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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/P46/033

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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1. Introduction

On 05 November 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 'Gaucher Disease during infancy and early childhood and experience with Enzyme Replacement Therapy (ERT) using Velaglucerase alfa (VPRIV): A Combined Retrospective and Prospective Cohort Study' (TAK-669-4019) 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.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- TAK-669-4019, Gaucher Disease during infancy and early childhood and experience with Enzyme Replacement Therapy (ERT) using Velaglucerase alfa (VPRIV): A Combined Retrospective and Prospective Cohort Study.

The study completion date is 31-March-2023 (last patient out). The MAH acknowledges that the submission date is not in line with the requirements of Article 46 of the Regulation (EC) 1901/2006 and states that corrective actions are in process.

2.3.2. Clinical study

TAK-669-4019, Gaucher Disease during infancy and early childhood and experience with Enzyme Replacement Therapy (ERT) using Velaglucerase alfa (VPRIV): A Combined Retrospective and Prospective Cohort Study

Description

Study TAK-669-4019 was an observational, retrospective / prospective, non-controlled, non-comparative, single-centre study conducted with a retrospective chart review and an observational prospective period. The study enrolled Gaucher disease (GD) infants and paediatric patients aged ≤5 years treated with velaglucerase alfa. Patients were followed up for up to 36 months and no less than 18 months after treatment initiation. They were studied by observing standard patient care.

The study was performed at a single centre in the USA, the Lysosomal & Rare Disorders Research & Treatment Center (LDRTC).

Methods

Study participants

The study enrolled infants and paediatric subjects ≤5 years old and treated with Velaglucerase alfa (VPRIV) as Enzyme Replacement Therapy (ERT). Patients were eligible if they started treatment at 4 years of age or younger and were followed up for up to 36 months and no less than 18 months after treatment initiation.

Inclusion criteria were participant's caregiver being able and willing to provide informed consent, participants to be ≤4 year of age at treatment initiation, having confirmed diagnosis of GD type 1 or type 3 (biochemically and/or genetically), and receiving IV velaglucerase alfa treatment for GD.

Exclusion criteria were being an immediate family member or being in a dependent relationship with a study site employee involved in the conduct of the study (e.g., child, sibling) or may have consented under duress, as well as judged by the investigator as being ineligible for any other reason.

Treatments

None of the patients was reported to have received treatment for GD before the start of velaglucerase alfa. Velaglucerase alfa was initiated at the age of ≤3 months in 3 patients, >3 to ≤6 months in 3 patients, >6 to ≤12 months in 1 patient, >12 to ≤18 months in 2 patients, and >36 to ≤48 months in 2 patients. Patients were treated for up to 57 months, with 9 patients treated for ≥12 months. Of the 8 patients who were not discontinued, 7 were treated with velaglucerase alfa for ≥20 months.

The initial prescribed dosage of velaglucerase alfa was 60 U/kg every other week (EOW).However, during the study, patients received doses according to the clinic practice and individual clinical needs. Three (3) patients received treatment EOW, with doses ranging from 59 to 71 U/kg, and the remaining 8 patients received treatment weekly, with doses ranging from 60 to 76.9 U/kg. One (1) patient initially received weekly infusions then transitioned to an EOW schedule.

Objective(s)

The primary objective was to evaluate real-world effectiveness of velaglucerase alfa in paediatric patients during infancy and early childhood by assessing improvement of growth (height / weight gain in percentile) and improvement in each of the 4 component domains haemoglobin (Hb) level, platelet count, spleen volume, and liver volume.

Secondary objectives were to assess benefits and limitations of velaglucerase alfa in early age (≤4 years of age), to understand the different disease presentations and response to ERT at different age groups (newborn/infancy, first year of life, childhood in 5 years of age and younger), and to describe the safety of velaglucerase alfa in a real-world setting in this population.

Outcomes/endpoints

The primary endpoints were changes from a point of ERT initiation (earliest available measurement defined as study enrolment or ERT initiation, whichever was earlier) and up to 5 years of age in Hb level (increase Hb levels up to 11.0 g/dL), in platelet count (percent change from baseline), in liver volume (percent change from baseline), and in spleen volume (percent change from baseline), as well as normalisation of growth retardation and improvement of bone (proportion of patients) and thrombocytopenia (proportion of patients). Data on GD-specific biomarkers, including chitotriosidase and glucosylsphingosine (Lyso-Gb1), were also recorded.

The secondary endpoint were the number of drug related adverse events recorded using parent statements and/or chart review. Data for the earliest available measurements were entered from historical records (subject to data availability) for patients who had already initiated treatment with velaglucerase alfa. Once enrolled, prospective data collection was based on the frequency of routine follow-up visits, for a period of up to 18 months.

Visits took place every 6 months during the Follow-up Period.

Sample size

Twenty (20) patients were estimated to be sufficient to investigate clinical and safety outcomes in GD patients ≤5 years of age, treated with velaglucerase alfa. No formal statistical sample size estimation was performed. However, the study was closed early with total enrolment of only 11 patients, according to the MAH owing to challenges with enrolment in part due to the coronavirus disease-2019 (COVID-19) pandemic.

Randomisation and blinding (masking)

N/A

Statistical Methods

All statistical analyses were descriptive, with no hypotheses tested and without imputation of missing values. Retrospective, baseline values as well as values during the possible follow-up periods of the included patients were included and analysed. Statistical Software System (SAS) version 9.4 (SAS Institute, Cary, NC, USA) was used for all data analysis.

Main outcome measures, different disease presentations and response to velaglucerase alfa at different age groups (newborn/infancy, first year of life, childhood up to 5 years of age) in real-world setting are presented based on the availability of the data in different age groups.

ADRs reported in the study as well as ADRs reported directly to authorities and to Takeda International Drug Safety and not captured in the study database were extracted from the overall safety database and the study database and listed or tabulated in the final report in the standard way of presenting such data in a Periodic Safety Update Report (PSUR).

Adverse events (AEs) were summarised using the safety analysis set.

Results

Participant flow

Twelve (12) patients were screened and 11 patients were enrolled; 2 patients were enrolled in the retrospective arm of the study and 9 were followed prospectively with available retrospective data also collected.

Three (3) patients (1 male, 2 female, all GD2) discontinued the study. Reported reasons were enrolment in an interventional trial (2 patients) and development of neurological symptoms consistent with GD2 that precluded study participation (1 patient).

Recruitment

Patients were enrolled between January 8, 2021 and December 13, 2022.

The study protocol was amended twice; amendment 1 is dated 09 April 2021 and amendment 2 02 August 2022. The following tables summarise the changes.

Table 1: Protocol Amendment 1: Summary of Changes

Description of Change	Original Language	Updated Language
Inclusion Criteria	The participant is male or female younger than or equal to *3 years of age at initial visit.*	The participant is male or female younger than or equal to *4 year of age at treatment initiation.*
Observation Period	Total treatment period to be evaluated for each patient will be minimum 18 months from the time of treatment initiation. • **Retrospective part up** *to ≤18 months* • **Prospective part** *18 months*	Total treatment period to be evaluated for each patient will be less or equal to 36 months and no less than 18 months from the time of treatment initiation. • **Retrospective part up** *to 36 months* • **Prospective part up** *to 18 month*

Table 2: Protocol Amendment 2: Summary of Changes

Description of Change	Original Language	Updated Language
Study design and primary objective	The primary objective is to evaluate the "Real World Effectiveness" of Velaglucerase alfa (VPRIV) in pediatric patients during infancy and early childhood, who are treated with Velaglucerase alfa *60 U/kg by IV infusion every other week as part of standard of care*	The primary objective is to evaluate the "Real World Effectiveness" of Velaglucerase alfa (VPRIV) in pediatric patients during infancy and early childhood, who are treated with Velaglucerase alfa.
Secondary objectives updated	To assess benefits and limitations of IV Velaglucerase alfa *60 U/kg* in early age by evaluating efficacy parameters in infants and pediatric patients who initiated ERT (VPRIV) in *5* years of age and younger	To assess benefits and limitations of IV Velaglucerase alfa in early age by evaluating efficacy parameters in infants and pediatric patients who initiated ERT (VPRIV) in *4* years of age and younger
Inclusion criteria updated	Patient has been receiving IV velaglucerase alfa *60 U/kg EOW ERT* treatment for GD	Patient has been receiving IV velaglucerase alfa treatment for GD

Protocol deviations associated with study inclusion criteria were noted during routine data review in June 2022; dosing and regimen of velaglucerase alfa were outside the protocol specified dose of 60 U/kg EOW. A corrective and preventive action (CAPA) plan was put in place, which included a patient safety assessment plan and documentation, documentation of the unified velaglucerase alfa dose escalation algorithm to describe the clinical rationale for the dose, as well as proposed changes in the protocol inclusion criteria given the observational nature of the study. No adverse events related to the treatment were identified; each patient's file was updated to document the dosing and frequency based on the clinician's judgement and patient's clinical status. The protocol was amended (Amendment 2) to remove language referencing 60 U/kg dosing and observational follow up was continued for patients whose clinical dosing was outside of the original study protocol specifications.

Baseline data

Of the 11 patients enrolled, 6 were male and 5 female. The age ranged from 3 to 71 months; mean age at diagnosis was 14 months (range: 2 weeks to 38 months). Four (4) of the patients were identified through newborn screening.

Of the 12 patients screened, 9 were white/European, and 1 each was white/Hispanic, black/African American, and South Asian/Pakistani.

Of 11 enrolled patients, 3 were assessed as clinical phenotype GD3, 2 as GD1/3, 3 as GD2, 2 as GD2/3, and 1 as GD3c.

Initial Hb levels and platelet counts ranged from 8.8 to 13.4 g/dL and from 113 × 10^9/L to 324 × 10^9/L, respectively. Lyso-Gb1 (normal values <0.05 ng/mL) were 14.5 to 874 ng/mL at presentation in the 8 patients with available measurements. CHITO activities (normal mean 20 nmol/h/mL; upper limit 120 nmol/h/mL) were 370 to 11,459 nmol/h/mL in 9 patients. Two patients had CHITO activity below the normal mean at presentation which was attributed to variants in the Chitinase 1 gene, and therefore CHITO levels for these patients were not further evaluated.

Most children presented with splenomegaly and 2 patients had spleen sizes at the upper limit of normal for their age.

The genotypes were varied and included the glucocerebrosidase gene (GBA) variants R163X, L444P, R463C, N462K, D409H, 55 bp deletion, and other recombinant alleles. One patient had a GBA genotype consistent with GD3 but lacked horizontal supranuclear palsy and was therefore considered to have GD1. This patient had a concomitant KIF-1-related disease that included white matter changes on magnetic resonance imaging and gait abnormalities.

At the last measurement before VPRIV treatment, head circumference percentiles ranged from 75% to 1%, height percentiles ranged from 80% to 1%, and weight percentiles for age ranged from 97% to <1%.

None of the patients were reported to have received treatment prior to the start of velaglucerase alfa.

For further details see tables below.

Table 3: Patient Demographics and Clinical Characteristics

	Patient ID										
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**
Study participation	**Completed**	**Ongoing at study closure**	**Completed**	**Ongoing at study closure**	**Ongoing at study closure**	**Discontinued**	**Completed**	**Discontinued**	**Completed**	**Discontinued**	**Ongoing at study closure**
Enrolment type	**Prospective**	**Prospective**	**Prospective**	**Prospective**	**Prospective**	**Prospective**	**Retrospective**	**Prospective**	**Retrospective**	**Prospective**	**Prospective**
Sex	Female	Female	Male	Male	Male	Female	Male	Female	Male	Male	Female
GD clinical phenotype	3	3	1/3	1/3	3c	2	2/3	2	3	2	2/3
GBA1 genotype Allele 1 Allele 2	 c.604C>T c.1246G>A	 c.1448T>C c.1503C>G	 c.1448T>C c.1504C>T	 c.1448T>C c.1448T>C	 c.1342G>C c.1342G>C	 c.1342G>C c.203dup	 c.1448T>C Recombinant*	 c.1265_1319del c.1448T>C	 c.1448T>C c.1448T>C	 c.203del c.1448T>C	 D409H Rec*NciI*
GCase activity at diagnosis, nmol/h/mg	0.5	0.17	N/A	101	0.00674	1	0.416†	0.00214	1.3	0.00031	0
Age at diagnosis, months‡	>36-≤50	>1-≤3	>24-≤36	≤1 (including NBS)	>6-≤9	>1-≤3	>9-≤12	≤1 (including NBS)	>12-≤18	≤1 (including NBS)	≤1 (including NBS)
Lyso-Gb1 levels at presentation, ng/mL	238 at >36-≤50 months	141 at ≤2 months	100 at >9-≤12 months	162 at >9-≤12 months	115 at >9-≤12 months	N/A	874 at >9-≤12 months	N/A	14.5	90 at ≤2 months	183 at >1-≤3 months
Chitotriosidase activity at presentation, nmol/h/mL	11 459 at >36-≤50 months	650 at ≤2 months	-§	413 at >9-≤12 months	768 at >9-≤12 months	370 at ≤2 months	-§	1733 at >1-≤3 months	6477 at >12-≤18 months	583 at ≤2 months	677 at >1-≤3 months
Weight at last measurement before velaglucerase alfa, kg (percentile)¶	16.3 (90%)	4.4 (N/A)	16.2 (75-90%)	3.9 (97%)	N/A (1%)	5.1 (25%)	7.5 (5-10%)	N/A (<2%)	9.3 (10%)	N/A (75%)	5.0 (25-50%)
Height at last measurement before velaglucerase alfa, cm (percentile)¶	93.5 (40%)	55.9 (N/A)	92.0 (10-25%)	60 (50-75%)	N/A (1%)	58.4 (25-50%)	72 (2%)	N/A (<2%)	72 (2%)	N/A (80%)	61.6 (50-75%)
Head circumference at last measurement before velaglucerase alfa, cm	N/A	N/A	+2 SD	N/A (25%)	N/A (1%)	N/A (24%)	43 (10-25%)	N/A (<2%)	N/A	N/A (75%)	38.1 (25-50%)

	Patient ID										
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**
(percentile)[¶]											

*Recombinant allele (several pseudogene derivative variants located in exon 9 and 10). †Value taken closest to diagnosis. ‡Age information is given in ranges to protect patient anonymity. [§]Attributed to variants in the *Chitotriosidase 1* gene. ¶N/A: the growth percentiles or the numerical values for the growth parameters were not available.
GBA1, glucosylceramidase beta 1 gene; *GCase*, glucocerebrosidase; *GD*, Gaucher disease; *Lyso-Gb1*, glucosylsphingosine; *N/A*, not available; *NBS*, newborn screening.

Table 4: Treatment patterns and clinical outcomes

Patient ID	A	B	C	D	E	F	G	H	I	J	K
Treatment											
Age at treatment initiation,* months	>36-≤50	>1-≤3	>36 50	>3-≤6	>12-≤18	>1-≤3	>6-≤12	>3-≤6	>12-≤18	>1-≤3	>3-≤6
Treatment duration, months	20	27	20	32	20	18	54	12	57	9	1.5
IV access	Mediport	Mediport	Mediport	Central line/ Mediport	Central line	PICC line/ Mediport	Mediport	Mediport	Central line/ Mediport	Mediport	Central line
Treatment location	Home	Home	Home	Home	Hospital	Home	Home	Home	Home	Home	Home
Dosage, U/kg	60 EOW	60 weekly	60 weekly	76.9 weekly	59 EOW	60 weekly	66 weekly	71 EOW	61 weekly	60 weekly	71 weekly
Clinical outcomes											
Haemoglobin level at earliest measurement, g/dL	11.9 (before treatment)	11.2 (before treatment)	12.8 (before treatment)	12.4 (before treatment)	13.4 (after treatment)	11.5 (after treatment)	8.8 (beforetreatment)	11.0 (after treatment)	11.9 (after treatment)	9.7 (before treatment)	11.4 (before treatment)
Haemoglobin level at the latest measurement, g/dL	12.6 (after treatment)	12.0 (after treatment)	12.3 (after treatment)	11.6 (after treatment)	11.5 (after treatment)	N/A	11.9 (after treatment)	N/A	13.0 (after treatment)	N/A	N/A
Platelet count at the earliest measurement,	132 (before treatment)	113 (before treatment)	129 (before treatment)	312 (before treatment)	179 (after treatment)	$324*10^9$/L (after treatment)	151 (before treatment)	217 (after treatment)	207 (after treatment)	281 (before treatment)	220 (before treatment)
Platelet count at the latest measurement,	202 (after treatment)	319 (after treatment)	229 (after treatment)	318 (after treatment)	109 (after treatment)	N/A	217 (after treatment)	N/A	207 (after treatment)	N/A	N/A
Liver size (cm)											
Liver size at presentation, cm (time before, after, or at treatment initiation)	11.4 (2 months before treatment initiation)	8.2 (1 month before treatment initiation)	Normal (31 months before treatment initiation)	7.8 (1 month before treatment initiation)	8.6 (6 months before treatment initiation)	Normal (1 month after treatment initiation)	10.5 (5 months after treatment initiation)	5.9 (3 months before treatment initiation)	11.0 (at treatment initiation)	9.5 (at treatment initiation)	10.0 (0.5 months before treatment initiation)
Intermediate measurements, cm (time after treatment initiation)	11.1 (5 months)		Mildly enlarged (10 months)				9.8 (15 months)		10.5 (10 months) 11.5 (32 months)		
Latest measurement, cm (time after treatment initiation)	9.5 (14 months)	9.0 (17 months)	12.1 (12 months)	298 mL (21 months)	Normal (29 months)	N/A	9.39 (39 months)	7.6 (5 months)	Normal (58 months)	Normal (2 months)	N/A
Spleen size (cm)											
Spleen size at presentation, cm (time before, after, or at treatment initiation)	10.5 (2 months before treatment initiation)	7.5 (at treatment initiation)	14.0 (at (31 months before treatment initiation)	7.0 (1 month before treatment initiation)	10.6 (6 months before treatment initiation)	7.4 (1 month after treatment initiation)	Normal (5 months after treatment initiation)	7.4 (3 months before treatment initiation)	15-16 (at treatment initiation)	6.2 (at treatment initiation)	7.1 (0.5 months before treatment initiation)
Intermediate measurements, cm (time after treatment initiation)	7.8 (5 months)		12.1 (10 months)				7.8 (15 months)		9.1 (10 months) 9.6 (32 months)		
Latest measurements, cm (time after treatment initiation)	8.4 (14 months)	7.9 (17 months)	13.6 (12 months)	7.1 (33 months)	9.0 (29 months)	N/A	7.6 (39 months)	Normal (5 months)	Normal (58 months)	N/A	N/A

*Age information is given in ranges to protect patient anonymity. †According to Waelti et al. BMC Pediatrics 2021:21;276[16], 5th-95th percentiles for right liver lobe craniocaudal diameter were 5.2-8.3 cm in children aged >1-≤6 months, 5.4-10.0 cm in children aged >6-≤12 months, 6.2-10.3 cm in children aged >1-≤2 years, 7.1-10.8 cm in children aged >2-≤3 years, 8.3-11.0 cm in children aged >3-≤4years, 8.8-11.2 cm in children aged >4-≤5 years, and 8.9-12.1 cm in children aged >5-≤6 years. ‡According to Rosenberg et al AJR Am J Roentgenol 1991:157(1):119-21[17], 10th-90th percentiles for spleen length were 3.3-5.8 cm in children aged >0-≤3 months, 4.9-6.4 cm in children aged >3-≤6 months, 5.2-6.8 cm in children in aged >6-≤12 months, 5.4-7.5 cm in children aged >1-≤2 years, 6.4-8.6 cm in children aged >2-≤4 years, 6.9 8.8 cm in children aged >4-≤6 years, and 7.0-9.6 cm in children aged >4-≤6 years.
EOW, every other week; IV, intravenous; N/A, not available; PICC, peripherally inserted central catheter.
[16] Waelti S, Fischer T, Wildermuth S, Leschka S, Dietrich T, Guesewell S, et al. Normal sonographic liver and spleen dimensions in a central European pediatric population. BMC Pediatrics 2021;21:276.
[17] Rosenberg HK, Markowitz RI, Kolberg H, Park C, Hubbard A, Bellah RD. Normal splenic size in infants and children: sonographic measurements. AJR Am J Roentgenol 1991;157:119-21.

Number analysed

See above.

Exposure

Treatment with velaglucerase alfa was initiated at the age of ≤3 months in 3, >3-≤6 months in 3, >6-≤12 months in 1, >12-≤18 months in 2, and >36-≤48 months in 2 patients. Patients were treated for up to 57 months, with 9 treated for 12 months or longer. Of 8 patients who remained in the study, 7 were treated with velaglucerase alfa for ≥20 months.

The initial prescribed dosage of velaglucerase alfa was 60 U/kg every other week (EOW); however, patients received doses of 59-77 U/kg according to clinic practice and individual clinical needs. The frequency of velaglucerase alfa administration was EOW in 3 and weekly in 8 patients. One (1) patient started receiving weekly infusions then continued with an EOW schedule (see table above).

Velaglucerase alfa was administered using central venous access, usually starting with a central line and switching to a mediport; all patients received home infusions except for 1 (treated at an infusion centre because of parental preference). The youngest age for port placement was 2 months.

Efficacy results

Haemoglobin and platelet count

Hematologic parameters (Hb and platelet count) improved or remained stable after start of velaglucerase alfa treatment in patients with available data before and after treatment (5 patients) and were maintained throughout the study. At the earliest measurement, Hb levels and platelet counts ranged from 8.8 to 13.4 g/dL and from 113 × 10^9/L to 324 × 10^9/L, respectively. At the latest measurement, Hb levels ranged from 11.5 to 13.0 g/dL and platelet counts from 109 × 10^9/L to 319 × 10^9/L. Individual data are presented in the table below.

Table 5: Haemoglobin Levels and Platelet Counts per Individual Patient

	Clinical Outcome			
	Hemoglobin level at earliest measurement (g/dL)	**Hemoglobin level at latest measurement (g/dL)**	**Platelet count at earliest measurement (thousand/µL)**	**Platelet count at latest measurement (thousand/µL)**
Patient ID				
A	11.9 (before treatment)	12.6 (after treatment)	132 (before treatment)	202 (after treatment)
B	11.2 (before treatment)	12.0 (after treatment)	113 (before treatment)	319 (after treatment)
C	12.8 (before treatment)	12.3 (after treatment)	129 (before treatment)	229 (after treatment)
D	12.4 (before treatment)	11.6 (after treatment)	312 (before treatment)	318 (after treatment)
E	13.4 (after treatment)	11.5 (after treatment)	179 (after treatment)	109 (after treatment)
F	11.5 (after treatment)	N/A	324* 10^9/L (after treatment)	N/A
G	8.8 (before treatment)	11.9 (after treatment)	151 (before treatment)	217 (after treatment)
H	11.0 (after treatment)	N/A	217 (after treatment)	N/A
I	11.9 (after treatment)	13.0 (after treatment)	207 (after treatment)	207 (after treatment)
J	9.7 (before treatment)	N/A	281 (after treatment)	N/A
K	11.4 (before treatment)	N/A	220 (before treatment)	N/A

Source: VPRIV TAK-669-4019 Final Study Report, Table 4.
N/A: not applicable.

Liver and Spleen Volumes

Liver and spleen sizes were assessed using ultrasonography, and results for organ lengths were provided in cm and compared with the normal measurements for the patient's age.

At the latest measurement, liver size was assessed for 9 patients. It decreased in 1 patient and was within normal limits in 7 patients at their latest measurement (see table above).

At the latest measurement, spleen size was assessed for 8 patients. It decreased relative to normal values in 7 patients who remained in the study and were treated with velaglucerase alfa for ≥6 months; 5 of these patients were treated weekly. Spleen size normalised for age in 5 patients overall. In 1 patient receiving ERT EOW, some residual splenomegaly remained despite decrease in spleen size (see table above).

Growth and Development

Growth was measured according to weight, height, and head circumference.

Height percentiles remained generally stable or improved, and head circumference percentiles remained stable in all patients. At the last measurement before treatment initiation, head circumference percentiles ranged from 75% to 1% and height percentiles ranged from 80% to 1%. At 12 months post-enrolment, height percentiles ranged from 40.5% to <3% (see table above).

Weight percentiles ranged from 89.2% to <3% at enrolment, and from 97% to <1% at the last measurement before treatment initiation. At 12 months post-enrolment, weight percentiles ranged from 78.4% to 4.6% (see table above).

Failure to thrive was seen in 2 patients, 1 patient with GD2 who discontinued the study and 1 patient whose weight increased from the first to fifth percentile during treatment (patient's growth followed normal growth curves and was within the predicted mid-parental heights).

Neurological Outcomes

Neurological outcomes were no endpoints prespecified in the protocol, but neurological assessments were documented when available. Two (2) patients had normal eye movements, 1 was considered to have GD1, while the other patient had a genotype consistent with GD3 (L444P/L444P). All other patients had horizontal supranuclear palsy, and 1 patient also had strabismus. Hearing abnormalities were the most common neurological sign, diagnosed in 6 patients with an abnormal auditory brainstem response at presentation. One (1) patient received cochlear implants. Gait abnormalities including ataxia and spasticity were observed in 3 patients among whom 1 was non-ambulatory. One (1) patient had an abnormal electroencephalogram, myoclonus, and generalised seizures. All other individuals did not have clinical seizures and had normal "sleep deprived" electroencephalograms.

Bone Disease

A skeletal survey was available for all but 1 patient before treatment initiation. None of the patients had bone abnormalities including congenital deformities, Erlenmeyer flask deformities, or cystic or lytic lesions. There were no events associated with GD-related bone involvement throughout follow-up. Skeletal x-rays, undertaken in 4 patients, showed bone age consistent with their chronological age. On follow-up radiological evaluation, 1 patient had developed mild metaphyseal broadening at the long bones; bone density abnormalities of the radius were noted for another patient whose bone density was at the 2.7^{th} percentile for age.

GD Biomarkers

At presentation to the study site, Lyso-Gb1 levels were reported for 9 out 11 enrolled patients and ranged from 14.5 to 874 ng/mL (patient age at presentation >1 month to ≤50 months). There was a rapid decrease in Lyso-Gb1 levels from presentation values in the 6 months after treatment initiation, with 4 to 26 ng/mL at the latest measurement. For the 1 patient who only received velaglucerase alfa for 6 weeks before study closure, Lyso-Gb1 levels decreased from 183 to 29 ng/mL.

CHITO activity levels decreased in all 9 patients and were below the upper limit of normal (120 nmol/h/mL) at the latest measurement in 5 patients. After an initial decrease, 1 patient had an increase in CHITO levels to 2272 nmol/h/mL, which was attributed to a recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection; it was sustained for some weeks before a resume in decline of CHITO activity levels.

Safety results

Adverse events (AEs) were recorded using parent statements and/or chart reviews. No drug-related AEs or infusion-related reactions were reported.

Serious adverse events (SAEs) were reported for 2 patients during the retrospective data collection:

- One (1) SAE of an upper respiratory infection reported for 1 patient.
- One (1) SAE of hospitalisation due to respiratory failure and sepsis, 1 SAE of cardiac arrest due to respiratory disorder, 3 SAEs of hospitalisation due to rhinovirus, 1 SAE of aspirator pneumonia,

increased oxygen demand, 1 SAE of hospitalisation due to COVID-19, and 1 SAE of scalp fungal infection reported for 1 patient.

SAEs were reported for 7 patients during the prospective data collection:

- One (1) SAE of hospitalisation due to fever, 1 SAE of multiple fever episodes in a 1 year period, 1 SAE of 1 month cold, and 1 SAE of tremors in the morning, residual cough, worse in the afternoon, reported for 1 patient.
- One (1) SAE of tremors, 1 SAE of respiratory syncytial virus (RSV) infection; 1 week of coughing and congestion, and 1 SAE of COVID-19 positive, reported for 1 patient.
- One (1) SAE of hand, foot, and mouth disease and 1 SAE of COVID-19 positive, reported for 1 patient.
- One (1) SAE of COVID19 and 1 SAE of RSV, reported for 1 patient.
- One (1) SAE of seizures and 1 SAE of rash on face, persistent diarrhoea, reported for 1 patient.
- One (1) SAE of hospitalisation, 1 SAE of frequent upper respiratory illnesses, daily seizures, and 1 SAE of hospitalisation due to rhinovirus, reported for 1 patient.
- One (1) SAE of RSV infection, 1 SAE of COVID-19, and 1 SAE of hospitalisation due to respiratory distress, reported for 1 patient.

No deaths, drug-related AEs, or infusion-related reactions were reported. Five (5) patients had a SARS-CoV-2 infection; 2 were hospitalised but did not require ventilation and 3 recovered from COVID-19 without sequalae.

AEs are summarised in the table below.

Table 6: Adverse Events

	Retrospective Events		**Prospective Events**	
Subject	**Serious Adverse Events**	**Drug-related Adverse Events**	**Serious Adverse Events**	**Drug-related Adverse Events**
A	-	-	2021-Nov-15: Fever, went to ER 2022-Jan-11: Multiple fever episodes in 2021 2021-Mar: 1 month cold 2022-Ap-07: Tremors in AM, residual cough, worse in PM	-
B	-	-	2021-Mar-02: Tremors 2021-Aug: RSV infection; 1 wk of coughing & congestion 2021-Dec-24: COVID-19 positive	-
C	-	-	2021-Jul-28: Hand, foot, mouth disease 2022-Sep-15: COVID-19 positive	-
D	-	-	2022-Jun-23: COVID-19 2022-Nov-13: RSV	-
E	-	-	-	-
F	-	-	2021-Dec: Seizures 2022-Feb-17: Rash on face, persistent diarrhoea	-

	Retrospective Events		Prospective Events	
Subject	**Serious Adverse Events**	**Drug-related Adverse Events**	**Serious Adverse Events**	**Drug-related Adverse Events**
G	2019-Mar-27: Hospitalisation due to respiratory failure & sepsis 2019-Apr-16: Cardiac arrest due to respiratory disorder 2019-Sep-25: Hospitalisation due to rhinovirus 2020-Jun-14: Aspirator pneumonia, increase oxygen demand 2021-Feb: Hospitalisation due to COVID-19 2021-May-17: Scalp fungal infection 2021-Jun: Hospitalisation due to rhinovirus 2021-Aug: Hospitalisation due to rhinovirus	-	2021-Dec: Hospitalisation 2022-Sep-21: Frequent upper respiratory illnesses, daily seizures 2022-Jul-Aug: Hospitalisation due to rhinovirus	-
H	n/a	n/a	2021-Dec-03: RSV infection 2021-Dec-18: COVID-9 2022-Jun-09: Hospitalisation due to respiratory distress	-
I	2018-Oct: Upper respiratory infection	-	-	-
J	-	-	-	-
K	-	-	-	-

2.3.3. Discussion on clinical aspects

Study TAK-669-4019, titled 'Gaucher Disease during infancy and early childhood and experience with Enzyme Replacement Therapy (ERT) using Velaglucerase alfa (VPRIV): A Combined Retrospective and Prospective Cohort Study', was an observational, retrospective / prospective, non-controlled, non-comparative, single-centre (USA) study conducted with a retrospective chart review and an observational prospective period. The study enrolled Gaucher disease infants and paediatric patients aged ≤5 years treated with velaglucerase alfa. Patients were followed up for up to 36 months and no less than 18 months after treatment initiation. They were studied by observing standard patient care.

The study completion date is given as March 2023 while the report has been submitted by the MAH on 05 November 2024.

Of the 11 enrolled patients, only 2 were assessed as Gaucher disease type 1/3 and non as Gaucher disease type 1. Velaglucerase alfa is only licensed for patients with Gaucher disease type 1 throughout the EU. Thus, no relevant information for the benefit-risk evaluation of VPRIV in children ≤years of age can be derived from the sparse data presented by the MAH.

Independent of the patient population included in the study, interpretation is limited by the small number of patients (even below the planned number of 20), by visits being based on physician's treatment plan rather than being protocol-defined, and the observational nature of the study.

Furthermore, assessment is hampered by the rather poor quality of the Final Study Report submitted by the MAH. Especially, presentation of study results is rather tenuous.

3. Rapporteur’s overall conclusion and recommendation

☒ **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
Gaucher Disease during infancy and early childhood and experience with Enzyme Replacement Therapy (ERT) using Velaglucerase alfa (VPRIV): A Combined Retrospective and Prospective Cohort Study	TAK-669-4019	31-March-2023 (last patient out)	05 November 2024