12 December 2024
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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

VPRIV

Velaglucerase alfa

Procedure no: EMEA/H/C/001249/P46/032

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 26 September 2024, the MAH submitted a completed paediatric study for VPRIV in accordance with Article 46 of Regulation (EC) No1901/2006 as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that 'Drug Use-results Survey for VPRIV® for I.V. Infusion 400 Units' (SHP-GCB-401) is a stand alone study.

A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

According to the data provided, the commercially available formulation of velaglucerase alfa was administered as per approved label (60 units/kg administered every other week).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- SHP-GCB-401, Drug Use-results Survey for VPRIV® for I.V. Infusion 400 Units.

2.3.2. Clinical study

SHP-GCB-401, Drug Use-results Survey for VPRIV® for I.V. Infusion 400 Units

Description

The postmarketing study SHP-GCB-401 was a survey to evaluate the safety and efficacy of VPRIV in patients with Gaucher disease (GD) in Japan, who were new to therapy or had been switched from another therapeutic agent for GD. The study used survey methods with a central enrolment system. The following steps were completed:

- Informed Consent Request to obtain and document permission from the patient for the use of patient data. The informed consent process involved both a conversation between the patient and the site staff.
- Conducted patient registration by completing the patient registration form.
- Conducted assessments as described in the study protocol and completed relevant case report forms (CRFs).

Safety and efficacy data that were available as part of routine clinical practices related to GD and the treatment with VPRIV were collected. CRFs were collected every 6 months for 2 years and then yearly thereafter; CRF collection was anticipated to be completed within 6 months after the end of the survey.

The study included 3 periods:

1. Enrolment period: From the initial marketing in Japan to December 2021 (until 9 months prior to the planned end of the observation period).
2. Observation period: From the initial marketing in Japan to September 2022 (until 8 years after launch).
3. Survey completion date: Date of completion of final statistical analysis (14 May 2024).

The maximum observation period in this study for an individual patient was 8 years.

Methods

Study participants

Study SHP-GCB-401 included patients with a confirmed diagnosis of GD (Types 1, 2, or 3), regardless of age or sex, who had no previous history of treatment or who were being treated with other drugs for GD and who were treated with VPRIV 400 Units powder for IV Infusion.

Treatments

VPRIV was administered as per the approved label (60 Units/kg administered every other week).

Objectives

The objectives of this survey were to collect and analyse data on the safety and efficacy of VPRIV in Japanese patients with GD who were new to therapy or had been switched from another therapeutic agent for GD. Data were 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 Types 2 and 3 GD.
- Additional long-term efficacy data in Japanese patients.
- Limited safety data of Japanese paediatric patients.
- Lack of safety data of Japanese elderly patients.

Outcomes / endpoints

The primary survey items were patient identification information, demographics, administration status of VPRIV, combination therapy, safety (adverse events, laboratory tests, etc.), important survey items (infusion reactions, laboratory tests), anti-velaglucerase alfa antibody tests (including IgG), and efficacy (haemoglobin concentrations, platelet counts, liver and spleen volumes, bone mineral densities, efficacy evaluation of anti-velaglucerase alfa antibodies, and the possibility of efficacy loss due to development of velaglucerase alfa neutralising antibodies).

Sample size

The MAH planned to enrol all patients who started treatment with VPRIV or transitioned from clinical studies with VPRIV during the enrolment period. Based on the estimated number of patients with GD in Japan, 30 patients were estimated to be reasonable assumption of the number of patients who would be available for enrolment.

Randomisation and blinding (masking)

N/A

Statistical Methods

Continuous variables (e.g., change from baseline in haemoglobin over time) were to be summarised using descriptive statistics (N, mean, standard deviation, minimum, median, maximum). Categorical variables (e.g., number and proportion of patients with infusion reactions over time) were to be summarised using the number and percentage of patients in each category. Two-sided 95% confidence intervals (CIs) for the parameters of interest were estimated as appropriate. No formal statistical tests were to be performed.

Safety and efficacy data were to be presented for the enrolled patients overall, by previous treatment status (treatment-naïve versus patients who previously received ERT for GD, e.g., imiglucerase or velaglucerase alfa), and by type of GD as appropriate.

The safety data were to be presented periodically for regulatory submissions per the regulation of the Safety Periodic Reporting System. If deemed necessary, summaries of the accumulating data including efficacy data may have also been assessed for exploratory and administrative purposes.

Results

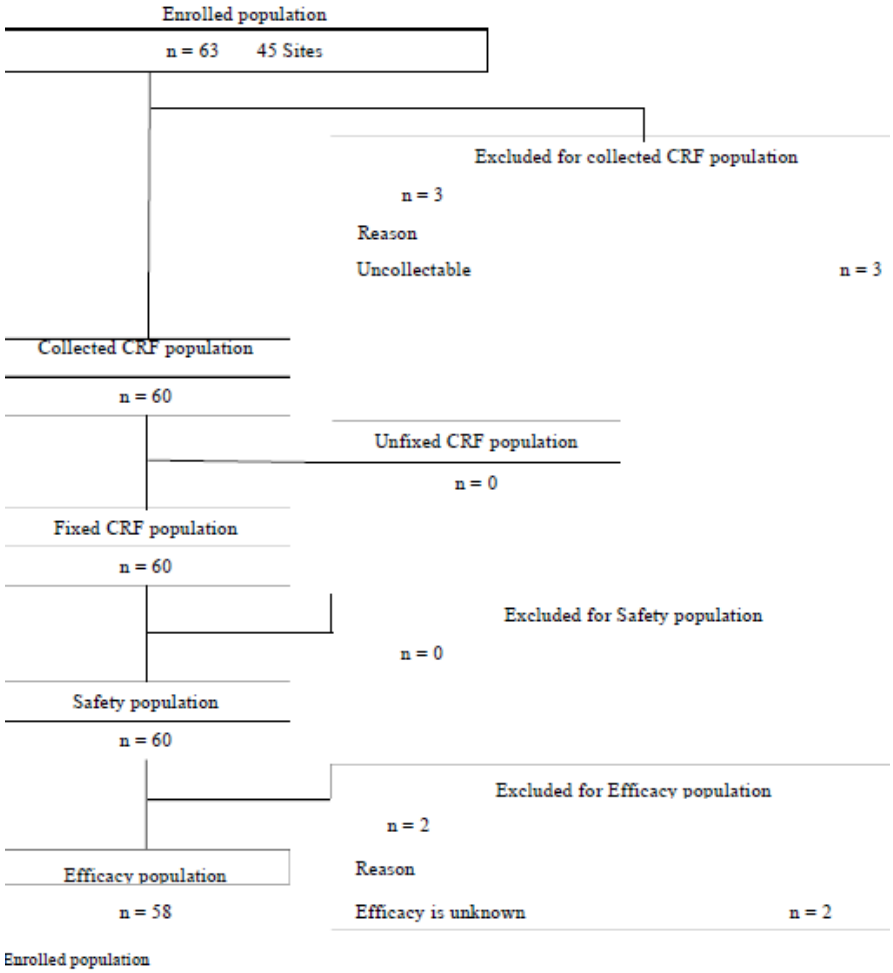
Participant flow

Since the number of enrolled patients exceeded the number of 30 stipulated in the protocol in September 2021, a consultation was held with the Pharmaceuticals and Medical Devices Agency and approval to complete the survey at the observation period through September 2022 was obtained if no registrations of patients newly administered the drug between October and the end of December 2021 are found. The collection of CRFs was subsequently completed on 30 June 2023. As of the data lock on 01 November 2023, 77 patients were enrolled at 58 sites. Among these, 14 were duplicated because of hospital transfer or cooperative medical care. Excluding these duplications, 63 patients were enrolled at 45 sites; the average enrolled population per site was 1.4 patients (minimum 1, maximum 5).

Of the 63 patients enrolled, 3 were excluded as they were uncollectable and 60 patients (36 paediatric, 24 adult) from whom CRFs were collected, were included in the safety population. Of these, 58 (35 paediatric, 23 adults) were included in the efficacy population, excluding 2 patients (1 paediatric, 1 adult) for whom efficacy was unknown.

As of the locking of records for all patients, the survey of 5 patients was ongoing and 55 of the 60 patients in the safety population had discontinued the survey. The reasons for discontinuation included adverse events (AEs) for 1 patient (1.67%), discontinuation due to decision by the physician for 4 patients (6.67%), no visit for 1 patient (1.67%), death for 13 patients (21.67%), hospital transfer for 4 patients (6.67%), and other (e.g., expiration of survey period) for 32 patients (53.33%).

Figure 1: Analysis Population



Recruitment

Patient enrolment period included the date of initial marketing in Japan up to December 2021, i.e. until 9 months prior to the planned end of the observation period. The observation period covered the date of initial marketing in Japan to September 2022, i.e. 8 years after launch of VPRIV. The date of completion of the survey, i.e. the date of completion of the final analysis, is 14 May 2024. The maximum observation period per patient in this survey was 8 years.

Version 1.0 of the study protocol is dated 18 August 2014. Revisions are listed in the table below.

Table 1: Revisions of Protocol

Edition/Version Number	Date of preparation	Item	Main Change
Ver.1.0	18-Aug-2014	—	—
Ver.1.1	01-Apr-2018	9 Organization Structure for the Conduct of Survey	• Change of the company name of the contractor Quintiles Transnational Japan → IQVIA Services Japan
		12 Other a. References	The word "(Draft)" was deleted in all documentation
Ver.2.0	27-Mar-2019	8. Items to Be Analyzed and Analysis Methods 2) Analysis methods	Changes to description of statistical tests
		9 Organization Structure for the Conduct of Survey	• The organizational structure for the conduct of survey was changed to "the same as the Risk Management Plan" • Addition of contractor 1 (Takeda Pharmaceutical Company Limited)
Ver.3.0	01-Oct-2020	Change of the name of survey company	Shire Japan KK was merged into Takeda Pharmaceutical Company Limited
		8. Items to Be Analyzed and Analysis Methods 2) Analysis methods	Changes to description of statistical tests
		9 Organization Structure for the Conduct of Survey	• Deletion of contractor 1 (Takeda Pharmaceutical Company Limited)
Ver.4.0	01-Nov-2020	9 Organization Structure for the Conduct of Survey	• Addition of contractor 2 (PRA Health Science Co., Ltd.)
Ver.5.0	15-Jan-2021	9 Organization Structure for the Conduct of Survey	• Addition of "Retention of site agreements, etc." to contracted tasks for Contractor 2 • Addition of contractor 3 (PharField Corporation)
Ver.6.0	19-Aug-2021	6 Estimated Duration of the Survey	The enrollment period was changed to the period from the date of initial marketing in Japan to December 2021 (until 9 months prior to the planned end of the observation period)
		11 Milestones and Rationale for Conducting the Survey, Evaluating Results or Reporting to the PMDA	Change of the survey enrollment completion to December 2021 (until 7 years and 3 months after launch)
Ver.7.0	12-May-2022	9 Organization Structure for the Conduct of Survey	Change of the phrase at the beginning, "The organizational structure for the conduct of the survey is the same as that of the Risk Management Plan," to "See the Attachment"
Ver.8.0	24-May-2023	1 Survey Objectives 7.1 Survey Items 7.2 Important Survey Items 8. Items to Be Analyzed and Analysis Methods	Change of "Infusion-related reactions" to "Infusion reactions" in the items to be examined (important survey items)
		9 Organization Structure for the Conduct of Survey	Addition of a "medical writing task" to the contracted tasks for Contractor 1
Ver.9.0	15-Sep-2023	6 Estimated Duration of the Survey	Addition of "Date of survey completion (date of final analysis completion): January 2024 (planned)"

Version 1.0 of the Statistical Analysis Plan is dated 20 October 2023. Revisions are shown in the table below.

Table 2: Revisions of Statistical Analysis Plan

Edition/Version Number	Date of preparation	Main Change
Ver.1.0	20-Oct-2023	–
Ver.1.1	21-Nov-2023	Addition of analysis for the bone mineral densities
Ver.1.2	13-Mar-2024	Addition of stratifications of patient demographics and efficacy aggregation Clarification of aggregations of patients and of the number of cases in adverse drug reaction aggregation
Ver. 1.3	08-May-2024	Clarification of aggregations by seriousness and by outcome in adverse drug reaction aggregation Revision of methods for calculating age and number of years since diagnosis with Gaucher's disease

Baseline data

Overall, the mean (SD) age of patients at inclusion was 19.8 (21.77) years and the median (range) 14.0 (0 to 70) years. Thirty-six (36) patients (60.00%) were <18 years [21 (35.00%) <4 years, 7 (11.67%) 4 to 11 years, 8 (13.33%) 12 to 17 years] and 4/60 patients (6.67%) were ≥ 65 years old.

Thirty (30) patients (50.00%) were male, and 30 (50.00%) female.

GD Type 1 were 17/60 patients (28.33%), Type 2 24/60 (40.00%), and Type 3 19/60 (31.67%). The diagnoses were made via leukocytes (whole blood only) with deficiency of leukocyte glucocerebrosidase activity in 10/60 patients (16.67%), genotype in 50/60 patients (83.33%), enzymatic activity in 50/60 patients (83.33%), and others (e.g., Gaucher cell detection in bone marrow biopsy) in 4/60 patients (6.67%). Thirteen (13)/60 patients (21.67%) had a medical history while 47/60 patients (78.33%) did not. Thirty-two patients (32/60, 53.33%) had complications while 28/60 patients (46.67%) did not; renal impairment was reported in 2/60 patients (3.33%) and hepatic function disorder in 5/60 patients (8.33%).

Overall, 37/60 patients (61.67%) received prior treatments for GD and 23/60 patients (38.33%) did not. Prior treatments (duplicate aggregation) included drug therapy in 36/60 patients (60.00%), enzyme replacement therapy (ERT) in 36/60 patients (60.00%), and substrate reduction therapy (SRT) in 2/60 patients (3.33%). In addition, splenectomy was performed in 6/60 patients (10.00%) and other prior therapeutic agents were performed in 9/60 patients (15.00%).

The mean (standard deviation) duration of exposure to VPRIV was 1522.4 (856.65) days and the median (minimum to maximum) was 1470.5 (57 to 2920) days. The mean (standard deviation) number of times of infusion was 94.9 (56.30) times and the median (minimum to maximum) was 97.0 (5 to 204) times.

Aggregated information on demographics and other baseline characteristics is summarised in the table below. Information on medical history is even more sparse.

Table 3: Demographic and Other Baseline Characteristics Safety population

		Total	**Type of GD**			
			Type 1	**Type 2**	**Type 3**	**Type 2 or 3**
Items	**Category**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of patients(population)		60 (100.00)	17 (100.00)	24 (100.00)	19 (100.00)	43 (100.00)
Sex	Male	30 (50.00)	8 (47.06)	11 (45.83)	11 (57.89)	22 (51.16)
	Female	30 (50.00)	9 (52.94)	13 (54.17)	8 (42.11)	21 (48.84)
Age(years)	n	60	17	24	19	43
	Mean	19.8	46.5	2.2	18.0	9.2
	SD	21.77	20.44	3.09	8.80	10.09

		Total	Type of GD			
			Type 1	Type 2	Type 3	Type 2 or 3
Items	**Category**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of patients(population)		60 (100.00)	17 (100.00)	24 (100.00)	19 (100.00)	43 (100.00)
	Minimum	0	2	0	0	0
	Median	14.0	51.0	1.0	17.0	4.0
	Maximum	70	70	13	36	36
Age category	< 4 years	21 (35.00)	1 (5.88)	18 (75.00)	2 (10.53)	20 (46.51)
	4 to 11 years	7 (11.67)	1 (5.88)	5 (20.83)	1 (5.26)	6 (13.95)
	12 to 17 years	8 (13.33)	0 (0.00)	1 (4.17)	7 (36.84)	8 (18.60)
	18 to 64 years	20 (33.33)	11 (64.71)	0 (0.00)	9 (47.37)	9 (20.93)
	≥ 65 years	4 (6.67)	4 (23.53)	0 (0.00)	0 (0.00)	0 (0.00)
	Missing	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Age category (< 18 years)	< 18 years	36 (60.00)	2 (11.76)	24 (100.00)	10 (52.63)	34 (79.07)
Type of GD	Type 1	17 (28.33)	17 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
	Type 2	24 (40.00)	0 (0.00)	24 (100.00)	0 (0.00)	24 (55.81)
	Type 3	19 (31.67)	0 (0.00)	0 (0.00)	19 (100.00)	19 (44.19)
Method of GD Diagnosis	Deficient GCB activity	10 (16.67)	3 (17.65)	3 (12.50)	4 (21.05)	7 (16.28)
	Genotype	50 (83.33)	11 (64.71)	21 (87.50)	18 (94.74)	39 (90.70)
	Enzyme activity	50 (83.33)	12 (70.59)	22 (91.67)	16 (84.21)	38 (88.37)
	Other	4 (6.67)	3 (17.65)	0 (0.00)	1 (5.26)	1 (2.33)
Method of GD type 2 and 3 diagnosis	Myoclonus	23 (53.49)	0 (0.00)	13 (54.17)	10 (52.63)	23 (53.49)
	Abnormal Eye Movement	21 (48.84)	0 (0.00)	15 (62.50)	6 (31.58)	21 (48.84)
	Abnormal Pupillary light Reflex	6 (13.95)	0 (0.00)	6 (25.00)	0 (0.00)	6 (13.95)
	Increased Muscle Tonus	18 (41.86)	0 (0.00)	16 (66.67)	2 (10.53)	18 (41.86)
	Other	11 (25.58)	0 (0.00)	6 (25.00)	5 (26.32)	11 (25.58)
Genotype (Multiple choice)	L444P	19 (31.67)	5 (29.41)	9 (37.50)	5 (26.32)	14 (32.56)
	F213I	7 (11.67)	4 (23.53)	1 (4.17)	2 (10.53)	3 (6.98)
	R496	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
	D409H	4 (6.67)	0 (0.00)	1 (4.17)	3 (15.79)	4 (9.30)
	Unknown	12 (20.00)	7 (41.18)	4 (16.67)	1 (5.26)	5 (11.63)
	Other	30 (50.00)	3 (17.65)	15 (62.50)	12 (63.16)	27 (62.79)
Weight(kg)	n	56	15	24	17	41
	Mean	31.822	52.533	10.589	43.524	24.245
	SD	22.9674	16.4120	8.2902	15.9662	20.2813
	Minimum	2.80	10.00	2.80	5.20	2.80
	Median	35.250	50.600	7.650	48.000	14.500
	Maximum	75.00	75.00	40.00	70.00	70.00
Height (cm)	n	36	8	18	10	28
	Mean	114.29	154.56	70.63	160.65	102.78
	SD	48.421	31.160	17.075	13.016	46.579
	Minimum	46.5	80.0	46.5	137.0	46.5
	Median	102.70	162.25	67.75	160.95	80.50
	Maximum	183.0	178.0	107.0	183.0	183.0
Family history of GD	Yes	11 (18.33)	1 (5.88)	2 (8.33)	8 (42.11)	10 (23.26)
	No	49 (81.67)	16 (94.12)	22 (91.67)	11 (57.89)	33 (76.74)
Past medical history	Yes	13 (21.67)	7 (41.18)	3 (12.50)	3 (15.79)	6 (13.95)
	No	47 (78.33)	10 (58.82)	21 (87.50)	16 (84.21)	37 (86.05)
Complication	Yes	32 (53.33)	10 (58.82)	16 (66.67)	6 (31.58)	22 (51.16)
	No	28 (46.67)	7 (41.18)	8 (33.33)	13 (68.42)	21 (48.84)
Complications (renal dysfunction)	Yes	2 (3.33)	0 (0.00)	0 (0.00)	2 (10.53)	2 (4.65)
	No	58 (96.67)	17 (100.00)	24 (100.00)	17 (89.47)	41 (95.35)

		Total	Type of GD			
			Type 1	Type 2	Type 3	Type 2 or 3
Items	**Category**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of patients(population)		60 (100.00)	17 (100.00)	24 (100.00)	19 (100.00)	43 (100.00)
Complications (liver dysfunction)	Yes	5 (8.33)	1 (5.88)	3 (12.50)	1 (5.26)	4 (9.30)
	No	55 (91.67)	16 (94.12)	21 (87.50)	18 (94.74)	39 (90.70)
Allergic history	Yes	47 (78.33)	15 (88.24)	21 (87.50)	11 (57.89)	32 (74.42)
	No	13 (21.67)	2 (11.76)	3 (12.50)	8 (42.11)	11 (25.58)
Prior treatments for GD (Therapeutics, Splenectomy, Other)	Yes	37 (61.67)	11 (64.71)	11 (45.83)	15 (78.95)	26 (60.47)
	No	23 (38.33)	6 (35.29)	13 (54.17)	4 (21.05)	17 (39.53)
Prior therapeutic agents	Yes	36 (60.00)	10 (58.82)	11 (45.83)	15 (78.95)	26 (60.47)
	No	24 (40.00)	7 (41.18)	13 (54.17)	4 (21.05)	17 (39.53)
Prior therapeutic agents (ERT / SRT)	ERT	36 (60.00)	10 (58.82)	11 (45.83)	15 (78.95)	26 (60.47)
	SRT	2 (3.33)	1 (5.88)	0 (0.00)	1 (5.26)	1 (2.33)
Splenectomy	Yes	6 (10.00)	5 (29.41)	0 (0.00)	1 (5.26)	1 (2.33)
	No	54 (90.00)	12 (70.59)	24 (100.00)	18 (94.74)	42 (97.67)
Other prior therapeutic agents	Yes	9 (15.00)	1 (5.88)	1 (4.17)	7 (36.84)	8 (18.60)
	No	51 (85.00)	16 (94.12)	23 (95.83)	12 (63.16)	35 (81.40)
Time since GD diagnosis (years)	n	56	16	23	17	40
	Mean	9.12	18.13	1.97	10.30	5.51
	SD	12.386	16.769	3.213	9.665	7.844
	Minimum	0.0	0.0	0.0	0.0	0.0
	Median	3.45	16.40	0.20	6.70	1.90
	Maximum	45.6	45.6	13.3	33.1	33.1

In the following tables, the status of survey discontinuation and of treatment with VPRIV are shown.

Table 4: Subject Disposition and Withdrawals Safety Population

Disposition	Number of patients (%)
Number of patients(population)	**60 (100.00)**
Completed	0 (0.00)
Ongoing	5 (8.33)
Withdrew	55 (91.67)
Reason for Withdrawal (primary)	
Adverse Events Including Serious Adverse Event	1 (1.67)
Adverse Laboratory Experience	0 (0.00)
Intercurrent Illness	0 (0.00)
Termination of Study by Investigator	4 (6.67)
Patient Lost to Follow-up	1 (1.67)
Death	13 (21.67)
Changing Hospital	4 (6.67)
Other	32 (53.33)

Table 5: Treatment Exposure Safety population

Items	Summary Statistics	Number of patients (%)
Number of patients(population)		**60 (100.00)**
Duration of exposure (days)	n	60
	Mean	1522.4
	SD	856.65
	Minimum	57
	Median	1470.5
	Maximum	2920
Number of times of infusion (times)	n	60
	Mean	94.9
	SD	56.30
	Minimum	5
	Median	97.0
	Maximum	204

Number analysed

See above

Efficacy results

For the analysis of efficacy, the visit interval was set as 12 weeks and the data at the date nearest to each visit were used.

Haemoglobin Concentrations

Overall, mean haemoglobin concentrations increased slowly through Visit 4 and subsequently remained almost stable at approximately 13 g/dL through Visit 30. Similar trends were observed in the age groups <18 years and <4 years.

Based on the changes from baseline, haemoglobin concentrations were classified as "good: increase of at least 1.5 g/dL", "moderate response: increase of at least 0.5 g/dL and less than 1.5 g/dL", and "ineffective (refractory cases): increase less than 0.5 g/dL". Evaluations of haemoglobin concentrations were reported as "good" in 11 (31.43%) patients, "moderate response" in 4 (11.43%) patients, and "ineffective (refractory cases)" in 20 (57.14%) patients. Most of the patients that contributed to the "good" category were paediatric patients (8/11 patients), specifically the age group <4 years (7/8 paediatric contributors). For the age groups <18 years and ≥18 years, "good" was reported in 8 (36.36%) and 3 (23.08%) patients, respectively; for the age group <4 years, "good" was reported in 7 (46.67%) patients (see table below).

Table 6: Evaluation of Haemoglobin Concentration in the Efficacy Population by Age Groups

	Evaluation		
	Good n (%)	**Moderate Response n (%)**	**Ineffective (Refractory Cases) n (%)**
Overall (N = 35)	11 (31.43%)	4 (11.43%)	20 (57.14%)
<4 years (N = 15)	7 (46.67%)	1 (6.67%)	7 (46.67%)
≥4 years (N = 20)	4 (20.00%)	3 (15.00%)	13 (65.00%)
<18 years (N = 22)	8 (36.36%)	2 (9.09%)	12 (54.55%)
≥18 years (N = 13)	3 (23.08%)	2 (15.38%)	8 (61.54%)
<65 years (N = 32)	10 (31.25%)	3 (9.38%)	19 (59.38%)
≥65 years (N = 3)	1 (33.33%)	1 (33.33%)	1 (33.33%)

Source: SHP-GCB-401 Study Report, Attached Figures / Tables: Table 13-1-2.
N: number of patients in the efficacy population (aggregated cases only); n: number of patients in the category.
Definition of evaluation: The change from baseline was classified as follows and tabulated.
- Good: increase ≥1.5 g/dL.
- Moderate response: increase ≥0.5 g/dL and <1.5 g/dL.
- Ineffective (refractory cases): increase <0.5 g/dL.

Platelet Counts

Mean platelet counts increased through Visit 2 and subsequently remained almost stable, ranging from approximately 200 to 300 × 10^9/L through Visit 32. Similar trends were observed in the age groups of <18 years and <4 years.

Based on the changes from baseline, platelet counts were classified as "good: increase of at least 30 × 10^9/L", "moderate response: increase of at least 15 × 10^9/L and less than 30 × 10^9/L", and "ineffective (refractory cases): less than 15 × 10^9/L" for evaluation. However, patients with normal baseline platelet counts (more than 150 × 10^9/L) were excluded. Evaluations of platelet counts were reported as "good" in 9 (47.37%) patients, "moderate response" in 6 (31.58%) patients, and "ineffective (refractory cases)" in 4 (21.05%) patients. The paediatric population showed greater improvement than the adult population. Most of the patients that contributed to the "good" category were paediatric patients (8/9), all in the age group <4 years. For the age groups <18 years and ≥18 years, "good" was reported in 8 (66.67%) patients and 1 (14.29%) patient, respectively; for the age group <4 years, "good" was reported in 8 (80.00%) patients (see table below).

Table 7: Evaluation of Platelet Count in the Efficacy Population by Age Groups

	Evaluation		
	Good n (%)	**Moderate Response n (%)**	**Ineffective (Refractory Cases) n (%)**
Overall (N = 19)	9 (47.37%)	6 (31.58%)	4 (21.05%)
<4 years (N = 10)	8 (80.00%)	1 (10.00%)	1 (10.00%)
≥4 years (N = 9)	1 (11.11%)	5 (55.56%)	3 (33.33%)
<18 years (N = 12)	8 (66.67%)	3 (25.00%)	1 (8.33%)
≥18 years (N = 7)	1 (14.29%)	3 (42.86%)	3 (42.86%)
<65 years (N = 17)	8 (47.06%)	5 (29.41%)	4 (23.53%)
≥65 years (N = 2)	1 (50.00%)	1 (50.00%)	0

Source: SHP-GCB-401 Study Report, Attached Figures / Tables: Table 13-2-2.
N: number of patients in the efficacy population (aggregated cases only); n: number of patients in the category.
Definition of evaluation: The change from baseline was classified as follows and tabulated.
- Good: increase ≥30 × 10^9/L
- Moderate response: increase ≥15 ×10^9/L and <30 × 10^9/L
- Ineffective (refractory cases): increase <15 × 10^9/L

Patients with normal baseline platelet count (>150 × 10^9/L) were excluded.

Liver Volumes

No clear trend was noted in changes in the mean liver volumes in the efficacy population.

Based on the changes from baseline, liver volumes were classified as "good: reduction of at least 30%", "moderate response: reduction of at least 10% and less than 30%", and "ineffective (refractory cases): less than 10% reduction". Evaluations of liver volumes were reported as "good" in none of the patients, "moderate response" in 1 patient (14.29%), and "ineffective (refractory cases)" in 6 patients (85.71%). Data were obtained from only a limited number of patients with easily palpable hepatomegaly at baseline and conclusions could not be drawn from distinct age groups (<18 years: n = 6; <4 years: n = 4).

Table 8: Evaluation of Liver Volume Efficacy population

	Evaluation	n	(%)
Overall	Efficacy population (Aggregated cases only)	7	-
	Good	0	(0.00%)
	Moderate response	1	(14.29%)
	Ineffective (refractory cases)	6	(85.71%)
Prior therapeutic agents - Yes	Efficacy population (Aggregated cases only)	2	-
	Good	0	(0.00%)
	Moderate response	0	(0.00%)
	Ineffective (refractory cases)	2	(100.00%)
Prior therapeutic agents - No	Efficacy population (Aggregated cases only)	5	-
	Good	0	(0.00%)
	Moderate response	1	(20.00%)
	Ineffective (refractory cases)	4	(80.00%)
Prior therapeutic agents - ERT	Efficacy population (Aggregated cases only)	2	-
	Good	0	(0.00%)
	Moderate response	0	(0.00%)
	Ineffective (refractory cases)	2	(100.00%)
Prior therapeutic agents - SRT	Efficacy population (Aggregated cases only)	0	-
	Good	0	(0.00%)
	Moderate response	0	(0.00%)
	Ineffective (refractory cases)	0	(0.00%)
Type of GD - Type 1	Efficacy population (Aggregated cases only)	1	-
	Good	0	(0.00%)
	Moderate response	1	(100.00%)
	Ineffective (refractory cases)	0	(0.00%)
Type of GD - Type 2 or Type 3	Efficacy population (Aggregated cases only)	6	-
	Good	0	(0.00%)
	Moderate response	0	(0.00%)
	Ineffective (refractory cases)	6	(100.00%)
< 4 years	Efficacy population (Aggregated cases only)	4	-
	Good	0	(0.00%)
	Moderate response	0	(0.00%)
	Ineffective (refractory cases)	4	(100.00%)
>= 4 years	Efficacy population (Aggregated cases only)	3	-
	Good	0	(0.00%)
	Moderate response	1	(33.33%)
	Ineffective (refractory cases)	2	(66.67%)
< 18 years	Efficacy population (Aggregated cases only)	6	-
	Good	0	(0.00%)
	Moderate response	0	(0.00%)
	Ineffective (refractory cases)	6	(100.00%)
>= 18 years	Efficacy population (Aggregated cases only)	1	-
	Good	0	(0.00%)
	Moderate response	1	(100.00%)
	Ineffective (refractory cases)	0	(0.00%)
< 65 years	Efficacy population (Aggregated cases only)	7	-
	Good	0	(0.00%)
	Moderate response	1	(14.29%)
	Ineffective (refractory cases)	6	(85.71%)

	Evaluation	n	(%)
>= 65 years	Efficacy population (Aggregated cases only)	0	-
	Good	0	(0.00%)
	Moderate response	0	(0.00%)
	Ineffective (refractory cases)	0	(0.00%)

Definition of evaluation: The change from baseline was classified as follows and tabulated.
Good: >=30% reduction
Moderate response: >=10% and <30% reduction
Ineffective (refractory cases): less than 10% reduction
However, according to the inclusion criteria, patients without readily palpable hepatomegaly at baseline were excluded.

Spleen Volumes

The mean spleen volume reduced at Visit 8 from baseline and subsequently remained almost stable ranging from 100 to 200 cm^3 through Visit 32. Due to the limited number of patients with spleen volume assessments in the age groups <18 years (n = 6) and <4 years (n = 4), no conclusions could be drawn for paediatric patients.

Based on the changes from baseline, spleen volumes were classified as "good: reduction of at least 30%", "moderate response: reduction of at least 10% and less than 30% reduction", and "ineffective (refractory cases): less than 10% reduction". However, patients without moderate splenomegaly, defined by the inclusion criteria 2-3 cm below the left costal margin by palpation at baseline were excluded. Evaluations of spleen volumes were reported as "good" (3 [37.50%] patients) or "ineffective (refractory cases)" (3 [37.50%] patients). All patients that contributed to the "good" category were paediatric patients (3/3), primarily <4 years (2/3).

Table 9: Evaluation of Spleen Volume - Efficacy population

	Evaluation	n	(%)
Overall	Efficacy population (Aggregated cases only)	8	-
	Good	3	(37.50%)
	Moderate response	2	(25.00%)
	Ineffective (refractory cases)	3	(37.50%)
Prior therapeutic agents - Yes	Efficacy population (Aggregated cases only)	2	-
	Good	0	(0.00%)
	Moderate response	1	(50.00%)
	Ineffective (refractory cases)	1	(50.00%)
Prior therapeutic agents - No	Efficacy population (Aggregated cases only)	6	-
	Good	3	(50.00%)
	Moderate response	1	(16.67%)
	Ineffective (refractory cases)	2	(33.33%)
Prior therapeutic agents - ERT	Efficacy population (Aggregated cases only)	2	-
	Good	0	(0.00%)
	Moderate response	1	(50.00%)
	Ineffective (refractory cases)	1	(50.00%)
Prior therapeutic agents - SRT	Efficacy population (Aggregated cases only)	0	-
	Good	0	(0.00%)
	Moderate response	0	(0.00%)
	Ineffective (refractory cases)	0	(0.00%)
Type of GD - Type 1	Efficacy population (Aggregated cases only)	2	-
	Good	0	(0.00%)
	Moderate response	1	(50.00%)
	Ineffective (refractory cases)	1	(50.00%)

	Evaluation	n	(%)
Type of GD - Type 2 or Type 3	Efficacy population (Aggregated cases only)	6	-
	Good	3	(50.00%)
	Moderate response	1	(16.67%)
	Ineffective (refractory cases)	2	(33.33%)
< 4 years	Efficacy population (Aggregated cases only)	4	-
	Good	2	(50.00%)
	Moderate response	0	(0.00%)
	Ineffective (refractory cases)	2	(50.00%)
>= 4 years	Efficacy population (Aggregated cases only)	4	-
	Good	1	(25.00%)
	Moderate response	2	(50.00%)
	Ineffective (refractory cases)	1	(25.00%)
< 18 years	Efficacy population (Aggregated cases only)	6	-
	Good	3	(50.00%)
	Moderate response	1	(16.67%)
	Ineffective (refractory cases)	2	(33.33%)
>= 18 years	Efficacy population (Aggregated cases only)	2	-
	Good	0	(0.00%)
	Moderate response	1	(50.00%)
	Ineffective (refractory cases)	1	(50.00%)
< 65 years	Efficacy population (Aggregated cases only)	7	-
	Good	3	(42.86%)
	Moderate response	2	(28.57%)
	Ineffective (refractory cases)	2	(28.57%)
>= 65 years	Efficacy population (Aggregated cases only)	1	-
	Good	0	(0.00%)
	Moderate response	0	(0.00%)
	Ineffective (refractory cases)	1	(100.00%)

Definition of evaluation: The change from baseline was classified as follows and tabulated.
Good: >=30% reduction
Moderate response: >=10% and <30% reduction
Ineffective (refractory cases): less than 10% reduction
However, as defined by the inclusion criteria at baseline (2 - 3 cm below from the left costal margin by palpation) excluded patients without moderate splenomegaly.

BMDs

No trend was noted for BMD (lumbar spine T-scores, lumbar spine Z-scores, lumbar spine BMD, femur neck T-scores, femur neck Z-scores, and femur neck BMD) since the number of evaluable patients was low (≤3 patients).

Antivelaglucerase Alfa and Neutralising Antibodies

Two (2) patients had positive antivelaglucerase alfa antibody test results; both were aged <18 years at baseline and treated for more than 6 years at the end of the survey period. No lack of efficacy or noteworthy effect on efficacy evaluation due to antibody production was recognised.

Safety results

Overall, the mean (SD) duration of exposure was 1522.4 (856.65) days and the mean (SD) number of times of infusion was 94.9 (56.30) times (see above).

Adverse Events

A total of 42 (70.00%) patients had 283 adverse events (AEs). The most frequently reported AEs (≥10% of patients) were pyrexia (9 [15.00%] patients), pneumonia (7 [11.67%] patients), and anaemia and hepatic function abnormal (6 [10%] patients each).

The majority of patients who had AEs were in the paediatric group (<18 years); the incidences of AEs in patients <18 years and ≥18 years were 77.78% (28/36) and 58.33% (14/24), respectively. The types of AEs (PTs) in patients aged <18 years were similar to those observed in the overall population. The most frequently reported AEs in the age group <18 years (≥10% of patients) were pneumonia and pyrexia (7 [19.44%] patients each), and anaemia, urinary tract infection, and hepatic function abnormal (4 [11.11%] patients each).

Occurrence of Adverse Drug Reactions / Infections

Fourteen (14, 23.33%) patients experienced 52 adverse drug reactions and infection events. The most frequently reported adverse drug reactions (≥2 patients) were pyrexia (4 [6.67%] patients), and respiratory failure, vomiting, hepatic function abnormal, and antibody test positive (2 [3.33%] patients each).

Most of the patients who had adverse drug reactions were in the paediatric group (<18 years); the incidences of adverse drug reactions in patients <18 years and ≥18 years were 36.11% (13/36) and 4.17% (1/24), respectively. The types of adverse drug reactions (PTs) in patients aged <18 years were similar to those observed in the overall population. The most frequently reported adverse drug reactions (≥2 patients) were pyrexia (4 [11.11%] patients), and respiratory failure, vomiting, hepatic function abnormal, and antibody test positive (2 [5.56%] patients each). The incidence of adverse drug reactions in the age group <4 years was 47.62% (10/21). The most frequently reported adverse drug reactions (PTs) in patients <4 years were pyrexia (4 [19.05%] patients) and respiratory failure (2 [9.52%] patients).

The observation of the incidence of adverse drug reactions by onset time indicated that the incidence of adverse drug reactions did not increase with long-term treatment. The incidence of adverse drug reactions was 3.33% (2 patients) for the period from the date of initial treatment to Day 1, 5.00% (3 patients) for Day 2 to Day 31, 10.00% (6 patients) for Month 1 to Month 6 (Day 32 to Day 182), 7.14% (4 patients) for Month 6 to Year 1 (Day 183 to Day 365), 10.91% (6 patients) for Year 1 to Year 2 (Day 366 to Day 730), and 10.42% (5 patients) from Year 3 onward (from Day 731 onward).

By outcome, the incidence of adverse drug reactions was 3.33% (2 patients) for fatal reactions, 10.00% (6 patients) for reactions that were not recovered / not resolved, 3.33% (2 patients) for reactions that were recovered / resolved with sequelae, 6.67% (4 patients) for recovering / resolving, 16.67% (10 patients) for recovered / resolved, and 5.00% (3 patients) for reactions with unknown outcome. The 2 patients with fatal reactions were due to serious adverse drug reactions of respiratory failure (1 paediatric patient, aged 1 year) and death (1 paediatric patient, aged 17 years). Short narratives have been provided.

Occurrence of Serious Adverse Events

Twenty-seven (27, 45.00%) patients experienced 73 serious adverse events (SAEs). The most frequently reported SAEs (≥2 patients) were pneumonia and respiratory failure (3 [5.00%] patients each) and sepsis, urinary tract infection, myoclonic epilepsy, and vesicoureteric reflux (2 [3.33%] patients each).

Most of the patients who had SAEs were in the paediatric group (<18 years); the incidence of SAEs in patients <18 years and ≥18 years was 58.33% (21/36) and 25.00% (6/24), respectively. The SAEs

rates by paediatric age group were 71.43% (15/21) in patients <4 years, 28.57% (2/7) in patients 4 to 11 years, and 50% (4/8) in patients 12 to 17 years. The types of SAEs (PTs) in patients <18 years of age were similar to those in the overall population. The most frequently reported SAEs in the age group <18 years (≥2 patients) were pneumonia and respiratory failure (3 [8.33%] patients each) and urinary tract infection and vesicoureteric reflux (2 [5.56%] patients each).

Occurrence of Serious Adverse Drug Reactions / Infections

Five (5, 8.33%) patients (all <18 years) experienced 14 serious adverse drug reactions and infection events. The reactions included respiratory failure in 2 (3.33%) patients; as well as peritonitis, colitis ischaemic, gastroenteritis eosinophilic; vomiting; and death in 1 patient each. The causal relationship was considered as "unlikely" related for all reactions, except for the reaction of vomiting, which was considered "likely" related. Four (4) of the 5 patients had Type 2 GD and 1 had Type 3 GD.

Safety Considerations in the Risk Management Plan

The occurrence of adverse drug reactions corresponding to the safety considerations in the risk management plan (RMP) is shown in the table below.

Summary of Adverse drug reactions / infections in additional Pharmacovigilance planning - Safety population

Safety analysis set	**60**			
Safety investigation items	**Seriousness**			
	Serious		**Non-serious**	
Important Identified Risks		-		-
Infusion reaction	1	(1.67%)	5	(8.33%)
Important Potential Risks		-		-
Anti-Velaglucerase Alfa Antibody	0	(0.00%)	2	(3.33%)
Important Missing Information		-		-
Lack of safety data in treatment-naïve Japanese patients	2	(8.70%)	6	(26.09%)
Limited safety data for patients with type 2 and 3 GD	5	(11.63%)	12	(27.91%)
Limited safety data of Japanese paediatric patients	5	(13.89%)	12	(33.33%)
Lack of safety data of Japanese elderly patients	0	(0.00%)	0	(0.00%)

Important Identified Risks: Infusion Reaction

The important identified risk of infusion reaction was defined as reactions occurring up to 24 hours of initial treatment. Regarding adverse drug reactions corresponding to infusion reactions, 6 (10.00%) patients (all paediatric patients aged 0-2 years) had 8 events. The events included pyrexia (3 events in 2 [3.33%] patients, aged 0 and 1 year); hypersensitivity and swelling of eyelid (both events once in the same patient, aged 1 year); and vomiting, urticaria, and injection site swelling (1 event in 1 [1.67%] patient each, aged 2, 1, and 0 years, respectively). All infusion reaction events were nonserious, except vomiting that was serious.

No noteworthy trends were noted during the period from the date of initial treatment with this drug to the onset of the event. For most of these reactions (7/8) the time from onset to outcome was up to 7 days with 4/7 reactions reaching an outcome within the first day. The outcomes of all cases were recovered / resolved. The causal relationship with VPRIV was "definitely related" or "probably related" for all cases.

Important Potential Risks: Antivelaglucerase Alfa Antibodies

As regards antivelaglucerase alfa antibody production, 2 (both paediatric patients) of the 15 patients tested were positive for antivelaglucerase alfa antibodies; titres of the 2 patients were 20 and 5120, respectively. One (1) patient (aged 5 years) with the titre of 20 had a negative neutralising antibody test. For this patient, a nonserious adverse drug reaction of rash was reported in addition to a positive antibody test; this adverse drug reaction was alleviated with no intervention while continuing treatment with VPRIV. Another patient (aged 1 year) with the titre of 5120 had a positive immunoglobulin E antibody test with titre of 80. For this patient, nonserious adverse drug reactions of swelling of eyelid and hypersensitivity were reported in addition to a positive antibody test result; both swelling of eyelid and hypersensitivity resolved without intervention while continuing treatment with VPRIV. No lack of efficacy or noteworthy safety issues due to antibody production were observed in these patients.

Important Missing Information

- Lack of safety data in treatment-naïve Japanese patients: The incidence of adverse drug reactions by status of prior therapeutic agents was 21.62% (8/37) in patients with and 26.09% (6/23) in patients without prior therapeutic agents (treatment-naïve). Adverse drug reactions that occurred in at least 2 patients with prior therapeutic agents were vomiting, pyrexia, and antibody test positive (5.41% [2/37] each), and those that occurred in at least 2 patients without prior therapeutic agents were pyrexia. No noteworthy safety issues were noted in patients without prior therapeutic agents.
- Limited safety data for patients with Type 2 and Type 3 GD: The incidence of adverse drug reactions by GD type was 5.88% (1/17) in patients with Type 1, 50.00% (12/24) with Type 2, 5.26% (1/19) with Type 3, and 30.23% (13/43) with Type 2 or Type 3, indicating a higher incidence with Type 2 or Type 3 GD (particularly Type 2). Adverse drug reactions reported in patients with Type 2 or Type 3 GD were pyrexia (9.30% [4/43]), respiratory failure, vomiting, hepatic function abnormal, and antibody test positive (4.65% [2/43] each), peritonitis, hypersensitivity, hypokalaemia, insomnia, hypertonia, myoclonus, swelling of eyelid, cardiac failure congestive, colitis ischaemic, constipation, diarrhoea, gastroenteritis eosinophilic, hyperchlorhydria, gastric hypomotility, erythema, rash, urticaria, albuminuria, proteinuria, death, injection site swelling, aspartate aminotransferase increased, femur fracture, hand fracture, tibia fracture, ulna fracture, and product preparation issue (2.33% [1/43] each). Type 2 GD is generally known to be more severe than GD Type 1 or 3.Based on the fact that many of the reported adverse drug reactions were caused by the primary disease, the difference in severity of the primary disease may have affected the difference in the incidence of adverse drug reactions.
- Limited safety data in Japanese paediatric patients: For paediatric patients, the incidence of adverse drug reactions in patients aged <18 years old was high at 36.11% (13/36); however, most of them were also considered to be affected by the primary disease or progression of the primary disease. The incidence of adverse drug reactions was 47.62% (10/21) in patients <4 years, 28.57% (2/7) in patients 4 to 11 years, and 12.5% (1/8) in patients 12 to 17 years. This indicates that higher incidences of adverse drug reactions were reported in the age groups of <4 years and <18 years compared with ≥18 years (4.17% [1/24]).
- Lack of safety data in Japanese elderly patients: The incidence of adverse drug reactions in patients ≥65 years of age was 0%. No particular safety concerns were noted for treatment of the elderly.

Additional details on safety considerations in the RMP are provided in the SHP-GCB-401 Study Report.

For the laboratory test values, changes in haemoglobin concentrations and platelet counts are described in the study report. No other laboratory test values were noteworthy.

2.3.3. Discussion on clinical aspects

Study SHP-GCB-401, titled 'Drug Use-results Survey for VPRIV® for I.V. Infusion 400 Units' was a post-marketing survey to evaluate the safety and efficacy of VPRIV in patients with Gaucher disease in Japan, who were either treatment naïve or had been switched from another therapeutic agent for Gaucher disease. The MAH declared that the study was neither part of the PIP nor part of the clinical development program of VPRIV.

The study used survey methods with a central enrolment system and included patients with a confirmed diagnosis of Gaucher disease Type 1, 2, or 3, regardless of age or sex. According to the MAH, VPRIV was administered as per the approved label, but as this was a purely Japanese study, this was according to the Japanese label. In Japan, the indication for VPRIV appears not to be restricted to specific types of Gaucher Disease. Safety and efficacy data that were available as part of routine clinical practices related to Gaucher disease were used; case report forms (CRFs) were collected every 6 months for 2 years and then yearly thereafter. The observation period of the study covered the period from the initial marketing in Japan to September 2022 (8 years after launch).

Overall, 63 patients were enrolled at 45 sites; data were analysed for 60 patients and efficacy data were available for 58 patients. Only about 28% (17/60) of analysed patients were classified as Gaucher disease Type 1; the majority of patients (40%, 24/60) had Gaucher disease Type 2 and about 32 % (19/60) were classified as Type 3. In the EU, VPRIV is however only licensed for Gaucher disease Type 1 and is not considered effective in Gaucher disease Type 2; the MAH received a paediatric waiver for Gaucher Disease Type 2 on the grounds that the specific medicinal product is likely to be ineffective.

As regards safety, the incidence of adverse drug reactions was 23.33% (14 patients), 3.33% (2 patients) for fatal reactions, 10.00% (6 patients) for reactions that were not recovered / not resolved, 3.33% (2 patients) for reactions that were recovered / resolved with sequelae, 6.67% (4 patients) for recovering / resolving, 16.67% (10 patients) for recovered / resolved, and 5.00% (3 patients) for reactions with unknown outcome.
According to the MAH, the 2 patients with fatal reactions were due to serious adverse drug reactions of respiratory failure (1 paediatric patient, aged 1 year) and death (1 paediatric patient, aged 17 years).However, although the study report distinguishes between adverse events (= no causality assessment) and adverse drug reactions (= at least a possible causal relationship), the MAH considered all serious adverse drug reactions (except events of vomiting) as unlikely related. None of the 5 patients with serious adverse drug reactions (including the 2 patients with fatal respiratory failure) suffered from Gaucher disease Type 1; 4 patients had Gaucher disease Type 2 and 1 Type 3.
The incidence of adverse drug reactions in paediatric patients was higher than in the overall population (36.11% and 23.33%, respectively). Many events were however considered to be due to the primary disease.
The incidence of adverse drug reactions did not increase with long-term treatment.
Based on the reported incidences, severity, and outcome of individual adverse drug reactions, in accordance with the MAH, no new safety measures are currently considered necessary; the provided data are not considered divergent to the known safety profile of VPRIV.

As regards efficacy, the mean haemoglobin concentrations and mean platelet counts increased with treatment and thereafter remained stable over time. Trends were similar between age groups of <18 years and <4 years of age. Most of the patients who reported "ineffective / refractory" response were adults (≥18 years), while patients aged <18 years, especially patients aged <4 years, contributed the

most to the category “good” response.
No clear trend was noted in changes in the mean liver volumes in the efficacy population, but data were only obtained from a very limited number of patients with easily palpable hepatomegaly at baseline.
Mean spleen volume was reduced from baseline to Visit 8 and remained almost stable thereafter. There was only a limited number of patients with spleen volume assessments in the age groups <18 years (n = 6) and <4 years (n = 4).
As regards BMD (lumbar spine T-scores, lumbar spine Z-scores, lumbar spine BMD, femur neck T-scores, femur neck Z-scores, femur neck), the number of evaluable patients was low (≤3 patients) and thus no trend could be evaluated.
Two (2) patients had positive anti-velaglucerase alfa antibody test results; both were aged <18 years at baseline; no lack of efficacy was recognised.
The reported efficacy results are not considered to significantly deviate from previous findings.

The provided ‘Safety Considerations in the Risk Management Plan’ does not appear to relate to the EU RMP for VPRIV and is not comprehensible for the EU licensing of VPRIV.

Overall, the reported information from study SHP-GCB-401 does not appear to significantly deviate from the known safety and efficacy profile of VPRIV, but transferability is questioned due to the inclusion of patients with Gaucher disease Type 2 and Type 3.
Furthermore, reporting of the data is very limited and does not allow for any meaningful analysis of the information provided. The majority of patients had Gaucher Type 2 (40%, 24/60) or Type 3 (32%, 19/60); only about 28% (17/60) of the patients were classified as Gaucher disease Type 1, although in the EU, VPRIV is only licensed in Type 1 Gaucher disease and VPRIV is considered ineffective in Gaucher disease Type 2. Overall, 36/60 patients included in the study were <18 years of age; the number of patients <18 years of age with Gaucher disease Type 1 has not been identified in the provided data. Interpretation of the safety and efficacy findings is also limited by the small sample size overall and the design of study.

Due to the study design aimed at the Japanese license including a majority of non-Type 1 Gaucher disease patients, it is considered that the study does not deliver any meaningful new information but rather confirms limiting the indication to Gaucher disease Type 1 in the EU.

No changes to the PI are warranted based on the data provided.

3. Rapporteur’s overall conclusion and recommendation

The benefit-risk ratio of VPRIV remains unchanged by the data provided and no changes to the PI are warranted based on these data.

☒ Fulfilled:

No regulatory action required.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

None

Clinical studies

Product Name: VPRIV Active substance: velaglucerase alfa

Study title	Study number	Date of completion	Date of submission of final study report
Drug Use-results Survey for VPRIV® for I.V. Infusion 400 Units	SHP-GCB-401	14 May 2024	26 September 2024