**Report on the Deliberation Results**

February 26, 2019
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

| | |
|---|---|
| **Brand Name** | Revcovi 2.4 mg for Intramuscular Injection |
| **Non-proprietary Name** | Elapegademase (Genetical Recombination) (JAN*) |
| **Applicant** | Teijin Pharma Limited |
| **Date of Application** | June 29, 2018 |

**Results of Deliberation**

In its meeting held on February 21, 2019, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 10 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

**Approval Conditions**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients studied in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a specified number of patients will be collected, in order to obtain information on the characteristics of patients treated with the product, to collect data on the safety and efficacy of the product as soon as possible, and to take necessary measures to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

**Review Report**

February 12, 2019
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

| | |
|---|---|
| **Brand Name** | Revcovi 2.4 mg for Intramuscular Injection |
| **Non-proprietary Name** | Elapegademase (Genetical Recombination) |
| **Applicant** | Teijin Pharma Limited |
| **Date of Application** | June 29, 2018 |
| **Dosage Form/Strength** | Aqueous injection: Each vial contains 2.4 mg of Elapegademase (Genetical Recombination). |
| **Application Classification** | Prescription drug, (1) Drug with a new active ingredient |
| **Definition** | Elapegademase is a recombinant bovine adenosine deaminase analogue in which Cys74 is substituted by Ser, to which an average of approximately 13 methoxy polyethylene glycol polymers (molecular weight: ca. 5,600) per mole of protein are bound via carbonyl groups (potential pegylation sites: Ala1 and Lys residues). Elapegademase is a pegylated protein (molecular weight: ca. 115,000) consisting of 356 amino acid residues. |

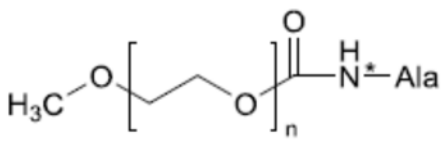
**Structure**

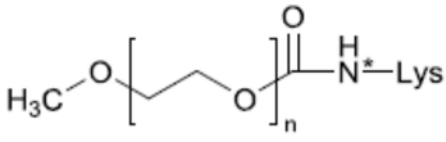
Amino acid sequence:

AQTPAFNKPK VELHVHLDGA IKPETILYYG RKRGIALPAD TPEELQNIIG
MDKPLSLPEF LAKFDYYMPA IAGSREAVKR IAYEFVEMKA KDGVVYVEVR
YSPHLLANSK VEPIPWNQAE GDLTPDEVVS LVNQGLQEGE RDFGVKVRSI
LCCMRHQPSW SSEVVELCKK YREQTVVAID LAGDETIEGS SLFPGHVKAY
AEAVKSGVHR TVHAGEVGSA NVVKEAVDTL KTERLGHGYH TLEDTTLYNR
LRQENMHFEV CPWSSYLTGA WKPDTEHPVV RFKNDQVNYS LNTDDPLIFK
STLDTDYQMT KNEMGFTEEE FKRLNINAAK SSFLPEDEKK ELLDLLYKAY
GMPSPA

A1, K8, K10, K22, K32, K53, K63, K79, K89, K91, K110, K146, K169, K170, K198, K205, K224, K231, K272, K283, K300, K311, K330, K322, K339, K340, K348: Potential pegylation sites

Binding mode of polyethylene glycol




*** α-Amino group of an alanine residue** *** ε-Amino group of a lysine residue**

Molecular formula: C1797H2795N477O544S12 (Protein moiety)
Molecular weight: ca. 115,000

**Items Warranting Special Mention** Orphan drug (Orphan drug Designation No. 377 of 2016 [*28 yaku*]; PSEHB/PED Notification No. 0316-3 dated March 16, 2016, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

**Reviewing Office** Office of New Drug I

**Results of Review**

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of adenosine deaminase deficiency, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions.

**Indication** Adenosine deaminase deficiency

**Dosage and Administration** The usual dosage of Elapegademase (Genetical Recombination) is 0.2 mg/kg administered as an intramuscular injection once weekly. The dose may be adjusted according to the patient's condition; however, a dose should not exceed 0.3 mg/kg. If adenosine deaminase activity needs to be increased rapidly, Elapegademase (Genetical Recombination) may be administered as an intramuscular dose of 0.2 mg/kg twice weekly.

**Approval Conditions**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients studied in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a specified number of patients will be collected, in order to obtain information on the characteristics

of patients treated with the product, to collect data on the safety and efficacy of the product as soon as possible, and to take necessary measures to ensure proper use of the product.

**Attachment**

# Review Report (1)

January 8, 2019

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | Revcovi 2.4 mg for Intramuscular Injection (changed in Japanese notation from the proposed application) |
| **Non-proprietary Name** | Elapegademase (Genetical Recombination) |
| **Applicant** | Teijin Pharma Limited |
| **Date of Application** | June 29, 2018 |
| **Dosage Form/Strength** | Aqueous injection: Each vial contains 2.4 mg of Elapegademase (Genetical Recombination). |

**Proposed Indication**

Adenosine deaminase deficiency

**Proposed Dosage and Administration**

The usual dosage of Elapegademase (Genetical Recombination) is 0.2 mg/kg body weight administered as an intramuscular injection once weekly.

The dose may be adjusted according to the patient's condition and laboratory values.

**Table of Contents**

**List of Abbreviations**

See Appendix.

## 1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Revcovi is a solution for injection containing elapegademase (genetical recombination) as the active ingredient, which was discovered by Leadiant Biosciences, Inc. (formerly Sigma-Tau Pharmaceuticals, Inc.) in the US. Elapegademase (genetical recombination) is a modified protein in which a recombinant adenosine deaminase (rADA) produced in *Escherichia coli* is covalently conjugated to polyethylene glycol (PEG) via carbonyl groups.

Adenosine deaminase (ADA) deficiency is an autosomal recessive disease caused by absence of the ADA enzyme, which is involved in purine metabolism, and catalyzes the conversion of adenosine and deoxyadenosine to inosine and deoxyinosine, respectively. The absence of ADA induces the intracellular accumulation of ADA substrates (i.e., adenosine and deoxyadenosine) and their phosphorylated forms (e.g., dAXPs), which damages various organs and tissues, notably immune cells, resulting in progressive immunodeficiency due to decreased numbers of T-, B-, and NK cells.

ADA deficiency is diagnosed at an average age of 4.4 months. Approximately 85% to 90% of patients develop immunodeficiency (*Clin Immunol.* 2007;123:139-47) and suffer from recurrent infections, developmental disturbance, diarrhoea, rash, decreased lymphocytes, hypogammaglobulinemia, etc. within several months after birth (*Blood.* 2009;114:3524-32). The prognosis of ADA deficiency accompanied by severe immunodeficiency is extremely poor, and many infants with ADA deficiency die from severe infections by around 1 year of age (*The Metabolic and Molecular Bases of Inherited Disease, 8th ed.* 2001:2585-625, *Congenital Malformation Syndrome Dictionary*. 2001:150-1). In Japan, ADA deficiency is categorized as an intractable disease "primary immunodeficiency syndrome." The estimated incidence of primary immunodeficiency syndrome is 2.3 cases in 100,000 births. A survey conducted in 2008 showed that 1,240 people are affected by primary immunodeficiency syndrome, 9 of whom were patients with ADA deficiency (*J Clin Immunol.* 2011;31:968-76).

In the US, "ADAGEN," which contains ADA that has been purified from the bovine intestine and conjugated to PEG, has been approved for the treatment of ADA deficiency. In Japan, the "Study Group on Unapproved and Off-label Drugs of High Medical Need" concluded in March 2012 that ADAGEN had high medical need, and the applicant expressed the intention of developing ADAGEN in Japan, through open recruitment. Subsequently, however, the fact that the development of Revcovi was ongoing overseas came to light, and in January 2014, the study group requested the applicant to develop Revcovi, rather than ADAGEN, in Japan. The present marketing application for Revcovi has been filed based on the results of a Japanese phase III study (Study STM-279-301) and another clinical study, which demonstrated the efficacy and safety of Revcovi in the treatment of ADA deficiency.

As of December 2018, Revcovi is marketed in the US.

In Japan, Revcovi was designated as an orphan drug (Orphan Drug Designation No. 377 of 2016 [*28 yaku*]), with the intended indication of ADA deficiency.

## 2. Data Relating to Quality and Outline of the Review Conducted by PMDA

### 2.1 Drug substance

Elapegademase (genetical recombination), the drug substance of Revcovi, is registered by Exelead, Inc. under the Drug Master File (MF registration No. 230MF10020). The drug substance is identical to the drug product in composition and is promptly formulated without being stored, as is, into the drug product through a sterile filtration/filling process. Therefore, the applicant has not proposed the drug substance specifications. The quality of the drug substance is controlled based on the specifications for a pre-pegylation intermediate of the drug substance (Intermediate A), the in-process control tests for the drug substance, and the specifications for the drug product.

#### 2.1.1 Generation and control of cell substrate

See Appendix.

#### 2.1.2 Manufacturing process

See Appendix.

#### 2.1.3 Safety evaluation of adventitious agents

No animal- or human-derived raw materials are used in the manufacturing process of the drug substance.

#### 2.1.4 Manufacturing process development

See Appendix.

#### 2.1.5 Characterization

##### 2.1.5.1 Structure and characterization

The drug substance was characterized as shown in Table 1. For a characterization of rADA, see Appendix.

Table 1. Characterization attributes for the drug substance[a)]

| | |
|---|---|
| Primary and higher order structures | Pegylation sites, number of pegylation sites, free thiol groups, and secondary and tertiary structures |
| Physicochemical properties | Molecular weight, Impurities A and B, and PEG degradation products |
| Biological properties | ADA enzyme activity |

a) Since the drug substance and the drug product are identical in composition, characterization were tested using the drug product.

##### 2.1.5.2 Product-related substances/Product-related impurities

Based on the results of characterization tests, as described in Section "2.1.5.1 Structure and characterization" and other data, [redacted] was identified as a product-related substance, while Impurities A and B were identified as product-related impurities. Both product-related impurities are appropriately controlled by the specifications for the drug product. For the product-related substances and impurities in Intermediate A, see Appendix.

#### 2.1.5.3 Process-related impurities

Process-related impurities include host cell proteins (HCPs), host cell-derived DNAs, Impurities C, D, E, F, and G, endotoxins, microorganisms, and insoluble particulate matter. HCPs, host cell-derived DNAs, Impurities C, D, and E, endotoxins, microorganisms, and insoluble particulate matter are controlled according to the specifications for Intermediate A. Insoluble particulate matter, Impurities F and G, and endotoxins are controlled according to the specifications for the drug product.

### 2.1.6 Control of drug substance

The drug substance is promptly formulated without being stored, as is, into the drug product, and the specifications for the drug substance have not been proposed [see Section "2.R.1 Quality control strategies for Revcovi"]. To control the quality of the drug substance, Intermediate A is controlled according to the specifications for Intermediate A, while post-pegylation drug substance is controlled according to the specifications for the drug product [see Section "2.2.4 Control of drug product"].

The proposed specifications for Intermediate A include content, description, identifications ([redacted], [redacted], [redacted], and [redacted]), [redacted], purity ([redacted] ([redacted]), [redacted], [redacted], [redacted], HCPs, host cell-derived DNAs, Impurities C, D, and E), [redacted], endotoxins, microbial limit, insoluble particulate matter, biological activity ([redacted]), specific activity, and assay ([redacted]). The proposed specifications for the drug product to control [redacted] include purity (Impurities G and F) and [redacted] ([redacted]).

### 2.1.7 Stability of drug substance

As the drug substance is formulated without being stored, as is, no long-term testing for the drug substance was conducted. For the stability of Intermediate A, see Appendix.

## 2.2 Drug product

### 2.2.1 Description and composition of drug product and formulation development

The drug product is a solution for injection. Each vial provides a 1.5 mL solution containing 2.4 mg of elapegademase (genetical recombination). The drug product also contains sodium phosphate dibasic heptahydrate, sodium dihydrogen phosphate monohydrate, sodium chloride, and water for injection as excipients.

### 2.2.2 Manufacturing process

The manufacturing process for the drug product consists of sterile filtration/filling and packaging/labeling/storage/testing processes. The critical steps are [redacted] and [redacted].

Process validation for the drug product has been conducted on a commercial scale.

### 2.2.3 Manufacturing process development

The major change in the manufacturing method that was made during the development stage for the drug product was a scale change. In a foreign phase III study (Study STP-2279-002), severe injection site pain occurred in 1 patient who received an earlier formulation manufactured from the drug substance containing [redacted]. Therefore, the manufacturing process of the drug substance was changed to use no [redacted]. In subsequent patients in the foreign phase III study and all patients in a Japanese phase III study, a drug product that was manufactured from the drug substance containing no [redacted] was used, which has been proposed as a to-be-marketed drug product in the present application [see Section "7.1.2 Foreign phase III study"]. When the manufacturing process was changed, a compatibility assessment was performed in terms of quality attributes, and the results demonstrated that the drug products before and after the change were comparable.

### 2.2.4 Control of drug product

The proposed specifications for the drug product include content, description, identifications ([redacted] and [redacted]), [redacted], purity ([redacted], [redacted], and Impurities G and F), [redacted] ([redacted]), endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, specific activity, biological activity ([redacted]), and assay ([redacted]). To these specifications, an identification ([redacted]), purity (Impurities G and F), and [redacted] ([redacted]) were added during the review process.

### 2.2.5 Stability of drug product

Key stability studies of the drug product are shown in Table 2.

Table 2. Summary of key stability studies of the drug product

| | Number of batches | Storage conditions | Testing duration | Storage package |
|---|---|---|---|---|
| Long-term testing | 3 | 5 ± 3°C | 24 months[b)] | A chlorobutyl rubber stopper, a glass vial, and an aluminium cap |
| | 3 [a)] | | 24 months | |
| Accelerated testing | 4 | 25 ± 2°C/60 ± 5% RH | 6 months | |
| Photostability testing | 1 | Overall illumination ≥1.2 million lux·h and total near ultraviolet energy ≥200 W·h/m$^2$ | | |

a) Pilot scale
b) The stability study will be continued for 36 months.

The long-term test showed a tendency for Impurity A to increase in [redacted] during storage; however, there were no clear changes in the other quality attributes.

The accelerated test showed a decrease in [redacted] at [redacted], and increases in the sum of Impurity A and other impurities.

The photostability study showed that the drug product was unstable in light.

Based on the above results, the applicant has proposed a shelf-life of 24 months for the drug product when stored at 2°C to 8°C, in a primary container consisting of an aluminum cap and a glass vial with a chlorobutyl rubber stopper, and protected from light in a paper carton.

## 2.R Outline of the review conducted by PMDA

Based on the data submitted and the following reviews, PMDA has concluded that the quality of the drug substance and the drug product is adequately controlled. For elapegademase, the master file registrant has separately submitted relevant information concerning the master file. For the results of reviews by PMDA regarding the master file, see Appendix.

### 2.R.1 Quality control strategies for elapegademase

The applicant's explanation:

The drug substance is identical to the drug product in composition and is promptly formulated without being stored, as is, into the drug product through a sterile filtration/filling process. Elapegademase is a modified protein, in which an rADA produced in *Escherichia coli* is covalently conjugated to PEG via carbonyl groups. The quality of the protein part is controlled by setting the specifications for a pre-pegylation intermediate, Intermediate A [see Section "2.1.6 Control of the drug substance"]. To ensure the quality of drug substance and the drug product after the pegylation of Intermediate A, a quality control strategy was established based on the specifications for the drug product in addition to including necessary controls in the manufacturing process as in-process controls, because manufacturing is performed continuously from the pegylation of Intermediate A to the drug product formulation process (sterile filtration/filling process) at the same manufacturing site.

Since the robustness of the manufacturing process has been demonstrated through the manufacturing history and other data, PMDA has concluded that the quality of the drug substance and the drug product can be secured by the proposed quality control strategy, in view of the manufacturing process after the pegylation of rADA.

## 3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

In primary pharmacodynamic studies, the effects of elapegademase on blood ADA activity in ADA-deficient mice, etc. were assessed. To evaluate the safety pharmacology of elapegademase, the effects on the central nervous, cardiovascular, and respiratory systems were evaluated in repeated dose toxicity studies. No secondary pharmacodynamic studies or pharmacodynamic interaction studies were conducted. The results of key studies are described below.

### 3.1 Primary pharmacodynamics

#### 3.1.1 Studies in ADA-deficient mice (CTD 4.2.1.1-1)

##### 3.1.1.1 Effects on blood ADA activity

Elapegademase or ADAGEN was administered to ADA-deficient mice (6 males and females/group) at 18 days of age as a single intraperitoneal dose of 5 U, and a blood sample was collected at 21 days of

age to determine blood ADA activity by enzyme electrophoresis. The results demonstrated the presence of blood ADA activity in both the elapegademase group and the ADAGEN group.

#### 3.1.1.2 Effects on trough plasma ADA activity

Elapegademase or ADAGEN was administered to ADA-deficient mice (6 males and females/group) every 4 days from 1 day to 21 days of age as repeated intramuscular doses of 5 U, and a blood sample was collected immediately before the final dose to determine trough plasma ADA activity by enzyme activity assay. The trough plasma ADA activity (mean ± standard error [SE]) was 0.02 ± 0.01 μmol/h/mL in the untreated group (7 males and females), 64.30 ± 7.91 μmol/h/mL in the elapegademase group, and 46.50 ± 8.21 μmol/h/mL in the ADAGEN group.

#### 3.1.1.3 Effects on adenosine concentration in bronchoalveolar lavage fluid (BALF)

Elapegademase or ADAGEN was administered to ADA-deficient mice (6 males and females/group) at 18 days of age as a single intraperitoneal dose of 5 U, and a BALF sample was collected at 21 days of age to determine the adenosine concentration by reverse-phase high performance liquid chromatography (RP-HPLC). The concentration of adenosine in BALF increased in the untreated group (6 males and females) and tended to decrease in the elapegademase group and the ADAGEN group, as compared with wild-type ADA mice.

#### 3.1.1.4 Effects on adenosine and deoxyadenosine concentrations, cell counts, and organ weights of the thymus and spleen

Elapegademase or ADAGEN was administered to ADA-deficient mice (7 males and females/group) every 4 days from 1 day to 21 days of age as repeated intramuscular doses of 5 U, and the thymus and spleen were isolated at 21 days of age to determine the organ weight and cell counts, and for measurement of adenosine and deoxyadenosine concentrations by RP-HPLC. The results are shown in Tables 3 and 4.

Table 3. Organ weight, cell counts, and adenosine and deoxyadenosine concentrations in the thymus

| | Organ weight (g) | Cell count ($\times 10^6$ cells) | Adenosine concentration (nmol/mg protein) | Deoxyadenosine concentration (nmol/mg protein) |
|---|---|---|---|---|
| Wild-type ADA | 0.100 ± 0.006 (N = 10) | 220.15 ± 37.26 (N = 8) | 0.0325 ± 0.006 (N = 10) | 0.002 ± 0.001 (N = 10) |
| Untreated | 0.023 ± 0.003 (N = 7) | 7.68 ± 2.10 (N = 6) | 11.946 ± 6.117 (N = 5) | 0.822 ± 0.371 (N = 5) |
| ADAGEN | 0.082 ± 0.009 (N = 7) | 132 ± 25 (N = 7) | 0.282 ± 0.112 (N = 7) | 0.014 ± 0.011 (N = 7) |
| Elapegademase | 0.105 ± 0.011 (N = 7) | 222.17 ± 48.11 (N = 7) | 0.045 ± 0.010 (N = 7) | 0.006 ± 0.002 (N = 7) |

Mean ± SE

Table 4. Organ weight, cell counts, and adenosine and deoxyadenosine concentrations in the spleen

| | Organ weight (g) | Cell count ($\times 10^6$ cells) | Adenosine concentration (nmol/mg protein) | Deoxyadenosine concentration (nmol/mg protein) |
|---|---|---|---|---|
| Wild-type ADA | 0.099 ± 0.009 (N = 10) | 76.35 ± 7.14 (N = 8) | 0.053 ± 0.020 (N = 10) | 0.003 ± 0.001 (N = 10) |
| Untreated | 0.025 ± 0.003 (N = 7) | 5.92 ± 1.45 (N = 5) | 7.013 ± 0.845 (N = 5) | 0.485 ± 0.096 (N = 5) |
| ADAGEN | 0.095 ± 0.006 (N = 7) | 73.4 ± 8.9 (N = 7) | 0.074 ± 0.030 (N = 7) | 0.012 ± 0.007 (N = 7) |
| Elapegademase | 0.100 ± 0.007 (N = 7) | 78.29 ± 14.02 (N = 7) | 0.043 ± 0.005 (N = 7) | 0.003 ± 0.001 (N = 7) |

Mean ± SE

#### 3.1.1.5 Effects on splenocyte count, T cell count, and B cell count in the spleen

Elapegademase or ADAGEN was administered to ADA-deficient mice (3 males and females/group) every 4 days from 1 day to 19 days of age, followed by once weekly from 20 days to 6 weeks of age, as repeated intramuscular doses of 5 U, and the spleen was isolated after the final dose to determine the splenocyte count, T cell count, and B cell count. The T cell count and B cell count were measured by flow cytometry, using T cell surface markers (CD3 and TCRβ) and B cell surface markers (CD45R and IgM) as indicators of the T cell and B cell populations. The results are shown in Table 5.

Table 5. Splenocyte count, T cell count, and B cell count in the spleen

| | Splenocytes | T cells ($CD3^+/TCR\beta^+$) | B cells ($CD45R^+$/IgM) |
|---|---|---|---|
| Wild-type ADA (N = 8)[a)] | 76.35 ± 7.14 | 44.5 ± 5.6 | 34.0 ± 6.0 |
| Untreated (N = 5)[a)] | 5.92 ± 1.45 | 0.25 ± 0.01 | 0.50 ± 0.02 |
| ADAGEN (N = 3) | 43.3 ± 4.4 | 25.7 ± 3.5 | 12.3 ± 1.5 |
| Elapegademase (N = 3) | 49.7 ± 3.2 | 28.0 ± 4.4 | 15.0 ± 1.7 |

Mean ± SE, ($\times 10^6$ cells)

a) The T cell counts and B cell counts were cited from a literature report *(J Biol Chem.* 2000;275:32114-21).

#### 3.1.1.6 Effects on body weight

Elapegademase or ADAGEN was administered to ADA-deficient mice (14 males and females/group) every 4 days from day 1 of age as repeated intramuscular doses of 5 U, and body weight was measured at 21 days of age. The body weight (mean ± SE) was 14.19 ± 0.60 g in wild-type AD mice (21 males and females), 8.74 ± 0.23 g in the untreated group (18 males and females), 15.37 ± 0.54 g in the elapegademase group, and 15.07 ± 0.66 g in the ADAGEN group.

#### 3.1.1.7 Effects on survival

Elapegademase or ADAGEN was administered to ADA-deficient mice (6 males and females/group) every 4 days from 1 day to 19 days of age, followed by once weekly from 20 days of age, as repeated intramuscular doses of 5 U to assess survival at 6 weeks of age. While untreated mice died at approximately 3 to 4 weeks of age (*J Exp Med.* 2000;192:159-70), 6 of 6 mice in the elapegademase group and 5 of 6 mice in the ADAGEN group were alive at 6 weeks of age.

### 3.2 Safety pharmacology

The effects of elapegademase on the central nervous, cardiovascular, and respiratory systems were assessed in repeated dose toxicity studies [see Section "5.2 Repeated dose toxicity studies"]. The results are shown in Table 6.

Table 6. Summary of safety pharmacology results

| Parameter | Test system | Observations/ examinations | Dose of elapegademase | Route of administration | Findings | CTD |
|---|---|---|---|---|---|---|
| Central nervous and respiratory systems | Sprague-Dawley rats (15/sex/group) | Clinical signs and histopathological examination | 0, 30, 100, and 300 U/kg | Intramuscular | No effects on the central nervous or respiratory system | 4.2.3.2-1 |
| | Dogs (5/sex/group) | Clinical signs and histopathological examination | 0, 30, 100, and 300 U/kg | Intramuscular | No effects on the central nervous or respiratory system | 4.2.3.2-2 |
| Cardiovascular system | Dogs (5/sex/group) | Electrocardiogram (unanesthetized) | 0, 30, 100, and 300 U/kg | Intramuscular | No effects on the cardiovascular system | 4.2.3.2-2 |

## 3.R Outline of the review conducted by PMDA

### 3.R.1 Mechanism of action of elapegademase

The applicant's explanation:

Elapegademase is a modified protein in which rADA is covalently conjugated to PEG via carbonyl groups, and which has an amino acid sequence at its active center that is identical to that of human endogenous ADA. ADA is an enzyme involved in the purine metabolic pathway that catalyzes the conversion of adenosine and deoxyadenosine to inosine and deoxyinosine, respectively. A deficiency of ADA due to an ADA genetic mutation causes the intracellular accumulation of ADA substrates (i.e., adenosine and deoxyadenosine) and their phosphorylated forms (e.g., dAXPs), resulting in immunodeficiency due to damage to cells, notably lymphocytes such as by the induction of apoptosis or the inhibition of DNA repair. Elapegademase administered intramuscularly is expected to promote the metabolism of adenosine and deoxyadenosine in the blood, thereby equalizing the gradients of substrate concentrations across the cell membrane, leading to normalization of the intracellular concentrations of adenosine and deoxyadenosine. *In vivo* studies showed that elapegademase increased plasma ADA activity, decreased adenosine and deoxyadenosine concentrations in the thymus and spleen, and inhibited the decline in splenocyte count in ADA-deficient mice. Based on the above study results, elapegademase was expected to be effective in the treatment of ADA deficiency.

PMDA has concluded that the data submitted demonstrate the pharmacological effects of elapegademase.

## 4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Elapegademase or ADAGEN was administered to rats and dogs as a single intravenous or intramuscular dose to evaluate the pharmacokinetics of the drugs. In addition, based on toxicokinetic data from toxicity studies in rats and dogs, the pharmacokinetics of elapegademase following repeated doses was evaluated.

Plasma concentrations of elapegademase and ADAGEN were determined by enzyme activity assay.[1)] The lower limit of quantification was 15, 25, or 50 mU/mL in rats, and 25 mU/mL in dogs. Anti-elapegademase antibodies and anti-PEG antibodies were measured by enzyme-linked immunosorbent assay (ELISA). Neutralizing antibodies were measured by enzyme activity assay.[1)] The results of key studies are described below.

## 4.1 Absorption

### 4.1.1 Single dose studies (CTD 4.2.2.2-1 to 2 and 4.2.3.1-1 to 2)

Table 7 shows the pharmacokinetic parameters following a single intravenous or intramuscular dose of elapegademase or ADAGEN in male and female rats and dogs.

[1)] Utilizing the fact that elapegademase or ADAGEN converts adenosine (a substrate) to inosine, drug concentrations were determined by absorption spectrophotometry. One unit (U) of ADA activity was defined as the enzyme activity that generates 1 μmol of inosine per minute, and 1 mU/mL was converted to 0.06 μmol/h/mL.

Table 7. Pharmacokinetic parameters following a single dose of elapegademase or ADAGEN

| Animal species | Drug | Sex | Route of administration | Dose (U/kg) | N | $C_{max}$ (U/mL) | $AUC_{0\text{-}336\ h}$ (U·h/mL) | $t_{max}$ (h) | $t_{1/2}$ (h) | CL/F[a)] (mL/h/kg) | $V_z$/F[b)] (mL/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Rats | Elapegademase | Female | Intravenous | 126 | 5 | 4.52 ± 0.56 | 136.57 ± 9.26[c)] | — | 37.5 ± 12.1[d)] | 0.93 ± 0.06 | 45.2 ± 7.9 |
| | ADAGEN | | | | | 5.09 ± 0.50 | 140.64 ± 10.26[c)] | — | 34.4 ± 3.5[d)] | 0.90 ± 0.07 | 42.1 ± 2.1 |
| Rats | Elapegademase | Male | Intramuscular | 150 | 6 | 0.92 ± 0.06 | 93.19 ± 4.63 | 24 ± 0 | 61.8 ± 4.1 | 1.57 ± 0.08 | 140 ± 10 |
| | | Female | | | 6 | 0.98 ± 0.13 | 98.56 ± 9.72 | 24 ± 0 | 60.3 ± 11.1 | 1.48 ± 0.15 | 129 ± 21 |
| | ADAGEN | Male | | | 5 | 0.82 ± 0.05 | 68.11 ± 5.61 | 24 ± 0 | 42.0 ± 3.5 | 2.12 ± 0.19 | 128 ± 7 |
| | | Female | | | 6 | 0.88 ± 0.11 | 70.01 ± 9.45 | 24 ± 0 | 38.6 ± 3.4 | 2.10 ± 0.29 | 117 ± 18 |
| Rats | Elapegademase | Male | Intramuscular | 30 | 9 | 0.24 ± 0.03 | 22.70 ± 3.83 | 24.0 ± 0.00 | 53.0 ± 5.98 | 1.25 ± 0.17 | 95.2 ± 12.2 |
| | | Female | | | 10 | 0.24 ± 0.03 | 20.40 ± 3.62 | 24.0 ± 0.00 | 49.4 ± 8.45 | 1.39 ± 0.20 | 97.9 ± 12.8 |
| | | Male | | 150 | 10 | 1.15 ± 0.19 | 124.00 ± 15.30 | 24.0 ± 0.00 | 61.0 ± 12.0 | 1.20 ± 0.17 | 104 ± 17.4 |
| | | Female | | | 10 | 1.07 ± 0.12 | 105.00 ± 14.90 | 22.4 ± 5.06 | 51.3 ± 4.18 | 1.41 ± 0.17 | 104 ± 12.9 |
| | ADAGEN | Male | | 30 | 10 | 0.19 ± 0.03 | 14.20 ± 3.85 | 22.4 ± 5.06 | 50.4 ± 13.1 | 1.75 ± 0.46 | 122 ± 21.8 |
| | | Female | | | 9 | 0.21 ± 0.05 | 12.90 ± 2.57 | 18.7 ± 8.00 | 36.1 ± 3.58 | 1.95 ± 0.39 | 101 ± 19.7 |
| | | Male | | 150 | 10 | 1.02 ± 0.12 | 83.20 ± 10.40 | 24.0 ± 0.00 | 40.6 ± 3.14 | 1.77 ± 0.21 | 104 ± 13.0 |
| | | Female | | | 9 | 0.95 ± 0.18 | 72.30 ± 13.90 | 18.7 ± 8.00 | 36.7 ± 2.47 | 2.04 ± 0.35 | 109 ± 20.8 |
| Dogs | Elapegademase | Male | Intramuscular | 30 | 5 | 0.32 ± 0.02 | 52.50 ± 1.69 | 17.6 ± 8.76 | 128 ± 20.0 | 0.48 ± 0.02 | 88.8 ± 9.77 |
| | | Female | | | 5 | 0.31 ± 0.02 | 53.90 ± 4.48 | 17.6 ± 8.76 | 134 ± 20.4 | 0.47 ± 0.06 | 88.5 ± 6.07 |
| | | Male | | 150 | 5 | 1.48 ± 0.12 | 252.00 ± 18.90 | 17.6 ± 8.76 | 138 ± 13.3 | 0.49 ± 0.04 | 96.9 ± 10.4 |
| | | Female | | | 5 | 1.43 ± 0.18 | 235.00 ± 27.90 | 17.6 ± 8.76 | 154 ± 15.2 | 0.51 ± 0.06 | 113 ± 13.5 |
| | ADAGEN | Male | | 30 | 5 | 0.30 ± 0.03 | 38.60 ± 3.23 | 20.8 ± 7.16 | 77.3 ± 1.92 | 0.73 ± 0.06 | 81.3 ± 5.56 |
| | | Female | | | 5 | 0.31 ± 0.02 | 39.50 ± 2.82 | 11.2 ± 7.16 | 79.0 ± 4.95 | 0.71 ± 0.04 | 80.9 ± 9.43 |
| | | Male | | 150 | 5 | 1.62 ± 0.11 | 191.00 ± 6.94 | 17.6 ± 8.76 | 68.3 ± 4.48 | 0.76 ± 0.03 | 74.7 ± 3.03 |
| | | Female | | | 5 | 1.46 ± 0.19 | 188.00 ± 9.53 | 17.6 ± 8.76 | 73.9 ± 2.84 | 0.77 ± 0.04 | 81.6 ± 5.29 |

Mean ± standard deviation (SD); —, Not determined

$C_{max}$, maximum plasma concentration; $AUC_{0\text{-}336\ h}$, area under the plasma concentration-time curve from 0 to 336 hours after administration; $t_{max}$, time to the maximum plasma concentration; $t_{1/2}$, elimination half-life; CL/F, apparent total body clearance; $V_z$/F, apparent volume of distribution

a) CL value when administered intravenously; b) $V_{ss}$ value when administered intravenously; c) $AUC_{inf}$ (area under the plasma concentration-time curve from 0 to infinity); d) β-phase elimination half-life

### 4.1.2 Repeated dose studies (CTD 4.2.3.2-1 to 2, 4.2.3.5.2)

Table 8 shows the pharmacokinetic parameters of elapegademase administered intramuscularly to male and female rats and dogs for 4 weeks.[2)] In 68 male and female rats (34/sex), anti-elapegademase antibodies were detected on Day 29 in all tested animals, and neutralizing antibodies were found in 1 of 12 males in the 30 U/kg group. In 6 male and female dogs (3/sex/group), anti-elapegademase antibodies were detected on Day 29 in 3 of 6 animals (1 male and 2 females) in the 30 U/kg group, 3 of 6 animals (3 males) in the 100 U/kg group, and 6 of 6 animals in the 300 U/kg group. Neutralizing antibodies were not found in any of the animals. Of 12 dogs subjected to a 4-week recovery period (2/sex/group), anti-elapegademase antibodies were detected in 2 of 4 animals in the 100 U/kg group (1 male and 1 female) and 2 of 4 animals in the 300 U/kg group (2 females), and neutralizing antibodies were found in 1 female of 4 animals in the 100 U/kg group.

Table 8. Pharmacokinetic parameters following repeated intramuscular doses of elapegademase

| Animal species | Dose (U/kg) | Sex | $C_{max}$ (U/mL) | | $AUC_{0\text{-last}}$ (U·h/mL) | | $t_{1/2}$ (h) | |
|---|---|---|---|---|---|---|---|---|
| | | | First dose | Final dose | First dose | Final dose | First dose | Final dose |
| Rats | 30 | Male | 0.21 | 0.06 | 12.20 | 0.85 | 98.1 | - [a)] |
| | | Female | 0.22 | 0.12 | 12.60 | 4.20 | 94.5 | 39.2 |
| | 100 | Male | 0.55 | 0.17 | 30.60 | 6.02 | 92.9 | 28.0 |
| | | Female | 0.69 | 0.62 | 36.00 | 61.10 | 53.8 | 65.7 |
| | 300 | Male | 2.26 | 2.58 | 107.00 | 281.00 | 42.9 | 53.6 |
| | | Female | 2.67 | 4.56 | 131.00 | 416.00 | 44.3 | 63.2 |
| Dogs | 30 | Male | 0.30 ± 0.04 | 0.81 ± 0.37 | 18.10 ± 2.56 | 107.00 ± 126.00 | 113 ± 20.1[b)] | 225, 229 [c)] |
| | | Female | 0.31 ± 0.03 | 0.91 ± 0.09 | 19.10 ± 2.22 | 115.00 ± 130.00 | 120 ± 20.9 [d)] | 192, 226[c)] |
| | 100 | Male | 1.33 ± 0.11 | 4.14 ± 0.23 | 85.50 ± 5.50 | 504.00 ± 570.00 | 167 ± 79.5[d)] | 170 ± 47.4[b)] |
| | | Female | 1.39 ± 0.06 | 4.16 ± 0.30 | 86.90 ± 5.76 | 305.00 ± 428.00 | 138 ± 27.8[d)] | 76.1, 168[c)] |
| | 300 | Male | 3.18 ± 0.37 | 9.21 ± 0.71 | 195.00 ± 10.50 | 1070.00 ± 1170.00 | 173 ± 71.0 | 202, 211[c)] |
| | | Female | 3.15 ± 0.19 | 9.72 ± 0.70 | 200.00 ± 9.55 | 969.00 ± 1030.00 | 144 ± 48.8 | 164, 183[c)] |

Rats, mean (3/timepoint); dogs, mean ± SD (5/sex); -, Not determined
$C_{max}$, maximum plasma concentration; $AUC_{0\text{-last}}$, area under the plasma concentration-time curve from 0 to the last quantifiable time; $t_{1/2}$, elimination half-life
a) Due to lack of a definite elimination phase, no $t_{1/2}$ value could be determined; b) 3 animals, excluding 2 animals whose $t_{1/2}$ values could not be determined due to lack of a definite elimination phase; c) 2 animals, excluding 3 animals whose $t_{1/2}$ values could not be determined due to lack of a definite elimination phase (individual values from these 2 animals are shown); d) 4 animals, excluding 1 animal whose $t_{1/2}$ value could not be determined due to lack of a definite elimination phase

Elapegademase was administered to pregnant rats (3/timepoint) on Gestation Days 7, 10, 13, and 16 as an intramuscular dose of 48, 143, or 238 U/kg. The $C_{max}$ values on Gestation Days 7 and 16, respectively were 0.66 U/mL and 0.87 U/mL in the 48 U/kg group, 1.83 U/mL and 2.10 U/mL in the 143 U/kg group, and 3.31 U/mL and 4.54 U/mL in the 238 U/kg group. The $AUC_{0\text{-last}}$ values on Gestation Days 7 and 16, respectively were 35.90 U·h/mL and 31.40 U·h/mL in the 48 U/kg group, 96.30 U·h/mL and 110.00 U·h/mL in the 143 U/kg group, and 183.00 U·h/mL and 229.00 U·h/mL in the 238 U/kg group. No anti-elapegademase antibodies or anti-PEG antibodies were found in any of the tested rats.

2) Elapegademase was intramuscularly administered on Days 1, 4, 7, 11, 14, 18, 21, 25, and 29.

### 4.2 Distribution

No distribution studies were performed.

### 4.3 Metabolism

No metabolism studies were performed.

### 4.4 Excretion

No excretion studies were performed.

### 4.R Outline of the review conducted by PMDA

#### 4.R.1 Effects of anti-elapegademase antibodies

The applicant's explanation:

In a 4-week repeated dose study in rats, exposure to elapegademase ($C_{max}$ and $AUC_{0\text{-last}}$) tended to increase after the final dose (Day 29) as compared with the first dose in the high dose group (males and females at 300 U/kg), but tended to decrease after the final dose (Day 29) as compared with the first dose in some animals in the lower dose groups (males and females at 30 U/kg and males at 100 U/kg) (Table 8). The following 2 factors might affect the exposure: (1) Multiple doses every 3 to 4 days led to an accumulation of elapegademase, in view of the half-life of elapegademase, which increased the exposure; (2) Anti-elapegademase antibodies were found after the final dose (Day 29) in all of the animals tested for the antibodies, suggesting that the formation of antibody-elapegademase complex reduced the plasma concentration of free elapegademase. In the high dose group (males and females at 300 U/kg), the exposure was considered to have been more greatly affected by the accumulation of elapegademase due to repeated doses than the development of anti-drug antibodies, resulting in increased exposure. In the lower dose groups (males and females at 30 U/kg and males at 100 U/kg), on the other hand, the formation of antibody-elapegademase complex was considered to have markedly lowered the plasma concentration of free-elapegademase, resulting in decreased exposure. The tendency for the exposure after repeated doses to differ between males and females in the 100 U/kg group could not be clearly explained, although both the accumulation of elapegademase and the development of anti-drug antibodies due to repeated doses might have affected the exposure. Of 5 patients enrolled in clinical studies of elapegademase (a Japanese phase III study and a foreign phase III study), excluding 1 patient who discontinued the study in the foreign phase III study,[9)] 2 patients were positive for anti-drug antibodies including anti-elapegademase antibodies. However, the development of anti-drug antibodies in these 2 patients was transitory during the treatment period. In addition, there were no clear changes in trough plasma ADA activity due to the development of antibodies and no adverse events that were attributable to the development of anti-drug antibodies. Based on the above, the development of anti-drug antibodies is unlikely to affect the pharmacokinetics, efficacy, or safety of elapegademase in humans.

PMDA's view:

The applicant has explained that the decreased exposure after repeated doses in some rats in the lower dose groups, which was not observed in the high dose group, was attributable to the development of anti-drug antibodies. However, (1) the exposure after repeated doses decreased only in males but not in females in the 100 U/kg group (Table 8), (2) a similar result was not observed in dogs, and (3) the number of rats tested was small. Thus, there are limitations in determining the appropriateness of the applicant's explanation. The effects of the immunogenicity of elapegademase on the efficacy and safety in human will also be discussed in Sections "7.R.1 Efficacy" and "7.R.2 Safety."

## 5. Toxicity and Outline of the Review Conducted by PMDA

The toxicity data on elapegademase included the results from single dose toxicity studies, repeated dose toxicity studies, reproductive and developmental toxicity studies, and other toxicity studies (toxicity studies of impurities). The results from some non-GLP toxicity studies were submitted as reference data. In this section, doses and concentrations of elapegademase, measured by enzyme activity assays[1)] are described as is. Doses and concentrations measured by enzyme activity assays using HPLC[3)] were converted into values measured by enzyme activity assays. Blood elapegademase concentrations were measured based on the blood enzyme activity of ADA including endogenous ADA.

### 5.1 Single-dose toxicity

Single dose toxicity studies were conducted in rats and dogs (Table 9). None of the tested animals died or showed signs of acute toxicity. The approximate lethal doses for elapegademase were >150 U/kg in both rats and dogs.

Table 9. Single dose toxicity studies

| Test system | Route of administration | Dose (U/kg) | Main findings | Approximate lethal dose (U/kg) | Attached CTD |
|---|---|---|---|---|---|
| Male and female rats (Sprague-Dawley) | Intramuscular | 30,[a)] 150[a)] | No toxicological changes | >150 | Reference 4.2.3.1-1 |
| Male and female dogs (Beagle) | Intramuscular | 30,[a)] 150[a)] | No toxicological changes | >150 | Reference 4.2.3.1-2 |

a) A 0.05 mol/L phosphate buffer-sodium chloride solution (pH 7.2-7.4) was used as the solvent.

### 5.2 Repeated-dose toxicity

In rats and dogs, 4-week repeated dose toxicity studies were conducted, and the results showed no toxicological findings (Table 10).

When elapegademase was administered to rats and dogs twice weekly for 4 weeks, the $AUC_{0\text{-}72h}$ values at the no observed adverse effect level (NOAEL, 300 U/kg) were 154,000 mU·h/mL in male rats, 231,000 mU·h/mL in female rats, 589,000 mU·h/mL in male dogs, and 597,000 mU·h/mL in female dogs, which corresponded to approximately 1.7-fold, 2.6-fold, 6.6-fold, and 6.7-fold, respectively, of

3) Utilizing the fact that both elapegademase and ADAGEN convert its substrate (i.e., adenosine) to inosine, the amount of inosine generated was measured by HPLC. One unit (U) of ADA activity was defined as the enzyme activity that generates 1 μmol of inosine per 1 minute.

the steady state $AUC_{\tau}$ observed in Japanese patients with ADA deficiency who received the recommended dose of elapegademase once weekly (89,251 mU·h/mL).

Table 10. Repeated dose toxicity studies

| Test system | Route of administration | Treatment duration | Dose of elapegademase (U/kg) | Main findings | NOAEL (U/kg) | Attached CTD |
|---|---|---|---|---|---|---|
| Male and female rats (Sprague-Dawley) | Intramuscular | 4-weeks (twice-weekly dosing) + 4-week washout | 0,[a] 30, 100, and 300 | No toxicological changes<br>Increased MPV[b] at ≥30 U/kg<br>Prolonged APTT[c] at ≥300 U/kg<br><br>Both of the changes were reversible. | 300 | 4.2.3.2-1 [d] |
| Male and female dogs (Beagle) | Intramuscular | 4-weeks (twice-weekly dosing) + 4-week washout | 0,[a] 30, 100, and 300 | No toxicological changes<br>Prolonged APTT[c] at ≥30 U/kg (males)<br>Prolonged APTT[c] at 300 U/kg (females)<br><br>Both of the changes were reversible. | 300 | 4.2.3.2-2 [d] |

MPV, mean platelet volume; APTT, activated partial thromboplastin time
a) 0.05 mol/L phosphate buffer-sodium chloride solution (pH 7.2-7.4)
b) The change was not accompanied by decreased platelet count, and was therefore of little toxicological significance.
c) The changes were of little toxicological significance, due to the absence of other changes suggestive of bleeding or coagulation disorders.
d) The stability of the test article and the concentrations of the dosing solutions were assessed in non-GLP studies.

### 5.3 Genotoxicity

No genotoxicity studies of elapegademase were conducted, because elapegademase is a modified protein in which rADA is covalently conjugated to PEG and is unlikely to interact directly with DNA or other chromosomal components.

### 5.4 Carcinogenicity

Considering the development of antibodies to elapegademase and the decrease in blood exposure observed in the 4-week repeated dose studies [see Section “4.1.2 Repeated dose studies”], the conduct of a carcinogenicity study involving a longer duration of treatment was considered unfeasible.

For the following reasons, the carcinogenic potential of elapegademase is considered to be low: (1) Elapegademase will be used as an enzyme replacement therapy for ADA deficiency and is unlikely from a pharmacodynamic viewpoint to cause any carcinogenic concern; (2) The dose of elapegademase may be adjusted; (3) ADAGEN, another ADA product, has been administered to patients with ADA deficiency for up to 22 years, with no reports suggesting the carcinogenic potential of elapegademase (*Blood.* 2009;114:3524-32); and, (4) PEG is not carcinogenic (*Drug Metab Dispos.* 2007;35:9-16).

## 5.5 Reproductive and developmental toxicity

The reproductive and developmental toxicity of elapegademase was assessed in an embryo-fetal development study in rats. Since no elapegademase-related changes in male or female reproductive organs were found and no concerns were identified about maternal or embryo-fetal toxicity in the 4-week repeated dose toxicity studies in rats and dogs or the embryo-fetal development study in rats, no studies were conducted regarding "fertility and early embryonic development to implantation" or "effects on pre- and postnatal development, including maternal function." In addition, successful pregnancy and childbirth has been reported in 2 patients treated with ADAGEN overseas, during the dosing period (*J Clin Immunol.* 2012;32:144, *J Clin Immunol.* 2016;36:242, etc.). Of 185 patients who have been treated with ADAGEN, approximately 70% start the therapy before 1 year of age. ADAGEN therapy has been well-tolerated, in general (*Blood.* 2009;114:3524-32).

The $AUC_{0\text{-}t}$ value at the NOAEL (238 U/kg) observed in the embryo-fetal development study in rats was 229,000 mU·h/mL, which was approximately 2.6-fold of the estimated steady state $AUC_{\tau}$ value in Japanese patients with ADA deficiency who received the recommended dose of elapegademase once weekly (89,251 mU·h/mL).

Table 11. Reproductive and developmental toxicity

| Study | Test system | Route of administration | Treatment duration | Dose of elapegademase (U/kg) | Main findings | NOAEL (U/kg) | Attached CTD |
|---|---|---|---|---|---|---|---|
| Embryo-fetal development study | Female rats (Sprague-Dawley) | Intramuscular | Gestation Days 7-16 (every 3 days; a total of 4 doses) | 0,[a)]48, 143, and 238 | Maternal animals: decreased body weight gain at 238 U/kg<br><br>Fetuses: incomplete ossification of the zygomatic arch[b)] at 238 U/kg | 238 | 4.2.3.5.2 |

a) Phosphate buffer (pH 6.9)
b) This finding was of little toxicological significance for the following reasons: (1) It was associated with fetal growth and not classified as a morphological defect; and, (2) there were no changes in other fetal growth parameters.

## 5.6 Local tolerance

The potential of elapegademase to induce local irritation was assessed in the 4-week repeated dose toxicity study (CTD 4.2.3.2-1 and 4.2.3.2-2). No local irritation attributable to elapegademase was observed.

## 5.7 Other toxicity studies

### 5.7.1 Toxicity studies of an impurity

Since Impurity A increased over time in the stability studies of elapegademase, a test article in which 10% of the elapegademase was changed into Impurity A and a test article containing no Impurity A were intramuscularly administered to rats in the 4-week repeated dose toxicity study. The results showed no toxicological differences between the 2 test articles (Table 12).

Table 12. Toxicity study of an impurity

| Test system | Route of administration | Treatment duration | Dose of elapegademase (U/kg) | Main findings | Attached CTD |
|---|---|---|---|---|---|
| Male and female rats (Sprague-Dawley) | Intramuscular | 4 weeks (twice weekly) | Elapegademase (500 U/kg, containing no Impurity A) and a test article in which 10% of elapegademase (500 U/kg) was changed into Impurity A[a)] | None | 4.2.3.7.6 |

a) Phosphate buffer (pH 6.9) was used as the solvent.

## 5.R Outline of the review conducted by PMDA

### 5.R.1 Safety of long-term treatment

The applicant's explanation about the rationale for setting the treatment duration at 4 weeks in the repeated dose toxicity studies and the possible risks of long-term treatment with elapegademase:

Conducting a repeated dose toxicity study with a duration of ≥4 weeks was considered to have little significance in the toxicological evaluation of elapegademase for the following reasons: (1) In the 4-week repeated dose studies (with a 4-week recovery period) of elapegademase in rats and dogs, the development of anti-drug antibodies was found on the last day of treatment or at the end of the recovery period; (2) In rats, the blood exposure on the last day of treatment was below the lower limit of detection in males and females in the 30 U/kg group, and males in the 100 U/kg group; and, (3) in dogs, the blood exposure on the last day of treatment had decreased significantly in 1 male in the 30 U/kg group and 1 female in the 100 U/kg group. With regard to the possible risks associated with long-term treatment with elapegademase, prolongation of the duration of treatment from 4 weeks to 8 weeks in the toxicity study of ADAGEN resulted in no new toxicological findings. Furthermore, ADAGEN has a successful clinical history of up to 22 years. Elapegademase was administered to patients with ADA deficiency for ≥101 weeks and ≥146 weeks in a Japanese phase III study (Study STM-279-301) and a foreign phase III study (Study STP-2279-002), respectively, both of which demonstrated the tolerability of elapegademase. In the Japanese phase III study (Study STM-279-301), although plasma ADA activity increased to approximately 50- to 125-fold of the normal range, no adverse reactions attributable to elapegademase were reported. Thus, no significant risks associated with long-term treatment with elapegademase have been identified. However, due to the small number of patients receiving elapegademase in clinical studies, safety information should continue to be collected after the market launch to evaluate the long-term safety of elapegademase.

PMDA's view:

Neither clinical experience with ADAGEN nor the results of clinical studies of elapegademase have provided information that suggests the occurrence of significant problems in association with long-term treatment with elapegademase. However, the treatment duration in the repeated dose toxicity studies was up to 4 weeks and the results of the non-clinical studies were not adequate to fully assess the risks of long-term treatment with elapegademase. Elapegademase is a replacement therapy for a deficient enzyme and is expected to be administered over an extended period of time. The clinical safety of elapegademase including long term administration, will be discussed in Section "7.R.2 Safety."

## 6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

### 6.1 Summary of biopharmaceutic studies and associated analytical methods

Plasma concentrations of elapegademase and ADAGEN were determined by enzyme activity assay[1)] with a lower limit of quantification of 9 μmol/h/mL. Anti-elapegademase antibodies, anti-ADAGEN antibodies, anti-elapegademase IgM antibodies, anti-ADAGEN IgM antibodies, and anti-PEG antibodies were detected by ELISA, and neutralizing antibodies were detected by enzyme activity assay.[1)]

### 6.2 Clinical pharmacology

The applicant submitted clinical pharmacological evaluation data, in the form of results data from a Japanese phase III study (Study STM-279-301) and a foreign phase III study (Study STP-2279-002).

#### 6.2.1 Japanese phase III study (CTD 5.3.5.2-1, Study STM-279-301, ongoing since March 2016 [data cutoff in March 2018])

An open-label, uncontrolled study was conducted to evaluate the efficacy, safety, and pharmacokinetics of elapegademase in Japanese patients with ADA deficiency (target sample size, 2) [for the detailed study design, and efficacy and safety results from the study, see Section "7.1.1 Japanese phase III study"].

Of 4 patients receiving elapegademase, 2 patients who tolerated frequent blood sampling were included in the pharmacokinetic analysis set.

The pharmacokinetic parameters during the Dose Maintenance Period in individual patients receiving repeated intramuscular doses of elapegademase once weekly are shown in Table 13.

Measurements of anti-elapegademase antibodies detected no anti-elapegademase antibodies at any timepoint in either of the patients.

Table 13. Individual pharmacokinetic parameters during the Dose Maintenance Period

| Patient number (sex/age) | Timepoint | Dose (mg/kg) | Body weight (kg) | $C_{max}$ (μmol/h/mL) | $C_{trough}$ (μmol/h/mL) | $AUC_{\tau}$ (h·μmol/h/mL) | $t_{max}$ (h) | $t_{1/2}$ (h) | CL/F (L/h) | $V_z$/F (L) |
|---|---|---|---|---|---|---|---|---|---|---|
| Patient 1 ([redacted]) | Dose Maintenance Period Week 6 | 0.167 | [redacted] | 41.91 | 33.50 | 6279.20 | 48.0 | 359.59 | 0.0140 | 7.3 |
| Patient 2 ([redacted]) | Dose Maintenance Period Week 12 | 0.233 | [redacted] | 34.91 | 20.15 | 4430.89 | 27.3 | 226.61 | 0.0108 | 3.5 |

Values from individual patients

$C_{max}$, maximum plasma concentration; $C_{trough}$, trough plasma concentration (plasma concentration at 168 hours after administration); $AUC_{\tau}$, area under the plasma concentration-time curve over the dosing interval (168 hours); $t_{max}$, time to the maximum plasma concentration; $t_{1/2}$, elimination half-life; CL/F, apparent total body clearance; $V_z$/F, apparent volume of distribution

### 6.2.2 Foreign phase III study (CTD 5.3.5.2-2, Study STP-2279-002, ongoing since January 2014 [data cutoff in April 2017])

An open-label, uncontrolled study was conducted to evaluate the efficacy, safety, and pharmacokinetics of elapegademase in non-Japanese patients with ADA deficiency accompanied by immunodeficiency (target sample size, 6) [for the detailed study design, and efficacy and safety results from the study, see Section "7.1.2 Foreign phase III study"].

Of 6 patients receiving elapegademase, 4 patients who were treated with elapegademase for ≥9 weeks and had pharmacokinetic data at Week 9 were included in the pharmacokinetic analysis set.

The pharmacokinetic parameters at Week 9 in individual patients receiving repeated intramuscular doses of elapegademase once weekly are shown in Table 14.

Anti-elapegademase antibodies, anti-ADAGEN antibodies, anti-elapegademase IgM antibodies, anti-ADAGEN IgM antibodies, and anti-PEG antibodies were measured. Among 5 patients excluding 1 patient who discontinued the study,[9)] 2 patients were positive for the antibodies at ≥1 timepoint before the data cutoff.

Table 14. Individual pharmacokinetic parameters at Week 9

| Patient number (sex/age) | Dose[a)] (mg/kg) | Body weight (kg) | $C_{max}$ (μmol/h/mL) | $C_{trough}$ (μmol/h/mL) | $AUC_{\tau}$ (h·μmol/h /mL) | $t_{max}$ (h) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|---|---|
| Patient 2 ([redacted]) | 0.188 | [redacted] | 44.6 | 29.0 | 6160 | 47.7 | 219 |
| Patient 3 ([redacted]) | 0.224 | [redacted] | 53.3 | 37.7 | 7630 | 71.9 | 177 |
| Patient 4 ([redacted]) | 0.200 | [redacted] | 58.3 | 46.2 | 8480 | 48.2 | 496 |
| Patient 5 ([redacted]) | 0.209 | [redacted] | 35.6 | 23.5 | 5260 | 72 | 145 |
| Mean ± SD (N = 4) | 0.205 ± 0.015 | 61.2 ± 24.8 | 47.9 ± 10 | 34.1 ± 9.97 | 6880 ± 1450 | 59.9 ± 13.9 | 259 ± 161 |

Values from individual patients

$C_{max}$, maximum plasma concentration; $C_{trough}$, trough plasma concentration (plasma concentration at 168 hours after administration); $AUC_{\tau}$, area under the plasma concentration-time curve over the dosing interval (168 hours); $t_{max}$, time to the maximum plasma concentration; $t_{1/2}$, elimination half-life

a) The dose administered at the time of pharmacokinetic assessment

### 6.R Outline of the review conducted by PMDA

The assessment of the pharmacokinetics of elapegademase in patients with ADA deficiency was limited. However, PMDA has concluded based on the study results submitted, that the pharmacokinetics of elapegademase do not differ largely between Japanese and non-Japanese patients.

## 7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of results data from 2 clinical studies as shown in Table 15.

Table 15. List of clinical studies on the efficacy and safety of elapegademase

| Data type | Geographical location | Study identity | Phase | Study population | N | Dosage regimen | Main endpoints |
|---|---|---|---|---|---|---|---|
| Evaluation | Japan | STM-279-301 | III | Patients with ADA deficiency | 4 | Dose Adjustment Period: Patients who had not been treated with ADAGEN received intramuscular elapegademase once weekly at a first dose of 0.1 mg/kg, followed by second and third doses of 0.133 mg/kg. Patients who had been treated with ADAGEN received intramuscular elapegademase once weekly at a dose calculated based on the most recent dose of ADAGEN for the first to third doses. In all of the patients, the fourth and fifth doses were determined after administration of the third dose.<br>Dose Maintenance Period: Patients received intramuscular elapegademase once weekly at a dose ranging from 0.067 and 0.2 mg/kg, which was selected after administration of the last dose in the Dose Adjustment Period. | Pharma-cokinetics<br>Efficacy<br>Safety |
| | Global | STP-2279-002 | III | Patients with ADA deficiency accompanied by immunodeficiency who were on ADAGEN therapy | 6 | Patients received intramuscular elapegademase once weekly at a dose that was calculated based on the most recent dose of ADAGEN. | Pharma-cokinetics<br>Efficacy<br>Safety |

The results of key studies are described below.

### 7.1 Phase III studies

#### 7.1.1 Japanese phase III study (CTD 5.3.5.2-1, Study STM-279-301, ongoing since March 2016 [data cutoff in March 2018])

An open-label, uncontrolled study was conducted to evaluate the efficacy, safety, and pharmacokinetics of elapegademase in Japanese patients with ADA deficiency (target sample size, 2) [for pharmacokinetic results, see Section “6.2.1 Japanese phase III study”].

Patients were enrolled in the study, if they were diagnosed by genetic testing or the investigator as having an ADA deficiency based on clinical symptoms and ADA activity, and if they required enzyme replacement therapy, at the discretion of the investigator.

The study included 2 phases: (1) the Evaluation Phase (21 weeks), consisting of a Dose Adjustment Period (5 weeks) and a Dose Maintenance Period (16 weeks); and, (2) the Continuous Administration Phase (continues until marketing approval).

Elapegademase was intramuscularly administered once weekly. During the Dose Adjustment Period, patients who had not been treated with ADAGEN within 4 weeks before providing informed consent received the first dose of elapegademase at 0.1 mg/kg, followed by second and third doses at 0.133 mg/kg. Patients who had been treated with ADAGEN within 4 weeks before providing informed consent received 3 doses of elapegademase calculated based on the most recent dose of ADAGEN using the conversion formula.[4), 5)] In all of the patients, the fourth and fifth doses in the Dose Adjustment Period were determined after administration of the third dose.[6)] The starting dose for the Dose Maintenance Period was set at a dose ranging from 0.067 to 0.2 mg/kg after the last dose in the Dose Adjustment Period.[7)] In addition, the subsequent doses were reselected after each of the fourth, eighth, and 12th doses in the Dose Maintenance Period.[8)] The starting dose in the Continuous Administration Phase was determined based on the information obtained during the Evaluation Phase, and, in principle, the dose was reselected after every 4 week period of administration at the same dose. The dose was adjusted by 0.033 mg/kg.

All 4 patients treated with elapegademase were included in the efficacy and safety analysis sets. One patient died and discontinued the study. A summary of the characteristics of these 4 patients is presented in Table 16, and the doses administered to individual patients during the Evaluation Phase are shown in Table 17.

Table 16. Summary of the characteristics of individual patients enrolled in Study STM-279-301

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 |
|---|---|---|---|---|
| Sex | [redacted] | [redacted] | [redacted] | [redacted] |
| Age | [redacted] years | [redacted] years | [redacted] months | [redacted] months |
| Body weight | [redacted] kg | [redacted] kg | [redacted] kg | [redacted] kg |
| Use of ADAGEN within 60 days before enrollment in the study and the most recent dose | None | 32 U/kg | 28 U/kg | None |

4) Conversion formula, Dose of elapegademase (mg/kg) = dose of ADAGEN (U/kg) × 1 mg elapegademase / 150 U ADAGEN

5) Since ADAGEN has not been approved in Japan, the use of ADAGEN before providing informed consent was not included in the inclusion criteria.

6) Dose adjustment criteria during the Dose Adjustment Period: If any of the following was found, the investigator decided whether the dose should be adjusted: (1) A trough erythrocyte dAXP concentration of >0.02 μmol/mL; (2) A trough serum ADA activity of <1100 U/L; (3) An onset, change, or deterioration of the clinical symptoms of ADA deficiency such as pneumonia or diarrhoea, or a change or abnormality in the results of laboratory tests (e.g., immune function and hepatic function tests); or, (4) A safety concern. In cases when an erythrocyte dAXP concentration was not available, a blood dAXP concentration could be used, instead.

7) If the investigator decided that the dose should be increased, and if the patient was not able to achieve a trough erythrocyte dAXP of ≤0.02 μmol/mL or a trough serum ADA activity of ≥1100 U/L, elapegademase could be administered at a dose of ≥0.233 mg/kg. In cases when an erythrocyte dAXP concentration was not available, a blood dAXP concentration could be used, instead.

8) Dose adjustment criteria during the Dose Maintenance Period: If any of the following were found, the investigator decided whether the dose should be adjusted: (1) Trough erythrocyte dAXP concentrations of >0.02 μmol/mL on the last 2 consecutive occasions; (2) Trough serum ADA activity of <1100 U/L at the last 2 consecutive occasions; (3) An onset, change, or deterioration of the clinical symptoms of ADA deficiency such as pneumonia or diarrhoea, or a change or abnormality in the results of laboratory tests (e.g., immune function and hepatic function tests); or, (4) A safety concern. In cases when an erythrocyte dAXP concentration was not available, a blood dAXP concentration could be used instead.

Table 17. Doses of elapegademase administered

<table>
<tr><td colspan="3"></td><td>Patient 1</td><td>Patient 2</td><td>Patient 3</td><td>Patient 4</td></tr>
<tr><td colspan="3">Dosing frequency</td><td>Once weekly</td><td>Once weekly</td><td>Once weekly</td><td>Twice weekly</td></tr>
<tr><td rowspan="25">Dose (mg/kg)</td><td rowspan="5">Dose Adjustment Period</td><td>First dose (Day 1)</td><td>0.1</td><td rowspan="8">0.2</td><td rowspan="3">0.167</td><td rowspan="16">0.2[a)]</td></tr>
<tr><td>Second dose (Day 8)</td><td rowspan="2">0.133</td></tr>
<tr><td>Third dose (Day 15)</td></tr>
<tr><td>Fourth dose (Day 22)</td><td rowspan="17">0.167</td><td rowspan="5">0.2</td></tr>
<tr><td>Fifth dose (Day 29)</td></tr>
<tr><td rowspan="16">Dose Maintenance Period</td><td>First dose (Day 36)</td></tr>
<tr><td>Second dose (Day 43)</td></tr>
<tr><td>Third dose (Day 50)</td></tr>
<tr><td>Fourth dose (Day 57)</td></tr>
<tr><td>Fifth dose (Day 64)</td><td rowspan="6">0.233</td><td rowspan="15">0.233[b)]</td></tr>
<tr><td>Sixth dose (Day 71)</td></tr>
<tr><td>Seventh dose (Day 78)</td></tr>
<tr><td>Eighth dose (Day 85)</td></tr>
<tr><td>Ninth dose (Day 92)</td></tr>
<tr><td>10th dose (Day 99)</td></tr>
<tr><td>11th dose (Day 106)</td><td rowspan="9">Discontinued (Died)</td></tr>
<tr><td>12th dose (Day 113)</td></tr>
<tr><td>13th dose (Day 120)</td><td rowspan="5">0.267</td></tr>
<tr><td>14th dose (Day 127)</td></tr>
<tr><td>15th dose (Day 134)</td></tr>
<tr><td>16th dose (Day 141)</td></tr>
<tr><td rowspan="2">Continuous Administration Phase</td><td>First - 16th doses</td></tr>
<tr><td>17th - 80th doses</td><td>0.3</td></tr>
</table>

a) Elapegademase was administered at a dose of 0.2 mg/kg twice weekly, because the patient's systemic condition was already poor at the start of the study. However, the patient died and discontinued the study on Day 107 after the last dose on Day 105.
b) The patient received the 72nd dose of the Continuous Administration Phase, as of the data cutoff.

No efficacy endpoints were set. Trough erythrocyte dAXP concentration was measured in 2 patients and trough blood dAXP concentration in 4 patients. The results are shown in Table 18.

Table 18. Trough erythrocyte dAXP concentrations and trough blood dAXP concentrations

(Efficacy analysis set)

| Endpoints | | Trough erythrocyte dAXP concentration | | Trough blood dAXP concentration | | | |
|---|---|---|---|---|---|---|---|
| Patients | | Patient 1 | Patient 2 | Patient 1 | Patient 2 | Patient 3 | Patient 4 |
| Screening | | 0.125 | <0.002 | 0.0952 | 0.000407 | 0.0107 | 0.0293 |
| Dose Adjustment Period | Second dose (Day 8) | 0.070 | <0.002 | 0.0477 | 0.00102 | 0.00861 | 0.017 |
| | Third dose (Day 15) | 0.046 | <0.002 | 0.0279 | <LLOQ | 0.0102 | 0.00775 |
| | Fourth dose (Day 22) | 0.021 | <0.002 | 0.0176 | 0.000474 | 0.00745 | 0.00429 |
| | Fifth dose (Day 29) | 0.019 | <0.002 | 0.0114 | <LLOQ | 0.0087 | 0.00329 |
| Dose Maintenance Period | First dose (Day 36) | 0.016 | <0.002 | 0.00838 | 0.000635 | 0.00391 | 0.00147 |
| | Second dose (Day 43) | 0.008 | <0.002 | 0.00584 | <LLOQ | 0.0057 | 0.00102 |
| | Third dose (Day 50) | — | — | — | — | 0.00463 | — |
| | Fifth dose (Day 64) | <0.002 | <0.002 | 0.00303 | <LLOQ | 0.00726 | 0.000609 |
| | Sixth dose (Day 71) | <0.002 | <0.002 | 0.0032 | 0.000677 | 0.0058 | 0.0019 |
| | Seventh dose (Day 78) | — | <0.002 | — | 0.000323 | 0.00295 | — |
| | Ninth dose (Day 92) | <0.002 | <0.002 | 0.0018 | 0.00141 | 0.00447 | 0.00267 |
| | 10th dose (Day 99) | <0.002 | <0.002 | 0.00135 | 0.000614 | 0.00432 | 0.00189[a)] |
| | 11th dose (Day 106) | — | — | — | — | 0.0041 | — |
| | 13th dose (Day 120) | <0.002 | <0.002 | 0.00189 | 0.000335 | 0.00478 | Discontinued (Died) |
| | 14th dose (Day 127) | <0.002 | <0.002 | 0.00117 | 0.00064 | 0.00506 | |
| | 15th dose (Day 134) | — | <0.002 | — | 0.000328 | — | |
| | Final observation (Day 148) | <0.002 | <0.002 | 0.00167 | 0.00114 | 0.00449 | |
| Continuous Administration Phase | 17th dose (Day 260) | <0.002 | <0.002 | 0.00109 | 0.00052 | 0.00218 | |
| | 33rd dose (Day 372) | <0.002 | <0.002 | 0.00242 | 0.000351 | 0.0021 | |
| | 49th dose (Day 484) | <0.002 | <0.002 | 0.00225 | 0.000282 | 0.00244 | |
| | 65th dose (Day 596) | <0.002 | <0.002 | 0.00152 | <LLOQ | 0.00233 | |
| | 81st dose (Day 708) | <0.002 | <0.002 | 0.000819 | 0.000961 | — | |

μmol/mL; LLOQ, lower limit of quantification

a) The patient died and discontinued the study on Day 107 after the last dose of 0.2 mg/kg on Day 105.

Trough plasma ADA activity was measured in 2 patients and trough serum ADA activity in 4 patients. The results are shown in Table 19.

Table 19. Trough plasma ADA activity and trough serum ADA activity (Efficacy analysis set)

| Endpoints | | Trough plasma ADA activity[a)] | | Trough serum ADA activity[b)] | | | |
|---|---|---|---|---|---|---|---|
| Patients | | Patient 1 | Patient 2 | Patient 1 | Patient 2 | Patient 3 | Patient 4 |
| Screening | | <9.0 | <9.0 | 20.7 | 223.7 | 884.0 | — |
| Dose Adjustment Period | Second dose (Day 8) | <9.0 | <9.0 | 421.1 | 476.8 | 525.0 | 846.0 |
| | Third dose (Day 15) | 14.51 | <9.0 | 733.5 | 540.2 | 655.5 | 1277.3 |
| | Fourth dose (Day 22) | 10.75 | 13.08 | 1014.0 | 741.5 | 762.0 | 1451.9 |
| | Fifth dose (Day 29) | 21.81 | 14.68 | 1438.0 | 724.0 | 1036.0 | 1830.0 |
| Dose Maintenance Period | First dose (Day 36) | 20.64 | 13.56 | 1327.7 | 622.5 | 796.0 | 1846.0 |
| | Second dose (Day 43) | 21.57 | 13.32 | 1475.0 | 717.5 | 1035.0 | 1666.7 |
| | Third dose (Day 50) | — | — | — | — | 1028.0 | — |
| | Fifth dose (Day 64) | 31.03 | 10.28 | 1782.0 | 717.0 | 1036.5 | 1554.8 |
| | Sixth dose (Day 71) | 29.51 | 12.38 | 1573.5 | 808.5 | 1086.8 | 2072.0 |
| | Seventh dose (Day 78) | — | 12.03 | — | 771.5 | 1334.0 | — |
| | Ninth dose (Day 92) | 31.92 | 19.77 | 1663.8 | 975.0 | 1281.2 | 2254.0 |
| | 10th dose (Day 99) | 25.67 | 18.04 | 1396.6 | 954.4 | 1296.4 | 1451.2c) |
| | 11th dose (Day 106) | — | — | — | — | 1302.4 | — |
| | 13th dose (Day 120) | 34.17 | 20.15 | 2010.0 | 949.3 | 1433.2 | Discontinued (Died) |
| | 14th dose (Day 127) | 33.44 | 20.77 | 1846.0 | 1027.0 | 1659.0 | |
| | 15th dose (Day 134) | — | 18.83 | — | 979.4 | — | |
| | Final observation (Day 148) | 28.73 | 18.66 | 1550.6 | 998.7 | 1482.0 | |
| Continuous Administration Phase | 17th dose (Day 260) | 38.90 | 32.67 | 1934.0 | 1206.3 | 1649.3 | |
| | 33rd dose (Day 372) | 31.97 | 20.34 | 1617.1 | 974.6 | 1644.2 | |
| | 49th dose (Day 484) | 31.04 | 22.32 | 1663.6 | 1288.5 | 1700.0 | |
| | 65th dose (Day 596) | 28.30 | 27.90 | 1501.2 | 1321.5 | 1942.0 | |
| | 81st dose (Day 708) | 26.41 | 20.48 | 1589.0 | 1162.4 | — | |

a) µmol/h/mL
b) U/L
c) The patient died and discontinued the study on Day 107 after the last dose of 0.2 mg/kg on Day 105.

Absolute Lymphocytes (CD45+) and CD19+ (B Cells) Absolute changed very little in 1 patient with the highest values at screening, but tended to increase after the start of treatment with elapegademase in the other 3 patients. CD3+ CD4+ (Helper Cells) Absolute remained unchanged or increased after the start of the treatment.

Adverse events were reported by 4 of 4 patients during the Evaluation Phase and 3 of 3 patients during the Continuous Administration Phase. The reported adverse events are shown in Table 20. A causal relationship to the study drug was denied for all of these events.

Table 20. Adverse events reported (Safety analysis set)

| Phase | Adverse events |
|---|---|
| Evaluation Phase | Otitis media, pneumonia, upper respiratory tract infection, device related infection, cholesteatoma, anaemia, neutropenia, interstitial lung disease, pulmonary haemorrhage, respiratory failure, upper respiratory tract inflammation, haematemesis, hepatic function abnormal, dermatitis contact, catheter site dermatitis, glucose urine present, protein urine present, tracheal haemorrhage, and procedural pain in 1 patient each |
| Continuous Administration Phase | Hypokalaemia in 2 patients, and cellulitis, dermatitis infected, hordeolum, impetigo, nasopharyngitis, onychomycosis, upper respiratory tract infection, upper respiratory tract infection bacterial, respiratory syncytial virus infection, aspergillus infection, neutropenia, dehydration, headache, deafness neurosensory, ear haemorrhage, eustachian tube patulous, upper respiratory tract inflammation, anal fistula, dental caries, gastrointestinal disorders, stomatitis, dermatitis contact, hepatic steatosis, arthralgia, back pain, neck pain, osteoporosis, pyrexia, blood creatinine increased, heat exhaustion, superficial injury of eye, fractured coccyx, contusion, and procedural pain in 1 patient each |

MedDRA/J ver. 19.1

One patient died from an adverse event (respiratory failure). Serious adverse events were reported by 2 patients (neutropenia/upper respiratory tract infection; and pulmonary haemorrhage/respiratory failure) during the Evaluation Phase and 2 patients (neutropenia/dehydration; and respiratory syncytial virus infection/aspergillus infection) during the Continuous Administration Phase.

With the exception of the patient who died, no patients discontinued treatment due to adverse events.

### 7.1.2 Foreign phase III study (CTD 5.3.5.2-2, Study STP-2279-002, ongoing since January 2014 [data cutoff in February 2014])

An open-label, uncontrolled study was conducted in the US to evaluate the efficacy, safety, and pharmacokinetics of elapegademase in patients with ADA deficiency accompanied by immunodeficiency (target sample size, 6) [for pharmacokinetic results, see Section "6.2.2 Foreign phase III study"].

Patients were enrolled in the study, if (1) they had ADA deficiency accompanied by immunodeficiency and had been receiving ADAGEN therapy at a stable dose for ≥6 months, (2) the clinical symptoms were stable, and (3) the trough plasma ADA activity was ≥15 μmol/h/mL and the trough erythrocyte dAXP concentration was ≤0.02 μmol/mL in the ADAGEN Induction Phase.

The study consisted of 3 phases: the ADAGEN Induction Phase (≥3 weeks), the Evaluation Phase (21 weeks), and the Maintenance Phase (continues until 3 patients in Cohort 1 have been treated with elapegademase for 4 years). Based on interim data from the first 3 patients (Cohort 1) who had undergone assessments up to Week 9 in the Evaluation Phase, the Independent Data and Safety Monitoring Committee established by the sponsor evaluated the efficacy, safety, and pharmacokinetics of elapegademase and decided whether an additional 3 patients would be enrolled (Cohort 2).

During the ADAGEN Induction Phase, patients received an intramuscular dose of ADAGEN once weekly for ≥3 weeks. The dose of ADAGEN started with the dose administered before enrollment in the study and was then adjusted depending on trough erythrocyte dAXP concentrations and trough

plasma ADA activity. When a trough erythrocyte dAXP concentration of ≤0.02 μmol/mL and a trough plasma ADA activity of ≥15 μmol/h/mL were maintained at the same dose for 2 weeks, the patients entered the Evaluation Phase. In the Evaluation Phase, patients received an intramuscular dose of elapegademase once weekly for 21 weeks. The starting dose of elapegademase was determined based on the last dose of ADAGEN in the ADAGEN Induction Phase, using the conversion formula.[4)] If the trough erythrocyte dAXP concentrations were >0.02 μmol/mL and the trough plasma ADA activity was <15 μmol/h/mL at Weeks 7 and 8, the dose for Week 9 was adjusted, and elapegademase therapy was continued at the adjusted dose for 4 weeks. Subsequently, if a trough erythrocyte dAXP concentration of >0.02 μmol/mL and a trough plasma ADA activity of <15 μmol/h/mL were again found during the last 2 of these 4 weeks, the necessity of a dose readjustment was considered. After the Evaluation Phase, patients received elapegademase at the same dose throughout the Maintenance Phase.

Of the 8 patients enrolled in the study, 1 patient was enrolled twice in the study and 1 patient rejected periodic blood samplings. The remaining 6 patients were treated with elapegademase and included in the As-treated population. Of these 6 patients, 1 patient discontinued treatment due to an adverse event.[9)] The 1 patient who was enrolled twice in the study failed to meet the protocol-specified criteria for entering the Evaluation Phase at the initial enrollment, but successfully met the criteria and entered the Evaluation Phase at the second enrollment. A summary of the characteristics of the 6 patients treated with elapegademase is presented in Table 21.

Table 21. Summary of the characteristics of individual patients treated with elapegademase

(As-treated population)

| Cohorts | Cohort 1 | | | | Cohort 2 | |
|---|---|---|---|---|---|---|
| Patients | Patient 1[a)] | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
| Body weight (kg) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Sex | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Age (years) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Dose of ADAGEN in the ADAGEN Induction Phase (U/kg) | 43.9 | 28.2 | 34.5 | 30 | 31.3 | 42.9 |
| Dose of elapegademase (mg/kg) | 0.292 | 0.188 | 0.224 | 0.2 | 0.209 | 0.285 |

a) The patient discontinued the study due to an adverse event.

The proportion of patients who achieved a trough erythrocyte dAXP concentration of ≤0.02 μmol/mL at all Weeks 15, 17, 19, and 21 (the primary endpoint) was 2 of the 3 patients in Cohort 1 who had results up to Week 21 of treatment with elapegademase. The remaining 1 patient had a trough erythrocyte dAXP concentration of 0.047 μmol/mL at Week 17 of treatment with elapegademase (Table 22).

9) The patient was the first patient enrolled, who experienced injection site pain after 2 doses of the earlier drug product containing [redacted], and discontinued the study. In subsequent patients, the proposed drug product containing no [redacted] was administered.

Table 22. Trough erythrocyte dAXP concentrations (As-treated population)

| | | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|---|---|---|---|---|---|---|
| Screening | | <0.002 | 0.020 | 0.014 | 0.008 | 0.002 |
| End of ADAGEN therapy | | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 |
| Evaluation Phase | Week 1 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 |
| | Week 3 | <0.002 | <0.002 | <0.002 | <0.002 | <0.002 |
| | Week 5 | <0.002 | <0.002 | <0.002 | — | — |
| | Week 7 | <0.002 | <0.002 | <0.002 | <0.002 | — |
| | Week 8 | <0.002 | <0.002 | <0.002 | <0.002 | — |
| | Week 9 | <0.002 | <0.002 | <0.002 | — | — |
| | Week 10 | <0.002 | <0.002 | <0.002 | <0.002 | — |
| | Week 11 | <0.002 | <0.002 | <0.002 | <0.002 | — |
| | Week 13 | <0.002 | <0.002 | 0.032 | — | — |
| | Week 15 | <0.002 | <0.002 | <0.002 | — | — |
| | Week 17 | 0.047 | <0.002 | <0.002 | — | — |
| | Week 19 | <0.002 | <0.002 | <0.002 | — | — |
| | Week 21 | <0.002 | <0.002 | <0.002 | — | — |
| Maintenance Phase | Week 34 | <0.002 | <0.002 | <0.002 | — | — |
| | Week 47 | <0.002 | <0.002 | <0.002 | — | — |
| | Week 73 | 0.006 | <0.002 | <0.002 | — | — |
| | Week 86 | <0.002 | <0.002 | <0.002 | — | — |
| | Week 99 | <0.002 | <0.002 | <0.002 | — | — |

μmol/mL

The trough plasma ADA activity (a secondary endpoint) is shown in Table 23. In the 3 patients in Cohort 1 who had results up to Week 21, trough plasma ADA activity was maintained at ≥15 μmol/h/mL from Week 3 to Week 21.

Table 23. Trough plasma ADA activity (As-treated population)

| | | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|---|---|---|---|---|---|---|
| Screening | | 17.3 | <1.8 | <1.8 | <LLOQ | 25.2 |
| End of ADAGEN therapy | | 14.5 | 17.6 | 22.4 | 9.0 | 16.1 |
| Evaluation Phase | Week 1 | 10.9 | 10.2 | 17.4 | 11.3 | 14.3 |
| | Week 3 | 30.2 | 21.2 | 28.2 | 11.9 | 25.0 |
| | Week 5 | 25.9 | 28.4 | 30.1 | — | — |
| | Week 7 | 33.9 | 35.7 | 40.3 | 33.2 | — |
| | Week 8 | 29.2 | 33.8 | 48.7 | 30.4 | — |
| | Week 9 | 32.9 | 36.4 | 44.4 | 32.1 | — |
| | Week 10 | 29.0 | 37.7 | 46.2 | 23.5 | — |
| | Week 11 | 33.9 | 37.7 | 42.0 | 19.3 | — |
| | Week 13 | 35.6 | 36.6 | 46.6 | — | — |
| | Week 15 | 35.5 | 33.1 | 43.3 | — | — |
| | Week 17 | 32.3 | 27.6 | 29.9 | — | — |
| | Week 19 | 34.1 | 32.0 | 26.1 | — | — |
| | Week 21 | 28.2 | 31.4 | 28.9 | — | — |
| Maintenance Phase | Week 34 | 31.1 | 31.1 | 29.8 | — | — |
| | Week 47 | 23.7 | 38.3 | 37.5 | — | — |
| | Week 73 | 40.0 | 47.6 | 42.2 | — | — |
| | Week 86 | 35.0 | 55.0 | 45.5 | — | — |
| | Week 99 | 27.3 | 49.0 | 57.1 | — | — |

μmol/h/mL; LLOQ, lower limit of quantification

Immune function was assessed based on the total lymphocyte count and lymphocyte subset (B, T, and NK cells) counts in the 3 patients in Cohort 1. The lymphocyte counts increased during the Evaluation Phase and through Weeks 86 to 99 of treatment with elapegademase in the Maintenance Phase as compared with those at screening.

In the ADAGEN Induction Phase, adverse events were reported by 5 of 6 patients. The reported adverse events [10)] were full blood count abnormal, back injury, groin abscess, dizziness, vomiting, lymphadenopathy, dyspepsia, upper respiratory tract infection, respiratory tract infection, back pain, crystal urine present, and gastroenteritis in 1 patient each. There were no serious adverse events. Among these adverse events, full blood count abnormal was classified as an adverse drug reaction.

In the Evaluation Phase and Maintenance Phase, during which elapegademase was administered, adverse events were reported by 5 of 6 patients. The reported adverse events[10)] were cough in 3 patients, vomiting in 2 patients, and conjunctivitis, gastrointestinal infection, influenza, otitis externa, tooth abscess, lymphadenopathy, migraine, ear disorder, impacted cerumen, epistaxis, nasal oedema, productive cough, oropharyngeal pain, dental caries, diarrhoea, haematochezia, tooth extraction, rash, swelling face, nephrolithiasis, asthenia, fatigue, injection site pain, injection site discomfort, and laceration in 1 patient each. The injection site pain and injection site discomfort reported in 1 patient each were classified as adverse drug reactions.

10) MedDRA/J ver. 19.1

No patients died. Serious adverse events were reported by 3 of 6 patients (injection site pain, migraine, and tooth extraction/tooth abscess). Among these events, injection site pain was classified as an adverse drug reaction.[9)]

No patients experienced adverse events leading to study discontinuation, except for 1 patient who experienced injection site pain classified as an adverse drug reaction.

## 7.R Outline of the review conducted by PMDA

### 7.R.1 Efficacy

The applicant's explanation about the efficacy of elapegademase observed in the clinical studies:
As with ADAGEN, elapegademase is expected to rapidly correct metabolic abnormalities caused by the deficiency of ADA enzyme, thereby improving immunodeficiency and leading to better infection control, a better prognosis for growth, etc. In the Japanese phase III study, 2 adult patients ([redacted] and [redacted] years of age) and 2 infant patients ([redacted] and [redacted] months of age) were enrolled, and 3 of these 4 patients completed the Evaluation Phase (21 weeks). The 1 infant patient who failed to complete the Evaluation Phase died due to respiratory failure on Day 107 and discontinued the study. This patient had an extremely poor systemic condition at the start of the study and received twice-weekly doses of elapegademase at 0.2 mg/kg. The estimated cause of death was the accumulation of pulmonary tissue damage, which had accumulated due to a number of factors such as interstitial pneumonia persisting from the start of treatment, resulting in fatal respiratory failure.

Trough erythrocyte dAXP concentration (an efficacy endpoint) was determined in 2 patients. In 1 patient who had not been treated with ADAGEN before enrollment in the study, trough erythrocyte dAXP concentration was >0.02 μmol/mL at screening, which declined after the start of treatment with elapegademase and was maintained at ≤0.02 μmol/mL from the fifth dose in the Dose Adjustment Period to the end of the Evaluation Phase. In 1 patient who had been treated with ADAGEN before enrollment in the study, trough erythrocyte dAXP concentration was maintained at ≤0.02 μmol/mL from screening to the end of the Evaluation Phase. Trough blood dAXP concentration was determined in 4 patients. In 2 patients who had not been treated with ADAGEN before enrollment in the study, trough blood dAXP concentration was >0.02 μmol/mL at screening in both patients, which declined after the start of treatment with elapegademase and was maintained at ≤0.02 μmol/mL from the fourth dose in the Dose Adjustment Period to the end of the Evaluation Phase in 1 patient and from the second dose in the Dose Adjustment Period to the time of death (i.e., until the 10th dose in the Dose Maintenance Period) in the other patient. In 2 patients who had been treated with ADAGEN before enrollment in the study, trough blood dAXP concentration was maintained at ≤0.02 μmol/mL from screening to the end of the Evaluation Phase. During the Continuous Administration Phase, trough erythrocyte and blood dAXP concentrations continued to be maintained at ≤0.02 μmol/mL in all evaluated patients and at all timepoints [see Section 7.1.1 "Japanese phase III study," Table 18].

Trough plasma ADA activity was determined in 2 patients. At screening, trough plasma ADA activity was below the LLOQ (9.0 μmol/h/mL) regardless of prior ADAGEN therapy, but increased after the start of treatment with elapegademase and was maintained in these patients at ≥15 μmol/h/mL from the fifth dose in the Dose Adjustment Period and the ninth dose in the Dose Maintenance Period, respectively, to the end of the Evaluation Phase. Trough serum ADA activity was determined in 4 patients. In 2 patients who had not been treated with ADAGEN before enrollment in the study, trough serum ADA activity was maintained at ≥1100 U/L after the third dose and the fifth dose, respectively, in the Dose Adjustment Period. Among 2 patients who had been treated with ADAGEN before enrollment in the study, trough serum ADA activity was maintained at ≥1100 U/L from the seventh dose in the Dose Maintenance Period to the end of the Evaluation Phase in 1 patient, while trough serum ADA activity in the second patient failed to increase to ≥1100 U/L within the Evaluation Phase, remaining around 950 to 1000 U/L in the latter part of the Dose Maintenance Period. Trough plasma ADA activity was maintained at ≥15 μmol/h/mL in both evaluated patients throughout the Continuous Administration Phase. Trough serum ADA activity was maintained at ≥1100 I/U at all timepoints and in both evaluated patients, except the 33rd dose in the patient who failed to achieve a trough serum ADA activity of ≥1100 U/mL within the Evaluation Phase [see Section "Japanese phase III study," Table 19.]

Of the 4 patients, 3 patients, except 1 patient who died, are continuing treatment with elapegademase in the Continuous Administration Period, and 2 patients and 1 patient were confirmed to be alive at Week 101 and Week 93, respectively.

In the foreign phase III study, 6 patients received ADAGEN and subsequently elapegademase, and 5 of these patients are still being treated with elapegademase, except the first enrolled patient.[9)] In 3 patients with results up to Week 21, trough erythrocyte dAXP concentrations were ≤0.02 μmol/mL through Week 21 of treatment with elapegademase, except 1 timepoint each in 2 patients. Trough plasma ADA activity began to increase in the ADAGEN Induction Phase and was maintained at 15 μmol/h/mL from Week 3 to Week 21 of treatment with elapegademase in all of these 3 patients. Also in the Maintenance Phase, trough erythrocyte dAXP concentrations were maintained at ≤0.02 μmol/mL, and trough plasma ADA activity was maintained at ≥15 μmol/h/mL, except 1 timepoint in 1 patient [see Section "7.1.2 Foreign phase III study," Tables 22 and 23.].

In the Japanese phase III study, anti-drug antibodies were detected in none of the evaluated patients. In the foreign phase III study, anti-drug antibodies were found in 2 of 5 evaluated patients, excluding the patient who discontinued the study[9)] [see Section "6.2.2 Foreign phase III study"]. However, no clear effects of anti-drug antibodies on trough erythrocyte dAXP concentration or trough plasma ADA activity were observed, and the trough erythrocyte dAXP concentration and trough plasma ADA activity showed neither a tend to increase or decrease in individual patients when they were positive for anti-drug antibodies, as compared with when they were negative.

PMDA asked the applicant to explain the clinical significance of maintaining trough erythrocyte and blood dAXP concentrations at ≤0.02 μmol/mL and maintaining trough plasma ADA activity at ≥15 μmol/h/mL and trough serum ADA activity at ≥1100 U/L.

The applicant's response:
The target thresholds for the above parameters were established as follows based on the results of clinical studies of ADAGEN and other data.

Trough erythrocyte dAXP concentration and trough blood dAXP concentration
ADAGEN was approved in the US in 1990, based on the results of a foreign clinical study in 6 patients with adenosine deaminase deficiency severe combined immunodeficiency (ADA-SCID). In the study, the dose of ADAGEN was started at 2 or 5 U/kg/week, and then increased to 15 U/kg/week or 20 U/kg/week. As a result, erythrocyte dATP concentration decreased from 0.056-0.899 μmol/mL to 0.007-0.015 μmol/mL, and immune function was improved. ADAGEN therapy was also reported to decrease erythrocyte dAXP concentration to ≤2 nmol/mL, 1 to 3 nmol/mL, or 7 ± 1 nmol/mL in patients with ADA deficiency (*Immunologic Disorders in Infants & Children. 5th ed.* 2004:480-504, *J Clin Invest.* 1993;92:596-602, etc.) These results suggested that maintaining a trough erythrocyte dAXP concentration below the target threshold of 0.02 μmol/mL is clinically significant. Blood dAXP concentrations are considered to be in equilibrium with erythrocyte dAXP concentrations. Thus, maintaining a trough blood dAXP concentration of ≤0.02 μmol/mL is also clinically significant.

Of 2 patients in whom trough erythrocyte dAXP concentrations and trough blood dAXP concentrations were measured in the Japanese phase III study, 1 patient who had not been treated with ADAGEN before enrollment in the study showed similar changes over time in trough erythrocyte dAXP concentration and trough blood dAXP concentration, reaching ≤0.02 μmol/mL almost simultaneously, while the other patient, who had been treated with ADAGEN, had trough erythrocyte dAXP concentrations and trough blood dAXP concentrations of ≤0.02 μmol/mL at all timepoints.

Trough plasma ADA activity and trough serum ADA activity
In a foreign clinical study of ADAGEN, trough plasma ADA activity increased to 15 to 35 μmol/h/mL after the start of treatment with ADAGEN. ADAGEN therapy increased plasma ADA activity to 21.2 to 62.7 μmol/h/mL in 17 patients with ADA deficiency (*J Clin Invest.* 1992;89:1643-51). In addition, ADAGEN administered to patients with ADA deficiency increased the average trough plasma ADA activity to 47.9 ± 11.7 μmol/h/mL at Weeks 7 to 25 in 1 patient, and to 65.8 ± 13.9 μmol/h/mL at Weeks 2 to 29 in another patient (*J Clin Invest.* 1993;92:596-602). Since the results of the clinical study of ADAGEN indicated that the decrease in dAXP concentration was sustained when trough plasma ADA activity was maintained at ≥15 μmol/h/mL, maintaining a trough plasma ADA activity of ≥15 μmol/h/mL was considered to be clinically significant.

The relationship between plasma ADA activity and serum ADA activity was assessed prior to initiation of the Japanese phase III study, and revealed that a plasma ADA activity of 15 μmol/h/mL was equivalent to approximately 1100 U/L of serum ADA activity. Therefore, maintaining a trough serum ADA activity of ≥1100 U/L was considered to be clinically significant.

In the Japanese phase III study, 2 patients had both trough plasma ADA activity and trough serum ADA activity data, and the changes in these 2 parameters over time were similar in both patients. Of the 2 patients who had both trough serum ADA activity and trough erythrocyte dAXP concentration data, 1 patient who had not been treated with ADAGEN achieved a trough erythrocyte dAXP concentration of ≤0.02 μmol/mL, which coincided with the time when a trough serum ADA activity of ≥1100 U/L was attained. In another patient who had been treated with ADAGEN, trough erythrocyte dAXP concentrations were <0.002 μmol/mL from the start of the study to the end of the Evaluation Phase, maintaining the targeted threshold of ≤0.02 μmol/mL. However, the trough serum ADA activity did not reach ≥1100 U/L within the Evaluation Phase, and remained around 950 to 1000 U/L during the latter part of the Dose Maintenance Period. As the patient had severe clinical symptoms from the start of the study, the dose of elapegademase was increased in the middle of the Dose Maintenance Period, and the trough serum ADA activity increased gradually with the increase in the dose of elapegademase.

The applicant's explanation about the effects of ADAGEN therapy, which has been approved for the treatment of ADA deficiency in the US, on the prognosis of patients with ADA deficiency:
ADA accompanied by severe immunodeficiency has an extremely poor prognosis, and patients often die from severe infections by approximately 1 year of age, if hematopoietic stem cell transplantation (HSCT) is not available (*The Metabolic and Molecular Bases of Inherited Disease, 8th ed.* 2001:2585-625, *Congenital Malformation Syndrome Dictionary.* 2001:150-1). One report about 185 patients with ADA deficiency who were treated with ADAGEN in 20 countries including the US indicated that 70% of these patients began ADAGEN therapy at <1 year of age (50% began at <6 months of age) and half of the remaining patients started treatment at 1 to 3 years of age (*Blood.* 2009; 114:3524-32). Figure 1 shows the survival curve for the patients. Of these 185 patients, 18% died while in therapy and 28% discontinued ADAGEN therapy to undergo HSCT or gene therapy. Of these deaths, 40% occurred within the first month and approximately half occurred within the first 6 months. The cause of death in these cases was considered to be infections. The probability of surviving >20 years in patients with ADA deficiency treated with ADAGEN is estimated to be 78%, and 90% of patients who are alive for 6 months after starting ADAGEN therapy will survive for the next 12 years. The causes of death occurring beyond 6 months of ADAGEN therapy include refractory hemolytic anaemia at 1 to 3 years, and chronic pulmonary insufficiency and lymphoproliferative disorders at 5 to 15 years. Approximately two-thirds of patients who are receiving ADAGEN therapy have been treated for ≥5 years, including 20% who have been treated for 15 to 22 years.

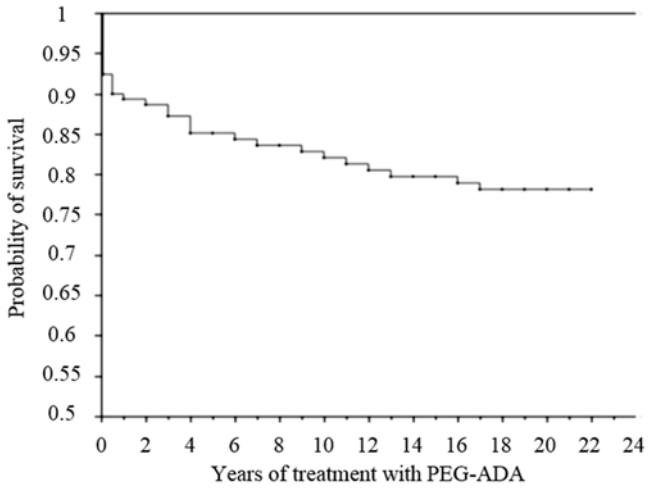



Figure 1. Survival curve in patients with ADA deficiency treated with ADAGEN (*Blood.* 2009;114:3524-32)

As described above, long-term treatment with ADAGEN, which is an enzyme replacement therapy for ADA deficiency that is similar to elapegademase, has been shown to contribute to survival of ≥20 years in patients with ADA deficiency. In addition, the results of the Japanese and foreign phase III studies using the target thresholds of various parameters such as trough erythrocyte dAXP concentration, established based on the results of clinical studies of ADAGEN and other available data have demonstrated the efficacy of elapegademase. Based on these findings, elapegademase is expected to be effective in patients with ADA deficiency.

PMDA's view:

The target thresholds of trough erythrocyte and blood dAXP concentrations and trough plasma and serum ADA activity, established by the applicant to evaluate the efficacy of elapegademase in the Japanese and foreign phase III studies are not sufficiently justified by evidence. However, these thresholds were established based on the results of clinical studies of ADAGEN and a certain amount of survival data have been collected from patients treated with ADAGEN. Therefore, the target thresholds of these parameters, as established by the applicant, may be used as reference to evaluate the efficacy of elapegademase.

In the Japanese phase III study in patients with ADA deficiency, 4 patients treated with elapegademase achieved or maintained both a trough erythrocyte dAXP concentration and a trough blood dAXP concentration of ≤0.02 μmol/mL during the Evaluation Phase. These 4 patients also achieved the target thresholds for trough plasma ADA activity and trough serum ADA activity (≥15 μmol/h/mL and ≥1100 U/L, respectively) during the Evaluation Phase, except 1 patient. The patient whose trough serum ADA activity did not meet the target threshold had been treated with ADAGEN before enrollment in the study. Even in this patient, both trough plasma ADA activity and trough serum ADA activity increased, and the trough erythrocyte dAXP concentration remained at or below the threshold after the start of treatment with elapegademase. In the 3 patients who successfully completed the Evaluation Phase, the responses to elapegademase have continued to be sustained in the Continuous Administration Phase. One infant

patient died from respiratory failure and was withdrawn from the Evaluation Phase. This death was considered to be attributable to pulmonary tissue damage such as interstitial pneumonia that persisted from the start of treatment, and did not deny the efficacy of elapegademase. In the foreign phase III study, erythrocyte dAXP concentrations were maintained at ≤0.02 μmol/mL, and trough plasma ADA activity increased from the ADAGEN Induction Phase and was maintained at ≥30 μmol/h/mL in 5 patients, except 1 patient who discontinued the study.[9)] In 3 patients whose data have been collected up to Week 21, similar responses to elapegademase continue to be sustained in the Maintenance Phase. The results of both studies demonstrated that elapegademase tended to increase lymphocyte counts, suggesting an improvement of the severe immunodeficiency associated with ADA deficiency.

Based on the above results, PMDA has concluded that elapegademase is expected to be effective for the treatment of metabolic abnormalities in patients with ADA deficiency.

In the Japanese phase III study, anti-drug antibodies were detected in none of the patients. In the foreign phase III study, anti-drug antibodies were detected in 2 patients; however, the development of the antibodies was sporadic and accompanied by no coincident effects on the efficacy of elapegademase. Thus, there have been no concerns that anti-drug antibodies may affect the efficacy of elapegademase. However, the effects of anti-drug antibodies on the efficacy of elapegademase should continue to be investigated, based on updated information on the development of anti-drug antibodies from the ongoing Japanese and foreign phase III studies, and other findings.

### 7.R.2 Safety

The applicant's explanation:

Table 24 shows the incidences of adverse events in patients with ADA deficiency who received elapegademase at a dose of 0.1 to 0.292 mg/kg once weekly[11)] in the Japanese and foreign phase III studies (during the Evaluation Phase and at the time of data cutoff in April 2017, respectively). A total of 63 adverse events were reported by 9 of 10 patients. Of these adverse events, 2 events of injection site pain in 1 patient and 7 events of injection site discomfort in 1 patient (i.e., 9 events in 2 patients) were classified as adverse drug reactions.

[11)] One patient in the Japanese phase III study had a poor systemic condition from the start of the study and received elapegademase at a dose of 0.2 mg/kg twice weekly. However, the patient died and discontinued the study on Day 107 after the last dose on Day 105.

Table 24. Incidences of adverse events in the Japanese and foreign phase III studies

(Safety analysis set and As-treated population, respectively)

| Events | | Japanese phase III study (N = 4) | Foreign phase III study (N = 6) | Total (N = 10) |
|---|---|---|---|---|
| All adverse events | | 100 (4) | 83.3 (5) | 90.0 (9) |
| All adverse drug reactions | | 0 (0) | 33.3 (2) | 20.0 (2) |
| Adverse events leading to death | | 25.0 (1) | 0 (0) | 10.0 (1) |
| Adverse drug reactions leading to death | | 0 (0) | 0 (0) | 0 (0) |
| Serious adverse events | | 50.0 (2) | 50.0 (3) | 50.0 (5) |
| Serious adverse drug reactions | | 0 (0) | 16.7 (1) | 10.0 (1) |
| Adverse events leading to treatment discontinuation | | 0 (0) | 16.7 (1) | 10.0 (1) |
| Adverse drug reactions leading to treatment discontinuation | | 0 (0) | 16.7 (1) | 10.0 (1) |
| Severity | Mild | 0 (0) | 16.7 (1) | 10.0 (1) |
| | Moderate | 100 (4) | 33.3 (2) | 60.0 (6) |
| | Severe | 0 (0) | 33.3 (2) | 20.0 (2) |

Incidence % (n)

One patient died from respiratory failure. The patient was diagnosed as ADA deficiency accompanied by severe immunodeficiency syndromes at [redacted] months of age and suffered from tracheal haemorrhage, pulmonary haemorrhage, interstitial lung disease, and other symptoms after being enrolled in the study. The patient experienced pulmonary haemorrhage, most likely due to cytomegalovirus infection at [redacted] months of age, and marked tachypnoea and hypoxaemia during treatment with elapegademase, leading to respiratory failure. Although a high concentration of oxygen and steroid pulse therapy were provided under artificial respiration, the patient died due to the progression of respiratory failure. The respiratory failure was considered attributable to pulmonary tissue damage due to a variety of factors including a prior history of bacterial pneumonia and pneumothorax, and cytomegalovirus infection, pulmonary haemorrhage, and administration of a high concentration of oxygen. Thus, a causal relationship to the study drug was denied. Serious adverse events were reported by 5 of 10 patients including neutropenia/upper respiratory tract infection, pulmonary haemorrhage/respiratory failure, injection site pain, migraine, and tooth extraction/tooth abscess in 1 patient each. Of these events, injection site pain was classified as an adverse drug reaction. The patient who experienced injection site pain received 2 doses of the earlier drug product containing [redacted], and discontinued treatment due to the event. An additional non-clinical study in mice showed that administration of a formulation containing [redacted], as compared with a formulation containing no [redacted], induced pain reactions and swelling, suggesting that the injection site pain was attributable to the [redacted] contained in the earlier drug product. Based on this result, the formulation of the drug product was changed to remove [redacted] (the proposed drug product). In the foreign phase III study, none of the patients receiving the proposed drug product reported injection site pain.

In the Japanese phase III study, 3 patients are continuing to receive elapegademase, as of March 2018. The doses (number of doses) of elapegademase administered in these 3 patients are 0.167 mg/kg (80 doses in the Continuous Administration Phase), 0.267 and 0.3 mg/kg (first to 16th doses at 0.267 mg/kg, and 17th to 80th doses at 0.3 mg/kg in the Continuous Administration Phase), and 0.233 mg/kg (72 doses in the Continuous Administration Phase). Adverse events reported during the Continuous

Administration Phase are shown in Table 20. Serious adverse events were reported by 2 patients including neutropenia/dehydration and respiratory syncytial virus infection/aspergillus infection in 1 patient each. There were no adverse drug reactions. In the foreign phase III study, 5 patients are continuing to receive elapegademase, as of November 2017. The doses (total duration of treatment) of elapegademase administered in these 5 patients are 0.188 mg/kg (146.1 weeks), 0.224 mg/kg (137.1 weeks), 0.2 mg/kg (141.1 weeks), 0.209 mg/kg (46.1 weeks), and 0.285 mg/kg (38.9 weeks). Adverse events reported from the data cutoff in April 2017 to November 2017 are abdominal pain upper, arthralgia, convulsion, ear lobe infection, fungal skin infection, gait disturbance, haemophilus infection, haemoptysis, nausea, nodule, oral candidiasis, stoma site infection, and upper respiratory tract infection in 1 patient each. There have been no adverse drug reactions or serious adverse events.

In the Japanese phase III study, no anti-drug antibodies were found in any of the patients. In the foreign phase III study, 2 of 5 patients, except 1 patient who discontinued the study,[9)] were positive for anti-drug antibodies at any timepoint [see Section "6.2.2 Foreign phase III study"]. However, the development of anti-drug antibodies while on treatment with elapegademase was transient, and had no effects on safety.

In a clinical study of ADAGEN conducted in the US, adverse drug reactions were reported by 3 of 6 patients with ADA-SCID receiving ADAGEN, including injection site pain in 2 patients and headache in 1 patient. Overseas post-marketing pharmaceutical safety information for ADAGEN includes the following adverse drug reactions: haemolytic anaemia, autoimmune haemolytic anaemia, thrombocythaemia, thrombocytopenia, autoimmune thrombocytopenia, injection site erythema, urticaria, and lymphoma. The US prescribing information for elapegademase states that these adverse drug reactions have been reported voluntarily from a very limited number of patients and that it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Consequently, the results of the Japanese and foreign phase III studies and other data have identified no events that require particular attention for safety reasons, in association with treatment with elapegademase.

PMDA's view:
Although the number of patients evaluated in the Japanese and foreign phase III study was small, the incidences of adverse events reported in the studies showed no consistent tendency. A causal relationship to elapegademase was ruled out for most of the events. The only serious adverse drug reaction was injection site pain, which occurred in 1 patient who received the earlier drug product of elapegademase. Moreover, there have been no immunogenic results arousing safety concerns. Therefore, PMDA has concluded that no events requiring particular attention have been identified in association with treatment with elapegademase, in patients with ADA deficiency. However, information on the long-term safety of elapegademase should continue to be collected after the market launch, because the

number of patients and the duration of treatment evaluated in the Japanese and foreign phase III studies were limited.

### 7.R.3 Clinical positioning

The applicant's explanation:

The first-line treatment of ADA deficiency is human leukocyte antigen (HLA)-matched HSCT, which is often a curative treatment. However, the estimated probability of finding an HLA-matched donor is approximately 30% (*Blood.* 2009;114:3524-32), and the success rate of HLA-mismatched HSCT is approximately from 50% to 85% (*Clin Immunol.* 2007;123:139-47, *N Engl J Med.* 2009;360:518-21). In Japan, no gene therapy product in which autologous stem cells are transduced with a retrovirus containing the human ADA gene[12] or an ADA enzyme replacement therapy (i.e., ADAGEN) has yet been approved. The latest clinical practice guidelines in the US and EU state that all patients should initiate enzyme replacement therapy immediately after being diagnosed with ADA deficiency, followed by either of 2 first-line options, HSCT from an HLA-matched related donor or gene therapy, and that if neither of these first-line options is available, enzyme replacement therapy should be continued (*J Allergy Clin Immunol*. 2018;doi:10.1016/j.jaci.2018.08.024.). In view of the above statement of the guidelines in the US and EU, combined with the situation in Japan, in which an approved gene therapy is currently unavailable, the clinical positioning of elapegademase should be the first-line treatment for all patients with ADA deficiency including those who are searching for a donor for HSCT or waiting for HSCT. Elapegademase therapy, unlike HSCT, will be available as an option for all patients. Elapegademase is expected to offer a novel treatment to patients with ADA deficiency, as an ADA enzyme replacement therapy, as with ADAGEN, to improve metabolic abnormalities by compensating for the depletion of ADA activity, thereby reducing dAXP.

PMDA's view:

Elapegademase is expected to become an ADA enzyme replacement therapy that improves metabolic abnormalities and various symptoms of severe immunodeficiency in patients with ADA deficiency. Although the number of patients with ADA deficiency evaluated in the Japanese and foreign phase III studies was limited, the assessment of trough erythrocyte and blood dAXP concentrations, trough serum ADA activity, lymphocyte counts, and other parameters demonstrated the promising efficacy of elapegademase in the treatment of ADA deficiency [see Section "7.R.1 Efficacy"]. Although 1 patient died in these studies, a causal relationship to elapegademase was denied for this death. No serious adverse events were reported by the patients, except 1 patient who received the earlier drug product of elapegademase. Thus, no particular safety concerns have been identified in association with elapegademase therapy [see Section "7.R.2 Safety"]. Considering that no approved pharmacological treatments for ADA deficiency are currently available in Japan, elapegademase, a genetical recombinant, can be positioned as a new enzyme replacement therapy for ADA deficiency. Therefore, offering elapegademase to clinical practice is of significance. The appropriateness of the above PMDA's view will be finalized after taking into account comments from the Expert Discussion.

12) Strimvelis, a pharmaceutical preparation approved in the EU

### 7.R.4 Indication

PMDA's view:

The results of the Japanese and foreign phase III studies showed that elapegademase had promising efficacy and acceptable safety in patients with ADA deficiency [see Sections "7.R.1 Efficacy" and "7.R.2 Safety"]. ADA deficiency is positioned as a primary immunodeficiency syndrome manifested by severe combined immunodeficiency in the "Study on the Establishment of Diagnostic Criteria and Severity Classification, and Clinical Practice Guidelines of Primary Immunodeficiency Syndrome" (Health and Labour Sciences Research Grants for Refractory Disease, etc. Policy and Research Project [Refractory Disease Policy and Research Project]). Therefore, PMDA has concluded that the indication of elapegademase should be "ADA deficiency," in view of the patients enrolled in the Japanese and foreign phase III studies.

### 7.R.5 Dosage and administration

The applicant's explanation:

For the reasons described in Sections 7.R.5.1 to 7.R.5.3, the dosage and administration of elapegademase should be "The usual dosage of Elapegademase (Genetical Recombination) is 0.2 mg/kg body weight administered as an intramuscular injection once weekly. The dose may be adjusted according to the patient's condition and laboratory test results" to allow the appropriate individualization of ADA activity. In addition, the maximum dose and the increment or decrement and procedure for dose adjustment, etc. should be stated in the "Precautions concerning Dosage and Administration" section.

#### 7.R.5.1 Necessity of dose titration in the early period of treatment

The applicant's explanation:

The US prescribing information for ADAGEN specifies the following dose titration, "The recommended dosing schedule is 10 U/kg for the first dose, 15 U/kg for the second dose, and 20 U/kg for the third dose." In the Japanese phase III study, the dose of elapegademase for patients who had not been treated with ADAGEN before enrollment in the study was planned to start at 0.1 mg/kg once weekly considering patient safety, followed by up-titration. However, one of the patients enrolled in the study required a rapid increase of ADA activity due to a poor systemic condition that was already present at the start of the study and the investigator decided to start elapegademase therapy at 0.2 mg/kg twice weekly, without subsequent up-titration, in view of clinical experience with the use of ADAGEN in the US. The patient died on Day 107, but reported no adverse drug reactions while on treatment with elapegademase. The maintenance dose of ADAGEN after up-titration is 30 U/kg/week (30 U ADAGEN is equivalent to 0.2 mg elapegademase in enzyme activity). However, ADAGEN has been administered to some patients with ADA deficiency at a dose of 30 U/kg twice weekly from the beginning of treatment, arousing no safety concerns regarding treatment with a high dose of ADAGEN (*J Clin Invest.* 1993;92:596-602, etc.) In patients with ADA deficiency, ADA activity has to be increased quickly at the beginning of treatment, with the aim of an early improvement of metabolic abnormalities. Therefore, up-titration from a low dose is unnecessary.

### 7.R.5.2. Usual dose of elapegademase

The applicant's explanation:

The recommended maintenance dose of ADAGEN is 30 U/kg/week, and 30 U of ADAGEN is equivalent to 0.2 mg elapegademase in enzyme activity. When elapegademase was administered to patients who were converted from ADAGEN to an equivalent dose of elapegademase (0.188 - 0.224 mg/kg/week in 3 patients who completed the Evaluation Phase) in the foreign phase III study, trough plasma ADA activity was approximately 30 μmol/h/mL from Weeks 3 through 21, which was roughly 2-fold higher than that observed at the last dose of ADAGEN (approximately 15 μmol/h/mL). In addition, the dose-normalized $AUC_{\tau}$[13)] at the steady state following repeated doses of elapegademase (mean ± SD, N = 4) was 5810 ± 1350 h·μmol/h/mL, which was roughly 2-fold higher than that observed following repeated doses of ADAGEN[13)] (2970 ± 399 h·μmol/h/mL, N = 4). These results suggested that elapegademase had a more stable PEG linker than ADAGEN, and thereby produced a higher exposure. Based on the facts that the therapeutic effects were likely to increase with an increase in trough plasma ADA activity and that no particular safety concerns had been identified in the study, the US prescribing information for elapegademase recommends that the usual dose of elapegademase should be 0.2 mg/kg/week, followed by dose adjustment to maintain trough plasma ADA activity at ≥30 μmol/h/mL. On the other hand, the prescribing information for ADAGEN recommends that the dose should be adjusted to maintain trough plasma ADA activity in the range from 15 to 35 μmol/h/mL.

In the Dose Maintenance Period of the Japanese phase III study, elapegademase was to be administered at a dose in the range from 0.067 to 0.2 mg/kg, based on the results from the Dose Adjustment Period. The doses of elapegademase administered to 3 patients who successfully completed the Evaluation Phase were 0.167, 0.2, and 0.2 mg/kg/week at the start of the Dose Maintenance Period, and 0.167, 0.267, and 0.233 mg/kg/week at the end of the Evaluation Phase. Trough plasma ADA activity increased in both of the 2 patients with trough plasma ADA activity data, and no particular safety concerns were identified.

Based on the above, the recommended usual dose of elapegademase should be 0.2 mg/kg administered as an intramuscular injection once weekly.

### 7.R.5.3 Dose adjustment and maximum dose of elapegademase

The applicant's explanation:

When elapegademase is administered to patients with ADA deficiency, the dose should be individualized based on plasma ADA activity, erythrocyte dAXP concentration, immune function, and other findings. In the Japanese phase III study, the dose of elapegademase was pre-defined to be adjusted by 0.033 mg/kg every 4 weeks according to the dose adjustment criteria established using these parameters [for details, see Section "7.1.1 Japanese phase III study"]. The doses administered during the Continuous Administration Phase in 3 patients who successfully completed the Evaluation Phase

13) Normalized to a 1500 U/week dose of ADAGEN or a dose of 10 mg/week of elapegademase

were 0.167, 0.233, and 0.3 mg/kg/week, with no adverse drug reactions reported. Also in the foreign phase III study, the dose of elapegademase was adjusted based on trough erythrocyte dAXP concentration, trough plasma ADA activity, and other findings. One patient, in whom the efficacy of elapegademase was maintained, received elapegademase at a dose of 0.285 mg/kg/week, with no particular safety concerns. Based on these results, the dose of elapegademase should be adjusted by 0.033 mg/kg every 4 weeks, and allowed to be increased up to 0.3 mg/kg once weekly in cases where the response is insufficient.

The administration of ADAGEN is recommended at a starting dose of 30 U/kg twice weekly in patients who have a low plasma ADA activity and severe clinical symptoms at the beginning of treatment. In the Japanese phase III study, elapegademase was administered to 1 patient with severe clinical symptoms at enrollment at a dose of 0.2 mg/kg twice weekly. Elapegademase therapy led to a decrease in trough blood dAXP concentration and an increase in trough serum ADA activity, and caused no adverse drug reactions. Based on these considerations, the dosage regimen of elapegademase should be determined to allow administration of a dose of up to 0.2 mg/kg twice weekly to increase ADA activity more rapidly in patients with severe immunodeficiency.

In the Japanese phase III study, dose adjustment was considered if the trough erythrocyte dAXP concentration was >0.02 μmol/mL or the trough serum ADA activity was <1100 U/L, according to the US prescribing information for ADAGEN and the dose adjustment criteria used in the foreign phase III study of elapegademase. The dose of elapegademase could also be adjusted based on the investigator's assessment of the patient's clinical symptoms. In the foreign phase III study of elapegademase, a trough plasma ADA activity level of <15 μmol/h/mL, rather than a trough serum ADA activity level of <1100 U/L was used as a criterion for dose adjustment. However, these two criteria were demonstrated to be equivalent. ADA enzyme replacement therapy for patients with ADA deficiency is expected to increase ADA activity, thereby reducing the dAXP concentration, and in fact, the results of the Japanese and foreign phase III study confirmed that erythrocyte dAXP concentration decreased with the increase in ADA activity. Considering that measurement of serum ADA activity is covered by insurance in Japan, the package insert for elapegademase in Japan will advise that the dose of elapegademase should be adjusted based on trough serum ADA activity, clinical symptoms, and laboratory test results.

PMDA’s view:
The applicant has explained about dose adjustment as follows:
(1) In the Japanese phase III study, elapegademase therapy started at a dose of 0.2 mg/kg in 1 patient with severe ADA deficiency, although the dose of elapegademase was to be up-titrated in the early period of treatment; (2) ADAGEN has been administered to some patients at a starting dose of 30 U/kg; and, (3) ADA activity has to be increased rapidly at the start of treatment in patients with ADA deficiency. The applicant's explanation is understandable and PMDA has concluded that the usual dosage of elapegademase should be 0.2 mg/kg once weekly, without setting dose-titration at the beginning of treatment. Elapegademase was also effective in a patient receiving a dose of 0.3 mg/kg

once weekly in the Japanese phase III study, with no particular safety concerns identified. Therefore, PMDA has concluded that the maximum dose may be set at 0.3 mg/kg and that the maximum dose should be stated in the "Dosage and Administration" section.

Furthermore, the package insert should also clearly state the increment or decrement for dose adjustment, the decision of dose adjustment based on trough serum ADA activity and other findings, and the selection of a dose of 0.2 mg/kg twice weekly according to the patient's clinical symptoms, etc., in view of the design and results of the Japanese phase III study and other data. Clinical experience with the use of elapegademase including administration at a starting dose of 0.2 mg/kg, has been limited, safety information in the early period of treatment and when administered at the maximum dose should be collected after the market launch. The appropriateness of the above PMDA's view will be finalized after taking into account comments from the Expert Discussion.

### 7.R.6 Post-marketing investigations

The applicant's explanation:

In the Japanese phase III study, no adverse drug reactions have been reported, and as of March 2018, elapegademase has been administered for up to 2 years, resulting in no safety problems. In the foreign phase III study, the reported adverse drug reactions were limited to injection site pain and injection site discomfort, which occurred in a patient treated with the earlier drug product, and as of November 2017, elapegademase has been administered for up to 2.8 years, resulting in no safety problems. However, the duration of treatment with elapegademase in the clinical studies was short compared with the expected duration of elapegademase therapy in clinical practice. In addition, the number of patients evaluated in the clinical studies was small. Therefore, the applicant will include the long-term safety and efficacy of elapegademase as safety and efficacy specifications in the risk management plan and plans to conduct a specified use-results survey after the approval of elapegademase. The enrollment period of the survey will be 6 years and the observation period will be 3 to 9 years (the observation period is 9 years from the market launch), covering all patients treated with elapegademase.

PMDA's view:

The information on the use of elapegademase collected from the Japanese and foreign clinical studies was limited. Therefore, PMDA has concluded that a specified use-results survey covering all patients treated with elapegademase should be conducted to collect information on the long-term safety and efficacy of elapegademase, as proposed by the applicant. The appropriateness of the above PMDA's view will be finalized after taking into account comments from the Expert Discussion.

## 8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

### 8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The inspections are ongoing, and the results and PMDA's conclusion will be reported in the Review Report (2).

### 8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The inspections are ongoing, and the results and PMDA's conclusion will be reported in the Review Report (2).

## 9. Overall Evaluation during Preparation of the Review Report (1)

On the bases of the data submitted, PMDA has concluded that elapegademase has efficacy in the treatment of ADA deficiency, and that elapegademase has acceptable safety in view of its benefits. Elapegademase is clinically meaningful because it offers a new treatment option, namely, enzyme replacement therapy, for patients with ADA deficiency.

PMDA has concluded that elapegademase may be approved if elapegademase is not considered to have any particular problems based on comments from the Expert Discussion.

**Review Report (2)**

February 12, 2019

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | Revcovi 2.4 mg for Intramuscular Injection |
| **Non-proprietary Name** | Elapegademase (Genetical Recombination) |
| **Applicant** | Teijin Pharma Limited |
| **Date of Application** | June 29, 2018 |

**List of Abbreviations**

See Appendix.

## 1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

### 1.1 Efficacy

PMDA's view:

(1) In the Japanese and foreign phase III studies, trough erythrocyte and blood deoxyadenosine nucleotide (dAXP) concentrations, and trough plasma and serum adenosine deaminase (ADA) activity were assessed using the target thresholds established based on the results from patients treated with ADAGEN in clinical studies, and most of the observed values of trough erythrocyte and blood dAXP concentrations and trough plasma and serum ADA activity met the target thresholds; (2) A certain level of improvement of survival has been demonstrated in patients with ADA deficiency treated with ADAGEN; and, (3) Elapegademase therapy tended to increase lymphocyte counts in both the phase III studies, suggesting that elapegademase may improve severe immunodeficiency accompanying ADA deficiency. Based on the above results, PMDA has concluded that the efficacy of elapegademase is expected in the treatment of metabolic abnormalities in patients with ADA deficiency.

At the Expert Discussion, the expert advisors supported the above PMDA's conclusion.

### 1.2 Safety

PMDA's view:

Although the number of patients evaluated in the Japanese and foreign phase III study was small, the incidences of adverse events reported in the studies had no consistent tendency. A causal relationship to elapegademase

was denied for most of the events. The only serious adverse event for which a causal relationship to elapegademase could not be ruled out was injection site pain occurring in 1 patient receiving the earlier drug product of elapegademase. In addition, there have been no immunogenic results that arouse safety concerns at present. Therefore, PMDA has concluded that no events have been identified to require particular attention in association with treatment with elapegademase in patients with ADA deficiency. However, information on the long-term safety of elapegademase should continue to be collected after the market launch, because the number of patients and the duration of treatment evaluated in the clinical studies were limited.

At the Expert Discussion, the expert advisors supported the above PMDA's conclusion.

### 1.3 Clinical positioning of elapegademase

PMDA's view:

In the Japanese and foreign phase III studies, elapegademase was shown to have promising efficacy and acceptable safety in patients with ADA deficiency, and it is therefore expected to become an ADA enzyme replacement therapy that improves metabolic abnormalities and various symptoms caused by severe immunodeficiency in such patients. In addition, considering that no approved pharmacological treatments for ADA deficiency are currently available in Japan, elapegademase, a genetical recombinant, can be positioned as a new ADA enzyme replacement therapy for ADA deficiency. Therefore, the PMDA has concluded that offering elapegademase to clinical practice is of significance.

At the Expert Discussion, the expert advisors supported the above PMDA's conclusion.

### 1.4 Indication

ADA deficiency is positioned as a primary immunodeficiency syndrome manifested by adenosine deaminase severe combined immunodeficiency (SCID) in the "Study on the Establishment of Guidelines for the Diagnostic Criteria and Severity Classification, and Clinical Practice of Primary Immunodeficiency Syndrome" (Health and Labour Sciences Research Grants for Refractory Disease, etc. Policy and Research Project [Refractory Disease Policy and Research Project]). In view of this situation of ADA deficiency, and based on the patients enrolled in the Japanese and foreign phase III studies, PMDA has concluded that the indication of elapegademase should be "ADA deficiency."

At the Expert Discussion, the expert advisors supported the above PMDA's conclusion.

### 1.5 Dosage and Administration

PMDA's view:

The applicant has explained about dose adjustment as follows:

(1) In the Japanese phase III study, elapegademase therapy was started at a dose of 0.2 mg/kg in a patient with severe ADA deficiency, although the dose of elapegademase was to be up-titrated in the early period of treatment; (2) ADAGEN, a drug of the same class as elapegademase, has been administered to some patients at a dose of 30 U/kg that is equivalent to 0.2 mg/kg elapegademase in enzyme activity (*J Clin Invest*.

1993;92:596-602, etc.); and (3) ADA activity has to be increased rapidly in the early period of treatment in patients with ADA deficiency. The above applicant's explanation is understandable, and PMDA has concluded that the usual dosage of elapegademase may be determined as 0.2 mg/kg once weekly, without setting dose-titration in the early period of treatment. In addition, the efficacy of elapegademase was demonstrated in a patient receiving a dose of 0.3 mg/kg once weekly in the Japanese phase III study, and no particular safety concerns were identified. Therefore, PMDA has also concluded that the maximum dose may be set at 0.3 mg/kg and that it is appropriate to state this maximum dose in the "Dosage and Administration" section.

In the Japanese phase III study, the dose of elapegademase was adjusted by 0.033 mg/kg every 4 weeks, based on trough serum ADA activity and other findings. PMDA has concluded that this detailed procedure for dosage regimen adjustment should be stated in the "Precautions Concerning Dosage and Administration" section. In the same study, elapegademase was administered to a patient with severe ADA deficiency at a dose of 0.2 mg/kg twice weekly and showed a certain level of efficacy, causing no particular safety concerns. Based on this fact, PMDA has concluded that elapegademase may be administered to patients with severe ADA deficiency at a dose of 0.2 mg/kg twice weekly.

At the Expert Discussion, the expert advisors supported the above PMDA's conclusion.

Based on the discussion at the Expert Discussion, and since a dosage regimen of 0.2 mg/kg twice weekly for patients with severe ADA deficiency exceeds the usual dosage, PMDA has concluded that the dosage regimen for patients with severe disease should be stated in the "Dosage and Administration" section. Accordingly, PMDA instructed the applicant to modify the proposed "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections as shown below, and confirmed that the applicant had handled this matter appropriately.

**Dosage and Administration**

The usual dosage of Elapegademase (Genetical Recombination) is 0.2 mg/kg administered as an intramuscular injection once weekly. The dose may be adjusted according to the patient's condition; however, a dose should not exceed 0.3 mg/kg. If adenosine deaminase activity needs to be increased rapidly, Elapegademase (Genetical Recombination) may be administered as an intramuscular dose of 0.2 mg/kg twice weekly.

**Precautions Concerning Dosage and Administration**

(1) During treatment with elapegademase, serum ADA activity, results of laboratory tests for immune function parameters such as lymphocyte counts, and clinical symptoms should be monitored periodically to adjust the dose depending on the patient's condition. Dose adjustment should be considered every 4 weeks, in principle, and should be adjusted within the range of ≤0.033 mg/kg (see "Clinical Studies" section).

(2) Elapegademase should usually be administered once weekly. Only when administered to patients who have severe immunodeficiency and need to increase ADA activity rapidly, elapegademase may be

administered at a dose of up to 0.2 mg/kg twice weekly (i.e., up to 0.4 mg/kg weekly, divided into 2 doses, every 3 to 4 days) (see the "Clinical Studies" section).

### 1.6 Risk management plan (draft)

In view of the discussions presented in Section "7.R.6 Post-marketing investigations" in the Review Report (1) and comments from the expert advisers at the Expert Discussion, PMDA has concluded that the safety and efficacy specifications listed in Table 25 should be included in the present draft risk management plan for elapegademase, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities summarized in Tables 26 and 27.

Table 25. Safety and efficacy specifications in the risk management plan (draft)

| Safety specification | | |
|---|---|---|
| Important identified risks | Important potential risks | Important missing information |
| None | None | • Safety of long-term treatment |
| Efficacy specification | | |
| • Efficacy of long-term treatment | | |

Table 26. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

| Additional pharmacovigilance activities | Additional risk minimization activities |
|---|---|
| • Post-marketing clinical study[a)]<br>• Specified use-results survey (all-case surveillance) | • None |

a) Study STM-279-301 (ongoing) will be reclassified as a post-marketing clinical study after approval, and continued until elapegademase is delivered to study sites.

Table 27. Outline of specified use-results survey (draft)

| | |
|---|---|
| Objective | To evaluate the safety and efficacy of elapegademase in clinical practice |
| Survey method | Central registration system |
| Population | Patients with ADA deficiency |
| Observation period | From the start of treatment with elapegademase to the end of the survey (≥3 years [≤9 years]) |
| Planned sample size | All patients treated with elapegademase |
| Main survey items | Patient characteristics, exposure to elapegademase, adverse events, serum ADA activity, immune function (total lymphocyte count, lymphocyte subset counts, immunoglobulins), erythrocyte dAXP concentration, blood dAXP concentration, and anti-drug antibodies |

## 2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

### 2.1 PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

### 2.2 PMDA's conclusion on the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

## 3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval conditions. The product is designated as an orphan drug. Therefore, the re-examination period is 10 years. The product is not classified as a biological product or a specified biological product. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

**Indication**

Adenosine deaminase deficiency

**Dosage and Administration**

The usual dosage of Elapegademase (Genetical Recombination) is 0.2 mg/kg administered as an intramuscular injection once weekly. The dose may be adjusted according to the patient's condition; however, a dose should not exceed 0.3 mg/kg. If adenosine deaminase activity needs to be increased rapidly, Elapegademase (Genetical Recombination) may be administered as an intramuscular dose of 0.2 mg/kg twice weekly.

(Underline denotes changes.)

**Approval Conditions**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients studied in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a specified number of patients will be collected, in order to obtain information on the characteristics of patients treated with the product, to collect data on the safety and efficacy of the product as soon as possible, and to take necessary measures to ensure proper use of the product.

**Appendix**

**List of Abbreviations**

| | |
|---|---|
| ADA | Adenosine deaminase |
| ADAGEN | A pharmaceutical preparation that has been approved for the treatment of ADA deficiency in the US, containing a modified protein in which ADA derived from bovine intestines is conjugated to PEG |
| adverse drug reaction | An adverse event for which a causal relationship to study drug could not be ruled out |
| [redacted] | [redacted] |
| AUC | Area under the plasma concentration-time curve |
| BALF | Bronchoalveolar lavage fluid |
| CD | Cluster of differentiation |
| $C_{max}$ | Maximum plasma concentration |
| dAXP | Deoxyadenosine nucleotides (a collective term for deoxyadenosine triphosphate [dATP], deoxyadenosine diphosphate [dADP], and deoxyadenosine monophosphate [dAMP]) |
| DNA | Deoxyribonucleic acid |
| [redacted] | [redacted] |
| earlier drug product | A drug product of elapegademase, manufactured from the drug substance containing [redacted] |
| elapegademase | Elapegademase (Genetical Recombination) |
| ELISA | Enzyme-linked immunosorbent assay |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| HCP | Host cell protein |
| HLA | Human leukocyte antigen |
| HPLC | High performance liquid chromatography |
| IgM | Immunoglobulin M |
| [redacted] | [redacted] |
| MedDRA/J | Medical Dictionary for Regulatory Activities, Japanese version |
| MF | Master file |
| [redacted] | [redacted] |
| PEG | Polyethylene glycol |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| rADA | Recombinant bovine adenosine deaminase analogue |
| RP-HPLC | Reversed phase high performance liquid chromatography |
| SC-PEG | Succinimidyl carbamate linker-polyethylene glycol |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| TCRβ | T cell receptor beta chain |
| The product | Revcovi 2.4 mg for Intramuscular Injection |
| U | Unit of enzyme activity, Enzyme activity that generates 1 μmol of inosine per minute, 1 U = 60 μmol/h/mL. |