Clinical Study Protocol

NCT Number: NCT03625882

Title: Drug Use-results Survey for VPRIV® for I.V. Infusion 400 Units

Study Number: SHP-GCB-401

Document Version and Date: Amendment 9 / 15-Sep-2023

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

Reexamination

VPRIV

Protocol of use-result survey

Takeda Pharmacutical Company Limited

Amendment 9

Document Date: 15 September 2023

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1 PURPOSE OF THE SURVEY

The objectives of this survey are to collect data to evaluate the safety and efficacy of velaglucerase alfa (VPRIV) in the post-marketing phase in patients with Gaucher disease who are new to therapy or have been switched from another therapeutic agent for Gaucher disease. Data will be collected to address the following specifications:

- Incidence of infusion reactions [Preferred Term (PT): Infusion-related reaction]
- Lack of safety data in treatment-naïve Japanese patients
- Limited safety data for patients with type 2 and 3 Gaucher disease
- Additional long term efficacy data in Japanese patients
- Limited safety data of Japanese pediatric patients
- Lack of safety data of Japanese elderly patients

2 ESTIMATED NUMBER OF PATIENTS AND RATIONALE

2.1 Target Number of Cases and Rationale

Target number of cases: All patients treated with this product.

Rationale: We plan to enroll all patients who start VPRIV treatment or transition from VPRIV clinical studies during the enrollment period of the DURS. Considering the estimated number of patients with Gaucher disease in Japan, 30 patients is a reasonable estimate of the patients who would be available for enrollment.

3 TARGET PATIENT POPULATION

Patients of any age or gender with confirmed diagnosis of Gaucher disease (types 1, 2, or 3) who are either naïve to treatment or patients that have been treated with another therapeutic agent for Gaucher disease.

The scope of patients is defined as patients who are treated with VPRIV.

4 PLANNED NUMBER OF CENTERS (DEPARTMENTS) WHICH WILL TAKE PART IN THE SURVEY

All treatment centers are in the scope of the survey.

5 SURVEYING METHOD

Survey methods employ a central enrollment system. The following steps will be completed:

1) Request Informed Consent. The purpose is to obtain and document permission from the patient for the use of patient data by the Sponsor company and other agencies. The informed consent process involves both a conversation between the patient and the site staff and the signing of the informed consent form to document the procedure.
2) Conduct patient registration by completing the patient registration form.

3) Conduct the assessments, as described in Section 7 and complete relevant case report forms (CRFs).

6 ESTIMATED DURATION OF THE SURVEY

Eight years after launch. Please see below for details regarding the specific period durations:

Enrollment period: Launch date to December 2021 (until nine months before the scheduled completion of observation period.

Observation period: Launch date to September 2022 (until 8 years after launch)

Survey Completion date (Estimated completion date of Statistical Analysis): January 2024 (plan)

The maximum observation period in this survey for an individual patient is 8 years.

7 WHAT IS INVESTIGATED IN THE SURVEY

Safety and efficacy data that are available as part of routine clinical practices related to Gaucher disease and the treatment with VPRIV will be collected.

7.1 Items for Investigation

a. Information for patient identification

- Patient initials
- Information that can identify the specific patient (e.g., Medical Record Number)

b. Patient background

- Date of birth
- Sex
- Race
- Diagnosis information including time point of definitive diagnosis of Gaucher disease, type of Gaucher disease, and method of Gaucher disease diagnosis including enzyme activity measurement.
- Genotype
- Height
- Weight
- Family history of Gaucher disease
- Clinical symptoms of Gaucher disease
- Complications not related to Gaucher disease
- Past medical and allergic history
- Prior treatments for Gaucher disease (other therapeutic agents, splenectomy, others).

c. Administration status

Details to be collected for each administration:

- Date of administration, time of infusion, dosage, body weight
- Rationale of selected dosage
- Whether pretreatment is used for the prevention or management of infusion reactions
- Status of administration: completed infusion or discontinuation (in the case of discontinuation, the date of the last infusion and the reason for discontinuation)

d. Concomitant therapy

- Presence or absence of concomitant therapy
- Names of concomitant drugs, administration route, start date, continuous use/end date, indication/purpose of use

e. Safety

Collected safety assessments include all adverse events (AEs) occurring following initiation of treatment with VPRIV regardless of the seriousness or relationship to VPRIV, and absence/presence of anti-velaglucerase antibodies. Please note the following definitions related to safety information:

Adverse event: An adverse event is any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction: An adverse reaction is an untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Seriousness criteria: An adverse reaction or adverse event is a serious adverse reaction or serious adverse event, respectively, if the reaction or event results in any of the following seriousness criteria:

- results in death
- life-threatening (NOTE: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or results in prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- a congenital anomaly/birth defect
- a medically important event or reaction

Causal Relationship: The relationship between VPRIV and the adverse event may be categorized as follows:

- Not Related

- Possibly Related
- Probably Related
- Definitely Related

Laboratory assessment may include; RBC, Hb, Ht, WBC, PLT, Total protein, AST, ALT, total bilirubin, BUN, creatinine, Na, K, Cl, angiotensin-converting enzyme (ACE), and acid phosphatase. These assessments will be performed at the physician's discretion per standard clinical practice. (approximately every 12 weeks as a guide).

Hypersensitivity reactions are defined as events of drug allergy, angioedema, anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, anaphylaxis prophylaxis, anaphylaxis treatment, drug reaction with eosinophilia and systemic symptoms.

Data about pregnancy testing for women of child-bearing potential will be collected throughout the survey. Data regarding occurrences of pregnancies/breastfeeding during the survey will also be collected.

f. Testing of anti-velaglucerase alfa antibodies (including IgGs) will be performed at the physician's discretion per standard clinical practice. IgE isotype-specific antibodies could also be measured when clinically indicated (e. g., AE, SAE or possible of lack of efficacy).

g. Efficacy

Data from the following assessments are be made at the physician's discretion per standard clinical practice:

- Hemoglobin concentration (approximately every 12 weeks as a guide)
- Platelet count (approximately every 12 weeks as a guide)
- Liver and spleen volume (approximately every 24 weeks as a guide)
- Bone density (approximately every 52 weeks as a guide)
- Evaluation of effects of anti-velaglucerase alfa antibody
- Potential for reduced efficacy due to development of neutralizing antibodies to velaglucerase alfa

7.2 Important Items for Investigation

Infusion reactions: Infusion reactions are defined as reactions occurring up to 24 hours after the start of the infusion. The most commonly observed symptoms of infusion- related reactions were: headache, dizziness, hypotension, hypertension, nausea, fatigue/asthenia, and pyrexia/body temperature increased.

Laboratory assessment may include: RBC, Hb, Ht, WBC, PLT, Total protein, AST, ALT, total bilirubin, BUN, creatinine, Na, K, Cl, ACE, and acid phosphatase. These assessments will be performed at the physician's discretion per standard clinical practice (approximately every 12 weeks as a guide).

8 ITEMS FOR ANALYSIS AND THE ANALYSIS METHOD

1) Items for analyses

a. Items on patient constitution

- Number of cases enrolled, Number of cases collected CRF,
- Number of cases evaluable for safety, Number of cases evaluable for efficacy,
- Evaluation of antibody effect on the efficacy and safety
- Number of cases excluded from the survey with reason

b. Safety issues

- Adverse reactions/infections (including unknown events), events, severity, incidence, etc.
- Adverse reactions/infections according to the background factor
- Serious adverse events by type of event
- Fetal/infant exposure via pregnancies and breastfeeding

c. Efficacy issues

- Assessment of related factors affecting on the efficacy in case of refractory
- Items on patients with special backgrounds
- Incidence ratio of adverse reactions/infections and clinical efficacy in patients with special backgrounds; pediatric, elderly, pregnant, treatment-naïve (ERT-naïve), and Gaucher type 2 or 3 patients

d. Items on important items for investigation

- Infusion reactions

2) Analysis method

Continuous variables (e.g., change from baseline in hemoglobin over time) will be summarized using descriptive statistics (N, mean, standard deviation, minimum, median, and maximum). Categorical variables (e.g., number and proportion of patients with infusion reactions over time) will be summarized using the number and percentage of patients in each category. In addition, the two-sided 95% confidence intervals (CIs) for the parameters of interest will be estimated as appropriate. No formal statistical tests will be performed. Safety and efficacy data will be presented for the enrolled patients overall, by previous treatment status (treatment-naïve versus patients who previously received ERT for Gaucher disease, e.g., imiglucerase or velaglucerase alfa) and by type of Gaucher disease as appropriate.

The safety data will be presented periodically for regulatory submissions per the regulation of the Safety Periodic Reporting System. In addition, summaries of the accumulating data including efficacy data may be assessed during the conduct of the survey for exploratory and administrative purposes, if deemed necessary. The statistical analysis methods will be prospectively specified in detail in the statistical analysis plan.

9 ORGANIZATION FOR IMPLEMENTING THE SURVEY

Same as described in the Risk Management Plan.

10 OUTSOURCE DETAILS

Contractor for the operations 1

[redacted]

Anticipated scope of services: Request the site to conduct the survey, Contract with the site, Status management of the survey, AE information collection, CRF and/or DCF collection Operation of specified use-result survey (Request to hospitals/clinics, making contracts with hospitals/clinics, enrollment of patients, collection of CRFs and review/follow-up, progress management, information collection of adverse reactions/infections, data compilation/analyses and medical writing).

Contractor for the operations 2

[redacted]

Anticipated scope of services: Receipt of paper CRFs, etc. sent from sites, confirmation of presence/absence of adverse event descriptions, transfer of original CRFs, etc. to contractor 1 and storage of site contract, etc.

Contractor for the operations 3

[redacted]

Anticipated scope of services: Monitoring

11 ADDITIONAL MEASURES WHICH MAY BE TAKEN DEPENDING ON THE OUTCOME OF THE SURVEY AND THE DECISION CRITERIA FOR INITIATING THE MEASURES

Depending on the outcomes of DURS, if new safety issues or risks are identified the additional pharmacovigilance and risk minimization measures will be planned.

12 MILESTONES FOR THE IMPLEMENTATION OF THE SURVEY AND THE ASSESSMENT OF THE RESULTS, OR REPORTING TO THE PMDA, AND THE JUSTIFICATION

Enrollment Completion: December 2021 (~about 7 years after launch)

Data collection: CRFs should be collected every 6 months for 2 years then yearly thereafter; CRF collection is anticipated to be completed within 6 months after the end of the survey.

Final Report: Within 6 months after data collection completion

13 OTHER NECESSARY ITEMS

a. Required/recommended reference materials.

- Contract
- Guideline for implementation of the survey
- Registration form for the survey
- CRF

14 SUMMARY OF CHANGES

Original Protocol: 26 June 2014
Amendment 1: 10 July 2014
Amendment 2: 14 August 2014
Amendment 3: 01 April 2018
Amendment 4: 01 April 2019
Amendment 5: 01 October 2020
Amendment 6: 01 November 2020
Amendment 7: 21 December 2020
Amendment 8: 19 August 2021
Amendment 9: 15 September 2023

Rationale for Amendment 2: Guidance for the frequency of assessment of safety laboratory assessments (Section 7.1e and Section 7.2) and efficacy assessments (Section 7.1g) was added.

The major changes are noted below. The deleted text is noted by ~~strikethrough~~ and the new text is **bolded**.

Summary of Changes for Amendment 2:
Section 7.1 Items for Investigation
Subsection e. Safety

Laboratory assessment may include ; RBC, Hb, Ht, WBC, PLT, Total protein, AST, ALT, total bilirubin, BUN, creatinine, Na, K, Cl, angiotensin-converting enzyme (ACE), and acid phosphatase. These assessments will be performed at the physician's discretion per standard clinical practice **(approximately every 12 weeks as a guide).**

Subsection g. Efficacy

Data from the following assessments are be made at the physician's discretion per standard clinical practice:

- Hemoglobin concentration **(approximately every 12 weeks as a guide)**
- Platelet count **(approximately every 12 weeks as a guide)**
- Liver and spleen volume **(approximately every 24 weeks as a guide)**
- Bone density **(approximately every 52 weeks as a guide)**
- Evaluation of effects of anti-velaglucerase alfa antibody
- Potential for reduced efficacy due to development of neutralizing antibodies to velaglucerase alfa

Section 7.2 Important Items for Investigation

Laboratory assessment may include; RBC, Hb, Ht, WBC, PLT, Total protein, AST, ALT, total bilirubin, BUN, creatinine, Na, K, Cl, ACE, and acid phosphatase. These assessments will be performed at the physician's discretion per standard clinical practice **(approximately every 12 weeks as a guide).**

Rationale for Amendment 3: Organization for Implementing the Survey (Section 9) was revised. The major changes are noted below. The deleted text is noted by strikethrough and the new text is **bolded**.

The name of trustee is changed. [redacted]

[redacted]

Rationale for Amendment 4: Organization for Implementing the Survey (Section 9) was revised.

Rationale for Amendment 5: Changes in Marketing Authorization Holder.

Outsource Details (Section 10) was revised.

Rationale for Amendment 6: Outsource Details (Section 10) was revised.

Rationale for Amendment 7: Outsource Details (Section 10) was revised.

Rationale for Amendment 8: Estimated Duration of the Survey & Milestones for the Implementation of the Survey (Section 6 & 12) was revised.

Rationale for Amendment 9: According to the change of term in the Risk Management Plan, 'Infusion-related reaction' was modified to 'Infusion reaction'. [Section 1, 7.1c, 7.2, 8.1)d and 8.2)]

'Survey Completion date' was added in Section 6.

The 'Medical writing' was added in the Anticipated scope services to Contractor for the operation 1: [redacted] [Section 10]