1.33	--	--
Helper/Supp. Ratio	0.21	0.24	0.21	0.24	0.29	0.33	0.32	0.34	0.31	--	--
Total lymphocytes, (x10^9/L)	1.71	1.61	1.77	1.76	2.19	1.74	2.23	2.43	2.26	--	--
Immunoglobulin A, (g/L)	0.52	0.48	0.50	0.46	0.50	0.46	0.47	0.45	0.48	0.51	--
Immunoglobulin G, (g/L)	12.60	11.10	12.60	9.19	10.50	10.60	12.60	12.70	12.80	11.60	--
Immunoglobulin M, (g/L)	0.30	0.27	0.22	0.26	0.22	0.21	0.19	0.16	0.16	0.24	--

Patient Assessment	PK Day 1	Week T-1	Week T-9	Week T-21	Maint. Week 34 [a]	Maint. Week 47 [a]	Maint. Week 60 [a]	Maint. Week 73 [a]	Maint. Week 86 [a]	Maint. Week 99 [a]	EOS/ Early D/C
Patient (b) (6)											
CD16+CD56 NK, ($x10^9$/L)	--	--	--	--	--	--	--	--	--	--	0.022
CD19, ($x10^9$/L)	--	--	--	--	--	--	--	--	--	--	<0.005
CD3, ($x10^9$/L)	--	--	--	--	--	--	--	--	--	--	0.34
CD4, ($x10^9$/L)	--	--	--	--	--	--	--	--	--	--	0.10
CD8, ($x10^9$/L)	--	--	--	--	--	--	--	--	--	--	0.24
Helper/Supp. Ratio	--	--	--	--	--	--	--	--	--	--	0.41
Total lymphocytes, ($x10^9$/L)	--	--	--	--	--	--	--	--	--	--	0.37
Immunoglobulin A, (g/L)	--	--	--	--	--	--	--	--	--	--	3.56
Immunoglobulin G, (g/L)	--	--	--	--	--	--	--	--	--	--	16.70
Immunoglobulin M, (g/L)	--	--	--	--	--	--	--	--	--	--	0.72
Patient (b) (6)											
CD16+CD56 NK, ($x10^9$/L)	0.056	0.108	0.073	--	--	--	--	--	--	--	--
CD19, ($x10^9$/L)	<0.005	<0.005	<0.005	--	--	--	--	--	--	--	--
CD3, ($x10^9$/L)	0.44	0.60	0.43	--	--	--	--	--	--	--	--
CD4, ($x10^9$/L)	0.12	0.18	0.13	--	--	--	--	--	--	--	--
CD8, ($x10^9$/L)	0.35	0.43	0.31	--	--	--	--	--	--	--	--
Helper/Supp. Ratio	0.34	0.42	0.41	--	--	--	--	--	--	--	--
Total lymphocytes, ($x10^9$/L)	0.50	0.72	0.51	--	--	--	--	--	--	--	--
Immunoglobulin A, (g/L)	3.31	3.63	4.79	--	--	--	--	--	--	--	--
Immunoglobulin G, (g/L)	15.00	15.90	14.70	--	--	--	--	--	--	--	--
Immunoglobulin M, (g/L)	0.55	0.60	0.66	--	--	--	--	--	--	--	--
Patient (b) (6)											
CD16+CD56 NK, ($x10^9$/L)	0.023	0.033	--	--	--	--	--	--	--	--	--
CD19, ($x10^9$/L)	0.018	0.020	--	--	--	--	--	--	--	--	--
CD3, ($x10^9$/L)	1.10	1.04	--	--	--	--	--	--	--	--	--
CD4, ($x10^9$/L)	0.66	0.70	--	--	--	--	--	--	--	--	--
CD8, ($x10^9$/L)	0.36	0.33	--	--	--	--	--	--	--	--	--
Helper/Supp. Ratio	1.83	2.15	--	--	--	--	--	--	--	--	--
Total lymphocytes, ($x10^9$/L)	1.17	1.12	--	--	--	--	--	--	--	--	--
Immunoglobulin A, (g/L)	2.84	--	--	--	--	--	--	--	--	--	--
Immunoglobulin G, (g/L)	14.50	--	--	--	--	--	--	--	--	--	--
Immunoglobulin M, (g/L)	0.43	--	--	--	--	--	--	--	--	--	--

EOS/Early D/C= End of Study/Early Discontinuation; --=data not available (patient discontinued prior to visit or visit data not available as of data cutoff date)
a Per protocol the scheduled assessment time ±3 weeks
Source: Module 5.3.5.2, Interim CSR STP-2279-002, Appendix 16.2.6, Listings 16.2.18.1 and 16.2.19.1

Patient (b) (6) and was withdrawn due to not meeting the inclusion criteria for ADA/dAXP levels during the Adagen® Lead-in phase, and the patient was later re-enrolled as Patient (b) (6) and continued in the study through SC-PEG- rADA dosing under this assigned number.

Appendix-2: Study STM-279-301: 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 Week 21 [Day 148])	CD16+CD56 NK, (x 10^9/L)	0.013	0.03	15	0.081	92	<LLN through Week 5 (Day 36); later near or above LLN [RR 0.070-0.76]
	CD19, (x 10^9/L)	0.001	0.006	15	0.07	64	All values <LLN [RR 0.11-0.66]
	CD3, (x 10^9/L)	0.779	0.836	64	1.076	36	All values WNL except for Screening and Week 9 (Day 64) [RR 0.840-3.06]
	CD4, (x 10^9/L)	0.143	0.151	64	0.25	120	All values <LLN [RR 0.490-1.74]
	CD8, (x 10^9/L)	0.552	0.557	120	0.759	36	All values WNL [RR 0.18-1.17]
	Helper/Supp. Ratio	0.3	0.3	15-92	0.4	120-148	All values <LLN [RR 0.86-5]
	Total Lymphocytes, (x 10^9/L)	0.651	0.97	15	1.18	36	All values WNL except at screening [RR 0.85-4.1]
	Immunoglobulin A, (mg/dL)	<10	<10	All	NA	NA	All values <10 mg/dL [RR 81-463]
	Immunoglobulin G, (mg/dL)	924	748	92	1058	120	All values WNL [RR 694-1618]
	Immunoglobulin M, (mg/dL)	<5	<5	15-36	8	120	All values <LLN [RR 48-271]
(b) (6) (Data available through Week 21 [Day 148])	CD16+CD56 NK, (x 10^9/L)	0.029	0.037	148	0.088	64	<LLN at screen and Days 15, 120, 148 [RR 0.060-0.43]
	CD19, (x 10^9/L)	0.013	0.015	15	0.045	148	All values <LLN [RR 0.13-0.80]
	CD3, (x 10^9/L)	0.084	0.062	120	0.122	36	All values <LLN [RR 0.860-2.42]
	CD4, (x 10^9/L)	0.054	0.027	92	0.06	36	All values <LLN [RR 0.510-1.45]
	CD8, (x 10^9/L)	0.028	0.028	15	0.039	36	All values <LLN [RR 0.24-0.89]
	Helper/Supp. Ratio	1.9	0.8	92	1.8	15	Most values WNL [RR 1.0-2.9]
	Total Lymphocytes, (x 10^9/L)	0.13	0.192	15	0.241	92	All values <LLN [RR 1.2-5.2]
	Immunoglobulin A, (mg/dL)	<10	<10	All	NA	NA	All values <10 mg/dL [RR 81-463]
	Immunoglobulin G, (mg/dL)	727	633	15	933	92	<LLN from Screen to Week 5 (Day 36); WNL Days 64-148 [RR 842-2013]
	Immunoglobulin M, (mg/dL)	<5	<5	All	NA	NA	All values <LLN [RR 23-281]
(b) (6) (Data available through Week 21 [Day 148])	CD16+CD56 NK, (x 10^9/L)	0.178	0.074	92	0.134	120	<LLN except at screening [RR 0.160-0.930]
	CD19, (x 10^9/L)	0.35	0.146	92	0.276	36	All values < LLN [RR 0.740-2.560]
	CD3, (x 10^9/L)	0.021	0.015	15	0.169	120	All values <LLN [RR 2.16-5.54]
	CD4, (x 10^9/L)	0.008	0.018	15	0.123	148	All values <LLN [RR 1.39-4.08]
	CD8, (x 10^9/L)	0	0.002	15	0.054	148	All values <LLN [RR 0.60-1.49]
	Helper/Supp. Ratio	--	2.3	92,148	9	15	Most values WNL [RR 1.7-3.9]
	Total Lymphocytes, (x 10^9/L)	1.087	0.384	92	0.726	64	All values <LLN [RR 4.0-10.5]
	Immunoglobulin A, (mg/dL)	<10	<10	All	NA	NA	All values <10 mg/dL [RR 24-121]
	Immunoglobulin G, (mg/dL)	601	540	36	954	64	Values were WNL [RR 533-1078]
	Immunoglobulin M, (mg/dL)	8	13	15	51	92,120	Values were <LLN at Screen and Day 15 [RR 26-218]
(b) (6) (Data available through Week 15 [Day 107])	CD16+CD56 NK, (x 10^9/L)	0.038	0.051	14	0.25	63	<LLN except at Week 9 (Day 63) [RR 0.160-0.930]
	CD19, (x 10^9/L)	0	0.028	14	0.557	91	All values <LLN [RR 0.740-2.560]
	CD3, (x 10^9/L)	0.003	0.003	14	0.38	63	All values <LLN [RR 2.16-5.54]
	CD4, (x 10^9/L)	0.003	0.002	14	0.059	63	All values <LLN [RR 1.39-4.08]
	CD8, (x 10^9/L)	0.002	0.001	14	0.308	63	All values <LLN [RR 0.60-1.49]
	Helper/Supp. Ratio	1.5	0.2	63,91	2.3	35	<LLN, except WNL Days 14, 35 [RR 1.7-3.9]
	Total Lymphocytes, (x 10^9/L)	0.1	0.2	14	0.9	63,91	All values <LLN [RR 4.0-10.5]
	Immunoglobulin A, (mg/dL)	41	<23	All	NA	NA	WNL at Screen. <23 mg/dL Days 14-91 [RR 24-121]
	Immunoglobulin G, (mg/dL)	956	756	14	971	91	Values were WNL [RR 533-1078]
	Immunoglobulin M, (mg/dL)	21	<17	35	253	91	All values <LLN until Week 13 (Day 91) (>ULN) [RR 26-218]

-- = data not available for interim analysis; LLN=lower limit of normal; RR=reference range; ULN=upper limit of normal; WNL=within normal limits
Source: Module 5.3.5.2, Interim Summary Report STM-279-301, Section 15.4, Listings 16.2.18 and 16.2.19

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/

SHUKAL BALA
08/14/2018

RENATA ALBRECHT
08/14/2018