Statistical Analysis Plan

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Study Number: SHP-GCB-401

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Note; This document was translated into English as the language on original version was Japanese.

STATISTICAL ANALYSIS PLAN

SHP-GCB-401

For reexamination application

VPRIV

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MODIFICATION HISTORY

Unique Identifier forthis Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	20 Oct 2023	[redacted]	Not Applicable - First Version New for Reexamination.
1.1	21 Nov 2023	[redacted]	Addition of analysis on bone density
1.2	13 Mar 2024	[redacted]	Stratification of patient characteristics and efficacy tabulation was added. Clarification of case tabulation and number of events in adverse reaction tabulation
1.3	8 May 2024	[redacted]	Clarification of tabulation by seriousness and outcome in the tabulation of adverse reactions Corrected the calculation method of age and years since diagnosis of Gaucher disease.

1. INTRODUCTION

This statistical analysis plan describes the rules and handling used in the efficacy and safety analyses of Protocol SHP-GCB-401. Describe the data for tabulation and analysis, including the type of statistical analysis to be performed.

This statistical analysis plan was prepared based on the protocol version 9.0 (dated September 15, 2023).

2. Objectives

The objective of this survey is to collect and analyze post-marketing safety and efficacy data of this drug in patients with Gaucher disease including both patients who start treatment with this drug for the first time and patients who switch from other drugs to start this drug treatment with.

Collect data on the following considerations:

- Incidence of Infusion Reactions (PT: Infusion related reaction)
- Safety in treatment-naïve Japanese patients
- Safety in patients with type 2 and type 3 Gaucher disease
- Long-term efficacy in Japanese patients
- Safety in Japanese pediatric patients
- Safety in Japanese elderly

3. Study design

3.1. General Matters

This is a post-marketing study of VPRIV and is conducted in accordance with Ministerial Ordinance on Good Post-marketing Study Practice for Drugs (GPSP). Analysis output forms based on this statistical analysis plan are applicable to the application for re-examination of VPRIV in Japan.

Target sample size and rationale for setting

Target sample size: All patients treated with this drug

Rationale for setting: All patients who started VPRIV Intravenous Infusion 400 U during the registration period of this survey and patients who continue to receive VPRIV Intravenous Infusion 400 U from the clinical study will be registered. Considering the estimated number of patients with Gaucher disease in Japan, it is estimated that 30 patients will be enrolled.

Patients to be surveyed

Patients of any age and sex with a confirmed diagnosis of Gaucher disease (Type 1, 2, or 3) who have

not received previous treatment or who are being treated with other therapeutic agents for Gaucher disease.

Patient population is defined as patients treated with VPRIV IV 400 units.

Planned number of study sites

All sites will be included in the survey.

Planned survey period

8 years after the launch. Specific survey periods are shown below.

Registration period: From the date of launch to December 2021 (until 9 months before the scheduled end of the observation period)

Observation period: From the date of initial marketing in Japan to September 2022 (8 years after launch)

Date of completion of investigation (date of completion of final analysis): January 2024 (planned)

The observation period for each patient in this investigation will be up to 8 years.

3.2. Investigation items

Are the investigation items in the protocol. See Section 1.

4. Planned Analyses

- In this survey, the following analyses will be performed.
- Analysis of Reexamination Application

5. Analysis Sets

5.1. Enrolled patients

All registered cases.

5.2. CRF not collected

All cases for which all CRFs collected have not been locked or no CRFs have been collected.

5.3. CRF collected

All registered patients for whom the CRF was collected.

5.4. Patients excluded from safety evaluation

All patients who have not received this drug or have no efficacy or safety evaluation data after treatment with this drug among patients for whom survey forms have been collected.

5.5. Subjects evaluable for safety

All registered patients who received this drug.

Statistical analyses for all safety endpoints will be based on the safety population.

5.6. Patients eligible for efficacy evaluation

Subjects excluded from the safety evaluation set are as follows:

- Off label use
- Efficacy assessment unknown
- The definition of "efficacy evaluation unknown" is detailed as follows.
- Patients meeting all of the following criteria:
    1) "Whether or not hematology test was performed" is not "Yes."
    2) "Whether or not biochemical tests are performed" is not "Yes."
    3) "Presence/absence of liver/spleen imaging" is not "Present."
    4) "Presence/absence of lumbar spine/femoral neck bone test" is not "Present."
    5) "Presence/absence of anti-velaglucerase alfa antibody test" is not "present."

Statistical analyses for all efficacy endpoints are based on the efficacy analysis set.

6. General Considerations

6.1. Reference Start Date & Relative Date

The reference date is calculated from the reference start date and is used to represent the start/end date of the assessment and event.

The reference start date is defined as the start date of the first this drug infusion (Day1 is the start date of the first this drug infusion) and will be displayed in any listing that provides a date of assessment or event.

- If the event date is on or after the reference date:

Relative date = (Date of event - Reference date) +1

- If the event date is before the reference date:

Relative date = (Event date - Reference date)

If the date of an event is partial or missing, the relative date and associated period will be displayed as missing in the listing.

6.2. Baseline

Unless otherwise specified, baseline is defined as the last non-missing value (including non-scheduled assessments) measured before the reference start date. If the last non-missing measurement and reference start date are the same, the measurement will be considered as baseline, but adverse events (AEs) and treatments starting at the reference start date will be considered per baseline.

6.3. Derivation time points

Since there are no planned time points in the protocol, all VISIT analyses will be performed using derived time points. The table below represents the visit windows for the following data for analysis: The latest date of the designated day should be adopted at each visit. In addition, if there are two subsequent candidate dates, the following date shall be adopted.

Table A: Laboratory parameter

Visit	Weeks	Target Days Specified Date	Assigned Relative Days	
			from	to
Baseline	0	1	-42	1
Visit 1	12	84	2	125
Visit 2	24	168	126	209
Visit 3	36	252	210	293
Visit 4	48	336	294	377
Visit 5	60	420	378	461
Visit 6	72	504	462	545
Visit 7	84	588	546	629
Visit 8	96	672	630	713
Visit 9	108	756	714	797
Visit 10	120	840	798	881
Visit 11	132	924	882	965
Visit 12	144	1008	966	1049
Visit 13	156	1092	1050	1133
Visit 14	168	1176	1134	1217
Visit 15	180	1260	1218	1301
Visit 16	192	1344	1302	1385
Visit 17	204	1428	1386	1469
Visit 18	216	1512	1470	1553
Visit 19	228	1596	1554	1637
Visit 20	240	1680	1638	1721
Visit 21	252	1764	1722	1805
Visit 22	264	1848	1806	1889
Visit 23	276	1932	1890	1973
Visit 24	288	2016	1974	2057
Visit 25	300	2100	2058	2141
Visit 26	312	2184	2142	2225
Visit 27	324	2268	2226	2309
Visit 28	336	2352	2310	2393
Visit 29	348	2436	2394	2477
Visit 30	360	2520	2478	2561
Visit 31	372	2604	2562	2645
Visit 32	384	2688	2646	2729

The window will be applied prior to the calculation of missing data.

Table B: Liver and Spleen Imaging

Visit	Weeks	Target Days Specified Date	Assigned Relative Days	
			from	to
Baseline	0	1	-84	1
Visit 2	24	168	2	251
Visit 4	48	336	252	419
Visit 6	72	504	420	587
Visit 8	96	672	588	755
Visit 10	120	840	756	923
Visit 12	144	1008	924	1091
Visit 14	168	1176	1092	1259
Visit 16	192	1344	1260	1427
Visit 18	216	1512	1428	1595
Visit 20	240	1680	1596	1763
Visit 22	264	1848	1764	1931
Visit 24	288	2016	1932	2099
Visit 26	312	2184	2100	2267
Visit 28	336	2352	2268	2435
Visit 30	360	2520	2436	2603
Visit 32	384	2688	2604	2771

6.4. Test

In principle, no statistical tests will be performed, and two-sided 95% confidence intervals will be calculated.

6.5. Common items

If quantitative, change from baseline will be calculated as follows:

- Test value at Visit X - Baseline value

If quantitative, the percent change from baseline will be calculated as follows:

- (Test value at Visit X - Baseline value)/Baseline value ×100

6.6. Software Version

All analyses were performed using SAS version 9.4 or higher or SAS Enterprise Guide (SAS Institute Japan) 82 or higher.

7. Form output method

Appendix 1 specifies the method for output of data in the output form.

The template of this statistical analysis plan shows the output method of this study, that is, the format and contents of summary tables, figures, and listings to be provided by the statistical analysis department of [redacted]

8. Patient composition and status of discontinuation

Patient composition and status of discontinuation will be tabulated for the patients evaluated for safety.

- Completed
- Continuing
- Discontinuation

9. Patient characteristics

Patient characteristics will be tabulated for patients evaluated for safety.

In this survey, the following patient background items will be summarized overall and by disease type of Gaucher disease.

Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation, minimum, median, maximum). Categorical variables will be summarized using the number and percentage of patients in each category.

- Gender
- Age (years) – calculated relative to first dose date
- Age category (years): infants (< 4 years), children (≥ 4 to < 12 years), adolescents (≥ 12 to < 18 years), adults (≥ 18 to < 65 years), elderly (≥ 65 years). Children aged < 18 years will be collectively handled as children for tabulation.
- Gaucher disease type
- Diagnostic Method of Gaucher Disease Including Enzyme Activity Measurement
- Diagnostic methods for type 2 and type 3 Gaucher disease
- Genotype
- Weight (kg)
- Height (cm)
- Family history of Gaucher disease (Yes/No)
- Past history (Yes/No), complication (Yes/No, Renal impairment Yes/No, Hepatic impairment Yes/No), and allergy history (Yes/No)

- Prior treatment for Gaucher disease (Yes/No, ERT/SRT), splenectomy (Yes/No), and other prior treatments (Yes/No)
- Years since diagnosis of Gaucher disease (years) – calculated relative to date of first dose

10.Past history and complications

Medical history and complications will be tabulated for patients evaluated for safety. Medical history and current medical conditions will be coded using the Medical dictionary for regulatory activities (MedDRA) version 26.0 or higher version.

Medical history and complications will be summarized by site using the number of patients and the hazard ratio for each category. Medical history and complications will be tabulated by case and type of Gaucher disease.

11.Administration status

The administration status of this drug will be tabulated for the patients evaluated for safety.

The start date of this drug administration will be collected from the paper CRF. This drug end dates will be collected from the paper CRFs.

Dose interruptions, compliance, and dose changes will not be considered for the duration of treatment.

11.1. Out-licensing

Duration of treatment (days) = Date of completion of this drug treatment (day) = Date of initiation of this drug treatment (day)

Number of doses: Total number of doses received throughout this drug treatment period

12.Safety Endpoints

Safety analysis will be performed in the safety evaluation set. For continuous variables, descriptive statistics including number of observations, mean, standard deviation (SD), minimum, median, and maximum will be summarized. Categorical variables will be summarized using frequencies and percentages. The time points to be output are defined in Chapter 63. Other items not defined in Section 12 will be tabulated (as necessary).

12.1. Adverse events

Adverse events (AEs) will be coded using MedDRA version 26.0 or higher.

The causal relationship to this drug based on the physician's judgment is classified as "not related," "unlikely related," and "highly related." An ADR is defined as an AE that is unlikely, highly, or definitely related to this drug. If the same AE is reported more than once in the same SOC/PT in the same case, the most related ADR should be used for ADR determination and the AE should be counted as 1 event.

12.1.1. Reaction/SAE/AE

ADRs are summarized by SOC and PT according to Appendix Form15 (Form15).

Adverse reactions and adverse events will be tabulated by severity and by SOC and PT. In tabulation, the number of events will be tabulated along with the number of subjects with events.

In the tabulation of the number of patients with events, if the same AE (same SOC/PT) is reported multiple times in the same patient, the event will be counted as 1 patient with 1 event, and no duplicate counting will be performed.

In the tabulation of the number of events, if the same AE (same SOC/PT) is reported more than once in the same case, it will be counted as duplicate.

However, if different seriousness of the same AE (same SOC/PT) are reported in the same case, the number of cases and the number of events will be counted for each seriousness.

Adverse reactions, adverse events, and serious adverse events will be tabulated by outcome by SOC and PT. For tabulation by outcome, if the same AE (same SOC/PT) is reported more than once in the same patient, it will be counted in the final outcome.

For adverse reactions, serious adverse events, and all adverse events, the following forms will be prepared by patient background:

- By prior treatment history (Yes/No, ERT/SRT).
- Each type of Gaucher disease (Type 1, 2, or 3).

For each patient with special background (Children (< 4 years/≥ 4 years, < 18 years/≥ 18 years), elderly patients (< 65 years/≥ 65 years), patients with renal impairment, patients with hepatic impairment, pregnancy test results)

12.1.2. Infusion reaction (IR)

An infusion reaction is defined as any reaction occurring within 24 hours of the start of the infusion.

The incidence and proportion of patients with infusion reactions in the safety analysis set were

summarized by PT.

Summarized separately. Infusion reactions will be listed by patient, SOC, and PT in the patients evaluated for safety.

In addition, data will be tabulated by SOC and PT. Data were summarized for overall infusion reactions and by prior treatment history (Yes/No, ERT/SRT), time from onset to outcome, and time from the start date of this drug treatment to the date of onset will be tabulated.

12.1.3. Exposure of fetus/infant in pregnancy and lactation

For patients who completed the pregnancy test, the results of the pregnancy test will be listed.

12.1.4. Changes over time in laboratory values

Summaries will be provided for RBC, Hb, Ht, WBC, PLT, total protein, AST, ALT, total bilirubin, BUN, creatinine, Na, K, Cl, ACE, and acid phosphatase. Actual values, change from baseline, and percent change from baseline will be summarized at each time point.

13.Efficacy Endpoints

Efficacy analysis will be performed in the efficacy evaluation population. For continuous variables, descriptive statistics including number of observations, N, mean, standard deviation (SD), minimum, median, and maximum will be summarized. Categorical variables will be summarized using frequencies and percentages. Summaries will be provided for all endpoints, by prior therapy (Yes/No, ERT/SRT) and by Gaucher disease type (Type 1, 2, or 3), by age (< 4 years/≥, < 18 years/≥, < 65 years/≥). The time points to be output are defined in Chapter 6.3. In addition, a time-course graph will be prepared.

Any other items not defined in Section 13 should be listed (as appropriate).

13.1. Hemoglobin concentration

Hemoglobin concentration will be summarized. Actual values, change from baseline, and percent change from baseline will be summarized at each time point. No imputation will be applied if baseline values are missing. Furthermore, changes in hemoglobin concentration from the final baseline will be classified as follows for tabulation.

Good: Increase by ≥ 1.5 g/dL

Moderate response: increase ≥ 0.5 g/dL and < 1.5 g/dL

Nonresponse (intractable cases): Increase of < 0.5 g/dL

13.2. Platelet count

Platelet counts will be summarized. Actual values, change from baseline, and percent change from baseline will be summarized at each time point.

Furthermore, changes in platelet count from the final baseline will be classified as follows and tabulated.

Good: >=30 $\times 10^9$/L increase

Moderate response: increase ≥ 15 $\times 10^9$/L and < 30 $\times 10^9$/L

Refractory: 15 $\times 10^9$/L

Patients with normal baseline platelet count (>150 $\times 10^9$/L) are excluded.

13.3. Liver volume

Liver capacity is required. Actual values, change from baseline, and percent change from baseline will be summarized at each time point. Differences in liver volume measurement methods will not be considered.

Changes in liver volume from baseline will be classified as follows and tabulated.

Good: Decrease ≥ 30% from baseline

Moderate response: ≥ 10% decrease and < 30% decrease

No response (intractable cases): Decrease of < 10%

However, patients without readily palpable hepatomegaly at baseline will be excluded according to the inclusion criteria.

13.4. Spleen volume

Spleen volume is required. Actual values, change from baseline, and percent change from baseline will be summarized at each time point. The internal consistency of measurement methods for each patient will be considered, but differences in measurement methods for spleen volume will not be considered.

In addition, changes in spleen volume from baseline will be classified as follows and tabulated.

Good: Decrease ≥ 30% from baseline

Moderate response: ≥ 10% decrease and < 30% decrease

No response (intractable cases): Decrease of < 10%

However, patients without moderate splenomegaly at baseline as defined in the inclusion criteria (2 ~3 cm below the left costal margin by palpation) will be excluded.

13.5. Bone density (lumbar spine/femoral neck bone test)

Bone mineral density (Z-score, T-score, and BMD of the lumbar spine or femoral neck) will be summarized. Actual values, change from baseline, and percent change from baseline will be summarized at each time point.

13.6. Anti-velaglucerase alfa antibody test, velaglucerase alfa neutralizing antibody

The results of anti-veragnoreselase alfa antibody test and veragnoreselase alfa neutralizing antibody test will be listed for each subject. If the results of the antibody test are worth examining, the observed adverse events and the rates of change in platelet count and hemoglobin concentration will be examined in patients who underwent the antibody test.

14.References

Guidance for Application for Re-examination (October 2021 version)

Appendix 1 Setting of the data output method in the output form

Date and Time

Depending on available data, the date and time can be in the format yyyy-mm-dd Thh: mm.

List

All listings should be in the following order (unless otherwise specified in the template):

- Case No.
- Date (if applicable)

Appendix 2 Requirements for partial dates

The imputed dates will not be displayed in listings.

Treatment Emergent Adverse Event (TEAE) Algorithm:

START DATE Start Date	**STOP DATE** End Date	**ACTION** Response
Full Date	Full Date	A TEAE if start date <If the start date of this drug infusion is the start date of the non-TEAE>= the start date of this drug infusion
	Partial Date	A TEAE if start date <If the start date of this drug infusion is the start date of the non-TEAE>= the start date of this drug infusion
	Missing	A TEAE if start date <If the start date of this drug infusion is the start date of the non-TEAE>= the start date of this drug infusion
It is a partial date but on or after the start date of this drug treatment.	Full Date	Not a TEAE
	Partial Date	Not a TEAE
	Missing	Not a TEAE
Partial date which may be on or after this drug Start Date	Full Date	If end date <End date that is not a TEAE if it is the start date of this drug infusion>= start date of this drug treatment, it is a TEAE
	Partial Date	With end date imputed as last possible date (i.e. last day of the month when day is unknown, December 31 when month and day are unknown): If end date <End date that is not a TEAE if it is the start date of this drug infusion>= start date of this drug treatment, it is a TEAE
	Missing	Expected to be a TEAE

Missing	Full Date	If end date <End date that is not a TEAE if it is the start date of this drug infusion>= start date of this drug treatment, it is a TEAE
	Partial Date	With end date imputed as last possible date (i.e. last day of the month when day is unknown, December 31 when month and day are unknown): If end date <End date that is not a TEAE if it is the start date of this drug infusion>= start date of this drug treatment, it is a TEAE
	Missing	Expected to be a TEAE

Prior/concomitant therapy algorithm:

START DATE Start Date	**STOP DATE** End Date	**ACTION** Response
Full Date	Full Date	If the end date is < the start date of this drug treatment, it will be regarded as prior treatment. If end date >= start date and start date of this drug treatment <= end of treatment, it should be a concomitant therapy If end date >= start date and start date of this drug treatment > end of treatment, it will be regarded as subsequent therapy
	Partial Date	With the end date imputed as the last possible date (i.e. last day of the month when day is unknown, December 31 when month and day are unknown): If the end date is < the start date of treatment with this drug, this will be regarded as prior treatment. If end date >= start date and start date of this drug treatment <= end of treatment, it should be a concomitant therapy If end date >= start date and start date of this drug treatment > end of treatment, it will be regarded as subsequent therapy
	Missing	If the end date is missing, the start date that cannot be assumed to be the prior treatment <= If end of treatment, start date of concomitant therapy>, and the end of treatment is the subsequent treatment.
Partial Date	Full Date	Imputation of the start date as the first possible date (i.e. first day of the month if day is unknown, January 1 if month and day are unknown): if end date < start date of this drug treatment, this will be regarded as prior therapy If end date >= start date and start date of this drug treatment <= end of treatment, it should be a concomitant therapy If end date >= start date and start date of this drug treatment > end of treatment, it will be regarded as subsequent therapy
	Partial Date	Start date imputed as first possible date (i.e. first day of the month if day is unknown, January 1 if month and day are unknown) and end date imputed as last possible date (i.e. last day of the month when day is unknown, December 31 when month and day are unknown): If the end date is < the start date of this drug treatment, it will be regarded as prior treatment. If end date >= start date and start date of this drug treatment <= end of treatment, it should be a concomitant therapy If end date >= start date and start date of this drug treatment > end of treatment, it will be regarded as subsequent therapy
	Missing	The start date is imputed as the first possible date (i.e. first day of the month if day is unknown, January 1 if month and day are unknown): if the end date is missing, a start date that cannot be assumed to be a prior therapy <= If end of treatment, start date of concomitant therapy>; if the end of therapy, it is regarded as subsequent therapy

Missing	Full Date	If the end date is < the start date of this drug treatment, it will be regarded as prior treatment. If end date >= start date of this drug treatment, it should be regarded as a concomitant therapy Cannot be assumed as "post-treatment"
	Partial Date	With the end date imputed as the last possible date (i.e. last day of the month when day is unknown, December 31 when month and day are unknown): If end date <If the start date of administration of this drug is the date of completion as prior therapy>= date of start of this drug treatment, this is a concomitant therapy Cannot be assumed as "post-treatment"
	Missing	Concomitant therapy