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APPLICATION NUMBER:

761092Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Office of Clinical Pharmacology Review

BLA Number	761092
Link to EDR	EDR Link
Submission Date	10/24/2017
Submission Type	Priority
Brand Name	REVCovi
Generic Names	Elapegademase, EZN-2279, STM-279, SC-PEG rADA, PEG-rADA
Dosage Form and Strength	Sterile solution for injection: 1.6 mg/mL solution
Route of Administration	Intramuscular
Proposed Indication	For treatment of adenosine deaminase severe combined immune deficiency (ADA-SCID)
Applicant	Leadiant Biosciences, Inc.
Associated IND	IND 100687
OCP Review Team	Abhay Joshi, Ph.D. <i>DCP IV Clinical Pharmacology Reviewer</i> Philip Colangelo, Pharm.D., Ph.D. <i>DCP IV Clinical Pharmacology Team Leader</i>
OCP Final Signatory	John A. Lazor, Pharm.D. <i>DCP IV Director</i>

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1. EXECUTIVE SUMMARY

This submission is a 351(a) BLA for REVCovi, which is elapegademase (code names: EZN-2279, STM-279, SC-PEG rADA) solution for intramuscular (IM) injection. EZN-2279 contains recombinant adenosine deaminase (rADA) enzyme and the proposed indication is treatment of adenosine deaminase severe combined immunodeficiency (ADA-SCID), which is a very rare genetic disorder.

The Applicant has developed EZN-2279 (b) (4)

(b) (4) Adagen is currently the only enzyme replacement therapy (ERT) for ADA-SCID patients (b) (4)

(b) (4) The product quality related attributes of EZN-2279 are purported by the Applicant to alleviate issues related to lack of assurance of a reliable and continuous supply of (b) (4) stability (i.e., shelf-life of (b) (4) months).

With this submission, the Applicant is seeking accelerated approval for EZN-2279 for the ADA-SCID indication and has submitted an interim analysis of efficacy and safety data from six patients enrolled in a Phase 3 study that is ongoing in the US. The Applicant has also submitted a supportive interim analysis of efficacy and safety data from four patients enrolled in a Phase 3 study that is ongoing in Japan. From these 10 patients enrolled in the two ongoing Phase 3 studies, the Applicant has submitted interim pharmacokinetic (PK) reports for six evaluable patients.

From a Clinical Pharmacology perspective, the key review issues are 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.

1.1.Recommendations

The Office of Clinical Pharmacology has reviewed the information provided by the Applicant in BLA 761092 for REVCovi and recommends approval of this BLA.

The Reviewer's proposed labeling changes to the Applicant's proposed labeling are listed in Section 2.4.

Table 1: Summary of OCP's Recommendations & Comments on Key Review Issues

Review Issue	Recommendations and Comments
Pivotal or 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/L/hr or greater, and deoxyadenosine nucleotide (dAXP; undesired marker) levels were maintained under 0.02 mmol/L.
General dosing instructions	For patients converting from Adagen to EZN-2279 treatment: the proposed starting weekly intramuscular (IM) dose for EZN-2279 is 0.2 mg/kg and the dose may be increased by 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.

Review Issue	Recommendations and Comments
	- From a clinical pharmacology perspective, the proposed starting weekly IM dose of 0.2 mg/kg is acceptable. Please see Section 2.2.1 for additional details. Regarding the plasma trough ADA activity level related criterion of 30 mmol/hr/L or greater to be used for EZN-2279 dose adjustment, this criterion is supported by published expert opinion and the current medical experience with Adagen. Therefore, the Clinical Pharmacology Reviewer defers review of this evidence to the Clinical Review Team. Please see Section 2.2.2 for additional details. 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). (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. - For Adagen-naïve patients, the available clinical pharmacology information is very limited to support the proposed starting EZN-2279 dose of 0.4 mg/kg/wk (b) (4). (b) (4) Therefore, the Clinical Pharmacology Reviewer defers to the Clinical Review Team regarding review of these proposals from the Applicant. Please see Sections 2.2.1 and 2.2.2 for additional details.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No clinical pharmacology studies were conducted that evaluated the effects of intrinsic or extrinsic factors. 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	The summary of clinical pharmacology related labeling recommendations are listed in Section 2.4.
Bridge between the to-be-marketed and clinical trial formulations	Not applicable. The to-be-marketed formulation of EZN-2279 is being used in the clinical studies that are supporting this application.
Bioavailability and dose conversion of a patient between formulations	Only one EZN-2279 formulation for IM injection is the to-be-marketed drug product. (b) (4) The Applicant has proposed a dose conversion factor of 1 mg EZN-2279 = 150 U Adagen. The proposed dose conversion factor is acceptable. Please see Section 3.3.2 for additional details.

1.1.Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1. Clinical Pharmacokinetics

The PK of both drug products are evaluated indirectly based on the plasma ADA activity levels.

In support of this application, the Applicant has conducted one interim clinical study that evaluated steady state pharmacokinetics, in terms of ADA activity levels, following IM administration of EZN-2279 in six ADA-SCID patients (age range: 8 to 37 years) who were stabilized on Adagen treatment. Therefore, each patient enrolled in this study served as his or her own control. In this study, following EZN-2279 treatment, all of the enrolled patients had total erythrocyte trough dAXP concentrations of ≤ 0.02 mmol/L at all timepoints, except for two patients, one who had a dAXP concentration of 0.032 mmol/L at treatment week 13 and the other who had a dAXP concentration of 0.047 mmol/L at treatment Week 17. The cause of these spurious dAXP levels in these two patients is apparently not known, since the Applicant did not attempt to provide an explanation.

At the time of interim analysis, four out of six patients were considered PK evaluable. The overall steady state PK information from these four patients indicated the following:

- All patients had trough plasma ADA activity levels greater than 15 mmol/L/hr.
- T_{max} estimates for plasma ADA activity levels from EZN-2279 treatment were not notably different from the estimates reported previously following Adagen treatment.
- On average, the dose normalized maximum ADA Activity and $AUC_{0-168hr}$ for ADA Activity following EZN-2279 treatment was approximately 66% and 90% higher compared to their respective values following Adagen treatment.

The Applicant has not conducted conventional single/multiple dose PK studies or any specific distribution or metabolism characterization assessments.

The Applicant attempted to determine the differences between terminal rate constant and half-life for plasma ADA activity levels at steady state from EZN-2279 and Adagen treatments. The Applicant has reported these estimates, but has noted that these estimates are not reliable.

2.2.Dosing and Therapeutic Individualization

2.2.1. General dosing

Patients transitioning from Adagen

The Applicant proposes that the starting weekly IM dose of EZN-2279 is 0.2 mg/kg of actual body weight, if a patient's Adagen dose is not known, or is at or lower than 30 Units/kg.

The Applicant also proposes that 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 equation provided below. The Applicant's proposed starting weekly IM dose of EZN-2279 for patients transitioning from Adagen treatment is acceptable.

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

For Adagen-naïve patients

For Adagen-naïve patients, the Applicant proposes a starting total weekly IM dose of EZN-2279 of 0.4 mg/kg of actual body weight, given as 0.2mg/kg two times a week. The available clinical pharmacology information is too limited to support the proposed dose of 0.4 mg/kg/week. Therefore, the Clinical Pharmacology Reviewer defers to the Clinical Review Team regarding the Applicant's proposed starting dose.

2.2.2. Therapeutic individualization

The Applicant is proposing to increase subsequent (to the starting dose) EZN-2279 doses by increments of 0.033 mg/kg weekly to maintain (1) plasma trough ADA activity at or above 30 mmol/hr/L for patients on Adagen treatment (b) (4) (2) total erythrocytes dAXP under 0.02 mmol/L, and/or (3) to maintain adequate immune reconstitution as judged the treating physician. The following is the summary of the clinical pharmacology assessment of the proposed plasma ADA activity based dose adjustment criterion.

Patients transitioning from Adagen

The Applicant is proposing to increase the dose at increments of 0.033 mg/kg weekly if plasma trough ADA activity is under 30 mmol/hr/L. This criterion is being supported by published expert opinion and the current medical experience with Adagen treatment. The Clinical Pharmacology Reviewer defers review of this evidence to the Clinical Review Team.

The plasma trough ADA activity level based dose adjustment criterion of 15 mmol/L/hr or greater is being used in the two ongoing pivotal clinical studies supporting this application. However, it is

noteworthy that in four out of six PK evaluable patients enrolled in these two pivotal studies, trough plasma ADA activity levels were maintained at or above 30 mmol/L/hr.

For Adagen-naïve patients

The clinical pharmacology information contained in the submission is not adequate to support the proposed dose adjustment criteria of maintaining plasma trough ADA activity at 50 mmol/L/hr or greater. The Clinical Pharmacology Reviewer also defers to the Clinical Review Team regarding review of this proposed minimum plasma trough ADA activity level by the Applicant.

2.3.Outstanding Issues

None.

2.4.Summary of Labeling Recommendations

The Reviewer's proposed specific additions to the Applicant's proposed labeling are in blue underlined text. The summary of the Reviewer's proposed labeling recommendations/revisions are provided below in *orange italics* text.

Section 2 DOSAGE AND ADMINISTRATION; 2.1 Recommended Dosage

The following addition is recommended by the Reviewer:

If a patient's weekly Adagen dose is not known or a patient's weekly Adagen dose is at or lower than 30 U/kg, the recommended minimum starting (b) (4) dose of REVCovi is 0.2 mg/kg (b) (4)
(b) (4)

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 equation:

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

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

Section 5 WARNINGS AND PRECAUTIONS; 5.2 (b) (4)

The proposed language by the Applicant in Sec 5.2 is not relevant under WARNINGS AND PRECAUTIONS and is better aligned under Section 2 as a new Section 2.3.

Section 6 ADVERSE REACTIONS; 6.2 Immunogenicity

The proposed language by the Applicant for Section 6.2 should be replaced with the following language:

As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity results from Study 1 and Study 2 suggest that patients who previously received Adagen may present an immunologic response to REVCovi (elapegademase). Therefore, monitoring for changes in ADA levels during REVCovi treatment is recommended. [see Dosage and Administration (2.3)]

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.

Section 7 DRUG INTERACTIONS and **Section 12 CLINICAL PHARMACOLOGY**; 12.3 Pharmacokinetics

The Clinical Pharmacology recommendations that were sent to the Applicant for these sections are attached in **Appendix 4.4**.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1. Regulatory Background and Overview of the Product

Adenosine deaminase severe combined immune deficiency (ADA-SCID) is a very rare genetic disorder. Current treatment options for US patients with ADA-SCID are bone marrow transplantation, enzyme replacement therapy (ERT), and/or enrollment in investigational gene-therapy studies. In the absence of ADA in ADA-SCID patients, adenosine accumulation occurs. ERT addresses this metabolic abnormality by preventing toxic levels of adenosine metabolites (i.e., dAXP) from accumulating in immune cells. At present, Adagen® (NDA 19818) is the only FDA approved ERT for ADA-SCID patients.

The proposed drug product REVCOVI is 1.6 mg/mL elapegademase (Code names: EZN-2279, STM-279, SC-PEG rADA) solution for intramuscular (IM) injection. The Applicant has developed EZN-2279 that contains recombinant adenosine deaminase (rADA) produced from the bacterium *Escherichia coli* (b) (4) (b) (4) instead of naturally derived adenosine deaminase (nADA) contained in Adagen. EZN-2279 and Adagen, both are PEGylated products, i.e., uses PEG for manufacturing. However, the SS linker used to link PEG to nADA in Adagen has been replaced by (b) (4) SC linker to link PEG to rADA in EZN-2279. The interim PK findings from Study STP-2279-002 indicate higher steady state plasma ADA activity levels following EZN-2279 treatment relative to the activity levels following Adagen treatment. The increased plasma ADA activity levels are attributed to improved stability of EZN-2279 at the site of injection. (b) (4)

These postulated improvements in stability at the site of injection are based on the findings from two single-dose nonclinical PK studies that showed higher plasma levels of ADA activity (AUC increase of approximately 45% in rats and 55% in dogs) compared to Adagen. In these non-clinical studies, the half-life for ADA activity was also reported to be longer (approximately 30% in rats and 80% in dogs) than Adagen. In a single dose rat study, the relative half-life of SC-PEG rADA, in terms of percent of the Adagen half-life, was calculated to be 152%, while SS-PEG rADA exhibited a relative half-life of 105% compared to Adagen.

3.2. General Pharmacology and Pharmacokinetic Characteristics

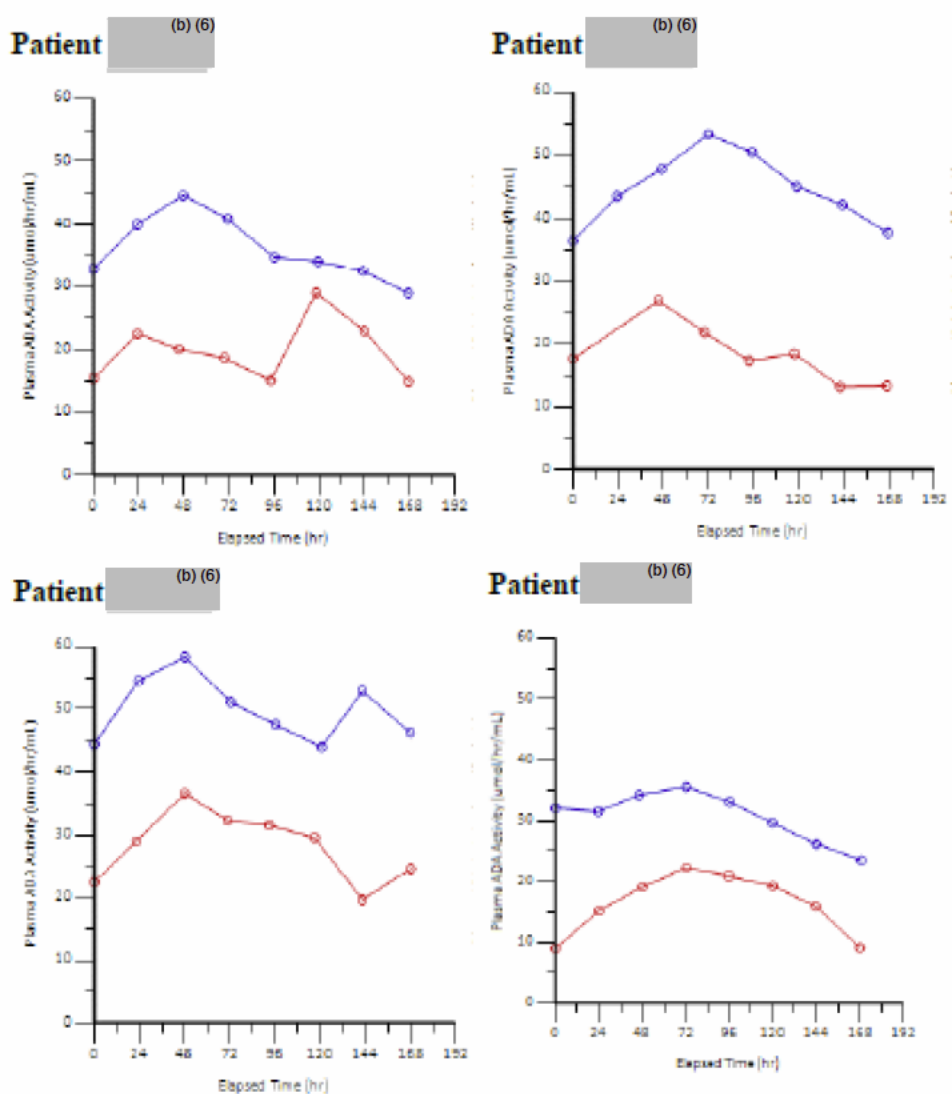
Mechanism of Action

ADA-SCID is a rare genetic condition that leads to complete or near complete absence of ADA that results in intracellular accumulation of purine metabolites (e.g. adenosine and 2'-deoxyadenosine) at toxic levels. EZN-2279 treatment replaces ADA into the plasma thereby breaking down the plasma adenosine rapidly. This effect is postulated to allow an outward movement of adenosine from intracellular space into the plasma and thereby reducing the formation of the toxic metabolites within the intracellular space.

Pharmacokinetics

The pharmacokinetics (PK) of EZN-2279 were evaluated indirectly based on the plasma ADA activity. The Applicant has conducted one clinical study that evaluated steady state PK of plasma ADA activity over the typical dosing interval of 168 hours. In total, six ADA-SCID patients who were on Adagen treatment were enrolled in this study and each patient served as his or her own control. Four out of six patients were considered PK evaluable. The overall steady state plasma ADA activity levels following Adagen and EZN-2279 treatment over the dosing interval of 168 hours are compared in Figure 1.

Figure 1: Steady State Plasma ADA Activity Levels-Time Profiles Over a Dosing Interval (168 hours) from PK Evaluable Patients: The Adagen Lead-in Period (Red) and the EZN-2279 Treatment Period (Blue): Study STP-2279-002 (Source: Adapted from 2.7.2 Summary of Clinical Pharmacology Studies, Figure 3, p16)



The observed plasma ADA activity levels were subjected to non-compartmental analysis and resultant parameter estimates are reported in **Table 2**. Given that the Applicant's proposed dose of EZN-2279 is on a mg/kg basis, these individual parameter estimates should be normalized to the actual mg/kg EZN-2279 dose that was administered. For the purposes of this review, the Reviewer re-analyzed the data to determine and compare the dose normalized estimates using the Adagen dose (converted to mg/kg) administered in the Adagen lead-in period and the EZN-2279 dose (mg/kg) (**Table 2**). The comparison indicated that, on average, the dose normalized maximum ADA Activity and $AUC_{0-168hr}$ for ADA Activity estimates from the EZN-2279 treatment period was approximately 66% and 90% higher compared to their respective average values from the Adagen lead-in period. The terminal rate constant and half-life for plasma ADA activity levels are not reported in **Table 2** as the available data are very limited and reliable estimates could not be determined.

Table 2: Individual and Summary Estimates from Non-Compartmental Analysis of Steady State ADA Activity Levels: Study STP-2279-

002 (Reviewer's Analyses)

Treat- ment	Patient ID	Dose	T _{max} for ADA Activity	Maximum ADA Activity	DN* Maximum ADA Activity [#]	AUC _{0-168 hr} for ADA Activity	DN* AUC _{0-168 hr} for ADA Activity	Trough ADA Activity
	Units	mg/kg	Days	μmol/hr/mL	(μmol/hr/mL)/ (mg/kg)	hr*μmol/hr/mL	(hr*μmol/hr/mL)/ (mg/kg)	μmol/hr/mL
Adagen	(b) (6)	0.19	5	29.00	154.28	3427.22	18232.79	14.90
		0.23	2	26.80	116.39	3238.41	14063.94	13.30
		0.20	2	36.60	183.00	4840.93	24204.66	24.60
		0.21	3	22.20	106.34	2911.00	13943.68	9.13
	N	4	4	4	4	4	4	4
	Mean	0.21	3	28.65	140.00	3604.39	17611.27	15.48
	SD	0.02	1.41	6.01	35.33	851.50	4826.80	6.55
	Min	0.19	2	22.20	106.34	2911.00	13943.68	9.13
	Median	0.20	2.50	27.90	135.33	3332.81	16148.37	14.10
	Max	0.23	5	36.60	183.00	4840.93	24204.66	24.60
	CV%	8.60	47.10	21.00	25.20	23.60	27.40	42.30
EZN-2279	(b) (6)	0.19	2	44.60	237.27	6179.96	32877.39	29.00
		0.23	3	53.30	231.47	7661.46	33272.61	37.70
		0.20	2	58.30	291.50	8474.45	42372.24	46.20
		0.21	3	35.60	170.52	5231.82	25060.42	23.50
	N	4	4	4	4	4	4	4
	Mean	0.21	2.50	47.95	232.69	6886.92	33395.66	34.10
	SD	0.02	0.58	9.99	49.48	1455.94	7079.05	9.96
	Minimum	0.19	2	35.60	170.52	5231.82	25060.42	23.50
	Median	0.20	2.50	48.95	234.37	6920.71	33075.00	33.35
	Maximum	0.23	3	58.30	291.50	8474.45	42372.24	46.20
	CV%	8.60	23.10	20.80	21.30	21.10	21.20	29.20

*DN = Dose normalized estimate based on the actual mg/kg dose reported in Dose column

Exposure-response

The Applicant has not conducted any formal exposure response-analysis between the plasma ADA activity and clinical efficacy or outcome. Internal discussions with the Review Team indicated that the plasma trough ADA activity levels of >15 mmol/L/hr is considered to be a predictive surrogate for effectiveness and or clinical outcome.

Immunogenicity

Immunogenicity assessments were conducted as the part of both studies, however, both studies are ongoing and very limited data are available from long term follow-up after EZN-2279 treatment to draw any definitive conclusions.

3.3.Clinical Pharmacology Review Questions

3.3.1. To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The Clinical Pharmacology information contained in this application provides supportive evidence of effectiveness.

The proposed drug product: EZN-2279 provides replacement of the ADA enzyme in plasma. The pivotal studies that are supporting this application evaluated whether therapy with EZN-2279 maintains trough plasma ADA activity $\geq 15 \mu\text{mol/hr/mL}$ (15 mmol/hr/L) in ADA-SCID patients. Therefore, the PK of EZN-2279 was evaluated indirectly based on the plasma ADA activity levels and was compared against the PK of plasma ADA activity levels from Adagen. Specifically, the Applicant has submitted steady state plasma ADA activity levels from the Adagen lead-in period and the EZN-2279 treatment period from four evaluable patients (out of six enrolled) that are enrolled in ongoing Study STP-2279-002 (**Figure 1, Section 3.2**). Trough plasma ADA activity level (Day 7) data from the maintenance period of this study are also available (**Figure 2**). The Applicant has also submitted steady state PK information from two evaluable patients (out of total four patients) enrolled in an ongoing Study STM-279-301 (**Figure 3**).

Information on the individual plasma trough ADA activity levels, i.e., ADA activity levels at Day 7, from six evaluable patients are summarized in **Table 3**. Please see **Section 4.1** and **Section 4.2** for additional details on these studies.

Figure 2: Trough Plasma ADA Activity Levels -Time Profiles from PK Evaluable Patients: EZN-2279 Treatment Weeks 1-21 Study STP-2279-002 (Source: Adapted from 2.7.2 Summary of Clinical Pharmacology Studies, Figure 4, p18)

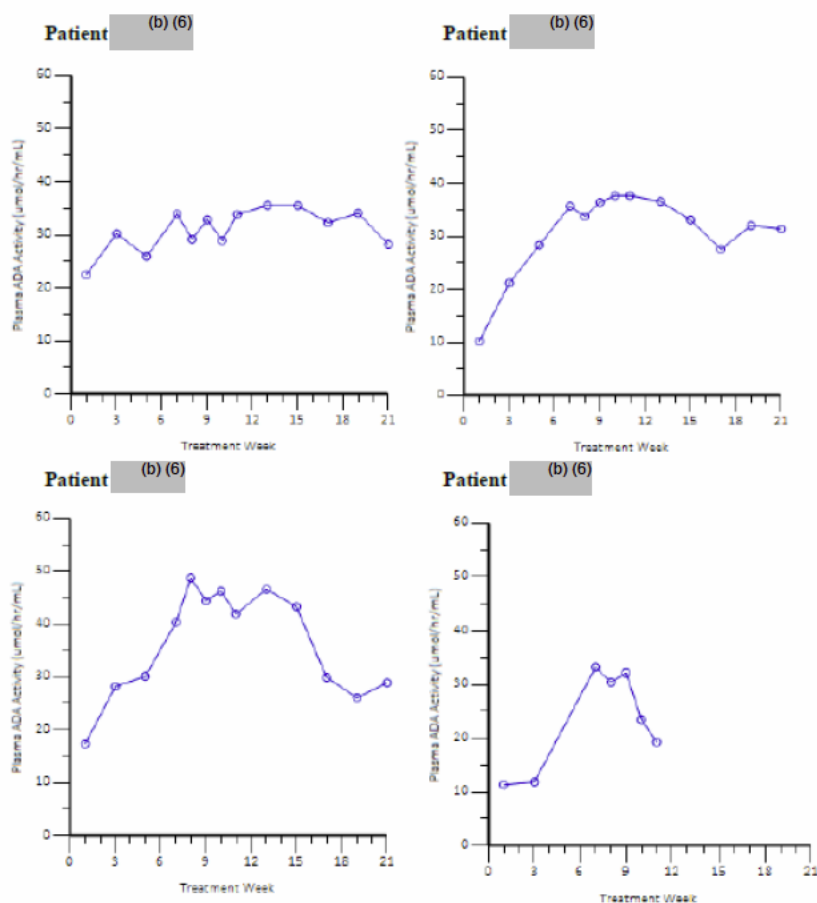


Figure 3: Steady State Plasma ADA Activity Levels-Time Profiles Over a Dosing Interval (168 hours) from PK Evaluable Patients: Study STM-279-301 (Source: Adapted from Pharmacokinetic Report – Interim Analysis, Version: FINAL (28 July 2017), Figure 7.1, p10)

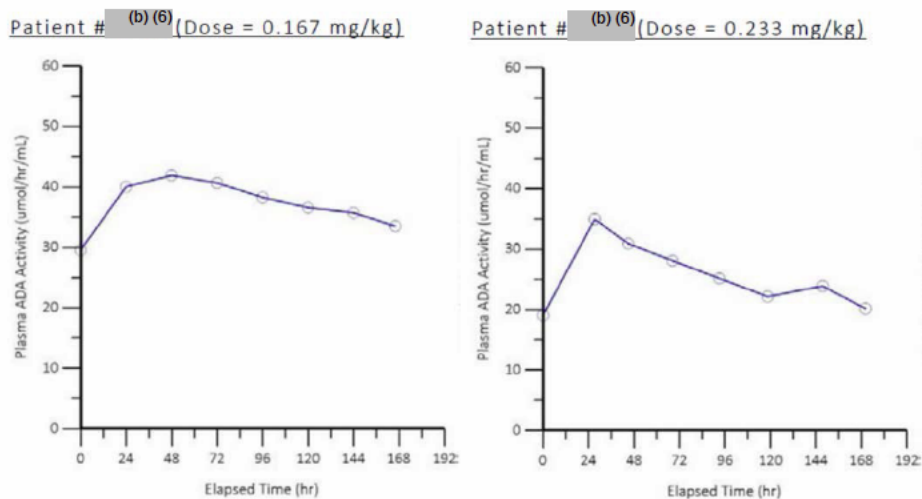


Table 3: Summary of Plasma Trough (Day 7) ADA Activity Levels from PK Evaluable Patients Enrolled in Studies STP-2279-002 and STM-279-301

Study	Patient ID	Trough (Day 7) ADA Activity (μmol/hr/mL)
STP-2279-002	(b) (6)	29.00
		37.70
		46.20
		23.50
STM-279-301	(b) (6)	33.50
		20.15
Summary	N	6
	Mean	31.68
	SD	8.73
	Minimum	20.15
	Median	31.25
	Maximum	46.2

It is noteworthy that the primary endpoint of Study STP-2279-002 is metabolic detoxification, defined as total erythrocyte dAXP concentrations of ≤ 0.02 mmol/L. Overall findings from the submitted interim report shows that at or after EZN-2279 treatment week five, all enrolled patients had trough total erythrocyte dAXP concentrations of ≤ 0.02 mmol/L at all timepoints, except for two patients, one (Patient IDs (b) (6)) who had a dAXP concentration of 0.032 mmol/L at treatment week 13 and the other who had a dAXP concentration of 0.047 mmol/L at treatment Week 17. The reasons for these apparently spurious increases are not known, however, the remaining trough dAXP levels for these two patients were ≤ 0.02 mmol/L at all other timepoints.

From Study STM-279-301, findings related to trough erythrocyte dAXP concentration were not available at the time of the interim report.

3.3.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Proposed Starting Dose

- *Patients transitioning from Adagen*

The Applicant's proposed starting weekly IM dose was 0.2 mg/kg of EZN-2279 in the original submission. The evidence for effectiveness is derived from six patients enrolled in Study STP-2279-002. Additional supportive evidence is derived from four patients enrolled in Study STM-279-301. From the 10 patients enrolled in these two studies, eight patients were transitioning from Adagen. The average starting weekly IM dose of EZN-2279 in these eight patients was 0.22 mg/kg (range: 0.17-0.29 mg/kg).

Therefore, the Applicant's proposed starting dose was found reasonable for patients transferring from Adagen treatment.

However, given that the pivotal studies supporting this application used the equation below to determine an equivalent weekly EZN-2279 dose when transitioning patients from Adagen to EZN-2279, the recommendation to include the equation in the labeling for EZN-2279 was sent to the Applicant.

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

The Applicant agreed and proposes revised language that is acceptable from a clinical pharmacology perspective. Please see Section 2.4 for additional details on the specific labeling language.

An additional information request (IR) was sent from the OCP Reviewer to the Applicant to provide the rationale for using the 150 U Adagen factor in the dose conversion equation. After review of the Applicant's reply to that IR, the proposed use of this factor is deemed to be acceptable. The following is a review summary of the pertinent information from the original submission and the Applicant's response to the IR from the Reviewer:

The dosing equation above was determined based on the following factors considerations:

(b) (4)

Overall, the conversion factor for Adagen dose from U/kg to EZN-2279 dose in mg/kg was derived using the following equation:

(b) (4)

Consequently, the conversion factor of 150 was obtained as follows:

$$\frac{0.2 \text{ mg EZN2279}}{30 \text{ U Adagen}} = \frac{1 \text{ mg EZN2279}}{150 \text{ U Adagen}}$$

The correlation factor (b) (4) between RP-HPLC and spectrophotometric methods used to determine enzyme activity was determined using data from five replicate samples from two different Adagen and EZN-2279 lots that were tested with both the spectrophotometric and RP-HPLC methods to determine the effect of the assay conditions on the resulting definition of a unit of enzymatic activity. The correlation factor from all replicates ranged from (b) (4) to (b) (4)

Enzymatic activity of two Adagen lots used for the treatment of four PK evaluable patients were (b) (4) U/mL. Enzymatic Activity of three EZN-2279 lots used for the treatment of four PK evaluable patients ranged from (b) (4) to (b) (4) U/mL. Therefore, the observed correlation between RP-HPLC and spectrophotometric methods used to determine enzyme activity of different Adagen and EZN-2279 lots used in the PK population ranged from (b) (4) to (b) (4). Therefore, the Applicant's use of correlation factor (b) (4) is acceptable.

In this study, enzymatic activity of three EZN-2279 lots used for the treatment of four patients that were in the PK population ranged from (b) (4) to (b) (4) U/mL. For the purpose of calculating the correlation factor, enzymic activity of EZN-2279 specifications for activity of EZN-2279 was considered to be (b) (4) U/ml, which is acceptable considering that this is a conservative (least value) value.

- *For Adagen-naive patients*

The available clinical pharmacology information is very limited to support the proposed dose of 0.4 mg/kg/week for the Adagen-naive patients. Therefore, the Clinical Pharmacology Reviewer defers to the Clinical Review Team regarding the Applicant proposed starting dose.

Within the pivotal studies mentioned in the previous section, only one Adagen-naive patient (age = 3.4 months) received the proposed starting dose of 0.4 mg/kg/week. This patient received treatment for 13 weeks and discontinued due to death from worsening of respiratory failure.

Dose Adjustments

The following is the review of the plasma trough ADA activity based dose adjustment criterion that is being proposed.

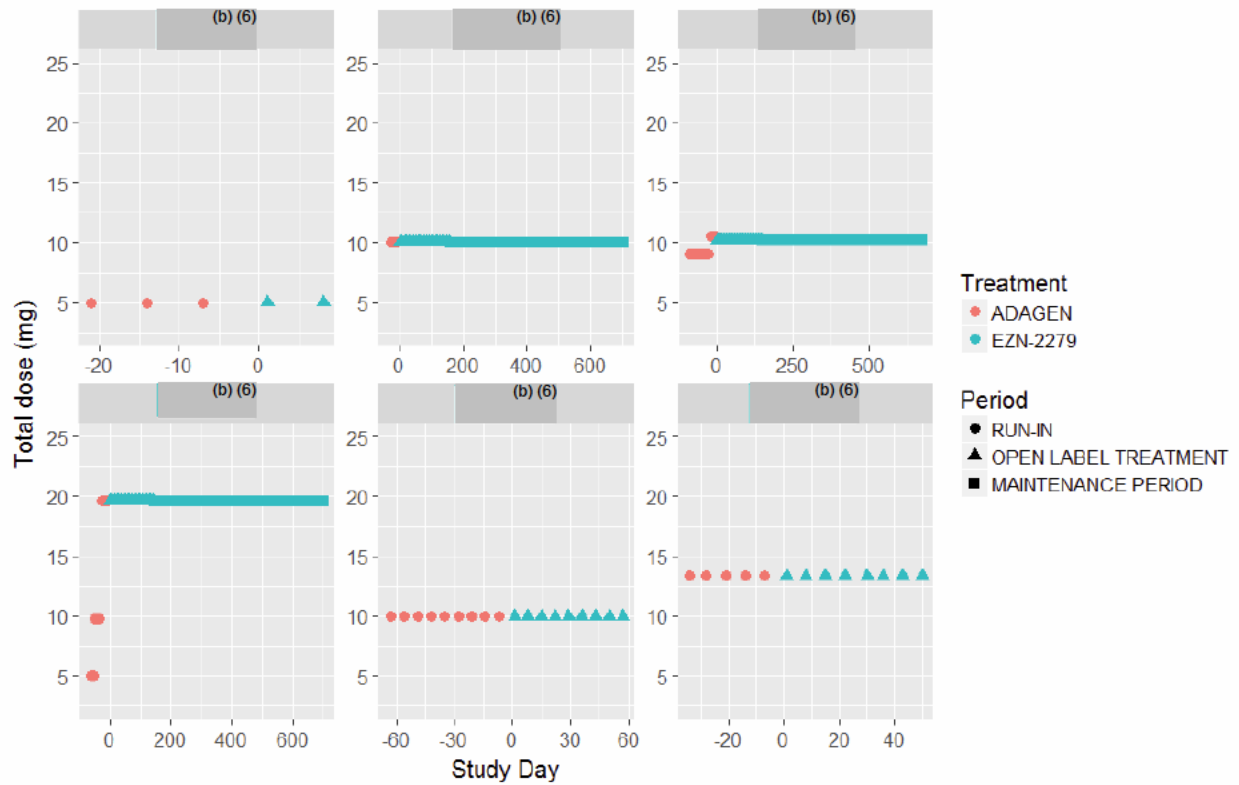
- *Patients transitioning from Adagen*

The Applicant is proposing to increase the dose in increments of 0.033 mg/kg weekly if plasma trough ADA activity is under 30 mmol/hr/L. The Applicant has not conducted any formal exposure response analysis between the plasma ADA activity and clinical efficacy in support of the proposed criterion. Instead, the Applicant appears to rely on published expert opinion and the current medical experience with Adagen treatment to support the proposed criterion above. Therefore, the Clinical Pharmacology Reviewer defers review of this evidence to the Clinical Review team.

The plasma trough ADA activity based dose adjustment criterion of <15 mmol/L/hr is being used in two ongoing clinical studies supporting this application. However, it is noteworthy that in four of six PK evaluable patients enrolled in two pivotal studies, plasma ADA activity levels were maintained at or above 30 mmol/L/hr. The available dose over time information for the Adagen non-naive patients enrolled in Study STP-2279-002 is presented in **Figures 4 and 5**.

Figure 4: Total Dose* (Mg) Over Time in Adagen Non-Naive Patients Enrolled in Study STP-2279-002

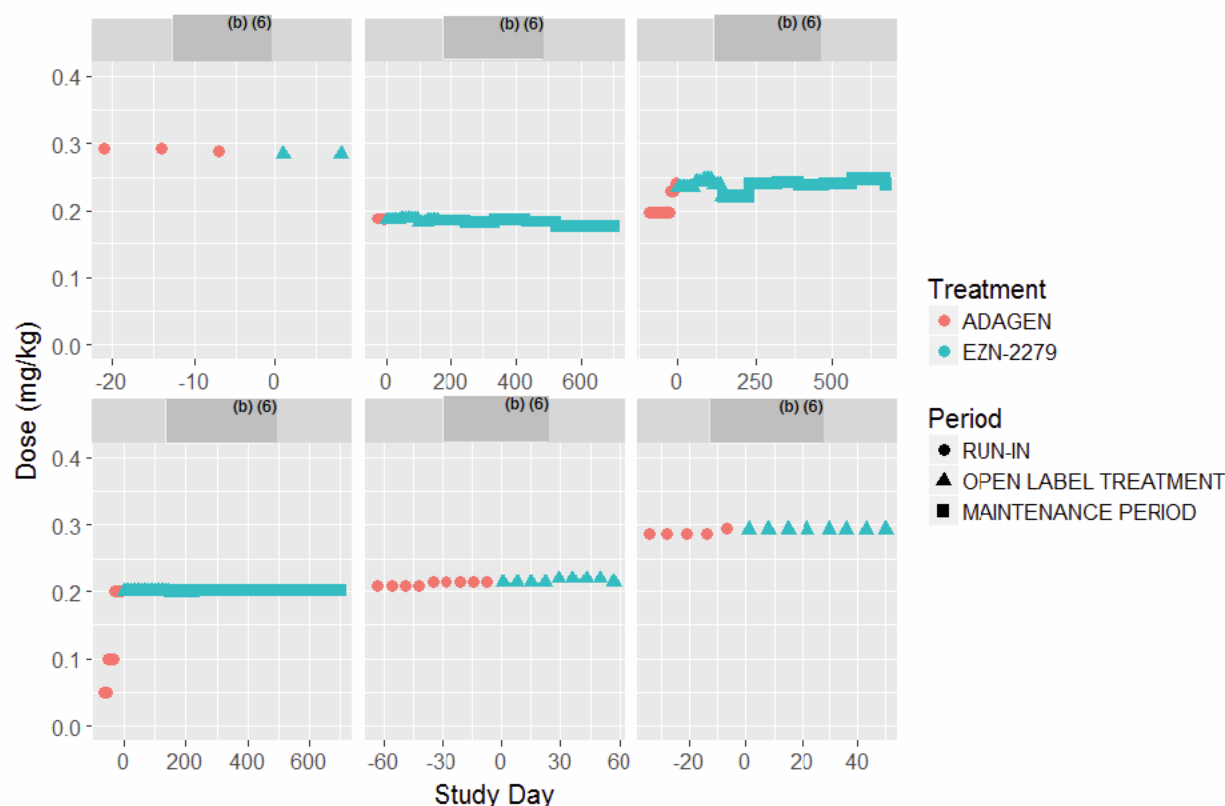
(Source: Reviewer's Analysis)



*Total Adagen dose presented above is converted from Unit dose to mg dose using 150 conversion factor that was used during the conduct of the trial, i.e., 150 U Adagen = 1 mg EZN-2279.

Figure 5: Dose (Mg/kg) Over Time in Adagen Non-Naive Patients Enrolled in Study STP-2279-002**

(Source: Reviewer's Analysis)



****Total Adagen dose presented above is converted from Unit/kg dose to mg/kg dose using 150 conversion factor that was used during the conduct of the trial, i.e., 150 U/kg Adagen = 1 mg/kg EZN-2279.**

- For Adagen-naive patients

The clinical pharmacology information contained in the submission is not adequate (b) (4). The Clinical Pharmacology Reviewer defers to the Clinical Review Team regarding this proposal from the Applicant.

Within the pivotal studies mentioned in the previous section, Study STM-279-301 enrolled Adagen-naive patient(s). Specifically, one Adagen-naive patient (age = 3.4 months) received the proposed starting dose of 0.4 mg/kg/week that was divided into two doses, i.e., 0.2mg/kg two times per week. This patient received the same dose throughout treatment for 13 weeks and discontinued due to death from worsening of respiratory failure. An additional patient (age = 25 years), who did not receive Adagen within four weeks prior to EZN-2279 treatment was also enrolled. This patient received the first dose at 0.1 mg/kg/week and the second and third doses at 0.133 mg/kg/week. From Week 4 onwards, this patient received 0.167/mg/kg/week through the cutoff date for the study report.

3.3.3. Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No, EZN-2279 dosing is adjusted (following to the starting dose) to maintain plasma trough ADA activity and total erythrocytes dAXP within the pre-specified criteria.

3.3.4. Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

The route of administration for the proposed drug product is intramuscular administration and therefore, the evaluation of food-drug interaction(s) is not relevant. The Applicant has not conducted any clinical pharmacology studies that evaluated drug-drug interactions (DDI).

4. APPENDICES

4.1. Study STP-2279-002

Title:

A study of EZN-2279 (polyethylene glycol recombinant adenosine deaminase [PEG-rADA]) administered as a weekly intramuscular injection in patients with adenosine deaminase (ADA)-deficient combined immunodeficiency

Trial Information:

Study centers	Bio-analytical Laboratory
5 US centers: Ongoing (First patient enrolled in 2014, Data cutoff month for interim analysis: April 2017)	(b) (4)

Primary Objective:

To evaluate whether therapy with EZN-2279 achieves metabolic detoxification, which was defined as a total erythrocyte deoxyadenosine nucleotide (dAXP) concentration from a trough blood sample equal to or below 0.02 $\mu\text{mol/mL}$ (0.02 mmol/L)

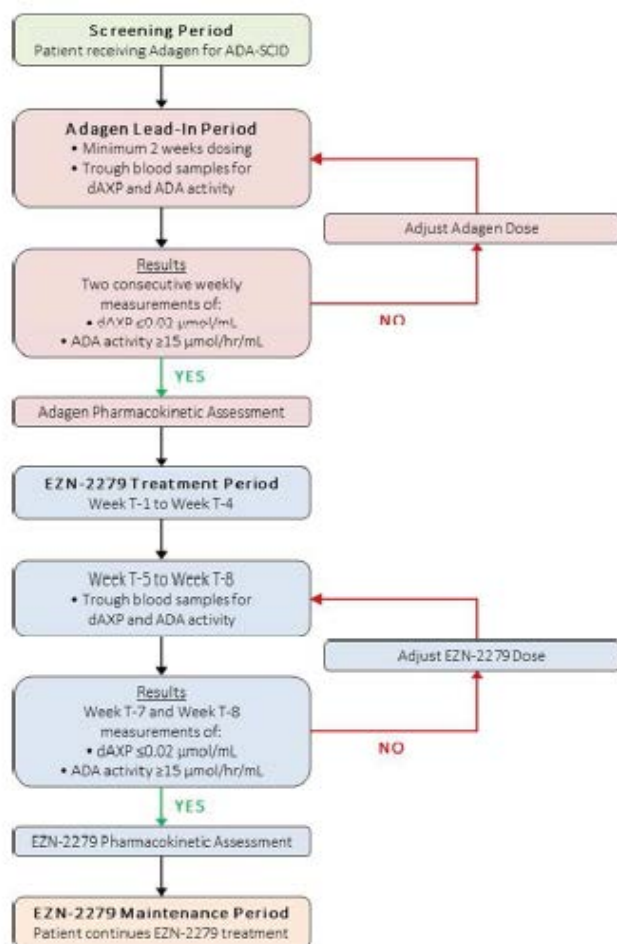
Secondary Objectives (Selected):

- To assess the immunogenicity to EZN-2279 and Adagen[®], including binding antibodies, neutralizing antibodies, and anti-PEG antibodies
- To evaluate whether therapy with EZN-2279 maintains trough plasma ADA activity of ≥ 15 mmol/L/h
- Determine the pharmacokinetic (PK) profile of EZN-2279 based on the observed ADA activity levels in plasma

Study Design:

This was an open-label, multicenter, single-arm, one-way crossover study that enrolled patients with ADA-deficient severe combined immunodeficiency (ADA-SCID) who were on Adagen treatment. Each patient served as his or her own control with respect to assessment of study endpoints. The study was conducted over 3 periods: the Adagen lead-in period (minimum of 3 weeks), the EZN-2279 treatment period (Weeks 1-21) and the EZN-2279 maintenance period. The maintenance period is expected to continue until the end of the study, i.e., until full regulatory approval of EZN-2279 or early study termination. The overall study design and PK assessment plan are presented in **Figure 1**.

Figure 1: Study Design of Study STP-2279-002 (Source: From Pharmacokinetic Report – Interim Analysis, Version: FINAL (3 August 2017), Figure 3.1, p45)



During the Adagen lead-in period, patients received a single intramuscular (IM) dose/week. Patients receiving Adagen doses more frequently than once a week prior to enrollment had his or her dose consolidated to a once-a-week regimen. During the Adagen lead-in period, further dose adjustments were made if a patient did not meet criteria for trough dAXP levels: ≤ 0.02 mmol/L and trough ADA activity: ≥ 15 mmol/L/h. Once a patient met these criteria, he or she was considered to be fully detoxified and the planned PK assessments were performed.

After completing the Adagen lead-in period and PK assessments, patients entered the EZN-2279 treatment period notated as treatment weeks 1-21. During this period, patients were transitioned from Adagen to EZN-2279 weekly IM injections. For transitioning, an equivalent weekly EZN-2279 IM dose was calculated using the following equation:

$$EZN2279 \text{ dose (mg/kg)} = \frac{\text{Adagen dose (U/kg)}}{150 \text{ U Adagen}} \times 1 \text{ mg EZN2279}$$

- *Reviewer's Comment: An information request (IR) was sent from the OCP reviewer to the Applicant to provide the rationale for using the 150 U Adagen factor in the dose conversion equation. After review of the Applicant's response to the IR above, this factor and the overall dose equation are deemed to be acceptable.*

During the EZN-2279 treatment weeks 7 and 8, if a patient's trough dAXP levels and trough ADA activity levels were within the criteria mentioned above, the planned PK assessments were performed during the EZN-2279 treatment Week 9. If not, further dose adjustments were made till he or she was considered to be fully detoxified and then the planned PK assessments were performed.

Following the treatment period, i.e., Week 21 onwards, patients entered the EZN-2279 maintenance period. During the EZN-2279 maintenance period, patients continued to receive single weekly IM doses of EZN-2279.

Treatments and Test Preparations:

Treatments	Description
Adagen	Adagen was supplied as single-use vials containing 375 U of Adagen (250 U/mL) Batch numbers: 3037A, 4017A, 5028A, 6039A, 6041A, 6043A
EZN-2279	EZN-2279 was supplied as 1.5 mL solution containing 2.4 mg of EZN-2279 (1.6 mg/mL) Batch numbers: 3073A, 4081A, 4091A, 5045A, 5046A, 5071A, 6046A.

Demographic Information:

At the cutoff time of the study report submitted by the Applicant, seven patients (4M/3F) were enrolled. One patient withdrew consent before the starting of study treatment. In total, six patients received EZN-2279, from which 1 patient discontinued due to an adverse event. Specifically, the first patient, i.e., patient ID (b) (6) was withdrawn after experiencing severe injection site pain. This adverse event was related to (b) (4) contained in the drug product formulation, and consequently, a new formulation (b) (4) was developed, which is being used in the remaining five patients enrolled in this study. At the cutoff time for this report, EZN-2279 treatment duration ranged from 8-115 weeks. Three patients have completed EZN-2279 treatment for ≥ 106 weeks. One patient, i.e., patient ID (b) (6) was withdrawn due to not meeting the inclusion criteria for ADA/dAXP levels during the Adagen lead-in period, however, was re-enrolled as patient ID (b) (6) at a later time.

Sample Collection and Bioanalysis:

Adagen lead-in period: Blood samples were collected each week immediately prior to Adagen administration. For PK assessment, eight blood samples were collected, pre-dose up to 168 hours following Adagen administration.

EZN-2279 treatment period: Blood samples were collected each week from weeks 1 to 9. If a patient was fully detoxified, i.e., dAXP level < 0.02 mmol/L and trough ADA activity level ≥ 15 mmol/L/h, eight blood samples were collected between Week 9 and Week 10, pre-dose and upto 168 hours following EZN-2279 administration. All four patients were detoxified by Week 9 and PK assessments were performed between Week 9 and Week 10.

Maintenance period: From Week 11 and onwards, biweekly samples were collected until Week 21.

In addition to PK assessments, EZN-2279 antibody titers (for neutralizing and binding antibodies), anti-PEG antibodies, trough total erythrocyte dAXP concentration, and trough plasma ADA activity were measured at every 3 months.

Regarding analytical sites, the study was initiated with (b) (4) as a central laboratory, which was responsible for immunogenicity, ADA activity, and dAXP levels. The Applicant changed the central laboratory to (b) (4). The information on the sample analysis is given in Table 1 and the review summary of the pertinent information on the bio-analytical methods that were used during the conduct of Study STP-2279-002 can be found in Section 4.3.

Table 1: Patient Level Bio-Analytical Method Site Information (Source: From Protocol STP-2279-002 Interim Clinical Study Report, p50)

Patient ID	Site: (b) (4)	Site: (b) (4)
(b) (6)	Screening, Adagen Lead-In, Treatment Weeks 1-2	No samples processed
	Screening, Adagen Lead-In, Treatment Weeks 1-21, Maintenance Phase	Maintenance Phase
	Screening, Adagen Lead-In, Treatment Weeks 1-21, Maintenance Phase	Maintenance Phase
	Screening, Adagen Lead-In, Treatment Weeks 1-21, Maintenance Phase	Maintenance Phase
	No samples processed	Screening, Adagen Lead-In
	No samples processed	Screening, Adagen Lead-In, Treatment Weeks 1-12
	No samples processed	Screening, Adagen Lead-In, Treatment Weeks 1-3

Pharmacokinetics:

Pharmacokinetics (PK) of EZN-2279 and Adagen were assessed based on ADA activity levels in plasma samples. The PK evaluable population was defined as patients who received EZN-2279 for at least nine weeks and participated in intensive PK sampling periods. At the time of interim data cutoff, i.e., 04/28/2017, four patients had completed the Adagen and EZN-2279 PK assessments (Table 2).

Table 2: Summary of Patients' Status at the Data Cutoff

Patient ID	Cutoff Date Status	Data Availability	PK Evaluable
(b) (6)	Discontinued	Screening through Week T-1	No
	Ongoing	Screening through Week 99	Yes
	Ongoing	Screening through Week 99	Yes
	Ongoing	Screening through Week 99	Yes
	Discontinued	Screening through lead-in Week 5	No
	Ongoing	Screening through Week T-9	Yes
	Ongoing	Screening through Week T-1	No

Within the PK dataset, from the Adagen lead-in period, Week 3 samples for two patients (ID (b) (6) and ID (b) (6)) and 24 hr sample for one patient (ID (b) (6)) were not collected. In addition, the lead-in phase Week 4 sample for one patient (ID (b) (6)) was inadvertently frozen and consequently was unable to be assayed. These missing samples were excluded from the PK dataset.

Plasma ADA activity-time data from four PK evaluable patients were used to determine terminal rate constant (λ_z), terminal half-life ($t_{1/2} = \ln(2)/\lambda_z$), $AUC_{0-168hr}$, C_{max} and C_{trough} . Exposure parameter estimates, i.e., $AUC_{0-168hr}$, C_{max} and C_{trough} , were dose normalized based on one of the following two equations:

For Adagen Exposure Estimate -

$$Dose\ Normalized\ Estimate = Estimate \times \frac{1500\ U}{Actual\ Adagen\ Dose\ (U)}$$

For EZN-2279 Exposure Estimate -

$$Dose\ Normalized\ Estimate = Estimate \times \frac{10\ mg}{Actual\ EZN2279\ Dose\ (mg)}$$

Results:

Applicant's Interim Safety and Efficacy Evaluations:

Primary endpoint of this study was metabolic detoxification, defined as total erythrocyte dAXP concentration of ≤ 0.02 mmol/L in trough blood samples, at treatment weeks 15, 17, 19, and 21. Two of three patients who received EZN-2279 treatment through Week 21, maintained detoxification. The third patient (ID (b) (6)) maintained detoxification at all time points except at treatment Week 17, when the reported trough dAXP total erythrocyte concentration was 0.047 mmol/L. Two patients could not be evaluated for dAXP levels because results through treatment Week 21 were not available for the interim analysis.

For the three patients, who entered the maintenance period, results for anti-Adagen®, anti-EZN-2279, and anti-PEG antibodies were mostly negative, with sporadic positive results shown for one patient.

- *Reviewer Comment: Please refer to the Medical Officer's review for additional details.*

Applicant's Interim PK Results:

Steady state plasma ADA activity levels over a dosing Interval (168 hours) from all four PK evaluable patients from the Adagen lead-in period and the EZN-2279 treatment period are presented in Figure 2. These steady state plasma activity levels were subjected to non-compartmental analysis and the resultant estimates for individual subjects as well as summary estimates are reported in Table 3. Exposure estimates, i.e., $AUC_{0-168hr}$, C_{max} , and C_{trough} , were normalized to a dose of 1500 U (for Adagen dose) or 10 mg (for EZN-2279 dose). These dose normalized estimates are also presented in Table 3. Trough (Day 7) plasma ADA activity levels from individual patients from the EZN-2279 maintenance period are reported in Figure 3. To assess if steady-state plasma trough ADA activity levels were achieved prior to the pharmacokinetic assessment component (i.e. Week 9), a linear mixed effects analysis of variance (ANOVA) model was used to perform statistical comparisons on natural log transformed, dose-normalized trough ADA activity at weeks 7, 8, 9, and 10. The findings from this indicated that dose normalized plasma trough ADA activity levels from the EZN-2279 treatment weeks 7, 8, and 10 were comparable to Week 9 levels (Table 4), which indicated that the steady state was attained.

Figure 2: Steady State Plasma ADA Activity Levels-Time Profiles from PK Evaluable Patients Over a Dosing Interval (168 hours): the Adagen Lead-in Period (Red) and the EZN-2279 Treatment Period (Blue) (Source: Adapted from 2.7.2 Summary of Clinical Pharmacology Studies, Figure 3, p16)

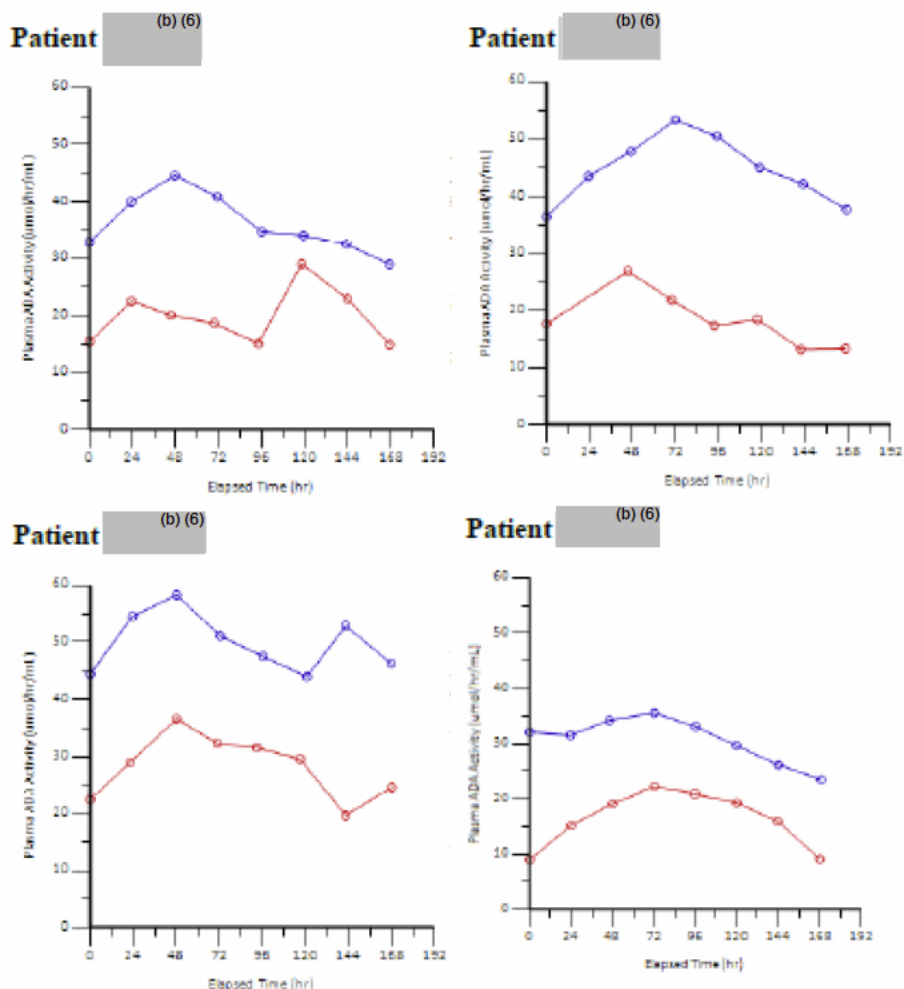


Table 3: Applicant's Pharmacokinetic Parameter Estimates for Steady State Plasma ADA Activity Levels: The Adagen Lead-in Period and the EZN-2279 Treatment Period (Source: Adapted from 2.7.2 Summary of Clinical

Pharmacology Studies, Table 5, p25)

Treatment	Patient ID	Dose	AUC _{0-168hr} (hr*µmol/hr/mL) ^a	C _{max} (µmol/hr/mL) ^a	C _{trough} (µmol/hr/mL) ^a	T _{max} (hr) ^a	T _{1/2} (hr) ^a	λ _z (1/hr) ^a	DN AUC _{0-168hr} (hr*µmol/hr/mL) ^a	DN C _{max} (µmol/hr/mL) ^a	DN C _{trough} (µmol/hr/mL) ^a
Adagen	(b) (6)	1500 U	3430	29.0	14.9	118	NE	NE	3430	29.0	14.9
		1575 U	3210	26.8	13.3	45.4	133	0.00520	3060	25.5	12.7
		2940 U	4840	36.6	24.6	48.1	166	0.00418	2470	18.7	12.6
		1500 U	2920	22.2	9.13	72.0	44.4	0.0156	2920	22.2	9.13
		N	4	4	4	4	3	3	4	4	4
		Mean	3600	28.7	15.5	71.0	115	0.00833	2970	23.9	12.3
		SD	850	5.99	6.55	33.8	62.9	0.00633	399	4.43	2.40
		Min	2920	22.2	9.13	45.4	44.4	0.00418	2470	18.7	9.13
		Median	3320	27.9	14.1	60.1	133	0.00520	2990	23.9	12.6
		Max	4840	36.6	24.6	118.3	166	0.0156	3430	29.0	14.9
		CV%	23.6	20.9	42.2	47.6	54.9	76.0	13.4	18.6	19.5
EZN-2279	(b) (6)	10 mg	6160	44.6	29.0	47.7	219	0.00317	6160	44.6	29.0
		10.2 mg	7630	53.3	37.7	71.9	177	0.00391	7480	52.3	37.0
		19.6 mg	8480	58.3	46.2	48.2	496	0.00140	4330	29.7	23.6
		10 mg	5260	35.6	23.5	72.0	145	0.00478	5260	35.6	23.5
		N	4	4	4	4	4	4	4	4	4
		Mean	6880	47.9	34.1	59.9	259	0.00331	5810	40.5	28.2
		SD	1450	10.0	9.97	13.9	161	0.00144	1350	9.92	6.35
		Min	5260	35.6	23.5	47.7	145	0.00140	4330	29.7	23.5
		Median	6900	49.0	33.3	60.0	198	0.00354	5710	40.1	26.3
		Max	8480	58.3	46.2	72.0	496	0.00478	7480	52.3	37.0
		CV%	21.0	20.9	29.3	23.2	61.9	43.4	23.2	24.5	22.5

DN: Dose-normalized to a dose of 1500 U Adagen/10mg EZN-2279; CV: coefficient of variation; min: minimum; max: maximum; NE: not estimated; SD: standard deviation

^aIndividual and summary PK data calculated over the dosing interval after administration of Adagen during the Adagen Lead-in PK Week, and after administration of EZN-2279 during treatment week 9.

Figure 3: Trough (Day 7) Plasma ADA Activity Levels-Time Profiles from PK Evaluable Patients: The Maintenance Period (Source: Adapted from 2.7.2 Summary of Clinical Pharmacology Studies, Figure 4, p18)

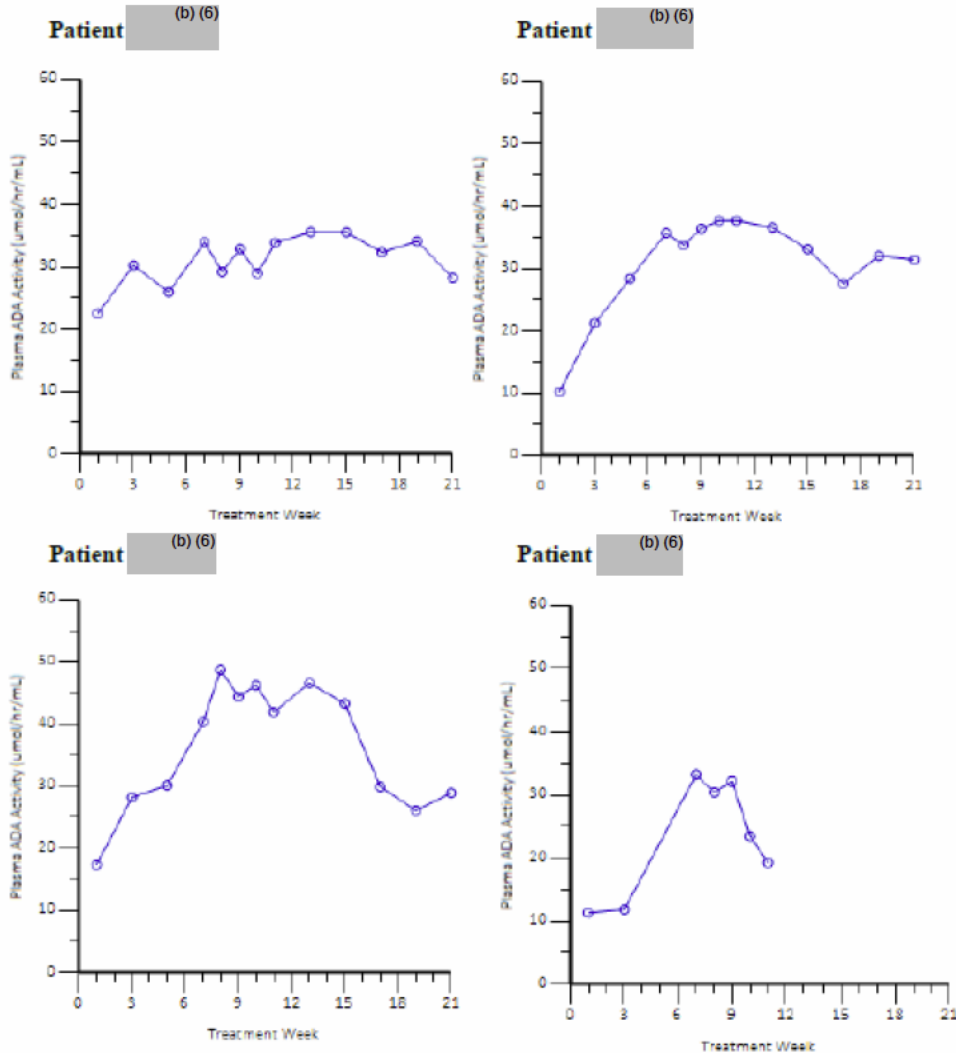


Table 4: Applicant's Comparison of Dose-normalized Trough ADA Plasma Activity During the EZN-2279 Treatment Period Weeks 7, 8, and 10 to Week 9 (Source: From Pharmacokinetic Report – Interim Analysis, Version: FINAL (3 August 2017), Table 7.2, p15)

Reference	Test	Geometric Mean ADA Activity (µmol/hr/mL)		Ratio (%Test/Reference)	90% Confidence Interval	p Value
		Reference	Test			
Week T-9	Week T-7		30.0	98.7%	86.1 – 113%	0.6351
	Week T-8	30.4	29.2	96.2%	83.9 – 110%	
	Week T-10		27.7	91.2%	79.6 – 105%	

Dose-normalized to a dose of 10 mg EZN-2279

Applicant's Conclusions from the Interim PK Report:

- T_{max} and $t_{1/2}$ estimates for plasma ADA activity levels in this study were 2-3 days and 3 to >6 days, respectively, which are consistent with the estimates reported previously for Adagen treatment.
- The data indicate that following the conversion to EZN-2279 dose (1 mg EZN-2279 = 150 U of Adagen), ADA activity levels were approximately 2-fold higher than the levels from the Adagen treatment.
- Although the terminal rate constant could not be reliably determined in all instances, there appears to be no substantial difference in the half-life of the two products.
- Whilst no definitive conclusions can be made from this interim analysis, it is feasible that the observed higher exposure with EZN-2279 treatment may be reflective of (b) (4) succinimidyl carbamate linker, with theoretically less dePEGylation than Adagen at the injection site, thereby increasing the amount of drug reaching the systemic circulation.

Reviewer's Assessments of Interim Reports:

- *Overall findings from the submitted interim report show that at or after EZN-2279 treatment week five, all enrolled patients had trough total erythrocyte dAXP concentrations of ≤ 0.02 mmol/L at all timepoints, except for two patients, one who had a dAXP concentration of 0.032 mmol/L at treatment week 13 and the other who had a dAXP concentration of 0.047 mmol/L at treatment week 17. The reasons for these apparently spurious increases are not known, however, the remaining trough dAXP levels for these two patients were ≤ 0.02 mmol/L at all other timepoints.*
- *Available immunogenicity results are limited to derive any definitive conclusions.*
- *From the Adagen lead-in period and the EZN-2279 treatment period, the steady state plasma ADA activity levels from four evaluable patients were subjected to non-compartmental analysis (NCA). The resultant individual and summary estimates from the NCA of ADA enzyme activity levels are reported in **Table 5**. Please note that the NCA estimates reported in **Table 5** are not for the systemic exposure to EZN-2279, instead, these estimates are for ADA activity levels.*
- *It is noteworthy that the estimates for maximum ADA Activity and $AUC_{0-168hr}$ for ADA Activity reported in the Applicant's interim PK report were compared after normalizing them with either a 1500 U or 10 mg dose of Adagen or EZN-2279, respectively.*

*Given that the Applicant's proposed EZN-2279 dosing is on a mg/kg basis, this reviewer requested that the Applicant normalize these parameter estimates from the EZN-2279 treatment period to the actual mg/kg EZN-2279 dose that was administered. The Applicant agreed with the request and provided revised estimates from the EZN-2279 treatment period dose normalized on a mg/kg dose basis. The review of Applicant's revised dose normalized estimates from the EZN-2279 treatment period indicated that they are in agreement with the Reviewer's analysis. The Reviewer's analysis was conducted using the Adagen dose (converted to mg/kg) administered in the Adagen lead-in period, and the EZN-2279 dose (mg/kg). The dose normalized estimates from both periods were derived and compared by the Reviewer (**Table 5**).*

This new comparison indicated that, on average, the dose normalized maximum ADA Activity and $AUC_{0-168hr}$ for ADA Activity estimates for the EZN-2279 treatment period were approximately 66% and 90% higher compared to their respective average values from the Adagen lead-in period.

- *During the EZN-2279 treatment period and the maintenance period, the observed trough ADA activity levels in all four PK evaluable patients were above 15 mmol/hr/L (15 μ mol/hr/mL), which was the protocol-defined criteria used to inform dose adjustment during the conduct of this study. This protocol-defined criterion is in agreement with the Adagen labeling, because, the Adagen labeling indicates that the Adagen dose adjustment should be aimed at maintaining plasma ADA activity (trough levels before maintenance injection) in the range of 15-35 μ mol/hr/mL (**Figure 4**).*
- *It is noteworthy that the mean and range of trough ADA activity levels following EZN-2279 treatment exceeded 20 mmol/hr/L, and the individual trough levels either exceeded or approached 30 mmol/hr/L in in all but one of the four patients from this study (**Figure 4**).*
- *The Applicant's conclusion related to the terminal rate constants for ADA activity levels is reasonable, i.e., the terminal rate constant could not be reliably determined in all patients. Consequently, half-life of ADA activity levels cannot be evaluated with the available limited data as well as the effect of the postulated (b) (4) succinimidyl carbamate linker on the half-life of ADA activity levels following the EZN-2279 treatment.*

Figure 4: Trough (Day 7) Plasma ADA Activity Levels-Time Profiles from Interim Report for Study STP-2279-002 (Source: Reviewer's Analysis)

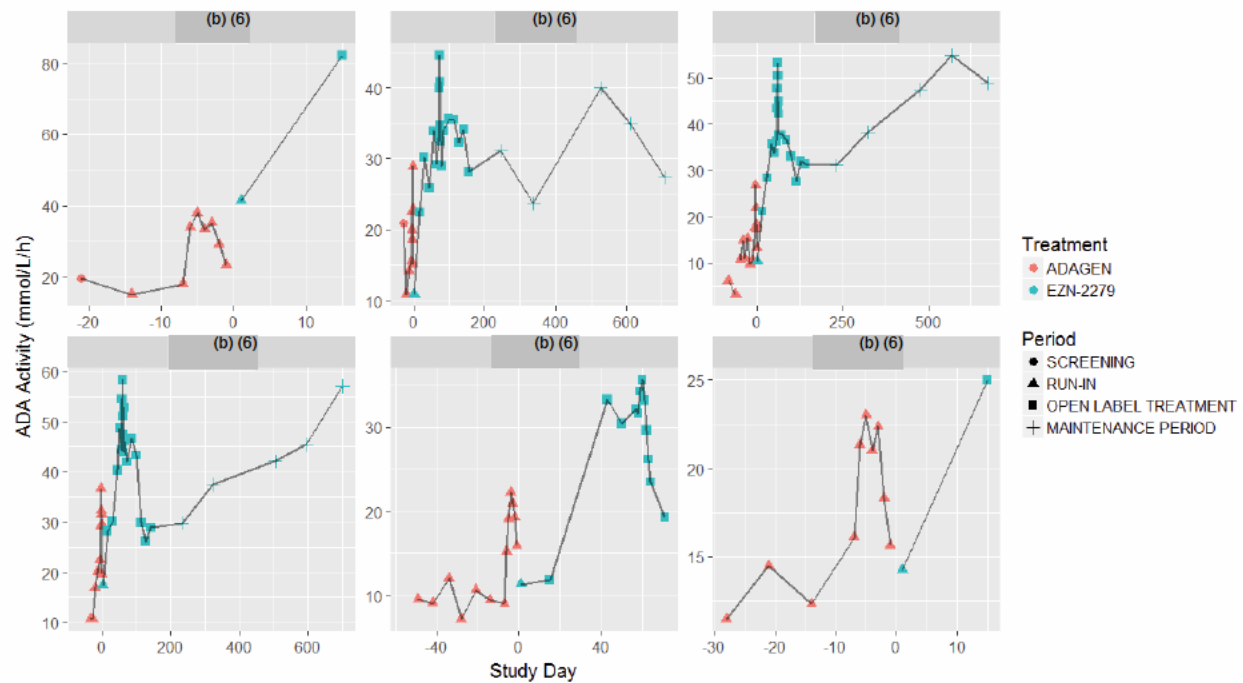


Table 5: Individual and Summary Estimates from Non-Compartmental Analysis of Steady State ADA Activity Levels (Reviewer's Analyses)

Treat- ment	Patient ID	Dose	T _{max} for ADA Activity	Maximum ADA Activity	DN* _Maximum ADA Activity#	AUC _{0-168 hr} for ADA Activity	DN* _AUC _{0-168 hr} for ADA Activity	Trough ADA Activity
	Units	mg/kg	Days	μmol/hr/mL	(μmol/hr/mL)/ (mg/kg)	hr*μmol/hr/mL	(hr*μmol/hr/mL)/ (mg/kg)	μmol/hr/mL
Adagen	(b) (6)	0.19	5	29.00	154.28	3427.22	18232.79	14.90
		0.23	2	26.80	116.39	3238.41	14063.94	13.30
		0.20	2	36.60	183.00	4840.93	24204.66	24.60
		0.21	3	22.20	106.34	2911.00	13943.68	9.13
	N	4	4	4	4	4	4	4
	Mean	0.21	3	28.65	140.00	3604.39	17611.27	15.48
	SD	0.02	1.41	6.01	35.33	851.50	4826.80	6.55
	Min	0.19	2	22.20	106.34	2911.00	13943.68	9.13
	Median	0.20	2.50	27.90	135.33	3332.81	16148.37	14.10
	Max	0.23	5	36.60	183.00	4840.93	24204.66	24.60
	CV%	8.60	47.10	21.00	25.20	23.60	27.40	42.30
EZN-2279	(b) (6)	0.19	2	44.60	237.27	6179.96	32877.39	29.00
		0.23	3	53.30	231.47	7661.46	33272.61	37.70
		0.20	2	58.30	291.50	8474.45	42372.24	46.20
		0.21	3	35.60	170.52	5231.82	25060.42	23.50
	N	4	4	4	4	4	4	4
	Mean	0.21	2.50	47.95	232.69	6886.92	33395.66	34.10
	SD	0.02	0.58	9.99	49.48	1455.94	7079.05	9.96
	Minimum	0.19	2	35.60	170.52	5231.82	25060.42	23.50
	Median	0.20	2.50	48.95	234.37	6920.71	33075.00	33.35
	Maximum	0.23	3	58.30	291.50	8474.45	42372.24	46.20
	CV%	8.60	23.10	20.80	21.30	21.10	21.20	29.20

*DN = Dose normalized estimate based on the actual mg/kg dose reported in Dose column

4.2. Study STM-279-301

Title:

A Multicenter, Open-Label, Uncontrolled Clinical Study of STM-279¹ in Patients with Adenosine Deaminase (ADA) Deficiency (Phase III Clinical Study)

Trial Information:

Study centers	Bio-analytical Laboratory (For Interim PK Report)
3 centers in Japan: Ongoing (First patient enrolled in 2016, Data cutoff month for interim analysis: March 2017)	(b) (4)

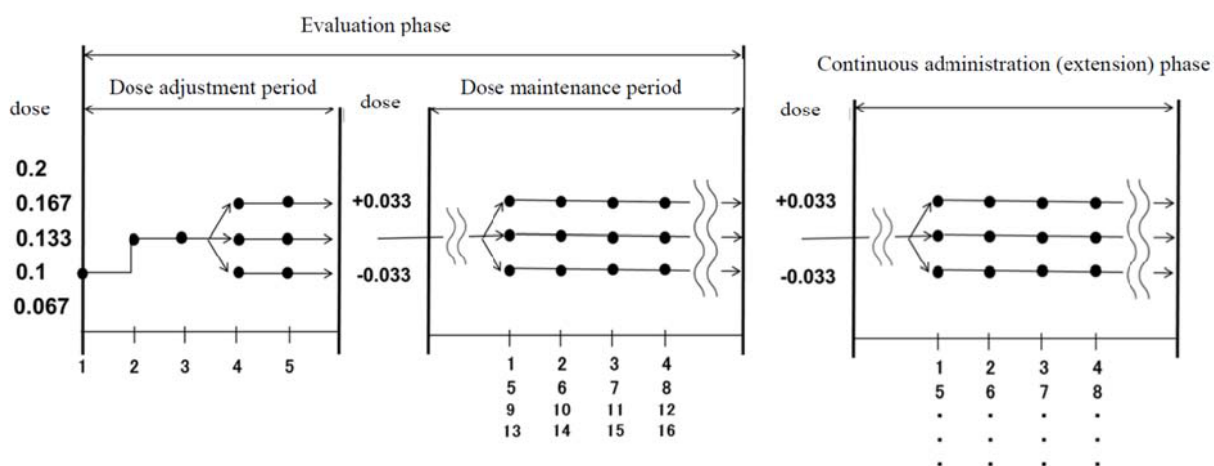
Primary Objective:

To evaluate efficacy and safety of STM-279 once a week IM administration in patients with adenosine deaminase severe combined immunodeficiency (ADA-SCID).

Study Design:

This was a multicenter, open-label, uncontrolled Phase 3 clinical study that enrolled patients with ADA-SCID. The study was conducted over 3 periods: dose adjustment period (five weeks), dose maintenance period (16 weeks), and extension period. The overall study design is presented in **Figure 1**. The extension period is expected to continue until marketing approval in Japan.

Figure 1: Study Design of Study STM-279-301 (Source: Pharmacokinetic Report – Interim Analysis, Version: FINAL (28 July 2017), Figure 4.1, p7)



During the dose adjustment period, the enrolled patients received a starting IM dose of 0.1 mg/kg of STM-279, after which doses were increased to 0.133 mg/kg for weeks 2 and 3. If a patient received Adagen® within the 4 weeks prior to study enrollment, an equivalent weekly starting STM-279 dose was calculated using the following equation:

¹ STM-279 name is used for EZN-2279 in Study STM-279-301

$$STM-279 \text{ dose (mg/kg)} = \frac{\text{Adagen dose (U/kg)}}{150 \text{ U Adagen}} \times 1 \text{ mg STM-279}$$

Reviewer Comment: An information request (IR) was sent from the OCP reviewer to the Applicant to provide a rationale for using the 150 U Adagen factor in the dose conversion equation. After review of the Applicant's reply, this factor and the overall dose equation are deemed to be acceptable.

Further dose adjustments were made at the increment of ± 0.033 mg/kg during Weeks 4 and 5, if a patient did not meet the protocol-defined detoxification related criteria, i.e., trough erythrocyte dAXP levels ≤ 0.02 $\mu\text{mol/mL}$ and trough plasma ADA activity ≥ 15 $\mu\text{mol/hr/mL}$.

During the dose maintenance and extension periods, patients received a weekly IM dose of STM-279 with ongoing safety and efficacy evaluations as well as necessary dose adjustments every 4 weeks. During the maintenance period, once a patient was on a stable dose for at least 5 consecutive weeks, pharmacokinetic (PK) assessment was performed by intensive blood sampling for quantification of plasma ADA activity over 168 hours dosing interval.

Treatments and Test Preparations:

Treatments	Description
STM-279 (EZN-2279)	STM-279 was supplied as 1.5 mL solution in 3.5-mL single-use vials containing 2.4 mg of STM-279 (1.6 mg/mL) Batch numbers: Batch numbers: STM001, STM002.

Demographic Information:

At the cutoff time of the study report, four patients (2M/2F) were enrolled. One patient, patient ID 02-03 (age = 3.4 months), discontinued from the study on Day 107 during the maintenance period due to death resulting from worsening of respiratory failure. This patient had received an exposure of 15 weeks of treatment. Two patients, patient ID (b) (6) (age = 16 years) and patient ID (b) (6) (age = 4.3 months), received Adagen within 60 days before obtaining informed consent, with the last dose within 1 week of the first STM-279 dose. Two patients, patient ID (b) (6) (age = 25 years) and patient ID (b) (6), had previously received gene therapy for ADA-SCID approximately 12 years prior to enrolling in the study.

Sample Collection and Bioanalysis:

PK samples: During the maintenance period, eight blood samples were collected including pre-dose and through 168 hours following STM-279 dose administration between two consecutive weekly doses after a patient was on stable dose for at least 5 weeks. The collected samples were analyzed for plasma ADA enzymatic activity (b) (4), and the review summary of the pertinent information on the bio-analytical methods that were used during the conduct of Study STP-2279-002 can be found in **Section 4.3**.

Immunogenicity: Samples were collected at screening; Week 3 of the adjustment period; and Weeks 1,5,9, and 13 of the maintenance period; by evaluating samples for binding antibodies, neutralizing

antibodies, and anti-PEG antibodies. During the extension phase, immunogenicity samples were collected at the times of injection such as weeks 17, 33, 49, and so on.

Pharmacokinetics:

The PK evaluable population excluded patients who weighed < 20 kg on the day of the first administration of the drug product and or if investigator(s) determined that frequent blood sampling should not be performed. Two infant patients, patient IDs (b) (6), met these criteria.

Therefore, the PK evaluable patients in this study included only two patients, patient IDs (b) (6).

Steady state plasma ADA activity-time data from the two PK evaluable patients were used to determine terminal rate constant (λ_z), terminal half-life ($t_{1/2} = \ln(2)/\lambda_z$), $AUC_{0-168hr}$, C_{max} and C_{trough} . Exposure parameter estimates for plasma ADA activity, i.e., $AUC_{0-168hr}$, C_{max} and C_{trough} , were dose normalized by the Applicant based on the following equation:

$$Dose\ Normalized\ Estimate = Estimate \times \frac{10\ mg}{Actual\ EZN\ 2279\ Dose\ (mg)}$$

Results:

Applicant's Interim Safety and Efficacy Evaluations:

Metabolic detoxification related endpoints that are being assessed in this study include trough erythrocyte dAXP concentrations and trough blood dAXP concentrations. As per the 2.7.3 Summary of Clinical Efficacy document, trough erythrocyte dAXP concentrations were not available at the time of the interim report. Instead, the Applicant has provided trough blood dAXP concentrations. Trough blood dAXP levels were <0.02 mmol/L at all assessment timepoints while on treatment in all patients except for one patient, who had trough blood dAXP concentrations of 0.0477 and 0.0279 mmol/L at Days 8 and 15, respectively.

Immunogenicity test results were negative for anti-STM-279 antibodies at screening and all other timepoints in all patients.

- *Reviewer Comment: Please refer to the Medical Officer's review for additional details.*
-

Applicant's Interim PK Results:

Steady state plasma ADA activity levels from the dose maintenance period are presented in **Figure 2**. These plasma ADA activity levels were subjected to non-compartmental analysis by the Applicant and the resultant estimates for individual subjects are reported in **Table 1**. Plasma ADA activity exposure estimates, i.e., $AUC_{0-168hr}$, C_{max} , and C_{trough} , were normalized to a dose of 10 mg STM-279 dose. These dose normalized estimates are also presented in **Table 1**.

Figure 2: Steady State Plasma ADA Activity Levels-Time Profiles Over a Dosing Interval (168 hours) from PK Evaluable Patients: The Maintenance Period [Source: Adapted from Pharmacokinetic Report – Interim Analysis, Version:

FINAL (28 July 2017), Figure 7.1, p10)

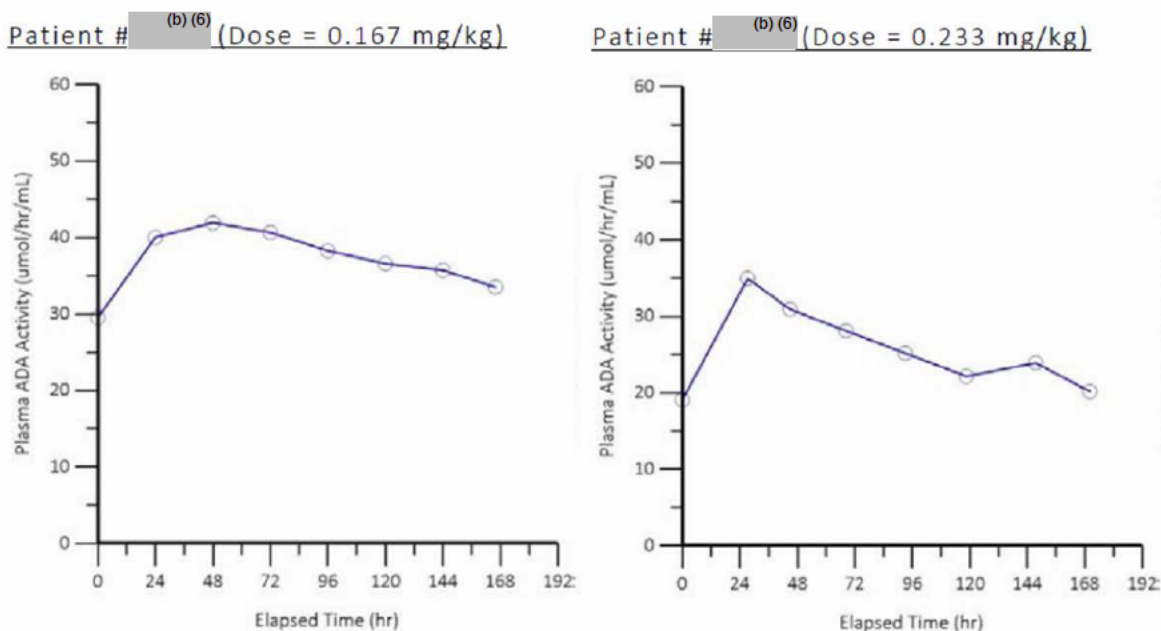


Table 1: Applicant's Pharmacokinetic Parameter Estimates for Steady State Plasma ADA Activity Levels: The Maintenance Period [Source: Adapted from 2.7.2 Summary of Clinical Pharmacology Studies, Table 11, p40)

Study	Pt ID	Dose in mg (mg/kg)	AUC _{0-168hr} (hr [*] umol/hr/mL)	C _{max} (umol/hr/mL)	C _{trough} (umol/hr/mL)	T _{max} (hr)	T _{1/2} (hr)	λ _z (1/hr)	DN AUC _{0-168hr} (hr [*] umol/hr/mL) ^a	DN C _{max} (umol/hr/mL) ^a	DN C _{trough} (umol/hr/mL) ^a
STM-279-301	(b) (6)	10.0 (0.167)	6280	41.9	33.5	48.0	360	0.00193	6270	41.8	33.4
		4.99 (0.233)	4430	34.9	20.2	27.2	227	0.00306	8890	70.0	40.4

DN: Dose-normalized to a dose of 10 mg STM-279

a Individual absolute and dose-normalized (to a dose of 10 mg) PK data calculated over the dosing interval after administration of SC-PEG rADA by weekly IM injection at a stable dose for at least five consecutive weeks.

Applicant's Conclusions from the Interim PK Report:

- Following the administration of STM-279 in two patients enrolled in this study, PK data of ADA activity levels at steady state are consistent with that previously reported for Adagen, with slow systemic absorption and a long terminal half-life.
- STM-279 treatment evaluated in this study maintained the trough plasma ADA activity above the protocol-defined minimum detoxification threshold (≥ 15 $\mu\text{mol/hr/mL}$).

Reviewer's Assessments of Interim Reports:

- Findings related to trough erythrocyte dAXP concentration were not available at the time of the interim report. Instead, the Applicant has provided trough blood dAXP concentrations. Trough blood dAXP levels were <0.02 mmol/L at all assessments during treatment for all patients except for one patient, who had trough blood dAXP concentrations of 0.0477 and 0.0279 mmol/L at Days 8 and 15, respectively. The reasons for these apparently spurious increases are not known, however, the remaining trough dAXP levels in blood samples from this patient were ≤ 0.02 mmol/L at all other timepoints.
- From the maintenance period, steady state plasma ADA activity levels from the two evaluable patients were subjected to non-compartmental analysis (NCA). The resultant individual estimates from NCA of ADA enzyme activity levels performed by this reviewer are reported in **Table 2**. Please note that the NCA estimates reported in **Table 2** are not for the systemic exposure to STM-279, instead, these estimates are for plasma ADA activity levels.
- It is noteworthy that the estimates for maximum ADA Activity and $AUC_{0-168hr}$ for ADA Activity reported in the Applicant's interim PK report were reported after normalizing them with a 10 mg dose of STM-279.

Given that the Applicant's proposed EZN-2279/STM-279 dosing is on a mg/kg basis, this Reviewer requested that the Applicant normalize these parameter estimates to the actual mg/kg STM-279 dose that was administered. The Applicant agreed with the request and provided revised estimates from the maintenance period. The review of Applicant's revised dose normalized estimates from the maintenance period indicated that they are in agreement with the Reviewer's analysis. Estimates from the Reviewer's analysis are presented in **Table 2**. The Reviewer's results are slightly different from the Applicant's results due to differences in methodologies that were used.

- During the maintenance period, the observed ADA activity levels in both patients were above 15 mmol/hr/L, which was the protocol-defined criteria used to inform dose adjustment during the conduct of this study. This protocol-defined criterion is in agreement with the Adagen labeling, because, the Adagen labeling indicates that the Adagen dose adjustment should be aimed at maintaining plasma ADA activity (trough levels before maintenance injection) in the range of 15-35 $\mu\text{mol/hr/mL}$.

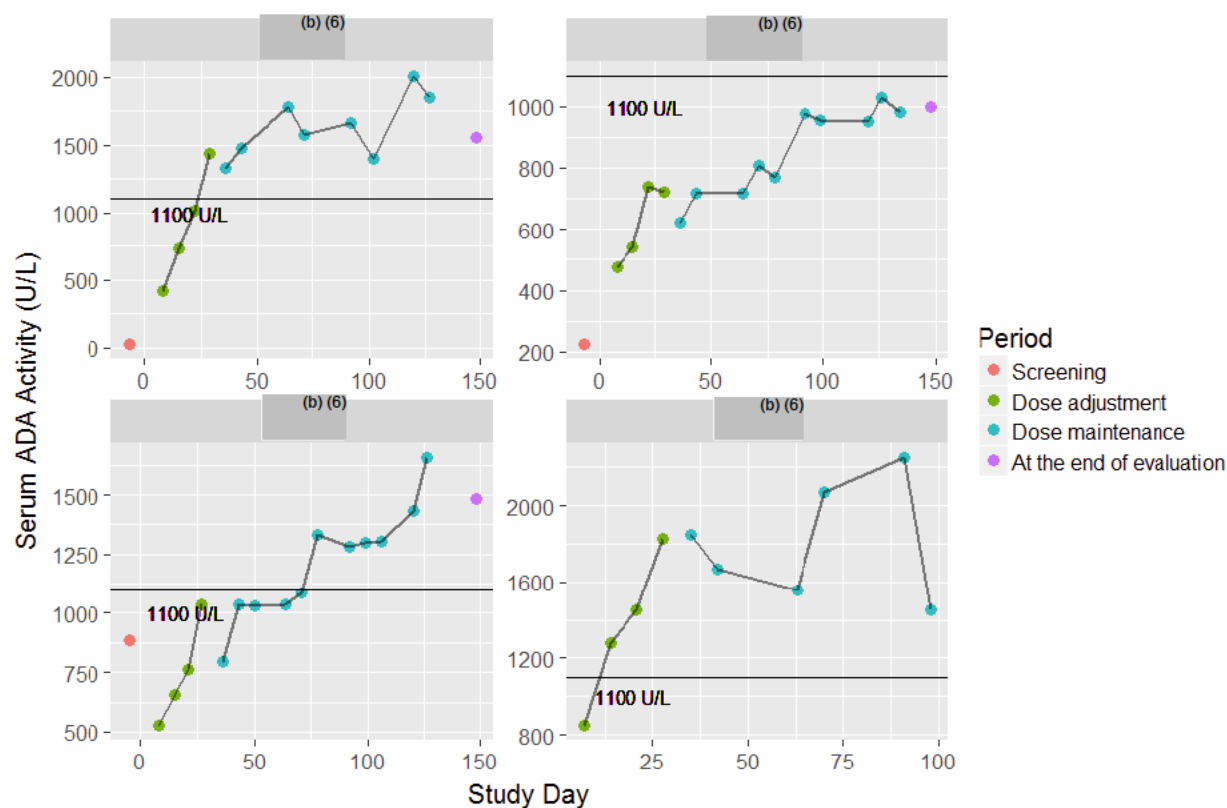
The interim efficacy and safety report contained information on trough (Day 7) serum ADA activity levels over time from all four patients enrolled in this study. These serum ADA activity levels are shown in **Figure 3**. Serum ADA activity is reported in unit of U/L and the protocol-specified threshold for adequate serum ADA activity is 1100 U/L, which is equivalent to plasma ADA activity of 15 mmol/L/h.

Table 2: Individual Estimates from Non-Compartmental Analysis of Steady State ADA Activity Levels

Patient ID	Dose	T _{max} for ADA Activity	Maximum ADA Activity	DN* Maximum ADA Activity [#]	AUC _{0-168 hr} for ADA Activity	DN* AUC _{0-168 hr} for ADA Activity	Trough ADA Activity
Units	mg/kg	Days	μmol/hr/mL	(μmol/hr/mL)/(mg/kg)	hr*μmol/hr/mL	(hr*μmol/hr/mL)/(mg/kg)	μmol/hr/mL
(b) (6)	0.167	2	41.91	250.96	6348.72	38016.28	33.50
	0.233	1	34.91	149.83	4426.68	18998.64	20.15

*DN = Dose normalized estimate based on the actual mg/kg dose reported in Dose column

Figure 3: Trough (Day 7) Serum ADA Activity Levels*-Time Profiles from Interim Report for Study STM-279-301 (Source: Reviewer's Analysis)



*As per the interim report STM-279-301, serum ADA activity is reported in U/L. The protocol-specified threshold for adequate serum ADA activity is 1100 U/L, which is equivalent to plasma ADA activity of 15 mmol/L/h.

4.3. Bioanalytical Method Validation and Performance

This application relies on the interim analysis of efficacy and safety data from two Phase 3 studies, i.e., Study STP-2279-002 and Study STM-279-301. Specifically, the interim efficacy analysis included the measurement of deoxyribonucleotides (dAXP) levels and adenosine deaminase (ADA) activity, which were used as the key endpoints. An inspection request was sent to the Office of Study Integrity and Surveillance (OSIS) for the inspection of the following US bioanalytical laboratories that performed the assays for the abovementioned analysis:

(b) (4)

Please see the Bioequivalence Establishment Inspection Report Review dated 07/13/2018 for the OSIS findings from the inspection of the above-mentioned laboratories. In summary, Form FDA 483 was issued to both sites at the inspection closeout. The final inspection classification was Voluntary Action Indicated (VAI). Objectionable conditions were observed during the inspections that could compromise the reliability of data from Study STP-2279-002. The specific concerns are listed below:

(b) (4)

The Clinical Pharmacology Reviewer requested additional information related to the above deficiencies that were identified from the OSIS inspection. The following is the review summary of the pertinent information on the bio-analytical methods that were used during the conduct of Study STP-2279-002. This information was submitted with the original submission and the Applicant's responses to the abovementioned IR from the Reviewer.

Analyte/Assessment	Plasma ADA Activity	
Method	Spectrophotometry	
Validation Report	Validation report provided	☒ Yes ☐ No
	Validation report acceptable Range: (b) (4) mU/mL, (b) (4) µmol/hr/mL to (b) (4) mU/mL, (b) (4) µmol/hr/mL Dilution: 128-fold for Adagen and 16-fold for SC-PEG rADA	☒ Yes ☐ No
Tech Transfer Report	Report acceptable	☒ Yes ☐ No
Performance Report	Samples analyzed within the established stability period The study protocol indicated that the samples were processed after collection at the clinical site. However, during the inspection it was noted that all samples were collected as whole blood and remained on ice and/or frozen gel pack for approximately 24-48 hours before being processed. The cumulative data submitted by the Applicant on sample stability in whole blood and plasma matrix are reasonable.	☒ Yes ☐ No
	Quality control samples range acceptable. QC: (b) (4) mU/mL, (b) (4) mU/mL, (b) (4) mU/mL	☒ Yes ☐ No
	Chromatograms provided	N/A
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No

	Overall performance reasonable	☒ Yes ☐ No
Inspection	Will the bioanalytical site be inspected?	☒ Yes ☐ No

Regarding the quantification of dAXP levels, these levels were not used in any exposure-response evaluations, nor were there any PK parameters calculated based on dAXP levels. Instead, a trough dAXP level of 0.02 µmol/ml was used as a threshold value to characterize a patient as detoxified or not-detoxified. The bioanalytical methodology and validation of the method to measure dAXP levels was deemed to be acceptable by the Reviewer.

4.4. Clinical Pharmacology Labeling Recommendations for Section 7 DRUG INTERACTIONS and Section 12 CLINICAL PHARMACOLOGY

1 page of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page

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/

ABHAY JOSHI
08/22/2018

PHILIP M COLANGELO
08/22/2018

JOHN A LAZOR
08/22/2018