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# Safety and efficacy results of switch from imiglucerase to velaglucerase alfa treatment in patients with type 1 Gaucher disease

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Gaucher disease (GD) is a lysosomal storage disorder; symptomatic patients with type 1 GD need long-term disease-specific therapy of which the standard of care has been enzyme replacement therapy (ERT). Thirty-eight of 40 patients (aged 9–71 years) clinically stable on ERT with imiglucerase, safely switched to a comparable dose of velaglucerase alfa (units/kg) during TKT034, a 12-month, open-label clinical study, and for 10–50 months in an extension study. The most common adverse events (AEs) judged to be drug-related in the extension were fatigue and bone pain. No drug-related serious AEs were reported. No AEs led to study withdrawal. At 24 months from baseline (baseline being TKT034 week 0), patients had generally stable hemoglobin, platelet, spleen, liver, and bone density parameters. Nevertheless, dose adjustment based on the achievement of therapeutic goals was permitted, and 10 patients, including seven patients who had platelet counts  $<100 \times 10^9/L$  at baseline, were given at least one 15 U/kg-dose increase during the extension. Trends indicative of improvement in platelet count and spleen volume, and decreasing levels of GD biomarkers, chitotriosidase and CCL18, were observed. Immunogenicity was seen in one patient positive for anti-imiglucerase antibodies at baseline. This patient tested positive for anti-velaglucerase alfa antibodies in TKT034, with low antibody concentrations, and throughout the extension study; however, the patient continued to receive velaglucerase alfa without clinical deterioration. In conclusion, clinically stable patients can be switched from imiglucerase to velaglucerase alfa ERT and maintain or achieve good therapeutic outcomes.

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## Introduction

Gaucher disease (GD), an inherited storage disorder of lysosomal glucocerebrosidase deficiency, caused by mutations in *GBA*, results in intracellular accumulation of glycosphingolipids. The vast majority of cases are classified as type 1 GD, which can present in either childhood or adulthood with hepatosplenomegaly, anemia, thrombocytopenia, and bone disease and is distinguished from other types by an absence of central neurological symptoms [1,2].

*Additional Supporting Information may be found in the online version of this article.*

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**Conflicts of interest:** DE currently receives reimbursement for travel expenses and honoraria for meetings from Shire. AM receives consultancy fees from Shire and his institution has received unrestricted research grants from Shire. DAH has received consultancy fees, travel and research grants, and honoraria for speaking from Shire, Genzyme, Protalix Biotherapeutics, and Amicus. PG has received consultancy fees from Shire, Genzyme, Protalix Biotherapeutics, and Actelion. JC is a member on Advisory Boards for Genzyme, Shire, Pfizer-Protalix Biotherapeutics, BioMarin, and Synageva; receives consultancy or speaker fees from Genzyme, Shire, Pfizer-Protalix Biotherapeutics, BioMarin, and Synageva; and has recently participated in clinical trials sponsored by Genzyme, Shire, Amicus, GSK, and BioMarin. LS has no competing interests to declare. SPS has received honoraria from Shire, Genzyme, and Protalix as a medical investigator and speaker. SPS's 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. TNH serves as a consultant to Shire. YK and NW are employees of Shire. EC is a former employee of Shire. AZ receives consultancy fees from Protalix Biotherapeutics, has options in Protalix Biotherapeutics, and is a member of its Scientific Advisory Board. AZ receives honoraria from Shire, Genzyme/Sanofi, and Pfizer, and his institution receives support from Genzyme/Sanofi for participation in the International Collaborative Gaucher Group Gaucher Registry and from Shire for participation in the Gaucher Outcome Survey. DE, AM, DAH, PG, JC, LS, SPS, and AZ were investigators in the clinical trial.

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Enzyme replacement therapy (ERT) is the approved first-line treatment approach for symptomatic type 1 GD. Imiglucerase (Cerezyme<sup>®</sup>, Genzyme, Cambridge, MA) and velaglucerase alfa (VPRIV<sup>®</sup>, Shire, Lexington, MA) are both replacement enzymes. Velaglucerase alfa is produced using gene activation technology in a human cell line; it has the same amino acid sequence as the naturally occurring human enzyme [3]. Imiglucerase is produced using recombinant DNA technology in Chinese hamster ovary cells, and the amino acid sequence differs from the human enzyme by a single amino acid substitution [4]. Velaglucerase alfa and imiglucerase have different glycosylation patterns; velaglucerase alfa contains longer chain high-mannose type glycans compared with the core mannose structures in imiglucerase [5]. Taliglucerase alfa ERT is also used to treat GD, but it was not commercially available at the time velaglucerase alfa was undergoing clinical trials as an investigational drug.

We previously reported that 40 patients were switched from ERT with imiglucerase to velaglucerase alfa in a phase II/III clinical trial, TKT034, wherein safety was the primary endpoint [6]. In that trial, one patient discontinued due to an anaphylactoid reaction during the first infusion of velaglucerase alfa that was classified as a serious adverse event (SAE) and considered to be related to the study drug. No other patient discontinued participation due to an adverse event (AE) or experienced a drug-related SAE. The four secondary-endpoint variables, hemoglobin concentration, platelet count, spleen volume, and liver volume, were stable over the 12-month trial. No patients developed anti-velaglucerase alfa antibodies, but two of three patients who tested positive for the presence of anti-imiglucerase antibodies at baseline (prior to velaglucerase alfa dosing), tested positive for the presence of very low titers of anti-velaglucerase alfa antibodies at baseline [6].

Patients who completed TKT034 were enrolled in an extension study, HGT-GCB-044. The primary objective of the extension study was to evaluate the long-term safety of every-other-week intravenous infusions of velaglucerase alfa in patients with type 1 GD. This is the first report of longer term switch-over to velaglucerase alfa in the context of a clinical trial.

## ■ Patients and Methods

**Extension study overview.** HGT-GCB-044 was an open-label extension of three clinical trials of velaglucerase alfa in patients with type 1 GD. Two of the three trials enrolled treatment-naïve patients, the results of which are reported elsewhere [7,8]. We report the extension study results of the cohort who completed the trial TKT034 [6], which was conducted in patients previously treated with imiglucerase.

Fifteen centers participated in TKT034 [6]; 14 of these were involved in the extension study, and due to a patient relocating, one additional center in South Korea took part. The extension study was conducted in compliance with the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice and Title 21 of the United States Code of Federal Regulations, part 56. At each site, an institutional review board or independent ethics committee approved the research. Each patient or their legally authorized representative(s) provided written, informed consent to participate in the study.

The extension study was registered in the ClinicalTrials.gov database (identifier NCT00635427).

**Patients.** Enrollment criteria for the clinical trial TKT034 are detailed elsewhere [6]. Briefly, adults and children with type 1 GD who were clinically stable and receiving a stable dose of imiglucerase were enrolled.

Patients were enrolled in the extension study after completing TKT034 (through week 53). Enrollment exclusion criteria for the extension study included treatment with an investigational device or drug (except velaglucerase alfa) in the 30 days before study entry, inability to comply with the protocol, being pregnant or lactating, and any significant comorbidity.

**Velaglucerase alfa.** Velaglucerase alfa was administered in a continuous intravenous infusion over 60 minutes every other week. Patients were eligible to participate in the extension study until commercial velaglucerase alfa became available to them or the study was discontinued.

Patients received the same dose of velaglucerase alfa that they had received in TKT034, which was dependent on the dose of imiglucerase that they had received before switching to velaglucerase alfa [6]. Dose adjustment by 15 U/kg was permitted once every 12 months based on the achievement of therapeutic goals [9], provided that the dose remained within the range 15–60 U/kg.

**Safety assessments.** Patients were monitored continuously for AEs, which could be discovered through observation or examination, questioning, complaint, or clinical laboratory tests. The investigators assessed the relationship of each AE to the study drug and its severity.

At each infusion visit, vital signs were measured and the use of concomitant medications (i.e., all nonprotocol treatments) was reviewed. Physical examinations and clinical laboratory tests were carried out approximately every 12 weeks.

Female patients of child-bearing potential had a urine pregnancy test before each infusion, which if positive, was to be confirmed by a human chorionic gonadotropin blood test and brought to the attention of the Shire medical monitor.

Blood samples were tested for anti-velaglucerase alfa antibodies approximately every 12 weeks (Supporting Information). An electrochemiluminescence assay was used to screen samples for the presence of anti-drug antibodies and an enzymatic activity neutralizing antibody assay was used to analyze samples that screened positive (methods described previously) [6,10].

**Efficacy measurements.** Blood hemoglobin concentration, platelet count, chitotriosidase activity, and chemokine (C-C motif) ligand 18 (CCL18) level were measured at a centralized laboratory, for consistency, approximately every 12 weeks.

The volumes of the spleen and liver were measured with yearly abdominal MRI scans. The scans were analyzed by one independent reviewer who was blinded to the patients' identities and the study time points when the scans were obtained. The volumes were normalized to body weight (% BW) and expressed as multiples of normal (MN) where 1 MN for the liver and spleen was considered 2.5% BW and 0.2% BW, respectively.

Bone mineral density (BMD) was assessed in adults only (patients aged at least 18 years at the time of consent in the trial TKT034). The lumbar spine and the proximal end of one or both femurs were scanned at yearly intervals using dual-energy X-ray absorptiometry (DXA).

Although different DXA scanners were used among the sites, scanners used in the study were cross-calibrated using a phantom (BMIL Quality Assurance/Quality Control phantom [11]; BioMedical Imaging Laboratory, Dayton, OH). Hologic scanners (Hologic, Bedford, MA) were cross-calibrated separately from GE Lunar scanners (GE Lunar, Madison, WI). Between-manufacturer calibration was achieved using published equations from clinical cross-calibration studies [12,13]. Where available, quality assurance data were collected from individual scanners, and correction equations were applied for longitudinal drifts if needed.

BMD measurements were converted to Z-scores using sex- and race-specific reference data and to T-scores using Caucasian female reference data, as suggested by the International Society for Clinical Densitometry [14]; reference data published by Hologic were used after standardizing the DXA data from GE Lunar scanners to the Hologic scale.

The DXA data were analyzed at the BioMedical Imaging Laboratory (Wright State University, Dayton, OH). A single reviewer blinded to treatment information executed the analysis of the DXA data under the supervision of the laboratory director (TNH).

Hemoglobin concentration, platelet count, and organ volumes were evaluated as secondary objectives and all other efficacy variables were evaluated as tertiary objectives.

**Statistical analysis of efficacy variables.** Summary statistics at regular time points were calculated for each efficacy variable. Mean within-patient changes and mean within-patient percentage changes from baseline were calculated, together with two-sided 95% confidence intervals. Baseline was defined as before the first dose in TKT034.

The changes in hemoglobin concentration, platelet count, spleen volume, and liver volume compared to baseline were the secondary endpoints of the extension study.

Changes from baseline in plasma chitotriosidase and CCL18 levels and changes in BMD within the adult cohort were tertiary endpoints. Chitotriosidase levels of subjects heterozygous for a 24-base-pair duplication in the chitotriosidase gene were doubled, because it has been established that the average enzyme activity of heterozygous patients is half that of patients homozygous for the wild type allele [15]. Homozygous, chitotriosidase-deficient patients were excluded from the chitotriosidase analysis [16].

During the course of the extension study, velaglucerase alfa was approved for use in the US and the EU and following this, a large number of patients transitioned to commercial therapy (after a cumulative 24-month treatment period in the studies). In addition to the analysis of the efficacy results from baseline to 24 months, a longitudinal data analysis was performed using all available data up to and including the end of the extension study.

Because the expectation was non-deterioration, the mean change from baseline to 24 months was expected to be <1 g/dL for hemoglobin concentrations, <20% for platelet counts, and <15% for the organ volumes (as in the trial TKT034) [6]. Two-sided confidence intervals around the mean changes were used for exploratory tests of these hypotheses; *P*-values were not calculated. A similar analysis using 90% confidence intervals was performed for the TKT034 trial [6]. For the change-from-baseline analysis at 24 months, a simple data imputation approach was used for intermittent missing values: last observation carried forward except for missing baseline values, which were substituted with the next available measurement.

**TABLE I.** Patients at Baseline (Before the First Dose in Clinical Trial TKT034)

	<i>n</i> = 38
Age, years	
Median	35
Range	9–71
Aged <18 years, <i>n</i> (%)	9 (24)
Male, <i>n</i> (%)	18 (47)
GBA genotype, <i>n</i> (%)	
N370S/N370S	13 (34)
N370S/84GG	2 (5)
N370S/L444P	6 (16)
N370S/Other	13 (34)
L444P/Other	1 (3)
Other/Other	3 (8)
Spleen status, <i>n</i> (%)	
Intact	35 (92)
Splenectomized	3 (8)
Pre-switch imiglucerase exposure, months	
Median	65
Range	22–192
Pre-switch imiglucerase infusion dose, <i>n</i> (%)	
<15 U/kg	1 (3) <sup>a</sup>
15–29 U/kg	16 (42)
30–44 U/kg	10 (26)
45–59 U/kg	7 (18)
≥60 U/kg	4 (11) <sup>b</sup>
Anti-imiglucerase antibody test, <i>n</i> (%)	
Negative	35 (92)
Positive	3 (8)
24-Base-pair duplication in chitotriosidase gene, <i>n</i> (%)	
Homozygous wild type	25 (66)
Heterozygous	12 (32)
Homozygous (chitotriosidase deficient)	1 (3)

<sup>a</sup> Lowest dose was 14 U/kg.

<sup>b</sup> Highest dose was 62 U/kg.

Covariate-adjusted linear mixed models were employed for the longitudinal data analysis. Adjustments were made for the following covariates: the baseline measurement and age at baseline. Because baseline platelet counts likely correlate with splenectomy status, the estimated platelet count means were also adjusted for splenectomy status. The estimated means for hemoglobin concentration were also adjusted for sex.

BMD analyses were repeated after excluding all patients who received concomitant bisphosphonates during the studies.

## Results

Thirty-eight of the 40 patients who received at least one full or partial infusion of velaglucerase alfa in TKT034 [6] were enrolled in the extension study (Table I). The median values at baseline for hemoglobin concentration, platelet count, and normalized liver volume were normal; however, several patients had platelet counts  $<150 \times 10^9/L$  and all 34 nonsplenectomized patients with baseline spleen volume measurements had some degree of splenic enlargement. Five patients had spleen volumes  $>8$  MN ( $\leq 8$  MN is a long-term therapeutic goal proposed by Pastores et al. for spleen size [9]) and each of these five patients had a platelet count  $\leq 74 \times 10^9/L$  at the start of TKT034.

The baseline platelet counts of the three splenectomized patients (Table I) were  $160 \times 10^9/L$ ,  $178 \times 10^9/L$ , and  $399 \times 10^9/L$  and their hemoglobin levels were 13.5, 13.1, and 12.9 g/dL.

Most patients continued to receive velaglucerase alfa in the extension study at the same dose that they had received in TKT034. There were no dose reductions, but 10 adult patients had their doses increased at least once in the extension study. These patients had one or more clinical parameters below the therapeutic goal and the investigators requested a dose increase. The patients were receiving between 15 and 35 U/kg before dose adjustment: seven of 10

**TABLE II.** Summary of AEs in the Extension Study

	Patients, <i>n</i> (%)	Events
At least one AE	35 (92)	375
At least one (possibly or probably) drug-related AE	8 (21)	9
At least one infusion-related AE	5 (13)	6
At least one serious AE <sup>a</sup>	6 (16)	14
Life-threatening or fatal	0	0
Possibly or probably drug-related	0	0
At least one severe AE <sup>b</sup>	4 (11)	12
Possibly or probably drug-related	0	0

Presentation of AEs that occurred any time from a patient's first infusion in the extension study until 30 days after their last infusion.

<sup>a</sup> Reported as serious based on outcome or action criteria usually associated with events that pose a threat to life or functioning.

<sup>b</sup> The severity of an AE was assessed with reference to the National Cancer Institute Common Terminology Criteria for AEs (version 3.0).

receiving  $\leq 20$  U/kg and three other patients on 27, 30, and 35 U/kg. No patient had their dose increased above 60 U/kg.

Low baseline platelet counts seemed to be associated with lower doses since six of eight patients with a baseline platelet count  $<120 \times 10^9/L$  and seven of 14 patients with a platelet count  $<150 \times 10^9/L$  were on an imiglucerase dose  $<30$  U/kg before switching.

The median duration of velaglucerase alfa exposure in the extension study was 21.25 months (range 10.1–50.1 months). Patients started to transition to commercial velaglucerase alfa after about 24 months of cumulative exposure (i.e., after the first 12 months of the extension study), following the drug's first marketing authorization.

Thirty patients completed the extension study. Six patients were considered to have discontinued when the sponsor decided to terminate the extension study at the end of 2012; five of these transitioned to commercial velaglucerase alfa. Two patients withdrew consent citing either a decision to focus on controlling comorbid diabetes (one patient) or dissatisfaction because of an expectation of improvement and the constraints of a clinical trial setting (one patient).

## Safety and tolerability in the extension study

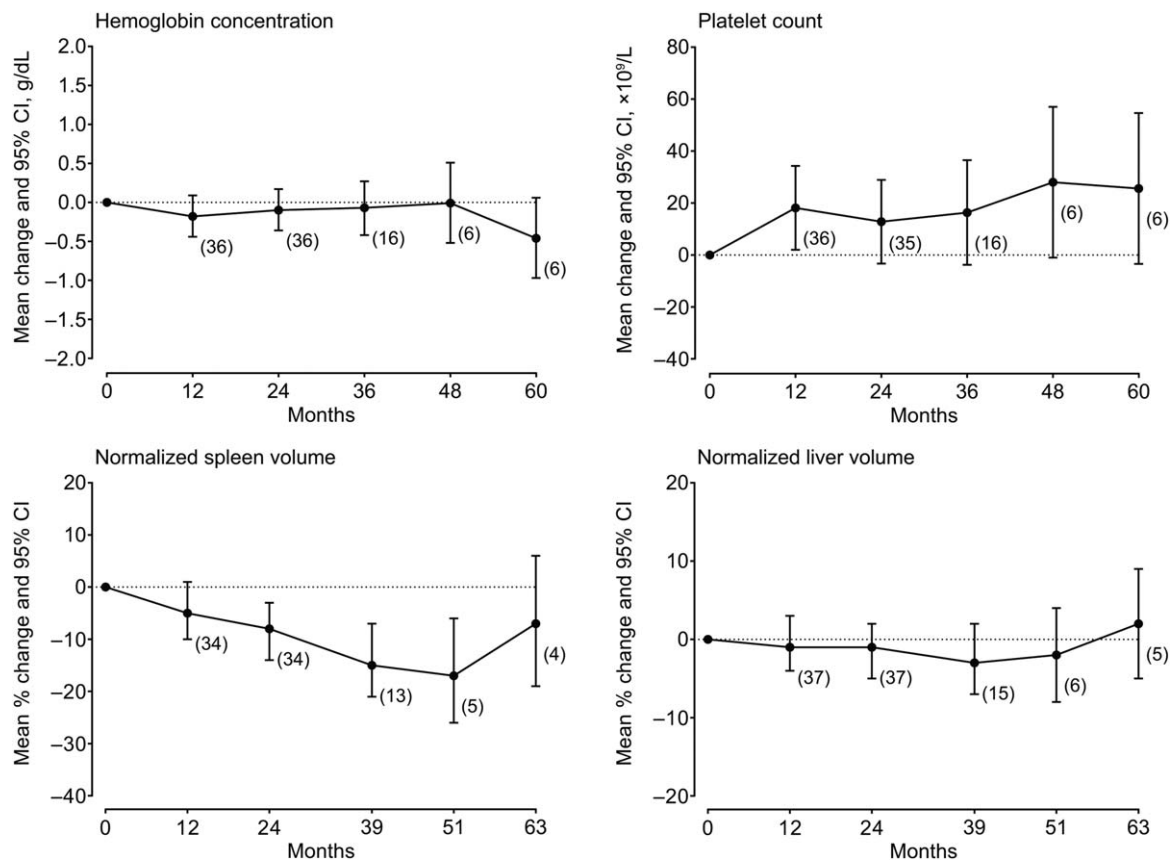
Three hundred and seventy-five AEs were reported in 35 patients (Table II). Only nine AEs in eight patients were considered (possibly or probably) related to velaglucerase alfa treatment. Fatigue ( $n = 2$ ) and bone pain ( $n = 2$ ) were the only AEs purported to be drug-related that were experienced by more than one person.

The drug-related AEs of fatigue were also categorized as infusion-related AEs. An infusion-related AE was defined as an AE that began within 12 hr of the start of an infusion and was judged to be drug-related. A total of six infusion-related AEs were reported in five patients during the extension study.

Infusion-related AEs were less common in the extension study than in TKT034 [6]. All 38 patients received at least one concomitant medication; however, only two patients required pre-infusion medication: one patient received loratadine and one patient received paracetamol. No patients discontinued from the extension study due to an AE.

None of the SAEs that were reported were considered related to velaglucerase alfa treatment (Supporting Information Table SI) and no study drug-related hypersensitivity reactions were reported. There were no trends in the physical examination findings, vital signs, or the clinical laboratory test results to indicate an increased safety risk with velaglucerase alfa treatment.

Only one patient tested positive for the presence of anti-velaglucerase alfa antibodies during the extension study. This patient had anti-imiglucerase antibodies at baseline, some of which



**Figure 1.** Hematological and visceral assessments: changes from baseline to annual assessments based on covariate-adjusted linear mixed models. Each number in brackets indicates the number of patients with available data at that time. Adjustments were made for the following covariates: the baseline measurement and age at baseline. The estimated means for hemoglobin concentration and platelet count were also adjusted for sex and splenectomy status, respectively.

apparently cross-reacted with velaglucerase alfa [6]. The titer (apparent concentration in ng/mL) for anti-velaglucerase alfa antibodies increased slowly during 3 years of dosing. At the end of the extension study, the titer was 1121 ng/mL, which was much lower than the titer for anti-imiglucerase antibodies that was measured at baseline (191,100 ng/mL) [6]. The anti-velaglucerase alfa antibody-positive samples from this patient were analyzed using an enzymatic activity neutralization assay and shown to have neutralizing antibody (NAb) activity; no effect was noted on hemoglobin concentration and platelet count and no drug-related AEs were reported for this patient.

Two patients became pregnant while enrolled in the extension study. One patient's pregnancy was confirmed just over 3 years into the extension study and the other was after 1.5 years. They elected to continue velaglucerase alfa treatment during their pregnancies and signed pregnancy informed consent forms (approved by an institutional review board or independent ethics committee), although one patient had a 4-month treatment interruption after the confirmation of pregnancy. Both patients experienced SAEs and nonserious AEs during pregnancy, but the events were considered to be unrelated to velaglucerase alfa treatment. The SAEs were oligohydramnios and postprocedural hematoma after a cesarean section (one patient) and two urinary tract infections (one patient). The platelet count of the patient who had a hematoma was  $106 \times 10^9/L$  around the time of this event. Both patients delivered full-term healthy babies.

### Efficacy evaluation

The mean changes from baseline to 24 months, and the 95% confidence intervals around the means, in hemoglobin concentration, pla-

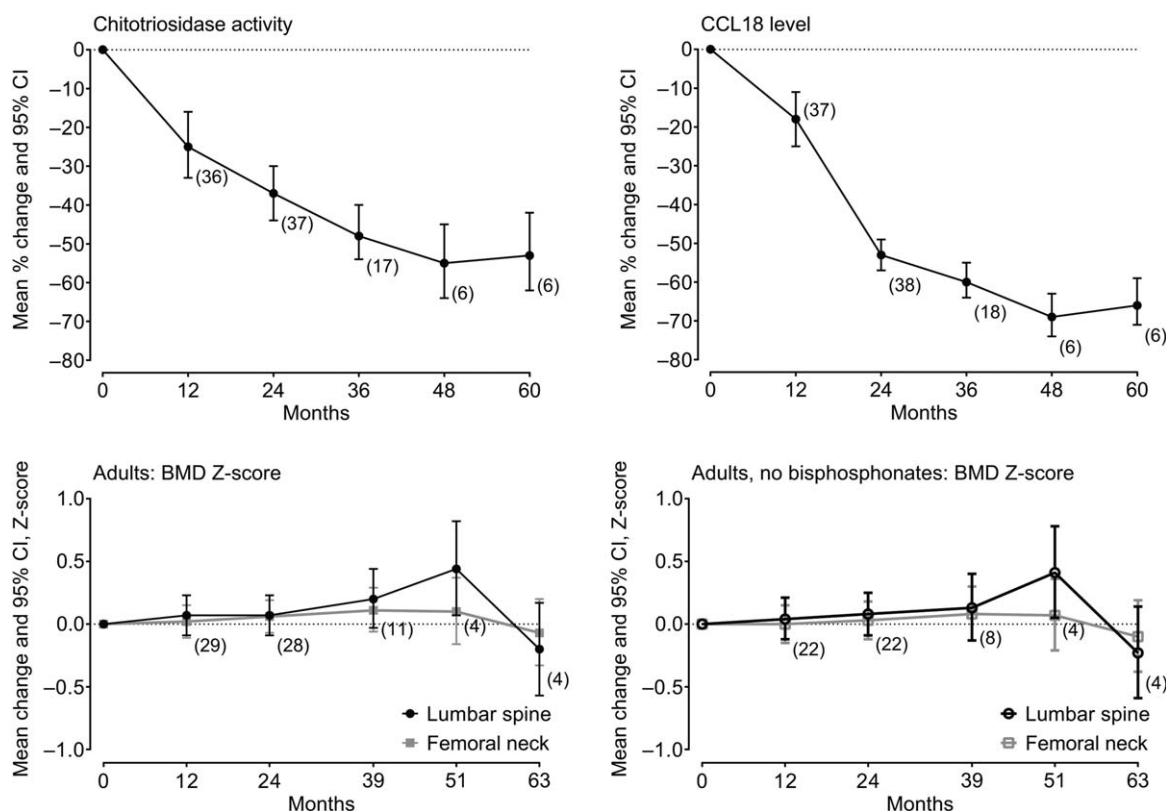
telet count, and the organ volumes were within the pre-specified, clinically significant ranges:  $-1$  to  $1$  g/dL,  $-20$  to  $20\%$ , and  $-15$  to  $15\%$ , respectively (Supporting Information Table SII).

However, there was some suggestion of improvement in platelet counts and spleen volumes (Fig. 1). In the individual patient data, we found that 13 patients had a  $>20\%$  increase (25–199%) in platelet count by their last assessment, including seven patients who had a baseline platelet count  $<150 \times 10^9/L$ . Eleven patients had a  $>15\%$  (17–60%) reduction in spleen volume, including three patients who had spleens  $>8$  MN at baseline.

Patients who did not have a dose increase are presented separately from those who did in by-patient line graphs for platelet count and spleen volume as well as the plasma biomarkers (Supporting Information Figs. S1–S4).

In the small group of patients with platelet counts  $<150 \times 10^9/L$  as well as treatment doses  $<30$  U/kg at baseline ( $n = 7$ ), the platelet measurements were generally stable during TKT034; five of them ultimately had their doses increased in the extension study, of whom four had a  $>20\%$  improvement in platelets at their last assessment.

One patient had a splenectomy during the extension study, after his infusion at week 149 (month 36 assessment), due to massive splenomegaly. He experienced an increase of  $>700\%$  in platelets (Supporting Information Fig. S1; probably due to decreased splenic sequestration of platelets). This patient's hematological measurements up to and including month 36 were with an intact spleen and he had hematological measurements up to month 45 only. Therefore, his post-splenectomy measurements are not included in Fig. 1 or Supporting Information Table SII.



**Figure 2.** Exploratory efficacy assessments: changes from baseline to annual assessments based on covariate-adjusted linear mixed models. Each number in brackets indicates the number of patients with available data at that time. Seven adults received bisphosphonates concomitantly at least once during the studies, and 22 adults (lower right panel) did not receive bisphosphonates. Adjustments were made for the following covariates: the baseline measurement and age at baseline. BMD: bone mineral density.

Mean decreases over time in levels of chitotriosidase and CCL18 were observed (Fig. 2); the two biomarkers decreased in almost all patients (Supporting Information Figs. S3 and S4).

Hemoglobin concentration, platelet count, spleen and liver volumes, and chitotriosidase and CCL18 levels in the patient who had a 4-month treatment interruption during pregnancy all deteriorated during the break (which was in her fifth year of trial participation). The patient then improved after resuming treatment (Supporting Information Figs. S1–S4 show platelets, spleen volume, and biomarkers).

All 29 adult patients had serial DXA scans, most of whom had a baseline T-score  $\geq -1$  at the lumbar spine ( $n = 19$ ), the femoral neck ( $n = 19$ ), or both, that is, within the normal range. BMD Z-scores were generally maintained over time, and there was little to no difference when patients who received bisphosphonates were excluded from the analysis (Fig. 2). At 51 and 63 months from baseline, there were only four patients with available data, and the mean change in lumbar spine Z-score peaked and then fell (Fig. 2).

## Discussion

We previously reported safety and efficacy results in 40 patients switching from imiglucerase to velaglucerase alfa treatment in the 12-month clinical trial TKT034 [6]. The extension study for patients who completed the trial provides longer-term safety and efficacy data for 24 up to 63 months.

The vast majority of AEs reported in the extension study were unrelated to velaglucerase alfa treatment. Infusion-related AEs affected only five patients and only two patients required pre-infusion

medication. No drug-related SAEs were reported and no patient discontinued due to an AE.

Only one patient tested positive for the presence of antivelaglucerase alfa antibodies; this patient did not deteriorate clinically.

Two patients became pregnant and continued to receive ERT during their pregnancies. Their experience of AEs does not change the risk-benefit profile of velaglucerase alfa and supports the decision not to interrupt treatment during pregnancy. In general, evidence regarding the safety of ERT use in pregnancy is limited, but good maternal and neonatal outcomes were reported based on records of 21 female patients receiving ERT, which were collected and examined retrospectively from six clinical sites [17], and the two cases in the present study are consistent with those findings.

The four clinical variables that were stable over 12 months in TKT034 (hemoglobin concentration, platelet counts, and spleen and liver volumes) remained stable in a subsequent 12-month period on velaglucerase alfa treatment, based on mean changes from baseline to 24 months that were within prespecified, clinically significant ranges.

Hemoglobin level, liver volume, and BMD Z-scores (age-standardized BMD) in adults were generally stable over time. However, there were trends toward improvement in platelet counts and spleen volumes, and the plasma biomarker levels were clearly reduced.

About half of the patients with baseline platelet counts  $< 150 \times 10^9/L$  and most patients with spleens  $> 8$  MN at baseline experienced what we judged to be a clinical improvement ( $> 20\%$  increase in platelets,  $> 15\%$  reduction in spleen volume). However, not all patients who experienced clinical improvements had low platelet counts or particularly large spleens on study entry; specifically, patients with low platelet counts and larger spleens made up seven of 13 patients

and three of 11 patients in total who experienced improvements in platelets and spleen volume, respectively.

Ten of 38 patients had their dose increased during the extension study. This probably contributed to the trends observed in platelet count and spleen volume, although clinically significant within-patient changes were also observed outside of the group who had dose adjustments. Specifically, seven of 13 patients who experienced an increase in platelets of >20% and five of 11 patients whose spleen volume decreased by >15% had their dose increased. Therefore, the results show that switching patients previously treated on a stable dose of imiglucerase to velaglycerase alfa was generally not associated with deterioration and for some patients, despite being apparently stabilized, there was room for clinical improvement, with dose adjustment for some patients and without it for others. Further investigation is needed to confirm the results and, if pertinent, look for patient- or drug-specific factors that might explain them.

Considering that low platelet counts seemed to associate with lower treatment doses or, perhaps more importantly, that most patients who had a dose adjustment achieved some clinical improvement, one might speculate that some pre-switch imiglucerase doses were not optimal. However, we cannot judge whether imiglucerase doses were optimal based on this study. Patients were not on imiglucerase treatment in the study.

Baseline chitotriosidase and CCL18 levels varied widely (108–30,785 nmol/mL/hr and 49–1582 ng/mL, respectively). The median values were clearly elevated compared with values reported for healthy controls or asymptomatic glucocerebrosidase-deficient

patients; since Gaucher cells secrete chitotriosidase and the chemokine CCL18 [18,19], these results may indicate that there may be significant glucosylceramide storage even after 2 or more years of previous imiglucerase treatment, and even though chitotriosidase is not glucosylceramide storage-specific.

Our analyses were limited by patient number attrition (less than half of the patients had 3 or more years of velaglycerase alfa exposure including time in TKT034), which was largely due to patients transitioning to commercial velaglycerase alfa. Linear mixed effects models that incorporated all available data and included covariate adjustments were used to analyze the longer-term efficacy data and minimize the impact of the missing data (missing mechanism was considered to be missing at random). We had to assume that there had been no longitudinal drift in DXA scanners if the quality assurance data were unavailable, which was another limitation; this may have affected the accuracy of the DXA results.

In conclusion, this study reinforces the safety profile and efficacy of velaglycerase alfa reported in previous studies [7,8,20] and the low incidence in the long term of anti-drug antibody production and hypersensitivity reactions. Clinically stable patients can be safely switched from imiglucerase to velaglycerase alfa ERT and maintain or achieve good outcomes.

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