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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/P46/031

Note

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

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1. Introduction

On 12 December 2023, 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 the 'Post Marketing Surveillance Study for VPRIV® in India' (SHP669-406) 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 study used the commercially available formulation of velaglucerase alfa (400 units of powder for solution for infusion).

2.3. Clinical aspects

2.3.1. Introduction

VPRIV (velaglucerase alfa) is a recombinant form of the human lysosomal enzyme glucocerebrosidase (GCB) indicated as a long-term enzyme replacement therapy (ERT) for adult and paediatric patients with confirmed type 1 Gaucher disease. At the time of the initial MAA, data from 5 clinical studies (TKT025, TKT032, TKT034, HGT-GCB-039, and the extension study TKT025EXT) were provided to assess the benefit-risk balance of VPRIV in patients who were treatment naïve to ERT for Gaucher disease and those who had previously received imiglucerase as ERT.

VPRIV was first approved in the USA on 25 February 2010 and in the EU on 26 August 2010. According to the MAH, as of February 2023, VPRIV has been approved in 69 countries worldwide.

The current application concerns study SHP669-406 titled 'Post Marketing Surveillance Study for VPRIV® in India'. It is a multicentre, uncontrolled, open-label, postmarketing surveillance study that collected retrospective and prospective data from subjects who were administered VPRIV under standard clinical practice in the postmarketing setting in India.

The MAH has submitted a final report for:

- SHP669-406 - Post Marketing Surveillance Study for VPRIV® in India.

2.3.2. Clinical study

Clinical study number and title

SHP669-406 - Post Marketing Surveillance Study for VPRIV® in India

Description

The current application concerns study SHP669-406 titled 'Post Marketing Surveillance Study for VPRIV® in India'. It is a multicentre, uncontrolled, open-label, postmarketing surveillance study that collected retrospective and prospective data from subjects who were administered VPRIV under standard clinical practice in the postmarketing setting in India for an approximately 12-month period. Start of data collection was July 2021 and end of data collection May 2023; the final CSR is dated 15 November 2023.

The period from the first time the subject was dosed in a charitable access program (CAP) until the signing of the informed consent form in study SHP669-406 was considered retrospective, and the period from informed consent to the end of the study / early discontinuation was considered prospective.

Methods

Study participants

The study aimed to recruit through a CAP up to 21 patients with Type 1 Gaucher disease, who had already received and continued to receive VPRIV. Patients were to be excluded if they met any of the contraindications included in the current Indian PI. Patients were followed for a total of approximately 12 months. Patients or legally authorised representatives had provided written informed consent to participate.

According to the CSR, the study was conducted in compliance with the protocol, the Declaration of Helsinki, International Society for Pharmacoepidemiology Guidelines for Good Epidemiology Practices, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Guidelines for Methodological Standards in Pharmacoepidemiology, Good Pharmacovigilance Practices, and all applicable regulatory requirements.

Treatment

The study used the commercially available formulation of velaglucerase alfa, i.e. 400 units of powder for solution for infusion.

Objectives

The primary objective of the study was to characterise the safety profile of VPRIV for patients with Type 1 Gaucher disease in standard clinical practice in India using both retrospective and prospective data.

The secondary objectives of the study were to describe effectiveness in patients with Type 1 Gaucher disease receiving VPRIV in standard clinical practice in India using both retrospective and prospective data, to collect and record genetic mutation data, if available, from patients with Type 1 Gaucher disease, and to collect retrospective data on treatment history, effectiveness, and safety data of the previous VPRIV treatment.

Outcomes / endpoints

Safety data were collected on serious adverse events (SAEs) / adverse drug reactions (ADRs), unexpected adverse events (AEs) / ADRs not listed on the current VPRIV Indian PI, and expected AEs, non-serious AEs / ADRs. AEs were categorised according to MedDRA dictionary and summarised by

system organ class (SOC) and preferred term (PT); they were cross-tabulated for relatedness, seriousness, and severity. AEs that occurred before VPRIV administration were listed separately.

The effectiveness of dosing of VPRIV was assessed by changes in haemoglobin concentration, platelet counts, and spleen and liver size. Spleen / liver length and volume were analysed separately, depending on the data available.

Genetic mutation data included the genetic mutations N370S (p.Asn409Ser), L444P (p.Leu483Pro), D409H (p.Asp448His), 84GG (c.84dupG), and IVS2 + 1 (c.115+1G>A); if available, other possible genetic mutations were to be captured as well.

Sample size

A sample size of up to 21 CAP patients was proposed, according to the MAH based on the prevalence and incidence of Type 1 Gaucher disease in India.

Randomisation and blinding (masking)

The study was conducted open-label without comparator.

Statistical Methods

All variables were summarised by descriptive statistics. No statistical comparison or inference was made. Continuous variables were summarised by number of patients (i.e. non-missing), mean, standard deviation (SD), 95% 2-sided confidence interval (CI) for mean, median, minimum, and maximum. The categorical variables were summarised using frequency tables (frequencies and percentages).

The safety analysis set (SAF) consists of all patients who were enrolled and received at least 1 infusion of VPRIV. The Safety Follow-Up Analysis Set (FSAF) was defined as a subset of the SAF and contains all patients who had at least one follow-up visit. Safety analyses were performed using both retrospective and prospective data separately; for the prospective data, safety analyses were carried out using FSAF analysis set.

The Effectiveness Full Analysis Set (EFAS) was defined as a subset of the SAF. Patients with baseline and at least one measurement of effectiveness during the study were included. This dataset was used for the effectiveness analysis. Summary statistics along with change from actual baseline to 12 months (observation period) were reported for this population.

Missing data in safety parameters or other categories were not imputed; the available dataset was used for analysis.

Eligible patients were enrolled sequentially to avoid selection bias.

Results

Participant flow

The original study protocol, dated 29 January 2019, was amended 4 times. Amendments 1 and 2 were instituted before the first patient was enrolled. Amendment 1, dated 18 Dec 2019, revised the secondary objectives and updated the safety reporting to the Indian Health Authority. Amendment 2, dated 31 Mar 2021, revised primary and secondary objectives, study design, and safety and effectiveness sections. Amendment 3, dated 16 Aug 2022, updated the study population to ensure only Type 1 Gaucher disease patient to be enrolled based on a requirement by the Health Authority.

Amendment 4, dated 07 Nov 2022, changed the name of the Sponsor from "Shire Biotech India Pvt. Ltd." to "Takeda Biopharmaceuticals, India Pvt. Ltd.".

No major protocol deviations were reported during the study. Two (9.5%) patients had minor protocol deviations, both related to a monitoring visit.

Recruitment

As targeted, 21 patients from the CAP, who had already received and continued to receive VPRIV, were recruited within 12 months. Participating sites were medical colleges and hospitals for the treatment of Type 1 Gaucher disease in India.

All 21 patients provided consent to participate in the prospective part of the study and received at least 1 infusion of VPRIV (SAF) and all of them had attended at least 1 follow-up visit (FSAF). Also, all 21 patients had at least 1 measurement of effectiveness following the baseline assessment during the study, including the prospective and retrospective periods.

None of the patients was re-diagnosed as Type 3 Gaucher disease post enrolment into the study.

Baseline data

Patient demographic and baseline characteristics for the SAF are presented in the table below. Out of 21 patients, 14 (66.7%) were male and 7 (33.3%) female. The mean (SD) of age, height, weight, and body mass index (BMI) of the overall population was 14.6 (8.37) years, 136.52 (20.732) cm, 35.884 (18.5964) kg, and 17.59 (4.955) kg/m^2, respectively. More than 25% of the patients were 4 to 11 (38.1%) or 18 to 40 years (33.3%) old.

Table 1: Demographic and Baseline Characteristics (Safety Analysis Set)

	Statistic	VPRIV (N=21)
Age (years)		
	n	21
	Mean (SD)	14.6 (8.37)
	Median	12.0
	95% CI (Mean)	10.8, 18.4
	Min - Max	3 - 34
Age group (years)		
< 4*	n (%)	1 (4.8)
4 - 11	n (%)	8 (38.1)
12 - 17	n (%)	5 (23.8)
18 - 40	n (%)	7 (33.3)
41 - 60	n (%)	0
61 and above	n (%)	0
Sex		
Female	n (%)	7 (33.3)
Pregnancy Status		
Yes	n (%)	0
No	n (%)	4 (57.1)
NA**	n (%)	3 (42.9)
Breastfeeding Status		
Yes	n (%)	0
No	n (%)	2 (28.6)
NA	n (%)	5 (71.4)
Male	n (%)	14 (66.7)
Partner Pregnancy Status		
Yes	n (%)	0
No	n (%)	0
NA***	n (%)	13 (61.9)
Height (cm)		
	n	19
	Mean (SD)	136.52 (20.732)
	Median	140.50
	95% CI (Mean)	126.53, 146.51
	Min - Max	88.0 - 167.0
Weight (kg)		
	n	21
	Mean (SD)	35.884 (18.5964)
	Median	30.600
	95% CI (Mean)	27.419, 44.349
	Min - Max	11.16 - 87.00
Body Mass Index (kg/m^2)		
	n	19
	Mean (SD)	17.59 (4.955)
	Median	16.50
	95% CI (Mean)	15.20, 19.98
	Min - Max	11.3 - 31.2

CI=Confidence Interval; Min=Minimum; Max=Maximum; SD=Standard Deviation; NA=Not Applicable
Percentages except for Female are based on the Safety Analysis Set. Percentages under Female are based on the female population
The data was collected and reported for prospective baseline
The prospective baseline was defined as the last non-missing measurement taken prior to prospective reference start date.
* Patient was already under CAP program and was enrolled on the study and the India PI does not specify any age specific contraindications
** The patients were underaged (did not reach the puberty)
*** For 1 patient, the data was not available in eCRF for partner pregnancy status

The majority of the patients were diagnosed with Gaucher disease by more than 1 method. All the patients except one were diagnosed by deficiency in enzyme activity; this patient was diagnosed by genotype mutation tests and liver biopsy. Genotypic mutation tests ranked second in the methods for diagnosis of Gaucher disease (16 of 21 patients). Out of 16 patients being diagnosed by genetic mutations, 14 patients had L444P mutation in the GBA gene, 1 patient had 2 genetic mutations (D409H and 145G>A[PA448T]), and for 1 patient, the genotype was unknown.

Table 2: Diagnosis of Gaucher Disease (Safety Analysis Set)

	Statistic	VPRIV (N=21)
Number of patients previously treated for Gaucher Disease	n (%)	0
Method of Gaucher Disease Diagnosis[1]		
Deficient glucocerebrosidase (GCB) activity in leukocytes	n (%)	18 (85.7)
Genotype	n (%)	16 (76.2)
Enzyme activity[2]	n (%)	8 (38.1)
Other[3]	n (%)	4 (19.0)
Genotype of Gaucher Disease Diagnosis		
N370S	n (%)	0
L444P	n (%)	14 (66.7)
D409H	n (%)	1 (4.8)
84GG	n (%)	0
IVS2	n (%)	0
Unknown	n (%)	1 (4.8)
Other[4]	n (%)	1 (4.8)

A patient might have more than one diagnosis method and genotype.
Percentage was based on the Safety Analysis Set.
Notes:
1.A patient might be diagnosed with the Type 1 Gaucher Disease by more than one method.
2. Out of 8 patients who were diagnosed with Type 1 Gaucher Disease by enzyme activity 7 patients were detected by more than 1 method and 1 patient was detected by only enzyme activity.
3.The other method of diagnosis included V460V(C.1497G>C), Liver biopsy, and elevated levels of chitotriosidase (106-fold elevation).
4. The other genotype included 145G>A(PA448T) D409H.

None of the enrolled patients had received any treatment prior to VPRIV (as a part of CAP) for Gaucher disease.

Medical history was collected from only 7 (33.3%) patients; 1 patient each had the medical history of myoclonic epilepsy; hydrocele, hepatic cirrhosis, proteinuria, anaemia, vitamin D deficiency, ascites, duodenitis, and portal hypertension; seizures and myoclonus; cholecystectomy; hypoalbuminaemia; rhinitis allergic and femur fracture; pregnancy and abortion spontaneous. Medical history of interest, namely splenectomy, medullary bone infarcts, and avascular necrosis, was evaluated. Three (3, 14.3%) patients had a medical history of splenectomy. None of the patients had the history of medullary bone infarcts or avascular necrosis.

A total of 8 (38.1) patients received at least 1 concomitant medication prior to, or / and which continued during retrospective period (retrospective reference start date). Eleven (11, 52.4%) patients received at least 1 concomitant medication during the prospective period (the medication start date was on or after the prospective reference start date). More than 1 patient was on paracetamol (6 patients) and ferrous ascorbate / folic acid (2 patients).

As regards study medication compliance, data is limited for the retrospective period since missed doses data during retrospective period was not collected. During the prospective period, VPRIV planned doses were 71 and mean (SD) dose was 51.3 (12.30) U/kg. The overall mean compliance with study medication was 92.169% (11.9815). More than 90% of the patients were continuing with VPRIV at all visits except at Month 9 (81%). The proportion of patients with dose change was 14.3% from Month 1 to 7 (except at Month 2), which further declined to 9.5% at Months 8 to 10 and 4.8% at Months 11 to 13. None of the patients had any change in dose frequency during the prospective period.

Numbers analysed

Of the 21 patients, 19 patients completed the study and 2 discontinued early; 1 patient withdrew consent and 1 was discontinued by the physician due to a non-drug related AE. Patient disposition is summarised in the table below.

Table 3: Patient Disposition (All Patients)

	Statistic	VPRIV (N=21)
Number of Patients Consented	n	21
Number of Treated Patient	n	21
Number of Patients in Safety Analysis Set (SAF)	n	21
Number of Patients re-diagnosed as GD Type 3 post enrollment	n	0
Number of Patients in Safety Follow-Up Analysis Set (FSAF)	n	21
Number of Patients in Effectiveness Full Analysis Set (EFAS)	n	21
Number of Patients who Completed the Study	n	19
Number of Patients who Discontinued the Study	n	2
Primary Reason for Discontinuation		
Adverse Event	n (%)	0
Death	n (%)	0
Participant withdrawal (withdrew consent)	n (%)	1 (50.0)
Discontinuation by physician	n (%)	1 (50.0)
Other	n (%)	0

n=Number of patients having an event
SAF=Safety Analysis Set; FSAF=Safety Follow-up Analysis Set; EFAS=Effectiveness Full Analysis Set
Percentage was based on the number of patients who discontinued the Study

Efficacy results

Haemoglobin Concentration

Overall, 17/21 (81%) patients had improvement in Hb concentration or maintained Hb concentration within normal range during the study.

Eleven (11) patients had Hb concentration < LLN at beginning of the study. Of these, 7 patients showed improvement to within normal ranges at the end of the study. Of the other 4 patients, 1 showed improvement but did not reach normal range; 2 maintained the same range, and 1 showed a further decline in Hb concentration at the end of the study.

Ten (10) patients had Hb concentration within normal range at the beginning of the study. Of these, 9 patients maintained a Hb concentration within normal range until the end of the study. One (1) patient was within normal range during the beginning of the study but did not have any further Hb concentration reported during the study.

Platelet Count

Overall, 18/21 (86%) patients had improvement or maintained normal platelet count values during the study. Fourteen (14) patients had low or normal platelet count at baseline and achieved a normal platelet count (8 improved, 6 maintained normal range) at the end of the study.

Twelve (12) patients had a low platelet count at the beginning of the study. Of these, 6 patients had improvement in platelet counts (low to normal range) until the end of the study. In the remaining 6 patients, the platelet count level remained below the normal range at the end of the study. One (1) patient showed an initial improvement in platelet count to normal levels followed by a decline but was still improved from baseline by the end of the study. Of the other 5 patients, 3 had an increasing trend in platelet count.

Seven (7) patients had a platelet count within normal range at the beginning of the study. Of these, 6 patients continued to have a platelet count within normal range until end of study and 1 patient did not have any further platelet counts reported during the study period.

Two (2) patients had platelet counts above ULN at beginning of the study, which normalised by the end of the study.

Out of 14 patients with abnormal platelet count levels at beginning of the study, 8 reported a normal platelet count at end of study.

Liver Size

Liver size by length (cm) was measured in 16 and by volume (mL) in 5 patients. Overall, 16/21 (76%) patients had improvement or maintained normal liver size during the study. Three (3) patients had liver size above normal range at the start of the study. Of these, 1 patient had reduction to normal range, followed by an increase by the end of the study. Two (2) patients did not have liver values measured during the study period after baseline assessments.

Thirteen (13) patients had either low or normal liver size at the beginning of the study. Of these, 4 patients had a further reduction in liver size, 9 continued to have liver size within normal range, and 5 had either low or normal liver volume at the beginning of the study. Of the latter, 3 patients had a reduction and 2 an increase in liver volume during the study period.

Liver Volumes in Multiple of Normal

The mean liver volume in multiple of normal at baseline was lower (0.666) during the prospective period as compared to the retrospective period (0.838). During the retrospective period, 1 patient had hepatomegaly (moderate or severe; multiple of normal > 1.25) at Months 19 and 77 and following Month 77, the patient had normal liver volume to body weight. During the prospective period, none of the patients had hepatomegaly.

Spleen Size

Spleen size was measured by length (cm) in 15 and by volume (mL) in 3 patients; no data were available for 3 patients (all 3 splenectomised). Overall, 14/18 (78%) patients with spleen size measurements had an improvement or maintained normal spleen size during the study.

Thirteen (13) patients had spleen size above normal range for their age group at the start of the study. Of these, 11 patients demonstrated reduction in spleen size and 4 of these had spleen size reduced to normal at the end of the study period. In the remaining 2 patients the size of the spleen did not change during the study.

Two (2) patients had normal spleen size at baseline; 1 had further reduction in the size of the spleen during the study and 1 had an increase during the study.

Three (3) patients had either low or normal spleen volume at the beginning of the study. Of these, 1 patient had a reduction and 2 an increase in spleen volume by end of study.

Spleen Volumes in Multiple of Normal

The mean spleen volume in multiple of normal at baseline during the prospective period (3.490) was slightly higher than during the retrospective period (2.967). During retrospective period, 1 patient had splenomegaly (moderate or severe; multiple of normal > 5) at Months 18, 37, 53, 58, and 65. During the prospective period, none of the patients had splenomegaly.

Laboratory Evaluation

No abnormal clinically significant haematological finding (haemoglobin concentration, platelet count) was reported during the retrospective or prospective period. Laboratory data at each visit were not captured in the eCRF.

Vital Signs

There were no major changes in vital signs across different months in the prospective period.

Safety results

Characterising the safety profile of VPRIV in standard clinical practice for patients with Gaucher disease in India was the primary objective of the study. Safety data were collected as SAEs / ADRs, unexpected AEs / ADRs (not listed in current VPRIV PI in India), expected AEs, and non-SAEs / ADRs. A summary of the AEs and incidences by SOC and PT during the retrospective and prospective periods are provided in the tables below.

During the retrospective period, 2 (9.5%) patients had at least 1 AE; 1 patient had cholelithiasis (SOC: Hepatobiliary disorders) and abdominal distension (SOC: GI disorders), and the other patient had post-procedural infection (SOC: Infections and infestations) and osteoporosis (SOC: Musculoskeletal and connective tissue disorders). All the AEs were considered mild, non-serious, and not related to treatment.
Out of 4 AEs, 2 had resolved (abdominal distention and post-procedural infection), 1 was recovering (osteoporosis), and 1 AE was not resolved (cholelithiasis) until end of study.
One (1) unexpected AE (post-procedural infection) was reported during the study.
None of the patients discontinued the treatment due to AEs.
There was no incidence of medically important AEs during the retrospective period.

During the prospective period, 8 (38.1%) patients had at least 1 AE; 5 patients had pyrexia (SOC: General disorders and administration site conditions), and 1 patient each had the AE of hydrocele (SOC: Congenital, familial and genetic disorders) and osteoporosis (SOC: Musculoskeletal and connective tissue disorders); mesenteric venous occlusion (SOC: GI disorders); and headache (SOC: Nervous system disorders).
Six (6, 28.6%) patients had mild AEs (hydrocele [1 patient], pyrexia [4 patients], headache [1 patient]), 1 (4.8%) patient had a moderate AE (pyrexia), and 2 (9.5%) patients had severe AEs (mesenteric venous occlusion [1 patient] and osteoporosis [1 patient]).
Two (2, 9.5%) patients had 3 unexpected AEs; hydrocele and osteoporosis (1 patient) and mesenteric venous occlusion (1 patient).
One (1) SAE (mesenteric venous occlusion) was reported in the prospective period. This SAE was severe, not considered related to treatment, and resolved.
All AEs were resolved except the severe and unexpected event of osteoporosis.
No treatment-related AEs were reported.
None of the patients discontinued treatment due to AEs.
No fatal events were reported.

None of the AEs led to dose modifications during either the retrospective or the prospective period.

Table 4: Summary of Adverse Events by Period

	Statistic	VPRIV (N=21)
Period: Retrospective (Safety Analysis Set)		
Number of Patients with at Least One AE	n (%)	2 (9.5)
Number of Patients with at Least One Related AE	n (%)	0
Number of Patients who Discontinued the Treatment for AE	n (%)	0
Number of Patients who Discontinued the Treatment for a Drug Related AE	n (%)	0
Number of Patients with at Least One Mild AE	n (%)	2 (9.5)
Number of Patients with at Least One Moderate AE	n (%)	0
Number of Patients with at Least One Severe AE	n (%)	0
Number of Patients with at Least One SAE	n (%)	0
Number of Patients with at Least One Drug Related SAE	n (%)	0
Number of Patients who Discontinued the Treatment for SAE	n (%)	0
Number of Patients who Discontinued the Treatment for a Drug Related SAE	n (%)	0
Number of Deaths due to any Cause	n (%)	0
Number of Patients with at Least One Unexpected AE	n (%)	1 (4.8)
Number of Patients with at least one reported IRR	n (%)	0
Period: Prospective (Safety Follow-up Analysis Set)		
Number of Patients with at Least One AE	n (%)	8 (38.1)
Number of Patients with at Least One Related AE	n (%)	0
Number of Patients who Discontinued the Treatment for AE	n (%)	0
Number of Patients who Discontinued the Treatment for a Drug Related AE	n (%)	0
Number of Patients with at Least One Mild AE	n (%)	6 (28.6)
Number of Patients with at Least One Moderate AE	n (%)	1 (4.8)
Number of Patients with at Least One Severe AE	n (%)	2 (9.5)
Number of Patients with at Least One SAE	n (%)	1 (4.8)
Number of Patients with at Least One Drug Related SAE	n (%)	0
Number of Patients who Discontinued the Treatment for SAE	n (%)	0
Number of Patients who Discontinued the Treatment for a Drug Related SAE	n (%)	0
Number of Deaths due to any Cause	n (%)	0
Number of Patients with at Least One Unexpected AE	n (%)	2 (9.5)
Number of Patients with at least one reported IRR	n (%)	0

n=Number of patients having an event; SAE=Serious Adverse Event; AE=Adverse Event; IRR=Infusion-related Reaction
Percentage was based on Safety Analysis Set for Retrospective period and Safety Follow-up Analysis Set for Prospective period.

Table 5: Incidence of Adverse Events by Period

System Organ Class Preferred Term	Statistic	VPRIV (N=21)
Period: Retrospective (Safety Analysis Set)		
Patients with at least one AE	n (%) E	2 (9.5) 4
Gastrointestinal disorders	n (%) E	1 (4.8) 1
Abdominal distension	n (%) E	1 (4.8) 1
Hepatobiliary disorders	n (%) E	1 (4.8) 1
Cholelithiasis	n (%) E	1 (4.8) 1
Infections and infestations	n (%) E	1 (4.8) 1
Post-procedural infection	n (%) E	1 (4.8) 1
Musculoskeletal and connective tissue disorders	n (%) E	1 (4.8) 1
Osteoporosis	n (%) E	1 (4.8) 1
Period: Prospective (Safety Follow-up Analysis Set)		
Patients with at least one AE	n (%) E	8 (38.1) 9
Congenital, familial and genetic disorders	n (%) E	1 (4.8) 1
Hydrocele	n (%) E	1 (4.8) 1
Gastrointestinal disorders	n (%) E	1 (4.8) 1
Mesenteric venous occlusion	n (%) E	1 (4.8) 1
General disorders and administration site conditions	n (%) E	5 (23.8) 5
Pyrexia	n (%) E	5 (23.8) 5
Musculoskeletal and connective tissue disorders	n (%) E	1 (4.8) 1
Osteoporosis	n (%) E	1 (4.8) 1
Nervous system disorders	n (%) E	1 (4.8) 1
Headache	n (%) E	1 (4.8) 1

n=Number of patients having an event; E=Number of events
Percentage was based on Safety Analysis Set for Retrospective period and Safety Follow-up Analysis Set for Prospective period.
Coded using MedDRA version 24.0

2.3.3. Discussion on clinical aspects

Study SHP669-406, titled 'Post Marketing Surveillance Study for VPRIV® in India' was a multicentre, uncontrolled, open-label post-marketing surveillance study in patients with Type 1 Gaucher disease that received VPRIV in India. It included 21 patients of whom 19 completed the study; 2 patients discontinued the study due to consent withdrawal or per physician's discretion. Patients received the commercially available formulation of velaglucerase alfa, i.e. 400 units of powder for solution for infusion.

Data were collected retrospectively and prospectively. The period from the first time the subject was dosed in a charitable access program until signing of the informed consent form in the current study was considered retrospective, and the period from informed consent to the end of the study / early discontinuation was considered the prospective period.

Results regarding effectiveness (haemoglobin, platelet count, liver size, spleen size) as well as genetic mutation data are considered to be in line with previous findings in studies with VPRIV. The benefit of VPRIV is not altered by the findings from study SHP669-406.

Safety findings in study SHP669-406 are also considered to be in line with previous safety data for VPRIV. There are no new or unexpected safety data. The risk of VPRIV is not altered by the results of this study.

The interpretation of the efficacy and safety results from study SHP669-406 however is limited by the very small sample size and the uncontrolled, open-label, observational design of the study. Furthermore, baseline data for the retrospective analysis were not completely available. Confounding factors affecting the efficacy and the safety outcome cannot be excluded.

The benefit-risk ratio of VPRIV remains unchanged.

No changes to the PI may be 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 may be 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
Post Marketing Surveillance Study for VPRIV® in India	SHP669-406	CSR dated 15 November 2023	12 December 23