CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-575

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA:	22-575
Type/Category:	New molecular entity
Brand Name:	VPRIV
Generic Name:	velaglucerase alfa
Proposed Indication:	Long-term enzyme replacement therapy (ERT) for pediatric and adult patients with type 1 Gaucher disease
Dosage Form:	Lyophilized powder for injectable solution
Route of Administration:	intravenous infusion
Dosing Regimen and Strength:	60 U/kg every other week as a 60-min infusion
Sponsor:	Shire
OCP Division:	Division of Clinical Pharmacology 3 (DCP3)
OND Division:	Division of Gastroenterology and In-Born Error of Metabolism Products
Submission Date:	August 31, 2009 (letter date)
Primary Clinical Pharmacology Reviewer:	Lanyan ('Lucy') Fang, Ph.D.
Secondary Pharmacometrics Reviewer:	Christoffer Tornoe, Ph.D.
Secondary Clinical Pharmacology Reviewer:	Jang-Ik Lee, Pharm.D., Ph.D.

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1 EXECUTIVE SUMMARY

Velaglucerase alfa (Gene-activated human glucocerebrosidase, GA-GCB) is a human glucocerebrosidase that is produced by gene activation in human fibroblast cell line. Velaglucerase alfa is being developed by Shire Human Genetic Therapeutics, Inc as a long-term enzyme replacement therapy (ERT) for patients with type 1 Gaucher disease. The current rolling NDA submission is a priority review submission (6-month review clock started on August 31, 2009) due to the supply shortage of the currently marketed Orphan product Cerezyme (imiglucerase) as a result of Genzyme's manufacturing facility contamination. Velaglucerase alfa is considered to be a new molecular entity (NME) and an alternative therapy to Cerezyme (imiglucerase).

The application includes 5 clinical studies in a total of 94 patients with type 1 Gaucher disease who were 2 years old or older. Studies TKT025, TKT032 and TKT039 were conducted in patients naïve to enzyme replacement therapy. Study TKT025EXT was an extension to study TKT025. Study TKT034 was conducted in patients who were receiving imiglucerase treatment. The pharmacokinetic (PK) characteristics of velaglucerase alfa were evaluated in studies TKT025, TKT025EXT and TKT032.

There were two manufacturing process changes during velaglucerase alfa clinical development process and resulted in three different drug products: —— b(4)
—— product (Phase I/II material), AF1 (Phase II/III material) and AF2 (to-be-marketed material). Patients received Phase I/II material in Study TKT025, and AF1 material in Studies TKT025EXT and TKT032. Based on preliminary CMC review, biochemical comparability was demonstrated between AF1 and AF2 drug substance, but not for Phase I/II material. Thus TKT025 was not reviewed in depth. In addition, most subjects in clinical studies received AF1 materials except 18 out of 94 patients were transitioned from AF1 to AF2 in Study 034.

A required inter-division-level Clinical Pharmacology briefing was held on Monday, January 25, 2010 with approximately 25 attendees.

1.1 RECOMMENDATIONS

As a result of Clinical Pharmacology and Biopharmaceutics review, it has been concluded that the in-process velaglucerase alfa assay performance, in the pivotal PK trial, was insufficient since duplicates rather than 5 replicates of quantity control (QC) samples were included in patient PK sample assay. As such, the PK parameters characterized by the sponsor and submitted in the current NDA can not be considered accurate and reliable for labeling purpose. However, considering the supply shortage of the currently marketed imiglucerase and the demonstrated clinical efficacy and safety of velaglucerase alfa, we recommend that the definitive PK characterization be deferred post approval as provided in 21 CFR §320.22 (e). A post marketing commitment (PMC) study was recommended in Section 1.2 below.

1.2 POST MARKETING COMMITMENTS

The Clinical Pharmacology Review Team recommends the following post marketing commitment (PMC):

1. Provided that you have retained the samples from Study TKT032, reanalyze all archived pharmacokinetic (PK) samples for Study TKT032 using adequate in-process quality controls and standard curves (see VII. C. Application to Routine Drug Analysis in Bioanalytical Guidance for Industry at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf.). Using these new assay results, prepare a new PK report that would adequately characterize velaglucerase alfa PK.

2. In case that the PK samples are not stable to be reanalyzed or there are significant number of missing samples such that velaglucerase alfa PK can not be adequately characterized (see PMC #1 above), conduct a prospective PK study in patients with Type 1 Gaucher disease. The study should include the following considerations:

    - Use of an accurate, precise, and validated analytical method (see referenced FDA Guidance document referred to in PMC #1 above).
    - The study should include a sufficient number of patients representing the entire range of the proposed age group
    - A sufficient number of time points for PK sampling in order to fully characterize the profile (i.e., sampling until velaglucerase alfa concentrations are undetectable using an appropriately established LOQ based on assay performance)

The recommended PMCs above need to be conveyed to the sponsor. If the new PK study is necessary (see PMC #2 above), the sponsor should submit the study protocol to the Agency for review and comments prior to study initiation.

1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Pharmacokinetics

In study TKT032, pediatric (N=7, 2 to 17 years old) and adult (N=18, 18 to 62 years old) patients with type 1 Gaucher disease were randomized to receive either 45 or 60 U/kg velaglucerase alfa as 1-hour intravenous (IV) infusion every two weeks for 51 weeks. PK evaluations were performed at Weeks 1 and 37. During the infusion, the velaglucerase alfa serum concentrations rose rapidly for the first 20 minutes after administration. The mean maximum concentration (C_{max}) were 3437 ng/mL (standard deviation [SD], 1283 ng/ml) and 5256 ng/mL (SD, 2323 ng/ml) for 45 and 60 U/kg, respectively, at Week 1. The mean C_{max} were 4033 ng/mL (SD, 2939 ng/ml) and 5721 ng/mL (SD, 2795 ng/ml) for 45 and 60 U/kg, respectively, at Week 37. At the end of infusion, velaglucerase alfa serum concentrations fell rapidly with a mean half life of 11 to 12 minutes for both dose groups at Weeks 1 and 37. The mean systemic clearance (CL) ranged from 6.72 to 7.56

mL/min/kg. The mean volume of distribution at steady state (Vss) ranged from 82 to 108 mL/kg (8.2% to 10.8% of body weight).

Consistent with the apparent short half life (approx. 11 to 12 minutes) and longer dosing interval (every two weeks), no significant accumulation in serum velaglucerase alfa concentrations was observed with repeated doses of 45 or 60 U/kg and velaglucerase alfa PK did not appear to change over time (Week 1 vs. Week 37).

The mean Cmax and area under the concentration-time curve (AUC_{inf}) of velaglucerase alfa were approximately 40% to 50% in the subjects received 60 U/kg than the subjects received 45 U/kg, which is slightly greater than the expected 33% increase assuming dose proportionality.

Hepatic impairment and drug interaction studies were not conducted. Renal impairment study was also not conducted. Such studies do not appear to be necessary for velaglucerase alfa, a large molecular protein product.

A study including transition from imiglucerase to velaglucerase alfa was conducted (Study TKT034), but the PK of veleglucerase alfa was not characterized.

Pharmacodynamics
Velaglucerase alfa administration resulted in clinical meaningful and statistically significant increase in mean hemoglobin concentration (primary efficacy endpoint), statistically significant change in secondary efficacy endpoints including increase in platelet count, statistically significant reduction in body weight normalized spleen and liver volume, and reduction in plasma biomarkers (see ***Exposure-Response Relationship*** below for more information).

Exposure-Response Relationship
In Study TKT032, the change in hemoglobin levels, platelet counts, normalized liver and spleen volume from baseline following 45 or 60 U/kg every-other-week administrations was assessed. Although the clinical efficacy of 45 and 60 U/kg dose levels was not statistically compared, the mean gain in hemoglobin levels (primary efficacy endpoint) observed following 60 U/kg every-other-week dosing was generally comparable to that following 45 U/kg every-other-week treatment (see Figure 1 in Section 2). An exploratory analysis for hemoglobin concentration increase (Week 53) from baseline versus AUC_{inf} of velaglucerase alfa (at Week 37 since no PK accumulation) confirmed the lack of exposure-response relationship. For other secondary efficacy end points, marginally better efficacy was observed in terms of platelet counts and comparable efficacy results in terms of normalized liver and spleen volume, for 60 versus 45 U/kg dosing regimens. No exposure-response relationship was established for safety. Therefore, the proposed dosing regimen (60 U/kg every two weeks) was not based on the result of the exposure-response relationship but was selected to be the same as that of the currently approved imiglucerase.

Intrinsic Factors

The appropriateness of dosing regimen of 60 U/kg every two weeks was evaluated through the effect of body weight on change in hemoglobin from baseline (primary efficacy endpoint). While velaglucerase alfa PK parameters (such as Cmax and CL) are dependent on body weight, these differences in exposure did not affect the efficacy response due to lack of exposure-clinical response relationship. Therefore, the proposed weight-based dosing regimen appears to be acceptable for all patients.

The relationship between velaglucerase alfa pharmacokinetics, and age or gender were assessed graphically bracketed into two dose groups (45 vs 60 U/kg) in study TKT032 (see Figure 11 in Section 2). In the 45 U/kg group, there was no apparent trend for AUC or CL change with increasing age. However, in the 60 U/kg group, there was a trend for lower AUC and higher CL values in subjects younger than 18 years of age compared to the adult subjects (19 to 42 years old). However, due to the small sample size (total n=7 for pediatric patients and n=18 for adult patients), the overall results were inconclusive when the two dose groups were combined. The safety and efficacy profiles were similar between pediatric and adult patients. As such, the same body weight-normalized dose of velaglucerase alfa (60 U/kg every 2 weeks) was recommended for both pediatric and adult patients. There are no apparent differences in PK parameters between male and female subjects.

Comparability

The CMC reviewer, Dr. Frederick Mills, confirmed the biochemical comparability between AF1 (Phase II/III material) and AF2 (to-be-marketed material) drug substance, but not for ——— process drug substance (Phase I/II material) (see the CMC review in DARRTS). It should be noted that the Sponsor is proposing to use the PK data obtained from studies conducted using Phase I/II material and AF1 drug substance for labeling purpose. Whereas it is considered appropriate to use PK results from AF1 drug substance, the PK results from Phase I/II is not relevant due to the lack of comparability. As such, only PK results with AF1 drug substance will be included in the labeling to be approved.

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Immunogenicity

Immunogenicity testing (using a validated electrochemiluminexcent bridging immunoassay) has been performed in all velaglucerase alfa clinical studies. The immunogenicity potential with velaglucerase alfa is low. Only one (out of 94) patient treated with velaglucerase alfa tested positive for anti-velaglucerase alfa IgG type antibodies (binding antibodies) at Week 53 (end of study), but the subject was negative for IgE antibodies at this time point (see note in 2. QBR on cut-point issue). Based on the only one patient who was positive to binding antibodies, the in vitro neutralizing antibody assay resulted in a 42% inhibition of enzymatic activity of velaglucerase alfa. None of the subjects were positive for anti-velaglucerase alfa antibodies on the days of PK evaluation; therefore, it is not possible to determine the relationship between the antibody formation and the change in velaglucerase alfa PK parameters.

2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Velaglucerase alfa (Gene-activated human glucocerebrosidase, GA-GCB) is a human glucocerebrosidase that is produced by gene activation in a human fibroblast cell line and contains the same amino acid sequence of the naturally occurring human enzyme, glucocerebrosidase. It is secreted as a monomeric glycoprotein of approximately 73 kDa containing 497 amino acids. There are 5 potential N-linked glycosylation sites, 4 of which are occupied. Natural GCB is expressed as a highly sialyated glycoprotein that contains complex carbohydrate chains and is poorly internalized by phagocytic cells. Velaglucerase alfa is manufactured to contain predominantly high mannose-type-linked glycans, which allows velaglucerase alfa to be effectively uptaken by the phagocytic cells via mannose cells.

Velaglucerase alfa drug product is supplied as powder for injectable solution in a single-use vial, either 200 or 400 Units/vial, in — sodium citrate —, containing — sucrose and — polysorbate 20, at pH 6.0. b(4)

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Gaucher disease is an autosomal recessive disorder caused by mutations in the GBA gene which results in a deficiency of the lysosomal enzyme beta-glucocerebrosidase. This enzymatic deficiency causes an accumulation of glucocerebroside primarily in macrophages, giving rise to foam cells or "Gaucher cells". In this lysosomal storage disorder (LSD), clinical features are reflective of the distribution of Gaucher cells in the liver, spleen, bone marrow, skeleton, and lungs. The accumulation of glucocerebroside in the liver and spleen leads to organomegaly. Bone marrow involvement results in skeletal abnormalities and deformities as well as bone pain crises. Deposits in the bone marrow and splenic sequestration lead to clinically significant anemia and thrombocytopenia.

Velaglucerase alfa supplements or replaces beta-glucocerebrosidase, the enzyme that catalyzes the hydrolysis of glucocerebroside, reducing the amount of accumulated glucocerebroside.

2.1.3 What are the proposed dosage and route of administration?

The proposed dose of velaglucerase alfa is 60 U/kg administered every other week as a 60-minute intravenous infusion. This dose regimen is the same as that of the currently approved imiglucerase.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The Clinical Pharmacology program was designed to characterize the pharmacokinetic (PK) profiles and parameters from patients diagnosed with Type 1 Gaucher disease following intravenous infusion of velaglucerase alfa. In the phase III clinical study TKT032, 25 patients were randomized to receive 1-hour intravenous infusion of velaglucerase alfa, either 45 or 60 U/kg, administered every other week for 37 weeks. PK evaluations were performed at Weeks 1 and 37.

In the phase I/II clinical study TKT025, 3 patients with Type 1 Gaucher disease were enrolled and received 1-hour infusion of velaglucerase alfa 15 U/kg at Week 1, 30 U/kg at Week 3, and 60 U/kg administered every other week from Weeks 5 to 39 (end of study). Nine additional patients subsequently received 60 U/kg administered every other week from Weeks 1 to 39. The initial 3 subjects had PK evaluations at Weeks 1 (15 U/kg), 3 (30 U/kg), 5 (60 U/kg) and 37/39 (60 U/kg), and the additional 9 subjects had PK evaluations at Weeks 1 (60 U/kg) and 37/39 (60 U/kg). These subjects were allowed to continue to receive velaglucerase alfa 60 U/kg every other week in an open-label extension study (TKT025EXT), and the dose of velaglucerase alfa was subsequently reduced to 30 U/kg for all subjects at Week 65. PK evaluations were conducted at Week 65 (30 U/kg). (*Note*: The Clinical Pharmacology and Biopharmaceutics studies are outlined in Section 4.1 of the Appendix.)

The safety and efficacy of velaglucerase alfa were assessed in 5 clinical studies in a total of 94 patients with Type 1 Gaucher disease who were aged 2 years old or older. Studies TKT025, TKT032 and TKT039 were conducted in patients naïve to enzyme replacement therapy. Study TKT039 was a head-to-head comparison study between velaglucerase alfa and imiglucerase, the currently approved product. Studay TKT025EXT was an extension to Study TKT025. A treatment-naïve patient was defined as the patient not receiving treatment for Type 1 Gaucher disease for at least 12 months. Study TKT034 was conducted in patients who were receiving imiglucerase treatment and switched to velaglucerease alfa treatment.

Study HGT-GCB-039 was a 9-month, randomized, double-blind, active-comparator (imiglucerase) controlled, parallel-group efficacy study conducted in 34 patients aged 2 years old or older. Patients received either 60 U/kg of velaglucerase alfa or the same dose of imiglucerase every other week. Study TKT034 was a 12-month, open-label safety study conducted in 40 patients aged 2 years and older who had been receiving treatment with imiglucerase at doses ranging between 15 to 60 U/kg for a minimum of 30 consecutive months. Patients were required to have a stable dose of imiglucerase for at least 6 months prior to study enrollment. Velaglucerase alfa was administered as the same dosing regimen as that of imiglucerase.

Study HGT-GCB-044 was an extension study in which patients were rolled over from TKT032, TKT034 or HGT-GCB-039, and is currently on-going.

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

Clinical Endpoints

Change in hemoglobin levels and platelet counts

Change in hemoglobin level is considered to be the primary clinical endpoint for Studies TKT032 and HGT-GCB-039. The clinical progress of Gaucher disease and the clinically relevant efficacy end points including hemoglobin levels are described well in the literature. For example,

In the Gaucher Registry, 76% of patients had platelet counts below 120 × 10^9/L and 26% had platelet counts below 60 × 10^9/L. Anemia (hemoglobin level < 12 g/dl) is found in two thirds of non-splenectomized patients. Progressive bone marrow failure may subsequently induce cytopenia. In these cases, anemia usually appears as the first symptom, and is followed by thrombocytopenia. In severe cases, patients may become transfusion dependent. During enzyme therapy, a difference in the rate of improvement in platelet count and the hemoglobin level can be established between splenectomized and non-splenectomized patients. This difference was clearly observed in the adult population in The Netherlands, where individualized low doses of enzyme supplementation therapy are used. It seems reasonable to set the goals for improvement in cytopenia to normalization of hemoglobin levels, and improvement of platelet counts to levels that are no longer associated with an increased bleeding tendency (C. E. M. Hollak, M. Maas and J. M. Aerts, J. Inherit. Metab. Dis. 24;2001:97–105).

Change in normalized liver and spleen size by magnetic resonance imaging

The following rationale was found in the literature:

Liver volumes are usually larger in splenectomized than in non-splenectomized patients. Data from the Gaucher Registry show that median liver volumes are 1.7 times normal in patients with intact spleens. Liver volumes are increased by a median of 2.2 times normal in splenectomized patients. Splenic volumes are grossly increased (median of 15.2 times normal), with a wide range from near normal to enormous proportions. Spleen and liver volumes decrease in size during enzyme supplementation therapy. After 6 months of treatment, the median decrease is approximately 20% for the spleen and 10% for the liver. Decreases in organ size are related to the extent of pretreatment organomegaly; larger organs show a more robust decrease in size than do smaller livers and spleens. Liver volumes usually normalize, whereas some degree of splenic enlargement commonly persists, even after long-term treatment (C. E. M. Hollak, M. Maas and J. M. Aerts, J. Inherit. Metab. Dis. 24;2001:97–105).

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

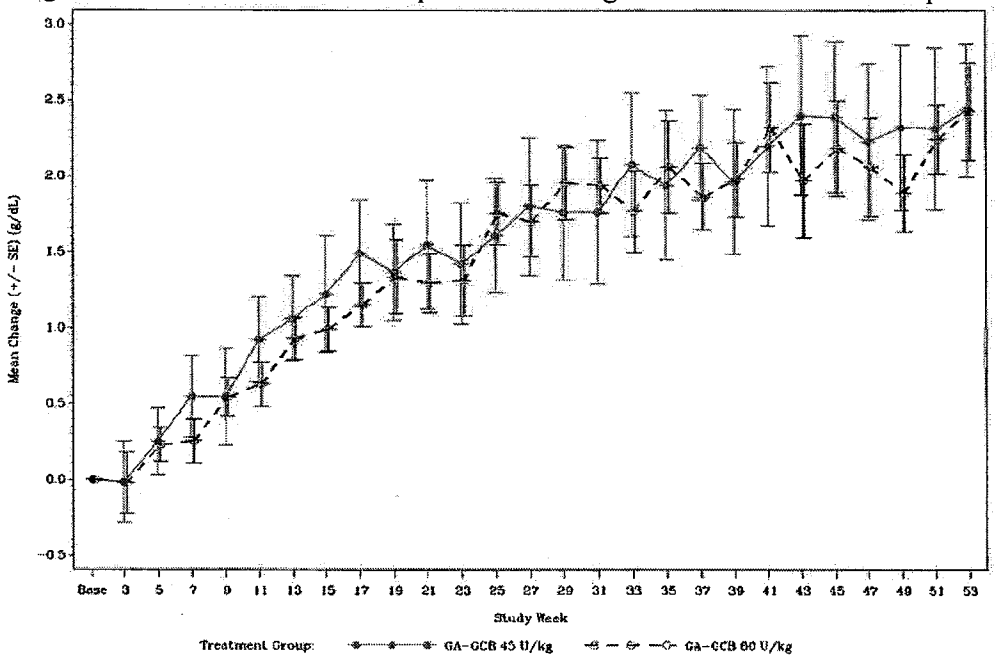
No. An inadequately validated, conventional sandwich enzyme-linked immunosorbent assay (ELISA) method was used to quantify serum velaglucerase alfa concentrations (see Section 2.6 for detail information).

2.2.4 2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

In Study TKT032, the change from baseline in hemoglobin levels, platelet counts, normalized liver and spleen size following 45 or 60 U/kg of velaglucerase alfa given every other week in Type 1 Gaucher disease was assessed. Velaglucerase alfa treatment was associated with clinically meaningful and statistically significant increase in hemoglobin levels and platelet counts, as well as statistically significant reduction in liver and spleen size. Although statistical comparison of clinical efficacies between 45 and 60 U/kg was not performed, the change from baseline in hemoglobin levels (primary efficacy endpoint) following 60 U/kg every other week dosing is comparable to that observed following 45 U/kg every other week dosing (Figure 1).

Figure 1: Mean Hemoglobin Levels (g/dL) (± SE) at Scheduled Visits by Randomized Velaglucerase Alfa Treatment Group – Mean Change from Baseline – ITT Population



An exploratory analysis for hemoglobin level increase (week 53) from baseline vs. Cmax and AUC_{inf} (at Week 37 since no PK accumulation is expected) confirmed the lack of exposure-response relationship (Figures 2 and 3).

Figure 2: Mean Hemoglobin Level (g/dL) Change from Baseline at Week 53 vs Cmax (ng/mL) at Week 37 following 45 or 60 U/kg 1-hour Intravenous Infusion Every Other Week (green circle indicates pediatric patients and red triangle indicates adults patients)

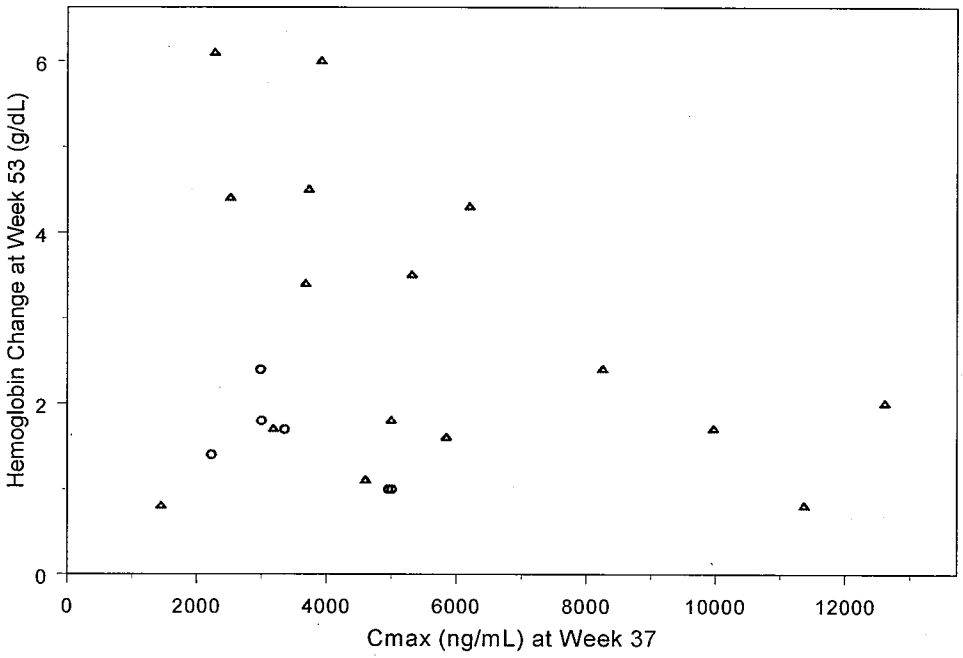
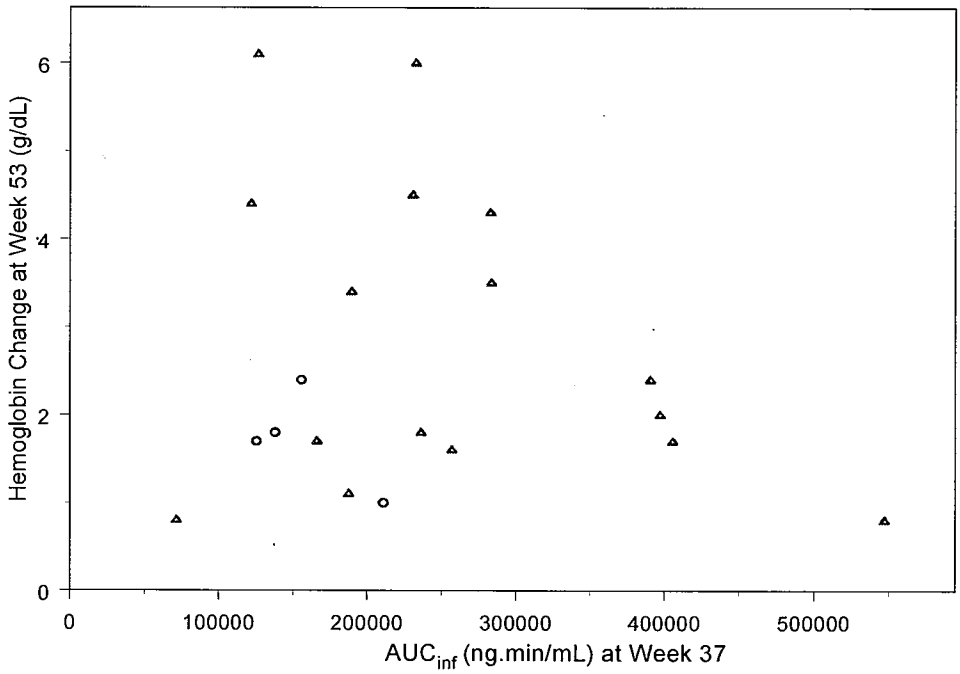


Figure 3: Mean Hemoglobin Level (g/dL) Change from Baseline at Week 53 vs AUC_{inf} (ng*min/mL) at Week 37 following 45 or 60 U/kg 1 hour Intravenous Infusion Every Other week (green circle indicates pediatric patients and red triangle indicates adults patients)



Regarding the secondary efficacy endpoints, marginally better clinical efficacy was observed in 60 U/kg compared to 45 U/kg dose group in terms of change from baseline in platelet counts (Figure 4), but inconsistent results (depending on the time of observation) were obtained for liver (Figure 5) and spleen size improvement (Figure 6). Altogether, based on the currently available but very limited data (total n=25 for two dose levels studied), no consistent dose-efficacy response relationship was established.

Figure 4: Mean Platelet Counts (x10^9/L) (± SE) at Scheduled Visits by Randomized Velaglucerase Alfa Treatment Group – Mean Change from Baseline – ITT Population

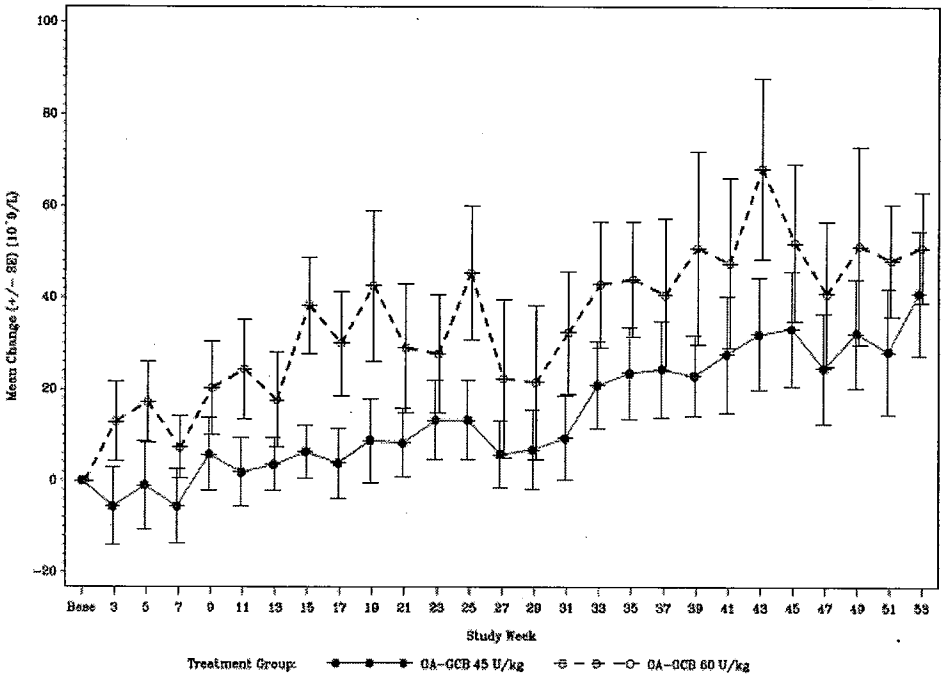


Figure 5: Mean Normalized (% of Body Weight) Liver Size (± SE) at Scheduled Visits by Randomized Velaglucerase Alfa Treatment Group – Mean Percent Change from Baseline – ITT Population

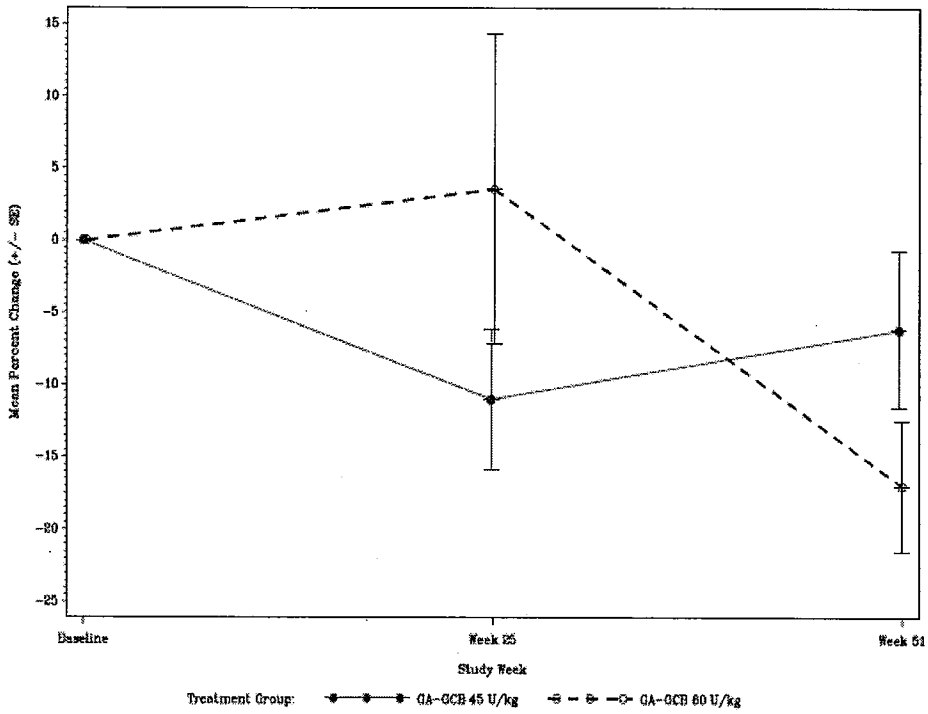
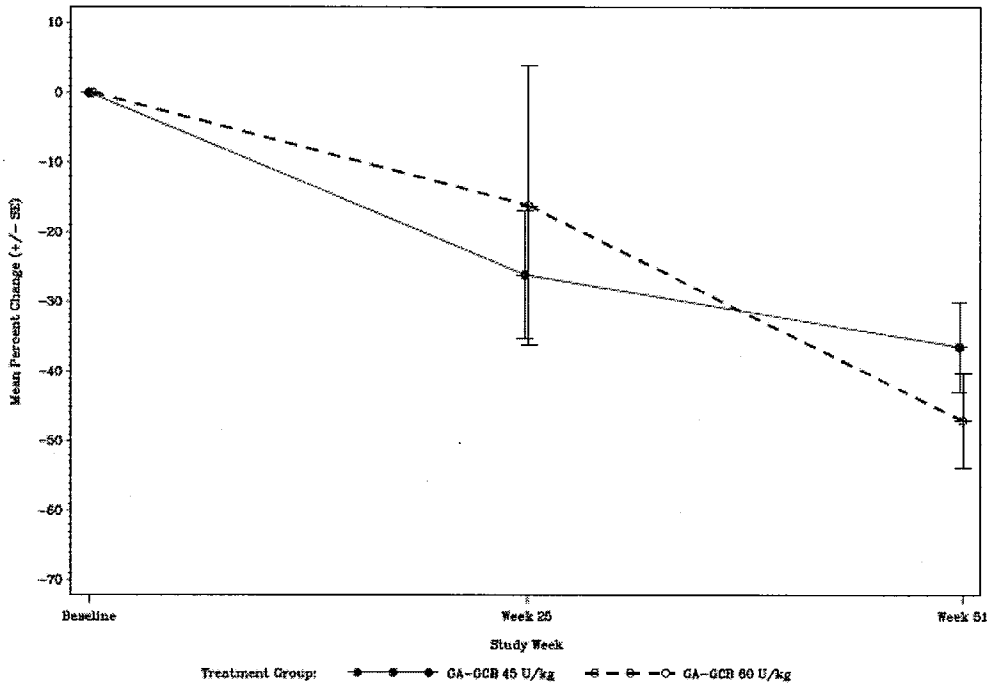


Figure 6: Mean Normalized (% of Body Weight) Spleen Size (± SE) at Scheduled Visits by Randomized Velaglucerase Alfa Treatment Group – Mean Percent Change from Baseline – ITT Population



2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

No dose-safety response relationship was determined and established.

2.2.4.3 Does this drug prolong the QT or QTc interval?

A thorough QT study is not required for velaglucerase alfa, a large molecular protein product.

2.2.4.4 Is the dose and dosing regimen selected by the Sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

An exploratory analysis for hemoglobin level increase (Week 53, primary efficacy endpoint) from baseline versus Cmax or AUC_{inf} (at Week 37 since no PK accumulation is expected) showed lack of exposure-efficacy response relationship (Figures 2 and 3) in Study TKT032. The efficacy results revealed no consistent dose-response relationship although statistical comparison was not performed between 45 and 60 U/kg dosing regimens. As such, the dose of 60 U/kg was selected based on the following considerations:

1) The active ingredient of valeglucerase alfa and imiglucerase are similar.
2) Velaglucerase alfa demonstrated to be clinically non-inferior to imiglucerase
3) The approved dose of miglucerase is 60 U/kg.

As illustrated in Figure 1, the mean increase from Baseline to Week 53 in hemoglobin levels (2.429 g/dL, 23.25%) in the 60 U/kg group was both clinically meaningful (i.e., ≥1.0 g/dL) and statistically significant ($p<0.0001$). Clinically meaningful mean increases from baseline in hemoglobin levels (i.e., 1 g/dL) were observed at Months 6, 9, and 12 following initiation of treatment (i.e., Weeks 25, 37, and 53) in the 60 U/kg group. The greatest mean increase in this group was observed at Week 53, the last evaluation time point in Study TKT032.

The appropriateness of body-weight-normalized dose regimen (60 U/kg every other week) was evaluated through both PK and pharmacodynamics (PD). From PK perspective, there was a trend of increasing exposure with increasing BW, i.e., pediatric patients tend to have lower exposure compared to adult patients (Figure 7). However, from PD perspective, the change from baseline in hemoglobin levels (the primary efficacy endpoint) appears to be comparable among studied patients following the administration of 60 U/kg every other week regardless of the baseline body weight, indicating that the proposed dosing regimen is appropriate for any patient with Type 1 Gaucher disease (Figure 8). The reference line in Figure 8 (1 g/dL) indicates the clinically meaningful change for hemoglobin concentration increase. This is consistent with the lack of exposure-efficacy response relationship in the dose levels studied (45 and 60 U/kg).

Figure 7: Relationship Between Velaglucerase Alfa Exposure (ng*min/mL) and Patient's Body Weight (kg) following Intravenous Infusion of 60 U/kg Every Other Week in TKT032

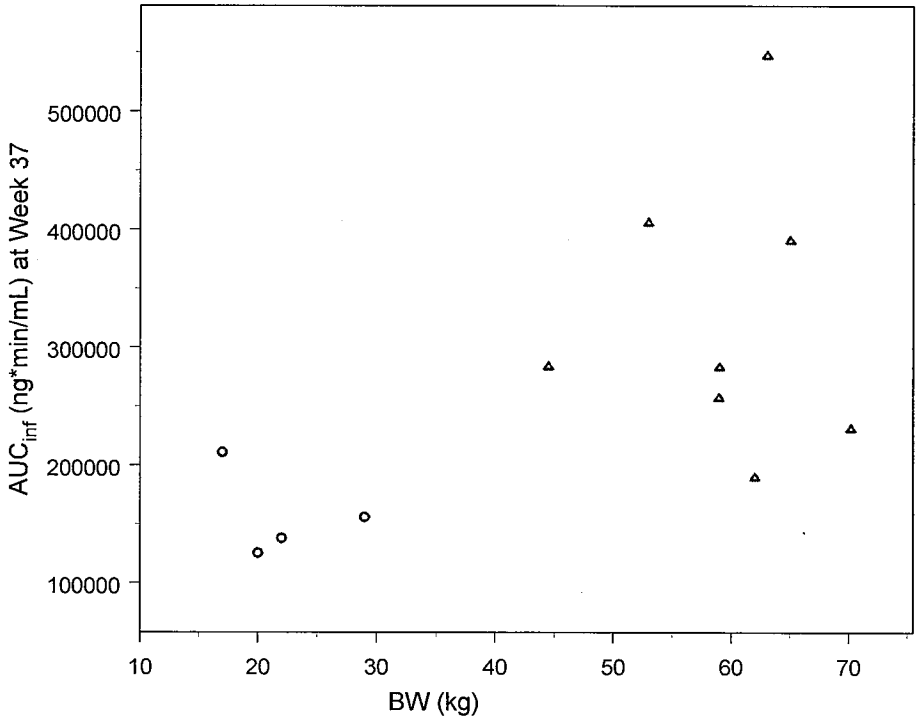
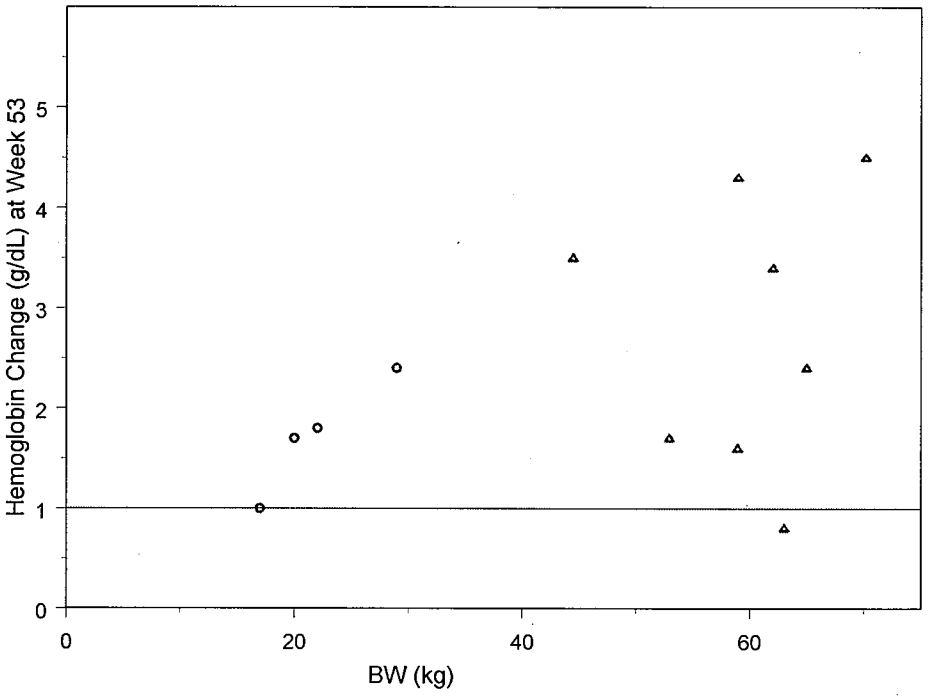


Figure 8: Relationship Between Velaglucerase Alfa and Hemoglobin Level Change from Baseline at Week 53 (g/dL) and Patient's Body Weight (kg) following Intravenous Infusion of 60 U/kg Every Other Week in TKT032



The velaglucerase alfa serum disposition half life (mean, 11 to 12 minutes) is considerably shorter than the 14-day dosing interval, and velaglucerase alfa was not expected to be accumulated in serum with repeated administration. For velaglucerase alfa, systemic clearance represents the distribution of velaglucerase alfa from the intravascular circulation into the intracellular uptake, a desired and necessary step for the enzyme to exert its clinical benefit. Although velaglucerase alfa was cleared from vascular circulation rapidly (undetectable at 3 hours post 1-hour infusion), it can retain its enzymatic activity in the target tissue (such as liver and spleen) for longer time as evidenced by the sustained clinical efficacy for the every-other-week dosing regimen.

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

2.2.5.1 What are the single dose (SD) and multiple dose (MD) PK parameters?

PK characterization in Type 1 Gaucher Disease Patients

In Study TKT032, pediatric (N=7, 2 to 17 years old) and adult (N=18, 18 to 62 years old) patients with Type 1 Gaucher disease, were randomized to receive either 45 or 60 U/kg velaglucerase alfa administered as 1-hour infusions every other week for 51 weeks. PK evaluations were performed at Weeks 1 and 37. The pharmacokinetic characterization was based on the protein content (ng/mL) of valeglucerase alfa. During the 1-hour IV infusion of velaglucerase alfa 45 or 60 U/kg, the velaglucerase alfa serum concentrations

rose rapidly for the first 20 minutes after administration. Velaglucerase alfa serum concentrations fell rapidly with a mean half life of 11 to 12 minutes for both dose groups at Weeks 1 and 37 (Figure 9). The mean velaglucerase alfa systemic clearance (CL) ranged from 6.7 to 7.6 mL/min/kg. The mean volume of distribution at steady state (Vss) ranged from 82 to 108 mL/kg (8.2% to 10.8% of body weight) (Table 1).

Figure 9: Mean (± SD) Serum Concentrations of Velaglucerase Alfa after Single Intravenous Infusion (45 or 60 U/kg) at Week 1 and Multiple Intravenous Infusions at Week 37 in Patients with Type 1 Gaucher Disease (Study TKT032)

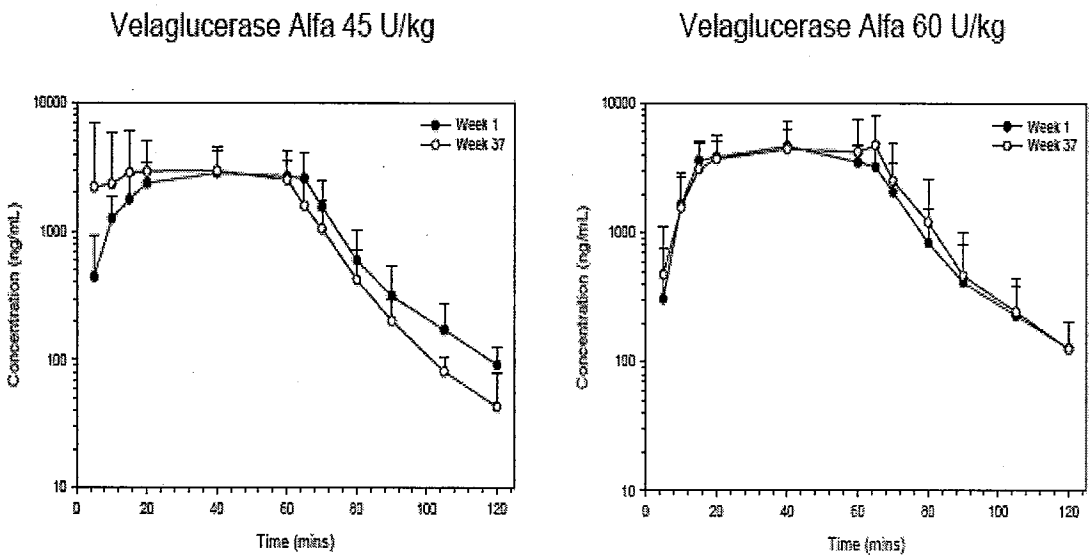


Table 1, Pharmacokinetic Parameter values Following the 1-hour Infusion of Velaglucerase Alfa 45 or 60 U/kg (Week 1 or Week 37) in Study TKT032

	C_{max} (ng/mL)	T_{max} (min)	AUC_{inf} (ng·min/mL)	CL (mL/min/kg)	$T_{1/2}$ (min)	V_{ss} (mL/kg)
45 U/kg Velaglucerase alfa (Week 1)						
Mean	3437	40	178318	7.02	12.4	104
± SD	± 1283	± 19	± 62162	± 2.59	± 3.1	± 66
N	13	13	10	10	10	10
45 U/kg Velaglucerase alfa (Week 37)						
Mean	4033	37	181056	7.56	11.9	108
± SD	± 2939	± 20	± 91591	± 3.56	± 5.5	± 59
N	12	12	10	10	10	9
60 U/kg Velaglucerase alfa (Week 1)						
Mean	5256	45	254148	7.16	11.5	106
± SD	± 2323	± 16	± 111749	± 3.54	± 3.5	± 60
N	12	12	12	12	12	12
60 U/kg Velaglucerase alfa (Week 37)						
Mean	5712	44	268085	6.72	11.4	82
± SD	± 2795	± 15	± 125438	± 2.91	± 3.2	± 39
N	12	12	12	12	12	12

Telve patients with Type 1 Gaucher disease aged from 19 to 70 years old were enrolled in Study TKT025 as two cohorts. In the initial cohort, 3 subjects received 1-hour infusion of velaglucerase alfa 15 U/kg at Week 1, 30 U/kg at Week 3, and 60 U/kg administered every other week from Week 5 to Week 39 (end of study). In the second cohort, 9 additional subjects subsequently received 60 U/kg administered every other week from Weeks 1 to 39. All subjects who completed TKT025 were allowed to continue to receive velaglucerase alfa 60 U/kg administered every other week in an open-label extension study (TKT025EXT), and the dose of velaglucerase alfa was subsequently reduced to 30 U/kg for all subjects by the time of PK evaluation at Week 65 of TKT025EXT (after a total of 105 weeks of treatment). In Study TKT025EXT, serum samples from 9 patients who continued therapy were assayed for velaglucerase alfa protein content (mcg/mL). As shown in Figure 10 and Table 2 below, at Week 65, following 1-hour 30 U/kg intravenous infusion, the mean velaglucerase alfa C_{max} of 2.3 mcg/mL (SD, 0.74 mcg/mL) was reached. Serum velaglucerase concentrations declined rapidly following first-order elimination kinetics in all 9 patients with a mean serum half life of approximate 9 minutes (SD, 2.2 minutes). Mean CL was approximately 6.5 mL/min/kg (SD, 2.0 mL/min/kg), and mean Vss was 83 mL/kg (SD, 19.5 mL/kg).

Figure 10: Mean (± SD) Serum Concentrations of Velaglucerase Alfa after Single-dose Intravenous Infusion (30 U/kg) Administration at Week 65 to 9 Patients with Type 1 Gaucher Disease (Study TKT025EXT)

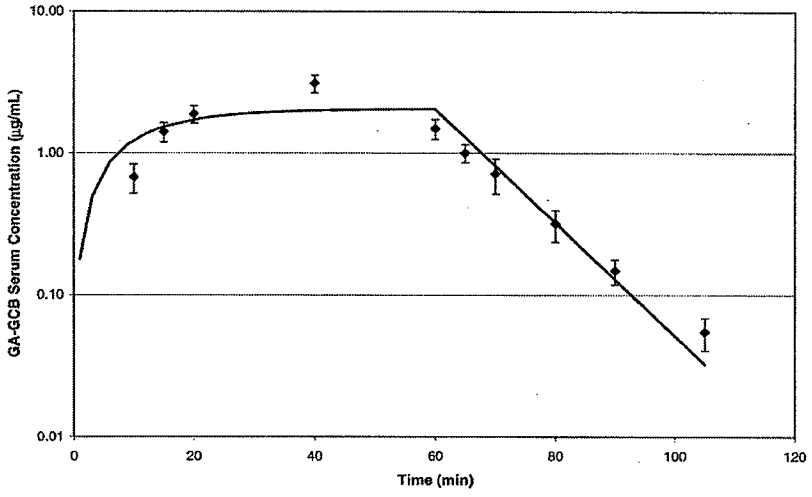


Table 2, Pharmacokinetic Parameter Values following the 1-hour Infusion of Velaglucerase Alfa 30 U/kg at Week 65 in Study TKT025EXT

	C_{max} (µg/mL)	T_{max} (min)	AUC_{inf} (µg·min/mL)	CL (mL/min/kg)	$T_{1/2}$ (min)	V_{ss} (mL/kg)
30 U/kg Dose of Velaglucerase alfa (Week 65 of the Extension, Overall Week 105)						
Mean	2.3	55.0	123.5	6.5	8.9	83
± SD	0.74	5.6	34.7	2.0	2.2	19.5
N	9	9	9	9	9	9

Reviewers Comment: This PK analysis was performed using 1-compartment infusion model. PK analysis used actual blood collection times for each patient rather than nominal time.

Velaglucerase alfa is manufactured to contain the predominantly high mannose-type-linked glycans, which allows velaglucerase alfa to be effectively uptaken by the phagocytic cells via mannose receptors. The consistently observed rapid clearance of velaglucerase alfa from serum in Studies TKT025EXT (6.5 mL/min/kg) and TKT032 (6.72 to 7.56 mL/min/kg) is considered to be consistent with the quick uptake of velaglucerase alfa into macrophages via mannose receptors.

Reviewer's Comment: The Phase I/II study TKT025 were conducted using drug substance produced using ——— process that is not comparable to the final to-be-marketed AF2 drug substance. Therefore, the PK results from Study TKT025 were not reviewed in details. However, the sponsor intended to use the PK results obtained from Study TKT025 using the 1 ——— process material and Studies TKT025EXT and TKT032 using AF1 process material, not AF2 drug substance in the proposed labeling. Whereas it is considered appropriate of using the PK data generated with AF1 drug substance since biochemical comparability between AF1 and AF2 drug substance was demonstrated based on CMC review (see the CMC review by Dr. Frederick Mills), the PK results obtained using the ——— process material are not considered to be appropriate for labeling purpose due to lack of comparability. b(4)

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

No PK studies were conducted in healthy subjects and therefore PK results can not be compared between healthy subjects and patients. No metabolite studies were conducted.

2.2.5.3 What are the characteristics of drug absorption?

The drug product was administered as an intravenous infusion and therefore drug absorption was not characterized.

2.2.5.4 What are the characteristics of drug distribution?

Plasma protein binding study has not been conducted. Based on non-compartmental analysis in Study TKT032 (45 or 60 U/kg), the mean V_{ss} is 82 to 108 mL/kg.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

No mass balance study is required for velaglucerase alfa, a large molecular protein drug product.

2.2.5.6 What are the characteristics of drug metabolism?

No metabolism study is required for velaglucerase alfa, a large molecular protein drug product..

2.2.5.7 What are the characteristics of drug excretion?

No excretion studies were conducted.

2.2.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

As stated in section 2.2.5.1, since only two doses were studies in study TKT032, dose-proportionality could not be adequately assessed. In Study TKT032, the mean velaglucerase alfa Cmax and AUC were approximately 40% to 50% higher in the patients receiving 60 U/kg than in the patients receiving 45 U/kg, which is slightly higher than the expected 33% increase assuming linear dose proportionality.

2.2.5.9 How do the PK parameters change with time following chronic dosing?

No accumulation in serum velaglucerase alfa concentrations was observed with repeated doses of 45 or 60 U/kg every other week, nor would it be expected to with an observed serum half-life of 11 to 12 minutes. Velaglucerase alfa PK did not appear to change following up to 1 year exposure (Study TKT032).

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

In TKT032, based on a non-compartment analysis, following 60U/kg every-other-week administration, the inter-subject variability (coefficient of variation %) were 44.2% and 44% for Cmax and AUC_{inf}, respectively, on Week 1; 48.9% and 46.8% for Cmax and AUC_{inf}, respectively, on Week 37.

2.2.6 What are the PD characteristics of velaglucerase alfa?

In Study TKT032, velaglucerase alfa administration resulted in clinical meaningful and statistically significant increase in mean hemoglobin levels, statistically significant increase in platelet counts, statistically significant reduction in normalized spleen and

liver size and reduction in plasma biomarkers. Please see more data in section 2.2.4.1 Exposure-Response Relationship.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

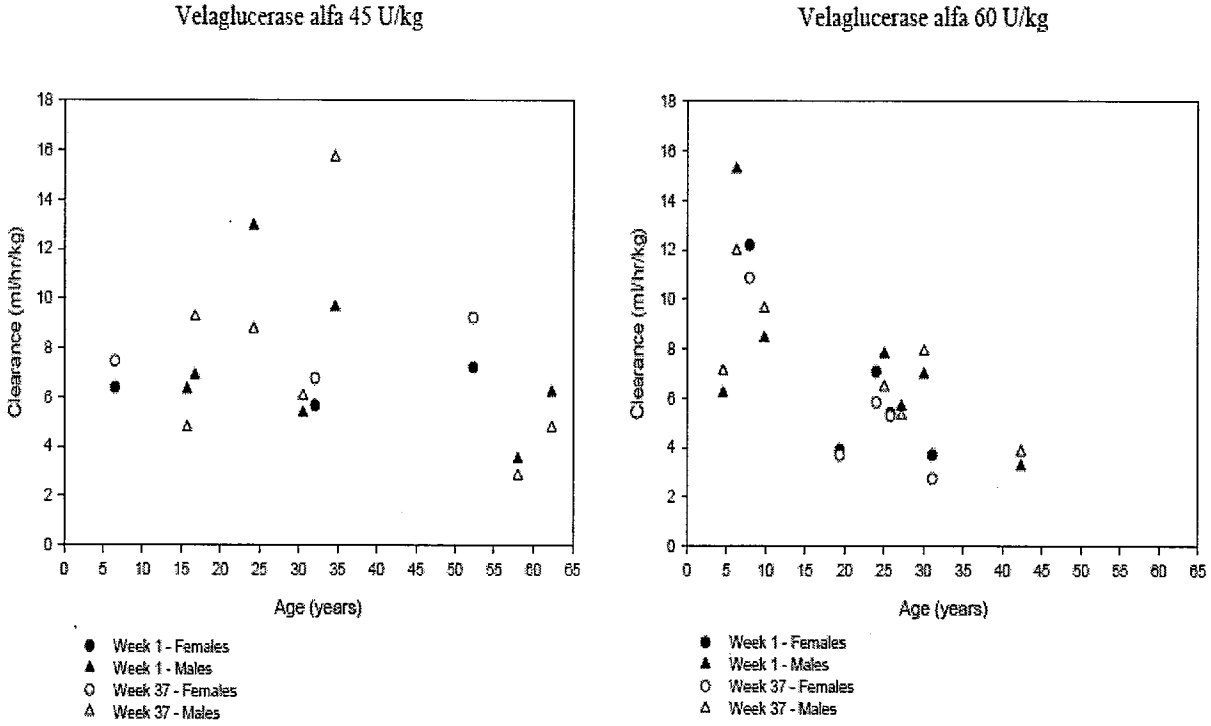
Body Weight
As indicated in 2.2.4.4, in Study TKT032, there was a trend of increasing exposure with increasing body weight (Figure 7) following 60 U/kg every-other-week administration. Due to the lack of exposure-response relationship, the efficacy observed in patients received 60 U/kg was comparable regardless of body weight. Therefore, body weight-normalized dosing regimen (60U/kg every other week) is considered appropriate.

Gender
There were no apparent pharmacokinetic differences between male and female patients with Type 1 Gaucher disease in Study TKT032 (Figure 11).

Age
The relationship between velaglucerase alfa PK parameters and age was assessed graphically bracketed into two dose groups (45 vs. 60 U/kg) in Study TKT032. In the 45 U/kg group, there was no apparent trend for AUC or CL to change with increasing age. However, in the 60 U/kg group, there was a trend for lower AUC values and higher CL values in pediatric patients (2-17 years old) compared to the adult patients (18 to 42 years old). The reason for such difference is not known. However, the overall results were inconclusive if the two dose groups are combined (Figure 9).

As stated in Section 2.2.4.4, although there is a trend of different PK (i.e., lower exposure and higher systemic CL for pediatric patients compared to adult patients following the administration of 60 U/kg every other week), the change from baseline in hemoglobin levels (the primary clinical efficacy endpoint) appears to be comparable among studied patients. As such, age does not appear to have an effect on the efficacy at the proposed dosing regimen.

Figure 11: Relationship Between Velaglucerase Alfa Clearance and Patient's Age and Gender (Study TKT032)



Other Intrinsic Factors

Due to the small sample size in the PK studies, other intrinsic factors were not adequately evaluable.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Pediatric patients

As stated in Section 2.3.1, the relationship between age and PK characteristics was inconclusive. However, the clinical efficacy observed in the pediatric patients (age range, 2-17 years old) receiving the same weight-normalized dosing regimen (60 U/kg every other week) was comparable to that of adult patients (age range, 18 to 62 years old). Thus, the same dosing regimen was proposed to pediatric patients.

2.3.2.2 Renal impairment

No studies have been conducted to evaluate the effect of renal impairment on the PK of velaglucerase alfa. Such studies would not be required considering that velaglucerase alfa is considered to be disintegrated into the amino acid level rather than renally excreted unchanged.

2.3.2.3 Hepatic impairment

No studies have been conducted to evaluate the effect of hepatic impairment on the PK of velaglucerase alfa. Such studies would not be required considering that velaglucerase alfa is considered to be disintegrated into the amino acid level rather than metabolized to product-specific metabolites.

2.3.2.4 What pregnancy and lactation use information is there in the application?

No data regarding the excretion of velaglucerase alfa in the milk of humans or animals was provided.

2.3.3 Immunogenicity (NOT applicable to small molecule drugs)

2.3.3.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

Overall, out of 94 subjects receiving velaglucerase alfa treatment, only one patient had positive anti-product antibody response (Study TKT032). This patient was positive for anti-velaglucerase alfa IgG type antibodies (binding antibodies) at Week 53 (end of study), but the patient was negative for IgE antibodies at this time. Samples were collected at adequate time points to assess anti-product antibody formation at early onset, during study, and during study follow-up. Table 3 summarizes the sample collection times in the pivotal trials.

Table 3: Immunogenicity Sample Collection Time Points in Pivotal Trials.

Pivotal Study #	Patient Population	Immunogenicity Sample Collection Times
Study TKT025EXT	Type 1 Gaucher disease	• Baseline collected in study TKT025 • Weeks 1, 13, 25, 37, 49/51, 65/67, 77, 89, 101/103, 117, 129, 141, 153/155, 169, 181, 193, 205/207, 219, 233, 245, 257/259, 271, 285, 297, 309/311, 323, 337, 349, and 365
Study TKT032	Type 1 Gaucher disease	• Weeks 7, 13, 19, 25, 31, 37, 43, 49 and 53

Reviewer's Comment: According to the CMC Review Team, the immunogenicity cut-point may not be appropriately selected. The Team did not reach the conclusion at the time that this review is completed (see CMC review in DARRTS in the future).

2.3.3.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

None of the patients were positive for anti-velaglucerase alfa antibodies on the days of pharmacokinetic evaluation; therefore, it was not possible to determine the impact of anti-product antibody on the change in velaglucerase alfa PK parameters. In addition, there is no evidence of altered PD in the subject who tested positive for binding antibodies at Week 53.

2.3.3.3 Do the anti-product antibodies have neutralizing activity?

Yes, based on one patient who was positive to binding antibodies, the *in vitro* neutralizing antibody assay resulted in 42% inhibition of enzymatic activity of velaglucerase alfa.

2.3.3.4 What is the impact of anti-product antibodies on clinical efficacy?

The velaglucerase alfa immunogenicity incidence was low (1 out of 94 patients) and therefore the impact could not be adequately determined.

2.3.3.5 What is the impact of anti-product antibodies on clinical safety? (e.g., infusion-related reactions, hypersensitivity reactions, cross-reactivity to endogenous counterparts, etc.)?

The velaglucerase alfa immunogenicity incidence was low (1 out of 94 patients). No evidence of altered safety profiles has been observed in the subject who tested positive for binding antibodies at Week 53 in study TKT032.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The impact of extrinsic factors on dose-exposure or exposure–response was not explored.

2.4.2 Drug-drug interactions

None of the drug-drug interaction questions in the standardized QBR is applicable to this protein product. No drug-drug interaction studies were conducted for velaglucerase alfa.

2.5 General Biopharmaceutics

Sections 2.5.1 through 2.5.9 are not applicable to therapeutic proteins.

2.5.10 What is the PK and PD comparability of the proposed to-be-marketed formulation to pivotal clinical trial?

Manufacturing process changes occurred twice during velaglucerase alfa clinical development and resulted in three different drug products: [redacted] (Phase I/II material), AF1 (Phase II/III material) and AF2 (to-be-marketed material). Patients received RB material in Study TKT025, and AF1 material in Studies TKT025EXT and TKT032. b(4)

According to the CMC Reviewer, Dr. Frederick Mills, biochemical comparability was demonstrated between AF1 and AF2 substance (see the CMC Review in DARRTS), but not for Phase I/II material. There were minor differences in glycosylation levels between AF1 and AF2 material. It is anticipated that there are no major glycosylation changes between the two processes and are unlikely to have an effect on clearance and other PK characteristics. As such, the PK comparability of velaglucerase alfa produced using AF1 and AF2 processes in human was not conducted. No PD comparability study was conducted, either.

2.6 Analytical Section

Sections 2.6.1 through 2.6.4 are not applicable to biologics.

2.6.5 What bioanalytical methods are used to assess *therapeutic protein* concentrations? Briefly describe the methods and summarize the assay performance.

Pharmacokinetic Assay for velaglucerase alfa

An inadequately validated, conventional sandwich enzyme-linked immunosorbent assay (ELISA) method was used to quantify serum velaglucerase alfa concentrations in clinical pharmacology studies. The assay method measures "free" velaglucerase alfa concentrations, since they rely on the capture of velaglucerase alfa with a human velaglucerase alfa-specific murine monoclonal antibody (mAb 9E4) bound to the assay plate and the detection of velaglucerase alfa with labeled mouse monoclonal antibody against human velaglucerase alfa (HRP-mAb 1E11).

b(4)

[redacted]

The in-process performance of PK sample assay for study TKT025EXT and TKT032 was summarized in Tables 4 and 5 below:

Table 4. In-Process Performance Summary for Patient PK Sample Assay in Study TKT025EXT (note: the concentration values are after 100 fold dilution during the assay)

Method	ELISA
Compound	Velaglucerase alfa
Matrix	Human serum
Standard curve range	0.6 to 20.0 ng/mL (R^2=0.987 to 1.000)
Accuracy (% Nominal) ***Intra-assay*** ***Inter-assay***	 Not accurate (only duplicates of QC samples included) 97.8%; 92.9%; 84.1% for high (3000 ng/mL), medium (1500 ng/mL) and low (800 ng/mL) controls, respectively
Precision (% CV) ***Intra-assay*** ***Inter-assay***	 Not calculable (only duplicates of QC samples included) 7.6%; 5.3%; 7.6% for high (3000 ng/mL), mid (1500 ng/mL) and low (800 ng/mL) controls, respectively
Limit of Quantitation (LOQ) **Limit of Detection (LOD)**	0.4 ng/mL 0.1 ng/mL
Specificity	Demonstrated with up to 1 mcg/mL of the human recombinant proteins iduronidase and agalsidase alfa in the presence and absence of velaglucerase alfa. Iduronidase and agalsidase alfa did not interfere with the detection of velaglucerase (accuracy = 99.1 to 103.9%), nor was recognized (<LOD) in the velaglucerase alfa assay.
Stability of velaglucerase alfa in Human serum	Velaglucerase alfa (250 to 1800 ng/mL) was demonstrated to be stable in human serum following three freeze/thaw cycles. The mean (SD) recovery after 3 freeze (<-65° C) – thaw (37° C) cycles was 92.5% (5.8%). Recovery was 101.3% (6.3%) at <-65°C for 12 months.

Conclusion	In-process assay runs met system suitability and assay specificity, however only duplicates of QC samples were included in the validation. Therefore, intra-assay accuracy and precision could not be determined.

Table 5. In-Process Performance Summary for Patient PK Sample Assay in Study TKT032 (note: the concentration values are after 100 fold dilution during the assay)

Method	ELISA
Compound	Velaglucerase alfa
Matrix	Human serum
Standard curve range	0.6 to 20.0 ng/mL (R^2=0.99465 to 0.99997)
Accuracy (% Nominal) ***Intra-assay*** ***Inter-assay***	 Not accurate (only duplicates of QC samples included) 114.5%; **116.3%**; **125.6%** for high (3000 ng/mL), mid (1500 ng/mL) and low (800 ng/mL) controls, respectively
Precision (% CV) ***Intra-assay*** ***Inter-assay***	 Not calculable (only duplicates of QC samples included) 5.0%; 5.0%; 5.2% for high (3000 ng/mL), mid (1500 ng/mL) and low (800 ng/mL) controls, respectively
Limit of Quantitation (LOQ) **Limit of Detection (LOD)**	0.4 ng/mL 0.1 ng/mL
Specificity	Demonstrated with up to 1 mcg/mL of the human recombinant proteins iduronidase and agalsidase alfa in the presence and absence of velaglucerase alfa. Iduronidase and agalsidase alfa did not interfere with the detection of velaglucerase (accuracy = 99.1 to 103.9%), nor was recognized (<LOD) in the velaglucerase alfa assay.
Stability of velaglucerase alfa in Human serum	Velaglucerase alfa (250 to 1800 ng/mL) was demonstrated to be stable in human serum following three freeze/thaw cycles. The mean (SD) recovery after 3 freeze (<-65° C) – thaw (37° C) cycles was 92.5% (5.8%). Recovery was 101.3% (6.3%) at <-65°C for 12 months.
Conclusion	In-process assay runs met system suitability and assay specificity, however only duplicates of QC samples were included in the validation. Therfore, intra-assay accuracy and precision could not be determined.

Reviewer's Comment:
The bioanalytical assay methods were determined to be unacceptable based on the criteria outlined in the FDA Guidance for Industry entitled "Bioanalytical Method Validation" (see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf). It was identified that only duplicates of the QC samples were included in patient PK sample runs. According to the Guidance, at least 5 replicates of the QC samples should be included. As a result, the intra-assay accuracy and precision could not be adequately determined. In addition, the inter-assay accuracy for medium (116.3%) and low (125.6%) QCs was unacceptable in Study TKT032. As a result, the PK parameters characterized by the sponsor and reviewed in this document may not be accurate and reliable for labeling purpose.

However, considering the supply shortage of the currently marketed imiglucerase and the demonstrated clinical efficacy and safety of velaglucerase alfa, the reviewer recommends that the definitive PK parameter characterization be deferred as a PMC (see 21 CFR §320.22 (e)).

2.6.6 What bioanalytical methods are used to assess the formation of the anti-product antibodies? Briefly describe the methods and assay performance including *sensitivity, specificity, precision, cut point, interference and matrix, etc.*

2.6.6.1 What is the performance of the binding assay(s)?

To detect anti-velaglucerase alfa antibodies in serum, biotin-conjugated velaglucerase alfa is immobilized onto a streptavidin-coated plate. When incubated with diluted serum sample, the biotinylated velaglucerase alfa/streptavidin complex captures any anti-velaglucerase alfa antibodies present in the serum. Next, sulfo-tagged velaglucerase alfa is added to each well resulting in the formation of a complex with the bound anti-velaglucerase alfa antibodies. This is followed by a wash step, in which unbound sulfo-tagged proteins are removed. The sulfo-tagged molecules near the plate surface emit light by electrochemiluminescence (ECL), which is measured by an [redacted] instrument. A mouse monoclonal anti-velaglucerase alfa antibody calibration curve is determined in the same assay, and the concentration of anti-velaglucerase alfa antibodies in serum samples is evaluated by comparison of the sample's measured ECL signal to the calibration curve. b(4)

The validation report is attached below:

Table 1. Method Validation Parameters

Validation Parameters	Acceptance Criteria	Validation Results
Selectivity / Specificity	Specificity for velaglucerase alfa protein: $R^2 \geq 0.990$	Specific antibody: $R^2 = 0.991$ Non-specific antibody: $R^2 = 0.009$
Repeatability: (Intra- and Inter-Assay Precision)	% RSD ≤ 15.0	% RSD $_{\text{Intra-assay}} \leq 6.2$ % RSD $_{\text{Inter-assay}} \leq 8.5$
Calibration Model	$R^2 \geq 0.990$	$R^2 = 0.995$
Limit of Detection (LOD) Limit of Quantitation (LOQ)	LOD = [3.3 x (SD of y-intercepts)] / slope of calibration curve LOQ = [10 x (SD of y-intercepts)] / slope of calibration curve Sensitivity < 500 ng/mL	LOD = 5.0 ng/mL LOQ = 15.0 ng/mL Sensitivity = 100.0 ng/mL
Intermediate Precision: (Inter-Analyst and Inter-Day Precision)	% Effect ≤ 15.0	% Analyst Effect ≤ 14.9 % Inter-Day Effect ≤ 9.0
Serum Anti-Velaglucerase Alfa Antibody Background	Based on mean ECL response from a minimum of 50 serum samples	Mean response = 127 ECL (N = 72)
Robustness: Variability in Sulfo-Tagged or Biotinylated Velaglucerase Alfa Protein Lots	Inter-Lot Variation % RSD ≤ 15.0	% RSD ≤ 3.6
Robustness: Effect of Plate Read Time	Overall Plate Read Time Variation % RSD ≤ 15.0	% RSD ≤ 10.6
Stability: • **Labeled Velaglucerase Alfa Overnight at 4 °C** • **Labeled Velaglucerase Alfa RT 3 hours**	Overall Variation % RSD ≤ 15.0	• % RSD ≤ 8.6 • % RSD ≤ 11.4
Stability: Long-Term Storage at -65 °C	% Recovery $_{\text{Long-term Stability}}$ = 85.0 – 115.0	% Recovery $_{\text{Long-term Stability}}$ = 93.5 – 112.5

2.6.6.2 What is the performance of the neutralizing assay(s)?

Samples confirmed positive for binding antibodies were tested for neutralizing activity along with their respective pretreatment samples, if available. It is based on a colorimetric assay that measures the ability of velaglucerase alfa to hydrolyze the substrate 4-nitrophenyl-β-D-glucopyranoside to p-Nitrophenol and D-glucopyranoside. Briefly, serum samples are pre-incubated with a fixed amount of velaglucerase alfa (250 ng/mL with enzymatic activity at 11 ± 2 mU/mL) for 30 minutes at 37 °C. The 4-nitrophenyl-β-D-glucopyranoside substrate solution is then incubated with the serum/enzyme mixture for 1 hour at 37 °C. The enzymatic reaction is stopped by addition

of a glycine/sodium carbonate buffer (pH 10.7) and the product, p-Nitrophenol (pNP), is measured at the absorbance wavelength of 405 nm. One unit of velaglucerase alfa activity is defined as the amount of enzyme required to hydrolyze 1 µmole of the substrate 4-nitrophenyl-β-D-glucopyranoside in 1 minute at 37 °C. Enzymatic activity is quantified by comparison of pNP in test samples and assay controls to the pNP calibration curve measured in the same assay plate. Results of the test samples are relative to the activity measured in 250 ng/mL velaglucerase alfa without serum and reported as % Inhibition.

The validation report was attached below:

Table 1. Validation Parameters, Acceptance Criteria, and Results

Validation Parameters	Acceptance Criteria	Validation Results
Repeatability (Intra- and Inter-Assay Precision)	% RSD ≤ 15.0	Intra-Assay % RSD: 0.2 – 12.9 Inter- Assay % RSD: 2.6 – 6.1
Intermediate Precision (Inter-Analyst and Inter-Day Precision)	% RSD ≤ 15.0	Inter-Analyst % RSD: 2.0 – 10.2 Inter-Day % RSD: 2.1 – 7.8 Overall % RSD: 2.9 – 8.1
Recovery	% Change ≤ 15.0	NHS vs. NC: 6.9% Change NHS+G140 vs. PC: 7.2% Change
Assay Cut Point	Mean Inhibition + 3 SD	NAb negative: ≤ 20% inhibition NAb positive: > 20% inhibition
Assay Linearity and Range	$R^2 \geq 0.990$	Calibration Curve: R^2 = 0.999-1.000 Dose Response: R^2 = 1.000 Assay Range: 0.3 - 33.3 mU/mL
Sensitivity: **Limit of Detection (LOD)** **Limit of Quantitation (LOQ)**	LOD = $(3.3 \times SD_{y\text{-intercept}}) / Mean_{slope}$ LOQ = $(10 \times SD_{y\text{-intercept}}) / Mean_{slope}$	LOD = 97% Inhibition (0.3 mU/mL) LOQ = 91% Inhibition (1.0 mU/mL) Maximum serum dilution factor = 1:40
Robustness: **Substrate Diluent's pH** **Pre-Incubation Time** **Enzymatic Reaction Time**	% RSD ≤ 15.0	Diluent's pH % RSD: 2.9 - 8.7 Pre-incubation % RSD: 1.9 - 4.7 Reaction Time % RSD: 2.8 - 8.9
Stability: **Freeze-Thaw (FT)** **pNP Stock Solution**	% Change ≤ 15.0 % RSD ≤ 15.0	FT % Change: 8.4 - 14.6 pNP stock: % RSD = 5.6

3 LABELING

The following are Clinical Pharmacology relevant parts of the Sponsor's proposed labeling with preliminary labeling recommendations from the Clinical Pharmacology review team. Labeling review will be completed later at the time of label negotiation with the Sponsor.

6.2 Immunogenicity

b(4)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Proposed:

b(4)

Recommended:

Gaucher disease is an autosomal recessive disorder caused by mutations in the GBA gene, which results in a deficiency of the lysosomal enzyme beta-glucocerebrosidase. Glucocerebrosidase catalyzes the conversion of the sphingolipid glucocerebroside into glucose and ceramide. The enzymatic deficiency causes an accumulation of glucocerebroside primarily in the lysosomal compartment of macrophages, giving rise to foam cells or "Gaucher cells". In this lysosomal storage disorder (LSD), clinical features are reflective of the accumulation of Gaucher cells in the liver, spleen, bone marrow, and other organs. The accumulation of Gaucher cells in the liver and spleen leads to organomegaly. Presence of Gaucher cells in the bone marrow and spleen lead to clinically significant anemia and thrombocytopenia.

Velaglucerase alfa catalyzes the hydrolysis of glucocerebroside, reducing the amount of accumulated glucocerebroside.

12.3 Pharmacokinetics

Proposed:

b(4)

Recommended:

In a multicenter study conducted in pediatric (N=7, 4 to 17 years old) and adult (N=15, 19 to 62 years old) patients with type 1 Gaucher disease, pharmacokinetic evaluations were performed at Weeks 1 and 37 following the 1-hour intravenous infusions of VPRIV 60 U/kg every other week. Serum velaglucerase alfa concentrations declined rapidly with a mean half life of 11 to 12 minutes. The mean velaglucerase alfa clearance ranged from 6.72 to 7.56 mL/min/kg. The mean volume of distribution at steady state ranged from 82 to 108 mL/kg (8.2% to 10.8% of body weight). However, because an inadequately validated analytical assay method was used in the evaluations, the pharmacokinetic parameter values do not appear to be accurate and can not be considered definitive.

No accumulation or change in velaglucerase alfa pharmacokinetics over time from Weeks 1 to 37 was observed upon multiple-dosing 60 Units/kg every other week.

Based on the limited data, there were no notable pharmacokinetic differences between male and female patients in this study. The effect of age on pharmacokinetics of velaglucerase alfa was inconclusive.

The effect of anti-drug antibody formation on the pharmacokinetic parameters of velaglucerase alfa was unknown.

***Reviewer's comment**: The sponsor is proposing to use PK data from Studies TKT025, TKT025EXT and TKT032 for labeling purposes. Since TKT025 was conducted with drug substance not comparable to the final to-be-marketed formulation (AF2), PK results from TKT025 should not be included in the label. PK parameters on the label should be from the most reliable single study (i.e., Study TKT032) rather than combining PK parameters from TKT025EXT and TKT032 since TKT025EXT was a continuous study from TKT025. Furthermore, because the in-process analytical validation was inadequate, the*

recommended labeling language needs to be replaced with acceptable PK data obtained from recommended PMC studies in the future.

4 APPENDIX

4.1 Synopsis of individual studies

Study TKT032 Title:
A Multicenter, Randomized, Double-Blind, Parallel Group, Two-Dose Study of Gene-Activated® Human Glucocerebrosidase (GA-GCB) Enzyme Replacement Therapy in Patients with Type 1 Gaucher Disease

Investigators and Study Centers: Multicenter

Publication (reference): None

Studied Period:
15 February 2007 (first patient enrolled) to 01 April 2009 (last patient completed)

Study Phase: III

Objectives: The primary objective of this study was to determine the efficacy of every other week dosing of velaglucerase alfa at a dose of 60 U/kg administered to patients with type 1 Gaucher disease, as measured by increases in hemoglobin concentration. The secondary objectives of this study were to evaluate the safety of every other week dosing of velaglucerase alfa at doses of 60 and 45 U/kg, to evaluate the efficacy of every other week dosing with 45 U/kg as measured by increases in hemoglobin concentration, to evaluate the efficacy of every other week dosing with velaglucerase alfa at 60 and 45 U/kg as measured by increases in platelet counts, decreases in spleen and liver volumes, and decreases in levels of plasma chitotriosidase and Chemokine ligand 18 (CCL18), to evaluate the effect on overall quality of life (QoL), as measured by the Short Form-36 (SF-36) for patients ≥18 years old and the Childhood Health Questionnaire (CHQ, PF50) for patients 5 to 17 years old, and to evaluate the single- and repeat-dose pharmacokinetics of every other week dosing of velaglucerase alfa when administered at doses of 60 and 45 U/kg. Tertiary objectives included time to hemoglobin response, pulmonary function tests in patients ≥18 years old, growth velocity and Tanner staging in patients 2-17 years old, and changes in skeletal age in patients 2-17 years old. Baselines for evaluation of bone disease were established.

Methodology: Randomized, double-blind, parallel dose group, multicenter Phase III efficacy and safety study where velaglucerase alfa was administered IV every other week for a total of 51 weeks (26 infusions) at doses of 60 U/kg and 45 U/kg.

Number of Patients (Planned and Analyzed):
12 patients/dose group were planned; 13 patients in the 45 U/kg group, 12 patients in the 60 U/kg group were analyzed for safety; 13 and 12 patients in the 45 U/kg group, 12 and 11 patients in the 60 U/kg group were analyzed for efficacy in the ITT and MITT populations, respectively.

Diagnosis and Main Criteria for Inclusion:
Patients at least 2 years of age with type 1 Gaucher disease documented by genotypic analysis or by deficient leukocyte glucocerebrosidase (GCB) activity and with disease-related anemia (hemoglobin reduced at least 1 g/dL below the lower limit of normal for age and gender), disease-related anemia, and at least 1 of the following: moderate splenomegaly (2 to 3 cm below the left costal margin) by palpation, Gaucher disease-related thrombocytopenia (platelet count <90 x 10^3 platelets/mm^3) or a Gaucher disease-related readily palpable enlarged liver. Patients were not to have received any treatment for Gaucher disease within 30 months of study entry.

Test Product, Dose and Mode of Administration, Lot Number:
Gene-Activated® Human Glucocerebrosidase (velaglucerase alfa), a human glucocerebrosidase, a monomeric glycoprotein of approximately 63 kD containing 5 potential N-linked glycosylation sites (one of which is unoccupied), produced by gene activation in a human cell line. Velaglucerase alfa was to be administered as an IV infusion given over 60minutes. The lot numbers used in this study were FEB06-001, FEC02-006, FEC06-002, FEC06-003, FEC06-004, FEC06-005, FEC07-001, FEC07-003, FEC07-005

Duration of Treatment: Patients were dosed with velaglucerase alfa once every other week for a total of 26 fusions (51 weeks).

Criteria for Evaluation:
Efficacy:
Primary endpoint:
- Hemoglobin concentration in 60 U/kg dose group

Secondary endpoints:
- Hemoglobin concentration in 45 U/kg dose group
- Platelet counts
- Liver and spleen volumes
- Chitotriosidase levels
- CCL18 levels
- QoL by SF-36 for patients ≥18 years old and CHQ-PF50 for patients 5 to 17 years old
- Single- and repeat-dose pharmacokinetics of velaglucerase alfa at Week 1 and Week 37

Tertiary endpoints:
- Time to first hemoglobin response
- Growth velocity and Tanner staging for patients 2 to 17 years old
- Skeletal age for patients 2 to 17 years old
- Pulmonary Function Tests (PFTs) for patients ≥18 years old

Endpoints Requested by the European Medicines Evaluation Agency
- Response categories for hemoglobin concentration, platelet count, liver and spleen volumes

Safety:

- Adverse events
- Vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiration rate, temperature)
- Physical examination
- Concomitant medications
- Electrocardiogram (ECG)
- Clinical laboratory tests (serum chemistry, hematology, urinalysis)
- Measurement of serum anti-velaglucerase alfa antibodies

Pharmacokinetics Results:

- Velaglucerase alfa PK profile was similar between Weeks 1 and 37 in most subjects.
- Velaglucerase alfa serum concentrations rose rapidly, with mean C_{max} at around 40 minutes after start of infusion.
- Mean C_{max} and AUC was approximately 40% to 50% higher in the 60 U/kg group compared with the 45 U/kg group
- Mean $t_{1/2}$ was 11 to 12 minutes for both dose groups.
- Rapid clearance of velaglucerase alfa from serum (mean 6.7 to 7.6 mL/min/kg) is consistent with the uptake into macrophages via mannose receptors.
- Mean velaglucerase V_{ss} ranged from 82 to 108 mL/kg (8.2% to 10.8% of body weight).
- There was no apparent trend for velaglucerase alfa C_{max}, AUC or CL to change with increasing age in the 45 U/kg dose group. However, in the 60 U/kg group, there was an apparent trend for lower C_{max} and AUC values and higher CL values in subjects below 10 years of age compared to the adult subjects (19 to 42 years old). However, if the two dose groups are combined, the range of CL values in the children is completely contained within the range of values in the adults.
- There are no apparent PK differences between male and female subjects in this study.
- No attempt was made to correlate antibody positivity with velaglucerase PK as no patients were antibody positive at the time of blood sampling fro PK analysis.

Reviewer's comment:

The sponsor reported that three Week 37 PK blood draws actually occurred at week 39 (subject 071-0005), and week 51 (subjects 191-0002 and 191-0003). Since there were no signs of accumulation based on the current data, including those three samples into week 37 calculation is considered acceptable.

Most subjects reached Cmax at the end of infusion (60 minutes post the start of infusion), however, there were some subjects who reached Cmax around 20 to 40 minutes. It is unknown whether this is due to the assay variability (ELISA assay tends to have larger variability compared to other analytical assays such as MS) or inter-subject variability in the velaglucerase alfa distribution.

It is worth noting that one subject is particularly different (subject 032-165-0001 at 45 U/kg). This subject reached Cmax at 5 minutes after the start of infusion at Week 37 although this same subject reached Cmax at the end of infusion (60 minutes after the start of infusion) at Week 1. The reason for this different PK was unknown; however, it is likely that there were some errors in the sample collection such as the blood samples were collected from the same arm of IV infusion.

It should be noted that 4 subjects had missing serum concentrations in the middle of PK profiles. It is unknown whether these missing or unreported concentrations were indeed PK samples missing or undetectable. Since those time points lay in the middle of the PK profiles, they were not likely to be under detection limit, especially PK samples right before and after these time points were well above the detection limit.

The sponsor claimed that velaglucerase afa follow approximately linear PK pattern with increasing dose. However, the current study only included two dose levels (45 or 60 U/kg) and 25 subjects, it is unreliable to make any conclusion based on the currently limited data.

For the effect of age on PK profiles, it was observed that there was no apparent trend for velaglucerase alfa C_{max}, AUC or CL to change with increasing age in the 45 U/kg dose group. However, in the 60 U/kg group, there was an apparent trend for lower C_{max} and AUC values and higher CL values in subjects below 10 years of age compared to the adult subjects (19 to 42 years old). Since only 25 subjects were enrolled and 5 of them were under 10 years old, the overall conclusion about the age's effect on PK is inconclusive.

Study TKT025EXT Title:
An Open-Label Extension of Study TKT025 Evaluating Long Term Safety in Patients with Type 1 Gaucher Disease Receiving DRX008A Enzyme Replacement Therapy

Investigators and Study Centers:
Ari Zimran, MD
Shaare Zedek Medical Center
(main study site)
Jerusalem, Israel

Dr. Maja Djordjevic
Mother and Child Health Care Institute of Serbia
Belgrade, Serbia

Prof. Florea Iordachescu
"Maria Sklodowska Curie" Children's Hospital
Bucharest, Romania

Publication (reference): Not applicable

Studied Period:
This study is currently ongoing. The safety data included in this report encompasses the time period of 03 February 2005 (first subject enrolled) to 01 June 2009 (date of data cut-off).

Phase of Development: I/II

Objectives:
The primary objective of this study is to:
• Evaluate the long term safety of Gene-Activated® glucocerebrosidase (velaglucerase alfa, GA-GCB, DRX008A), when administered at doses of 60 and 30 U/kg every other week by intravenous (IV) infusion to patients with type 1 Gaucher disease.
The secondary objectives of this study are to:
• Assess the effects of velaglucerase alfa (GA-GCB) enzyme replacement therapy (ERT) on hemoglobin and platelet counts, liver and spleen size, and disease biomarkers in patients with type 1 Gaucher disease.
• Analyze pulmonary function tests, magnetic resonance imaging (MRI) of the femora and lumbar spine, skeletal survey and bone densitometry to evaluate clinical activity.
An analysis of clinical activity is not included in this abbreviated clinical study report.

Methodology: TKT025EXT is an open-label extension study of Study TKT025. Ten patients, who were previously enrolled in Study TKT025, enrolled in Study TKT025EXT. All patients were to receive 60 U/kg velaglucerase alfa administered IV every other week for a minimum of one year including treatment in Study TKT025. Patients were then evaluated to determine whether they could receive velaglucerase alfa at a transitional reduced dose of 45 U/kg administered every other week for 13 weeks, followed by 30 U/kg thereafter, for the remainder of the treatment period. To receive the reduced dose, patients had to meet at least two of four, year-one therapeutic criteria for ERT treatment of type 1 Gaucher disease. Patients are to continue treatment with velaglucerase alfa until commercial velaglucerase alfa is available, the patient's participation is discontinued, or the study is discontinued.

Number of Subjects (Planned and Analyzed):
11 subjects were planned; 10 subjects were enrolled and analyzed for safety in this abbreviated clinical study report.

Diagnosis and Main Criteria for Inclusion:
All patients with type 1 Gaucher disease who completed the Phase I/II Study TKT025 and elected to continue to receive treatment with velaglucerase alfa were permitted to participate in Study TKT025EXT.

Test Product, Dose and Mode of Administration, Lot Number:
Velaglucerase alfa, IV, initially dosed at 60 U/kg. If a patient met the criteria for dose reduction, the dose was reduced to 45 U/kg EOW for 13 weeks, then to 30 U/kg EOW until study treatment was terminated. Lot numbers for velaglucerase alfa were FE924-001, FEB04-001, FEB05-001, FEB06- 001, FEC06-002, FEC06-003, FEC07-004, FEC08-001, and FEC07-005.

Duration of Treatment: Treatment in this study is intended to continue until velaglucerase alfa is commercially available. The safety data included in this report encompasses the time period of 03 February 2005 (first subject enrolled) to 01 June 2009 (date of data cut-off).

Criteria for Evaluation:
Efficacy:
Not applicable to this report
Safety:
Safety was evaluated by assessments of adverse events (including infusion-related adverse events), concomitant medications, and vital signs. Additional safety assessments include 12-lead electrocardiograms (ECG), echocardiograms, physical examinations, and collection of samples for clinical laboratory tests (hematology, serum chemistry, and urinalysis). Determination of the presence of anti-velaglucerase alfa antibodies and enzyme neutralizing antibodies were conducted approximately every 12 weeks and will continue to be collected until a patient's participation in the study ends. Patients who were found to be positive for anti-velaglucerase alfa antibodies were to have pharmacokinetics assessed within 6 weeks of positive antibody status. This abbreviated report contains the safety data up to 01 June 2009 for adverse events, concomitant medications, hematology and clinical chemistry laboratory tests, and antibody testing.

Statistical Methods:
The safety analysis population consists of all enrolled patients who received at least one infusion of study drug (partial or full). No formal statistical tests were performed on the safety parameters.

Summary of Results
Efficacy:
Not applicable to this report.
Safety:
Overall, 10 patients have been treated for a median of 59.00 months including treatment in Studies TKT025 and TKT025EXT, and for a median of 49.80 months in Study TKT025EXT alone. Overall, the median actual average dose was 38.40 U/kg, and in Study TKT025EXT alone, the median actual average dose was 34.65 U/kg. All 10 patients (100.0%) experienced at least one treatment-related adverse event. The most frequent adverse events were arthralgia, back pain, pyrexia, headache, pharyngolaryngeal pain, upper abdominal pain, influenza, pain in extremity, abdominal pain, gingival bleeding, nausea, and fatigue. Only two patients (20.0%) experienced a total of 3 adverse events (severe headache, severe arthralgia and osteonecrosis) that were severe. No patient experienced a life threatening adverse event.

Only two patients (20.0%) experienced a total of 3 adverse events (tremor, pain in extremity, and fatigue) that were considered by the Investigator possibly or probably related to study drug. The majority of those events (tremor and pain in extremity) were infusion-related. Only two patients (20.0%) experienced infusion-related adverse events. The two infusion-related events, tremor and pain in extremity, were mild and moderate, respectively. No patient received preinfusion medications. Four patients experienced a total of 7 treatment-emergent SAEs. All SAEs were considered by the Investigator as not related to study drug. No deaths were reported during the study. No patient experienced an adverse event that led to discontinuation of treatment. No consistent clinically significant changes were seen in the key clinical chemistry and hematology parameters. All patients tested negative for anti-velaglucerase alfa antibodies.

OVERALL CONCLUSIONS
In this ongoing study, based on the data collected through 01 June 2009, long-term treatment with velaglucerase alfa (GA-GCB) for patients with type 1 Gaucher disease was safe and well tolerated.
Final Report Date: 28 July 2009

Reviewer's comment:
This is a continous study from study TKT025, a 9-month open-label, Phase I/II safety study with IV administration of GA-GCB every 2 weeks, followed by a long term extension study TKT025EXT. Twelve patients were enrolled in TKT025 and received Phase I/II raw materials. The dose of velaglucerase alfa (switched to AF1 material in TKT025EXT) was subsequently reduced to 30 U/kg for all subjects by the time of the PK evaluation at Week 65 of TKT025EXT and nine patients had blood collected for PK analysis at Week 65.

At week 65, the serum concentrations at predose and 5 minutes after the start of infusion were under the detection limit (0.03 μg/mL) except one subject (071-0010) had detectable serum concentration (0.4 μg/mL) at 5 minutes. The PK profiles across all 9 subjects were quite comparable and one-compartment IV infusion model fitted the data reasonably well. Following 1-hour 30 U/kg intravenous infusion, the mean maximum serum velaglucerase alfa concentrations (C_{max}) of 2.3 μg/ml (standard deviation [SD]: 0.74 μg/ml) was reached with the end of the 1-hour infusion period (mean Tmax: 55 minutes; standard deviation [SD]: 5.6 minutes). After C_{max}, serum velaglucerase concentrations declined rapidly following first-order elimination kinetics in all 9 patietns continuing therapy with a mean half life of approximate 9 minutes (SD: 2.2 minutes). Mean CL was approximately 6.5 mL/min/kg (SD: 2.0 mL/min/kg), and mean Vss was 83 mL/kg (SD: 19.5 mL/kg). None of the subjects was positive for anti-velaglucerase alfa antibodies at any time during this study.

4.2 Clinical Pharmacology Filing Memo

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	22-575	Brand Name	Glucocerebrosidase
OCP Division (I, II, III, IV, V)	DCP III	Generic Name	velaglucerase alfa
Medical Division	DGIP	Drug Class	Enzyme Replacement Therapy
OCP Reviewer	Lanyan Fang, Ph.D.	Indication(s)	Type 1 Gaucher disease
OCP Secondary Reviewer	Jang-Ik Lee, PharmD, Ph.D.	Dosage Form	Lyophilized powder
Pharmacometrics Reviewer	N/A	Dosing Regimen	60 U/kg every other week as 60-minute i.v. infusion
Date of Submission	August 31, 2009	Route of Administration	I.V.
Estimated Due Date of OCP Review	December 31, 2009	Sponsor	Shire
Medical Division Due Date	January 29, 2010	Priority Classification	P
PDUFA Due Date	February 26, 2010	Dosing Strength	200 U/vial and 400 U/vial

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	13		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	3		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	X	1		
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	no			
gender:	X			

Age:	X			
pediatrics:	X	2-17 and adults (18-62)		
geriatrics:				
renal impairment:				
hepatic impairment:				
Immunogenicity:	X			
PD -				**No biomarker**
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
PK and PD comparability:				**Not conducted**
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**16**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted PK and PD comparability data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		X		
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			The routine drug-analysis report was not submitted. Update: The required in-process validation report was submitted on 10/23/09 following the

					teleconference on 10/22/09. The submission fulfilled the filing requirements.
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?		X		Some embedded hyperlinks bring the document to wrong places
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?		X		No clin pharm information submitted in preNDA mtg package
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			Maybe a review issue
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			Weight-based dosing
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?		X		
	General				

18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
__Yes_____

Fileable.

However, the to-be-marked product (AF2) may not be approvable if CMC review determines that there is major manufacture changes, different glycosylation levels or analytically incomparable between AF1 and AF2 products.

In the original submission, the sponsor did not submit the routine drug analysis report. Therefore, the sponsor needed to submit the report before the 60-day filing date. Drug analysis site inspection may also be needed.

Update: The required in-process assay validation report was submitted on 10/23/09 following the teleconference on 10/22/09. Preliminary review indicated that the submission fulfilled the filing issues.

Lanyan Fang, Ph.D.

Clinical Pharmacology Reviewer Date

Jang-Ik Lee, Pharm.D., Ph.D.

Acting Team Leader Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LANYAN FANG
01/29/2010

JANG IK LEE
01/29/2010

EDWARD D BASHAW
02/01/2010