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Regular Article

Long-term velaglucerase alfa treatment in children with Gaucher disease type 1 naïve to enzyme replacement therapy or previously treated with imiglucerase

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ABSTRACT

Background: Gaucher Disease type 1 (GD1) often manifests in childhood. Early treatment with enzyme replacement therapy (ERT) may prevent disease complications. We report the assessment of velaglucerase alfa ERT in pediatric GD1 patients who participated in a long-term extension study (HGT-GCB-044, ClinicalTrials.gov Identifier NCT00635427).

Methods: Safety and efficacy were evaluated in pediatric patients receiving velaglucerase alfa 30–60 U/kg by intravenous infusion every other week. In addition to key hematological and visceral efficacy assessments, exploratory assessments conducted specifically in pediatric patients included evaluation of height, bone age, bone marrow burden, and Tanner stage of puberty.

Results: The study included 24 pediatric patients. Fifteen patients were naïve to ERT on entry into the preceding trials TKT032 (12-month trial) or HGT-GCB-039 (9-month trial): in the preceding trials, ten of these 15 patients received velaglucerase alfa and five patients received imiglucerase ERT. Nine patients in the study were previously treated with imiglucerase for >30 months and were switched to velaglucerase alfa in the preceding trial TKT034 (12-month trial). Cumulative ERT exposure in the clinical studies ranged from 2.0 to 5.8 years. Three serious adverse events, including a fatal convulsion, were reported; none were deemed related to velaglucerase alfa. One patient tested positive for anti-velaglucerase alfa antibodies. An efficacy assessment at 24 months showed that velaglucerase alfa had positive effects on primary hematological and visceral parameters in treatment-naïve patients, which were maintained with longer-term treatment. Disease parameters were stable in patients switched from long-term imiglucerase ERT. Exploratory results may suggest benefits of early treatment to enable normal growth in pediatric patients.

Conclusion: The safety profile and clinical response seen in pediatric patients are consistent with results reported in adults.

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Abbreviations: AE, adverse event; BMB, bone marrow burden; BW, body weight; CCL18, chemokine (C–C motif) ligand 18; EOW, every other week; ERT, enzyme replacement therapy; GD, Gaucher disease; ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; IgG, immunoglobulin G; IRAE, infusion-related adverse event; LS, lumbar spine; MN, multiples of normal; MRI, magnetic resonance imaging; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

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1. Introduction

Gaucher disease (GD) is a lysosomal storage disorder caused by a deficiency of β-glucocerebrosidase that leads to accumulation of glucocerebroside in the cells of the monocyte–macrophage system. Many patients with GD type 1 (GD1) have signs or symptoms during childhood, which include anemia, thrombocytopenia, hepatosplenomegaly, bone disease, pubertal delay and growth retardation [1–3].

GD has a broad spectrum of clinical presentation for which three subtypes are described: GD1 is characterized by the lack of neurologic involvement, whereas GD2 and GD3 present with acute and chronic neurologic involvement, respectively. As chronic neurologic symptoms may not develop until late childhood or adolescence, children presenting with GD should be treated with a high index of suspicion for GD3, particularly in cases of non-N370S genotypes (as carrying at least one N370S allele is negatively associated with neuronopathic disease) or homozygosity for L444P (as this genotype is commonly seen in GD3) [4,5].

Early intervention with glucocerebrosidase enzyme replacement therapy (ERT) during childhood can avoid complications from disease symptoms, and may prevent progression of irreversible skeletal manifestations [6]. ERT does not slow progression of the neurologic symptoms of GD3, but can alleviate systemic symptoms, greatly improving quality of life [7].

Velaglucerase alfa (VPRIV®) and imiglucerase (Cerezyme®) are indicated as ERTs for the treatment of GD1. Analyses of registry data on pediatric patients treated with imiglucerase (and/or alglucerase) have shown that normalization or near-normalization of clinical parameters can be achieved with long-term therapy [8,9]. There are currently limited data on the effects of velaglucerase alfa in children, and clinical trial evidence on pediatric-specific parameters such as growth and development, is lacking.

Velaglucerase alfa was assessed in adult and pediatric patients in three clinical trials that were followed by a single extension study: TKT032 [10] and HGT-GCB-039 [11] were Phase III parallel-group clinical trials conducted in treatment-naïve patients with GD1. TKT032 was an assessment of two doses of velaglucerase alfa, whereas HGT-GCB-039 was a non-inferiority study comparing velaglucerase alfa with imiglucerase. TKT034 [12] was a Phase II/III trial assessing velaglucerase alfa in GD1 patients previously treated with imiglucerase.

HGT-GCB-044 was an extension study of the preceding trials TKT032, HGT-GCB-039 and TKT034; the primary objective was to evaluate the long-term safety of velaglucerase alfa ERT. We report the safety and efficacy of velaglucerase alfa in the pediatric population of the extension study (25% of the study population), including assessments conducted specifically in children to evaluate bone disease.

2. Methods

2.1. Patients

HGT-GCB-044 was an open-label, multicenter extension study conducted from March 2008 to December 2012. Patients who completed one of three preceding trials, TKT032 (two-dose assessment; 51 weeks), HGT-GCB-039 (non-inferiority trial; 39 weeks) or TKT034 (switch trial; 51 weeks), were eligible to enroll (Fig. 1). A documented diagnosis of GD was required for inclusion in the preceding trials as determined by either deficient glucocerebrosidase activity, or by genotype analysis. Patients were examined by their treating physician and were clinically judged to have GD1 based on the absence of neurologic signs or symptoms. Patients with GD2 or GD3, or who were suspected of having GD3, were excluded; patients who had significant comorbidities or were unable to comply with the protocol were also excluded. *GBA* genotyping of all patients was conducted at a central laboratory following enrollment (Emory Genetics Laboratory, Decatur, GA) [10,11].

The extension study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Pediatric patients provided written informed consent (and assent where applicable) to participate via a parent or legal guardian.

Patients who completed the TKT032 two-dose assessment and HGT-GCB-039 non-inferiority trial were assigned to receive velaglucerase alfa at 60 U/kg every other week (EOW). Patients who completed the TKT034 switch trial were assigned to receive velaglucerase alfa at the same dose they received during TKT034 (range 15–60 U/kg).

Velaglucerase alfa was administered by intravenous infusion over 60 min. Patients could remain in the extension study until commercial velaglucerase alfa became available to them or the study was discontinued, or until early discontinuation from the study.

2.2. Safety assessments

Evaluation of the long-term safety of velaglucerase alfa was the primary objective of the extension study. Safety was evaluated by continuous monitoring for adverse events (AEs) and assessment of vital signs at each infusion visit. Treatment emergent AEs (TEAEs) were those that occurred within the time of or after the first infusion in the extension study until 30 days after the last infusion in the study. Infusion-related AEs (IRAEs) were those that began during or within 12 h of an infusion start time, and deemed possibly or probably related to velaglucerase alfa.

Approximately every 3 months, patients underwent physical examination and safety-related laboratory testing, and had blood samples screened for anti-velaglucerase alfa antibodies. Antibody-positive samples were isotyped and assessed for enzyme neutralizing activity.

2.3. Efficacy assessments

The secondary objectives of the extension study were to evaluate the effects of velaglucerase alfa on hemoglobin concentration, platelet count, and spleen and liver volumes. The exploratory objectives were to assess the effects of velaglucerase alfa on the GD plasma biomarkers chitotriosidase and chemokine (C–C motif) ligand 18 (CCL18); bone mineral density and serum bone biomarkers in adults (not described here); and growth velocity (height), bone age, bone marrow burden (BMB) and Tanner stage in pediatric patients. Efficacy results were determined from the start of the preceding trials.

Blood samples were collected every 3 months and evaluated for hemoglobin concentration, platelet count, chitotriosidase activity and CCL18 level. Spleen and liver volumes were measured annually using quantitative abdominal magnetic resonance imaging (MRI).

Height measurements were recorded every 3 months. For comparison across ages and sexes, measurements were converted to Z-scores using World Health Organization 2007 growth reference data. Growth velocity was calculated as change in height from baseline over regular intervals (Supplementary material).

Bone age was evaluated annually by radiographs of the left hand and wrist. Radiographs were interpreted by one radiologist with no knowledge of the patient's chronological age. Bone ages were converted to Z-scores based on standards recommended by Greulich and Pyle [13].

BMB was evaluated annually by MRI of the lumbar spine (LS) and femur (Supplementary material).

Patients who turned 18 years of age during the study continued to have their height, bone age and BMB assessed as described above.

Tanner Stage of Puberty [14] was assessed annually. Assessments ceased once a patient reached the final stage of the Tanner scale (stage 5), or turned 18 years of age.

2.4. Statistical analysis

Pediatric patients were those 2 to <18 years of age at entry into the preceding trials. The safety population was defined as all patients who

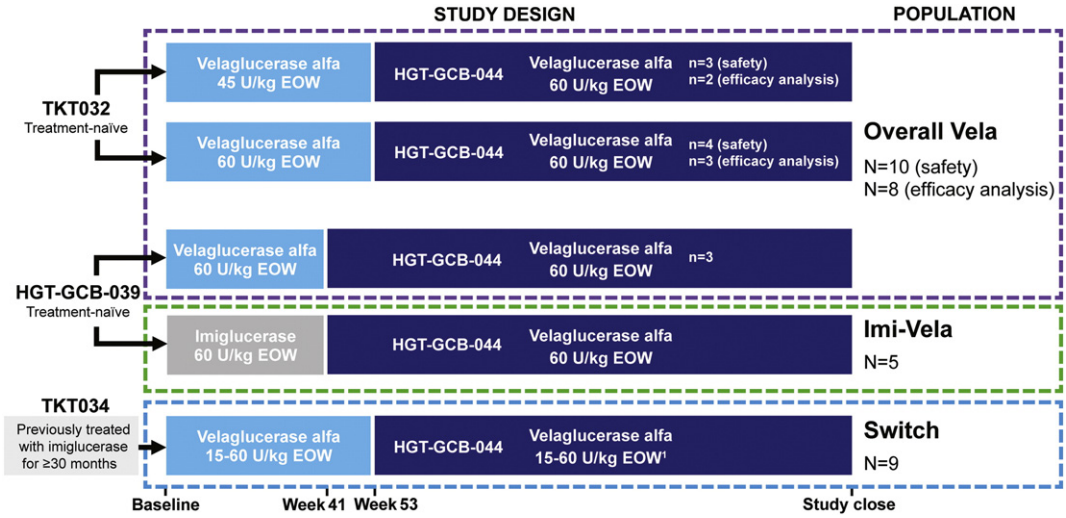

Fig. 1. Study design and grouping of pediatric patients in HGT-GCB-044. For all analyses, patients were grouped into three populations according to their participation in the preceding trials. The Overall Vela population comprised ten patients who received at least one dose of velaglucerase alfa in the TKT032 two-dose assessment (7 patients) or HGT-GCB-039 non-inferiority trial (3 patients). Two patients in this group were the carriers excluded from the efficacy analysis. The Imi-Vela population comprised five patients who received imiglucerase in the HGT-GCB-039 non-inferiority trial and transitioned to velaglucerase alfa in the extension study. The Switch population comprised nine patients previously treated with imiglucerase who switched to velaglucerase alfa in the TKT034 switch trial and continued to receive velaglucerase alfa in the extension study. [1]Patients who completed TKT034 received velaglucerase alfa at the same dose they received during TKT034, which could range from 15 to 60 U/kg.

received at least one dose of velaglucerase alfa during the extension study. Safety data are presented from the start of the extension study. No formal statistical tests were performed on safety parameters.

Two pediatric patients from TKT032 (two-dose assessment) were diagnosed with GD1 based on a false-positive dried-blood-spot test showing glucocerebrosidase deficiency. Later testing determined these patients to be genetic carriers and they were immediately withdrawn from the study [10]. These carriers were excluded from the efficacy analysis population defined as all patients with GD1 enrolled in the extension study. However, by the conservative safety principle (any subject who received at least one dose of the study drug) and per the ICH E9 guidelines 'Statistical Principles for Clinical Trials', they were included in the safety population.

Changes and mean changes from baseline in efficacy parameters were calculated. Baseline was defined as data obtained prior to receiving the first dose of study drug at the start of TKT032, HGT-GCB-039 or TKT034. An efficacy analysis was conducted at 24 months, in addition to a longitudinal analysis calculating changes from baseline at each study time point.

Three analysis populations were defined based on participation in the preceding trials: Overall Vela, Imi-Vela and Switch.

3. Results

3.1. Patients

Twenty-four pediatric patients enrolled in the extension study (95 patients enrolled in total). The Overall Vela population comprised 10 patients who received velaglucerase alfa in TKT032 (two-dose assessment) or HGT-GCB-039 (non-inferiority trial). Two individuals, who were carriers in TKT032, were excluded from the final efficacy analysis population of eight patients. The Imi-Vela population comprised five patients who received imiglucerase in the HGT-GCB-039 non-inferiority trial. The Switch population comprised nine patients previously treated with imiglucerase who switched to velaglucerase alfa in the TKT034 switch trial (Fig. 1).

Pediatric patients ranged in age from 3 to 16 years at baseline (Table 1). Imi-Vela patients were younger than those in the other two groups. N370S was the most prevalent *GBA* mutation present in the Switch population. Mutations that have been associated with more severe disease or neuronopathic GD were present in the Overall Vela and Imi-Vela populations, including L444P/L444P, F213I/F213I and D409H/L444P; all patients were clinically judged to have GD1 at study enrollment. Treatment-naïve patients (Overall Vela and Imi-Vela) showed more severe disease at baseline than patients previously treated with imiglucerase (Switch) (Table 2).

All patients completed 24 months of treatment from baseline; time in the study after 24 months was variable as patients transitioned to commercial velaglucerase alfa (first available in February 2010). The median duration of exposure to study drug from baseline to last infusion was 53 (range 47–69) months for the Overall Vela population, 52 (33–54) months for the Imi-Vela population (combined exposure to imiglucerase and velaglucerase alfa) and 33 (24–63) months for the Switch population. The shorter duration of exposure in the Switch group is due to six of nine patients being in the United States and transitioning sooner to commercial therapy, whereas Overall Vela and Imi-Vela patients were in countries where velaglucerase alfa received market approval later.

Overall Vela patients received velaglucerase alfa at 45 U/kg (two patients) or 60 U/kg (six patients) during the TKT032 two-dose assessment or HGT-GCB-039 non-inferiority trial whereas Imi-Vela patients received imiglucerase at 60 U/kg during HGT-GCB-039 (Fig. 1). All Overall Vela and Imi-Vela patients received velaglucerase alfa at 60 U/kg during the extension study.

Switch patients received velaglucerase alfa at 30 U/kg (two patients), 45 U/kg (three patients) and 60 U/kg (four patients); these doses were the same as the doses of imiglucerase received prior to switching to velaglucerase alfa in TKT034.

3.2. Safety in the extension study

All 24 patients experienced at least one AE during the extension study (Supplemental Table 1). The most common TEAEs were upper respiratory tract infection, nasopharyngitis and headache. Seven patients experienced at least one study drug-related AE. Three patients experienced at least one IRAE. One patient experienced three serious AEs (SAEs) of respiratory tract infection, bronchopneumonia and a convulsion, all deemed unrelated to velaglucerase alfa. The convulsion was fatal; it was considered by the investigator to be related to GD progression. The patient was a male with *GBA* genotype F213I/F213I, aged 3 years at baseline and 6 years at the time of the convulsion. He

Table 1
Patient ages at baseline, start of extension study and last study visit.

Patient	Sex, *GBA* genotype	Age at baseline (years)	Age at start of extension study (years)	Age at final study visit (years)
Overall Vela				
1	F, D409H/L444P	7	8	11
2	M, D409H/L444P	6	7	10
3	M, N370S/Rec*Nci*I[a]	9	10	15
4	M, N370S/Rec*Nci*I	16	17	22
5	F, D409H/F411I	6	7	11
6	M, N370S/N370S	14	14	18
7	M, L444P/L444P[b]	14	15	18
8	M, L444P/L444P[b]	7	8	11
Imi-Vela				
9	F, N370S/L444P	7	8	10
10	M, L444P/L444P[b]	4	5	8
11	M, L444P/L444P[b]	3	4	8
12	M, F213I/F213I	3	4	8
13	M, F213I/F213I	3	4	6
Switch				
14	F, G46E/L444P	9	10	14
15	F, N370S/L324P	14	15	17
16	F, N370S/L444R	14	15	20
17	F, N370S/84GG	12	13	15
18	M, N370S/L444P	13	14	16
19	F, N370S/L444P	13	14	16
20	F, N370S/Rec*Nci*I	10	12	12
21	F, N370S/Rec*Nci*I	16	17	18
22	M, N370S/Rec*Nci*I	14	15	16

Baseline is the start of preceding trials TKT032, HGT-GCB-039 or TKT034.
[a] The Rec*Nci*I allele results from recombination between *GBA* and its downstream pseudogene, and carries the pseudogene-derived L444P and A456P amino acid substitutions.
[b] Although this genotype is commonly seen in GD3, a diagnosis of GD type cannot be made based on genotype alone and these patients were clinically judged by their treating physician to have GD1 at study enrollment.

experienced a seizure 3 days after an imiglucerase infusion in the HGT-GCB-039 non-inferiority trial, and a second seizure 10 days after a velaglucerase alfa infusion in the extension study. Both seizures were moderate, non-serious and deemed unrelated to the study drug. He also experienced a non-serious event of gait disturbance during the extension study unrelated to velaglucerase alfa. The patient received 24 months of velaglucerase alfa treatment; his last dose was administered 12 days before the fatal convulsion. The patient was diagnosed with GD1 at entry into HGT-GCB-039, though it is noted that the neurologic symptoms he developed during study participation are suggestive of GD3.

Thirteen bone-related AEs were experienced by eight patients during the extension study, including one event of bone pain, two of

Table 2
Baseline characteristics of the efficacy analysis pediatric population.

Baseline factor	Overall Vela	Imi-Vela	Switch
	N = 8	N = 5	N = 9
Males			
n (%)	6 (75%)	4 (80%)	2 (22%)
Age			
Median (range), years	8 (6–16)	3 (3–7)	13 (9–16)
GBA genotype			
N370S/N370S	1	0	0
N370S/84GG	0	0	1
N370S/L444P	0	1	2
L444P/L444P[a]	2	2	0
N370S/Rec*Nci*I	2	0	3
N370S/L324P	0	0	1
N370S/L444R	0	0	1
D409H/L444P	2	0	0
G46E/L444P	0	0	1
D409H/F411I	1	0	0
F213I/F213I	0	2	0
Splenectomized			
n	1	1	0
Efficacy variables			
Median (range)			
Hemoglobin concentration, g/dL	10.75 (10.0, 12.4)	9.50 (8.1, 11.5)	13.30 (11.5, 15.3)
Platelet count, $\times 10^9$/L	116 (44, 292)	73 (63, 188)	169 (139, 277)
Spleen volume, multiples of normal	14.3 (4.8, 35.0)	40.35 (6.5, 44.4)	3.2 (1.7, 4.3)
Liver volume, multiples of normal	1.6 (1.1, 2.1)	2.2 (1.5, 2.8)	0.8 (0.6, 1.0)
Chitotriosidase, nmol/mL/h	38,718 (19,856, 63,182)	56,625 (27,438, 99,390)	4169 (1465, 12,460)
CCL18, ng/mL	1713 (1094, 2793)	1750 (960, 5902)	211 (67, 935)

Baseline is the start of preceding trials TKT032, HGT-GCB-039 or TKT034.
[a] Although this genotype is commonly seen in GD3, a diagnosis of GD type cannot be made based on genotype alone and these patients were clinically judged by their treating physician to have GD1 at study enrollment.

foot fracture (in the same patient), three of pain in an extremity, and seven related to injury. All were mild or moderate in intensity and all were deemed unrelated to velaglucerase alfa except for one incidence of muscular pain in the calf at rest that was deemed possibly related.

No patients withdrew from the study due to an AE. The AE profile of pediatric patients in the extension study did not identify additional safety concerns compared with the complete extension study population (Supplemental Table 2).

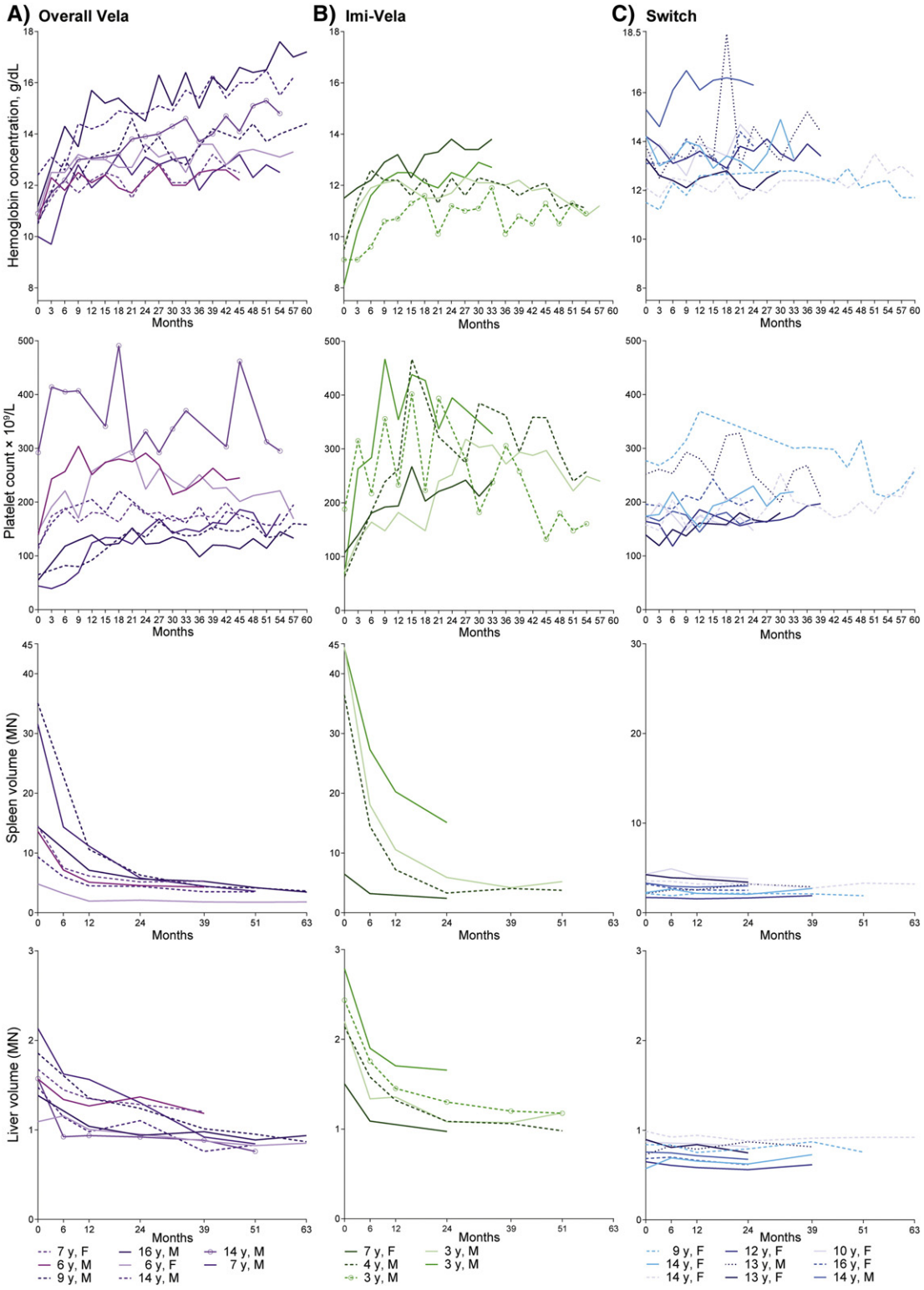

Fig. 2. Observed values of primary efficacy parameters in individual patients over time. (A and B) In Overall Vela and Imi-Vela patients, increases in hemoglobin concentration and platelet count, and decreases in spleen and liver volume were seen within 24 months, and changes were generally maintained for the duration of the study. (C) The efficacy parameters of patients previously treated with imiglucerase were stable following transition to velaglucerase alfa. Organ volumes were expressed normalized to body weight (% BW); one multiple of normal was defined as 0.2% BW for spleen volume and 2.5% BW for liver volume. Lines marked with circles (○) indicate splenectomized patients. MN: multiples of normal.

There were no clinically significant trends in vital signs or physical examination findings to suggest an increased safety risk with velaglucerase alfa.

One 12-year-old Switch patient, positive for anti-imiglucerase IgG antibodies with a high titer of 191,100 ng/mL at baseline [12], tested positive for anti-velaglucerase alfa IgG antibodies at week 77 and continued to test positive for the remainder of the study. The samples from this patient that tested anti-velaglucerase alfa antibody positive were further analyzed using an enzymatic activity neutralization assay and were shown to have neutralizing antibody activity. No apparent impact was noted on the efficacy of velaglucerase alfa as assessed by changes in hemoglobin concentration and platelet count. The patient did not experience any drug-related AEs.

3.3. Efficacy evaluations

The 0–24 month analysis in Overall Vela and Imi-Vela patients showed favorable changes from baseline in all primary efficacy parameters (Supplemental Table 3). Mean changes from 0 to 24 months in Switch patients indicated that parameters were generally stable (Supplemental Table 3). Longitudinal measurements over up to 5.8 years of treatment showed that positive changes in primary efficacy parameters in Overall Vela and Imi-Vela patients were maintained (Fig. 2A and B). Primary efficacy parameters in Switch patients continued to be stable for up to 5.3 years of treatment (Fig. 2C).

Chitotriosidase activity decreased in Overall Vela and Imi-Vela patients, and also continued to decrease in Switch patients following transition to velaglucerase alfa (Supplemental Table 3). These reduced activity levels were maintained in the extension study (data not shown). Similarly, decreases in CCL18 level were seen in all three populations (Supplemental Table 3).

From 0 to 24 months, mean height Z-scores increased in the Overall Vela and Imi-Vela populations and were stable in the Switch population (Supplemental Table 3). Beyond 24 months, height Z-scores continued to increase in the Overall Vela population and were maintained in the Imi-Vela and Switch populations, though the number of patients with evaluable assessments was small (Table 3).

At 24 months, the mean change from baseline in bone age Z-scores was +1.3, −0.1 and +0.7 for the Overall Vela, Imi-Vela and Switch populations, respectively (Supplemental Table 3). Bone age Z-scores increased beyond 24 months in the Overall Vela population and were stable in the Switch population (Table 3). Longer-term changes from baseline in the Imi-Vela population were not statistically significant.

Sixteen of 22 patients were old enough to enter puberty during the extension study (≥7 years of age at baseline). One 13-year-old female patient had completed pubertal development at baseline. Tanner stage assessments indicated that patients were at an appropriate stage of puberty for chronological age.

4. Discussion

Velaglucerase alfa showed a positive safety profile in children and adolescents throughout the extension study. The safety results from this subgroup analysis are consistent with those in the complete extension study population of 95 adult and pediatric patients [15,16]. No new safety concerns were identified in the pediatric subgroup. No SAEs were deemed related to velaglucerase alfa, and no patients withdrew from the study because of an AE.

One patient died following a SAE of convulsion. The patient was a 6-year-old male from India with a history of anticonvulsant-treated seizures. He received velaglucerase alfa for 2 years before the terminal seizure. As reported by his mother, he had involuntary movements and breathlessness for 2–3 min and then stopped breathing. There was no associated vomiting, cough or fever. No medical advice was sought. The investigator did not consider the fatal convulsion to be related to velaglucerase alfa but instead a result of progression of the patient's GD. The patient met the eligibility criteria at study entry for the HGT-GCB-039 non-inferiority trial, as he was diagnosed by his treating physician as having GD1. During study participation, he developed neurologic symptoms suggestive of GD3 and his *GBA* genotype, F213I/F213I, has been described in other cases of GD3 [17]. This patient retained a diagnosis of GD1 at the time of his death. This is the only death reported in a velaglucerase alfa clinical trial to date.

In the Overall Vela and Imi-Vela populations, increases in hemoglobin concentration and platelet count, as well as decreases in spleen and liver volumes were seen, indicating beneficial effects of velaglucerase alfa in pediatric GD1 patients. In the Switch population, primary efficacy parameters were stable over time. The efficacy results in the pediatric population reflect those seen in the complete extension study population, where Overall Vela and Imi-Vela patients showed significant improvements in hematological parameters and organ volumes during the first 24 months that were maintained with longer-term treatment [16]; these efficacy parameters were generally stable in the complete Switch population [15].

The results obtained here with velaglucerase alfa are also comparable to those seen with imiglucerase; in retrospective analyses of registry data of pediatric patients treated with imiglucerase and/or alglucerase, normal or near normal values of key disease parameters could be achieved within 8 years of therapy, and often sooner [8,9].

Changes from baseline in exploratory efficacy parameters over time displayed trends toward improvement or maintenance. The GD plasma biomarkers chitotriosidase and CCL18 decreased considerably in Overall Vela and Imi-Vela patients within the first year of ERT and also decreased in Switch patients following their transition to velaglucerase alfa. Chitotriosidase and CCL18 are secreted from the activated pathologic macrophages characteristic of GD [9,18].

Bone involvement is considered the most debilitating aspect of GD, and can lead to complications such as growth retardation and skeletal

Table 3
Median observed values for height and bone age at baseline, and 24, 39 and 51 months.

Time point	Efficacy parameter	Overall Vela		Imi-Vela		Switch	
		N = 8		N = 5		N = 9	
		n	Median (range)	*n*	Median (range)	*n*	Median (range)
Baseline	Height Z-score	8	−1.5 (−2.7, −0.4)	5	−3.6 (−4.6, −0.7)	9	0.7 (−1.1, 1.3)
	Bone age Z-score	8	−2.4 (−6.6, 0.0)	4	−2.4 (−4.7, −2.2)	9	−0.1 (−2.5, 0.9)
24 months	Height Z-score	8	−1.1 (−1.7, −0.3)	5	−2.1 (−3.5, 0.0)	8	0.7 (−1.3, 1.4)
	Bone age Z-score	7	−0.9 (−3.7, 2.9)	5	−2.2 (−4.2, −1.4)	8	0.4 (−1.7, 1.5)
39 months	Height Z-score	7	−0.6 (−1.5, 0.1)	3	−2.2 (−2.7, −1.9)	4	0.4 (−1.8, 0.7)
	Bone age Z-score	7	−0.2 (−1.1, 2.7)	3	−2.3 (−4.3, −1.5)	4	−0.1 (−0.6, 0.8)
51 months	Height Z-score	5	−0.2 (−2.0, 0.2)	3	−2.3 (−3.0, −1.2)	2	0.5 (0.4, 0.5)
	Bone age Z-score	3	−0.5 (−2.2, 4.1)	3	−3 (−3.7, −2.9)	1	0 (0, 0)

No imputation was applied.
Abnormally advanced bone age was defined by a Z-score >2, whereas abnormally retarded bone age was defined by a Z-score <−2.

deformity in children [19–21]. In this study, eight of 13 treatment-naïve patients were below the 5th percentile for height Z-score at baseline. Increases were seen in the Overall Vela and Imi-Vela mean height Z-scores, consistent with a positive treatment effect on linear growth. Switch patients had a greater mean height Z-score at baseline than treatment-naïve patients, which was stable over time. These results suggest the benefit of early treatment to enable normal growth.

Increases in bone age Z-scores in the Overall Vela population were observed with long-term velaglucerase alfa treatment, and velaglucerase alfa maintained bone age Z-scores in Switch patients.

No AEs of bone pain or bone crises were reported for any pediatric patient prior to starting velaglucerase alfa treatment in the preceding trials; over the course of the extension study only one AE of bone pain was reported. Andersson et al. also observed a low frequency of new bone crises in a study of pediatric GD1 patients receiving ERT [8].

Our study is limited by the small number of patients, especially at later study time points due to patients transitioning to commercial velaglucerase alfa. Although age- and sex-matched standards were used for comparison where possible, there was a wide age range and imbalance in sex representation that must be considered when interpreting growth parameters. With a minimum age of 2 years for inclusion in the trials and subsequent enrolment of 3- and 4-year-old patients, the inclusion age may have been too low to determine whether patients suffered from GD3, as neurologic signs may only manifest later. Finally, all pediatric-specific parameters assessed in the study were exploratory. While they show trends toward improvement with velaglucerase alfa treatment, additional confirmatory research is required to validate the findings.

5. Conclusions

Velaglucerase alfa ERT was well-tolerated, and no new safety concerns were identified for pediatric patients compared with adults. Velaglucerase alfa had a positive effect on key efficacy parameters in treatment-naïve pediatric patients and maintained parameters in patients previously treated with imiglucerase.

Conflicts of interest

L. Smith has no competing interests to declare. W. Rhead has received speaker fees from UCYCLYD and has received clinical trial support from Genzyme, Hyperion and Shire. J. Charrow is a member of Advisory Boards for BioMarin, Genzyme, Protalix Biotherapeutics, Shire and Synageva, has received consulting or speaker fees from BioMarin, Genzyme, Protalix Biotherapeutics, Shire and Synageva, and has recently participated in clinical trials sponsored by Amicus, BioMarin, Genzyme, GSK and Shire. S. P. Shankar has received honoraria from Shire, Genzyme, and Protalix as a medical investigator and speaker, and her institution receives grants for participation in clinical trials and education grants for patients with Gaucher disease from Shire, Genzyme, and Protalix, and participates in the Gaucher Registries and Gaucher Outcome Survey. A. Bavdekar's institution received a research grant from Shire for a study in patients with type 3 Gaucher disease. N. Longo is a member of the Advisory Board for BioMarin and has participated in clinical trials sponsored by Shire, Amicus, BioMarin, Genzyme, and Hyperion. R. Mardach has no competing interests to declare. P. Harmatz has received consulting and speaker fees, as well as research support from BioMarin, consulting and speaker fees from Shire, consulting fees from Alexion, PTC, Johnson and Johnson and Chiesi, and speaker fees from Genzyme. T. Hangartner serves as a consultant to Shire. HM. Lee is an employee of Shire. E. Crombez is a former employee of Shire. G. M. Pastores has received consulting or speaker fees from Pfizer and has participated in clinical trials sponsored by Amicus, BioMarin, Genzyme, Protalix Biotherapeutics and Shire.

Role of the funding source

Shire was involved in the design of the clinical trials and in the analysis of the data. Shire funded medical writing support provided by Julia Cope, PhD, of Excel Scientific Solutions, and reviewed the manuscript for scientific accuracy.

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Appendix A. Supplementary data

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