CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022458Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ADDENDUM TO OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	**22-458**
Original Submission Dates	**Stamp (4/26/10), Amendment 0002 (12/8/09), Amendment 0003 (12/16/09)**
Resubmission Dates	**8/1/2011, 11/1/2011, 11/15/2011**
PDUFA Due Date	**5/1/2012**
Brand Name	**Elelyso**
Generic Name	**Taliglucerase alfa**
Primary Reviewer	**Lanyan Fang, Ph.D.**
Team Leader	**Yow-Ming Wang, Ph.D.**
Primary PM Reviewer	**Kevin Krudys, Ph.D.**
Team PM Leader	**Christine Garnett, Ph.D.**
OCP Division	**DCP 3**
OND Division	**DGIEP**
Sponsor	(b) (4)
Relevant IND(s)	**69,703**
Submission Type	**NME NDA**
Formulation; Strength(s)	**Lyophilized solid for intravenous infusion; 200 U/vial**
Proposed indication	**Treatment of Gaucher disease**
Proposed Dosage and Administration	(b) (4) **60 U/kg every 2 weeks**

This addendum documents the revision to Table 6 in the clinical pharmacology review for NDA 22458 and serves as a replacement to previous addendum dated 4/12/12.

Revised Table 6

Table 6: Pharmacokinetic parameters of taliglucerase alfa determined in Gaucher patients (Study PB-06-001)

Dose Group (Units/kg)		30		60	
Study Visit		Day 1	Week 38	Day 1	Week 38
Number of Patients		10	14	16	15
C_{max} (ng/mL)	Median (Range)	1,504 (637 – 3,275)	1,382 (720 – 4,989)	3,650 (1,792 – 10,351)	4,565 (1,834 – 12,504)
	Mean ± SD	1556 ± 742	1656 ± 1116	4250 ± 2230	5153 ± 3099
AUC_{last} (ng·hr/mL)	Median (Range)	2,411 (807 – 3,082)	1,989 (1,002 – 9,546)	6,350 (2,877 – 10,077)	6,751 (2,545 – 20,496)
	Mean ± SD	2,229 ± 669	2,654 ± 2,130	6,349 ± 2,200	7,665 ± 4,578
AUC_{∞} (ng·hr/mL)	Median (Range)	2,459 (810 – 3,119)	2,007 (1,007 – 10,092)	6,372 (2,885 – 10,265)	6,459[a] (2,548 – 21,020)
	Mean ± SD	2,244 ± 674	2,706 ± 2,270	6,383 ± 2,229	7,814 ± 5157[a]
CL (L/hr)	Median (Range)	23.2 (16.8 – 56.4)	30.5 (6.8 – 68.0)	19.7 (10.0 – 35.6)	18.5[a] (6.2 – 37.9)
	Mean ± SD	29.4 ± 13.9	30.7 ± 14.5	20.5 ± 7.1	19.9 ± 9.6[a]
V_{ss} (L)	Median (Range)	9.6 (4.0 – 26.5)	11.7 (2.3 – 22.7)	7.3 (0.4 – 19.4)	10.7[a] (1.4 – 18.5)
	Mean ± SD	11.0 ± 7.3	12.1 ± 6.0	9.06 ± 5.32	10.5 ± 4.8[a]
$t_{½}$ (min)	Median (Range)	23.6 (10.0 – 42.4)	18.9 (9.2 – 57.9)	21.9 (13.3 – 43.7)	28.7[a] (11.3 – 104)
	Mean ± SD	25.9 ± 11.8	25.1 ± 15.5	25.0 ± 10.1	34.8 ± 22.9[a]

[a] n=14

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
04/17/2012

YOW-MING C WANG
04/19/2012

ADDENDUM TO OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	**22-458**
Original Submission Dates	**Stamp (4/26/10), Amendment 0002 (12/8/09), Amendment 0003 (12/16/09)**
Resubmission Dates	**8/1/2011, 11/1/2011, 11/15/2011**
PDUFA Due Date	**5/1/2012**
Brand Name	**Elelyso**
Generic Name	**Taliglucerase alfa**
Primary Reviewer	**Lanyan Fang, Ph.D.**
Team Leader	**Yow-Ming Wang, Ph.D.**
Primary PM Reviewer	**Kevin Krudys, Ph.D.**
Team PM Leader	**Christine Garnett, Ph.D.**
OCP Division	**DCP 3**
OND Division	**DGIEP**
Sponsor	(b) (4)
Relevant IND(s)	**69,703**
Submission Type	**NME NDA**
Formulation; Strength(s)	**Lyophilized solid for intravenous infusion; 200 U/vial**
Proposed indication	**Treatment of Gaucher disease**
Proposed Dosage and Administration	(b) (4) **60 U/kg every 2 weeks**

This addendum documents the revision to Table 6 in the clinical pharmacology review for NDA 22458.

Revised Table 6

Table 6: Pharmacokinetic parameters (median and range) of taliglucerase alfa determined in Gaucher patients (Study PB-06-001)

Dose Group (Units/kg)	30		60	
Study Visit	Day 1	Week 38	Day 1	Week 38
Number of Patients	10	14	16	15
C_{max} (ng/mL)	1,504 (637 – 3,275)	1,382 (720 – 4,989)	3,650 (1,792 – 10,351)	4,565 (1,834 – 12,504)
AUC_{last} (ng·hr/mL)	2,411 (807 – 3,082)	1,989 (1,002 – 9,546)	6,350 (2,877 – 10,077)	6,751 (2,545 – 20,496)
AUC_{∞} (ng·hr/mL)	2,459 (810 – 3,119)	2,007 (1,007 – 10,092)	6,372 (2,885 – 10,265)	6,459[a] (2,548 – 21,020)
CL (L/hr)	23.2 (16.8 – 56.4)	30.5 (6.8 – 68.0)	19.7 (10.0 – 35.6)	18.5[a] (6.2 – 37.9)
V_{ss} (L)	9.6 (4.0 – 26.5)	11.7 (2.3 – 22.7)	7.3 (0.4 – 19.4)	10.7 [a] (1.4 – 18.5)
$t_{½}$ (min)	23.6 (10.0 – 42.4)	18.9 (9.2 – 57.9)	21.9 (13.3 – 43.7)	28.7[a] (11.3 – 104)

[a] n=14

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
04/12/2012

YOW-MING C WANG
04/12/2012

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	**22-458**
Original Submission Dates	**Stamp (4/26/10), Amendment 0002 (12/8/09), Amendment 0003 (12/16/09)**
Resubmission Dates	**8/1/2011, 11/1/2011, 11/15/2011**
PDUFA Due Date	**5/1/2012**
Brand Name	**Elelyso**
Generic Name	**Taliglucerase alfa**
Primary Reviewer	**Lanyan Fang, Ph.D.**
Team Leader	**Yow-Ming Wang, Ph.D.**
Primary PM Reviewer	**Kevin Krudys, Ph.D.**
Team PM Leader	**Christine Garnett, Ph.D.**
OCP Division	**DCP 3**
OND Division	**DGIEP**
Sponsor	(b) (4)
Relevant IND(s)	**69,703**
Submission Type	**NME NDA**
Formulation; Strength(s)	**Lyophilized solid for intravenous infusion; 200 U/vial**
Proposed indication	**Treatment of Gaucher disease**
Proposed Dosage and Administration	(b) (4) **60 U/kg every 2 weeks**

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

ELELYSO™ (taliglucerase alfa, formerly prGCD) is a recombinant β-glucocerebrosidase (β-D-glucosyl-N-acylsphingosine glucohydrolase), which is expressed in transformed carrot plant root cells. β-Glucocerebrosidase is a lysosomal glycoprotein enzyme that catalyzes the hydrolysis of the glycolipid glucocerebroside to glucose and ceramide. Taliglucerase alfa is proposed for a long-term enzyme replacement therapy (ERT) for patients with Gaucher disease. Taliglucerase alfa for injection is proposed to be administered by intravenous infusion over 1-2 hours. The proposed initial dosages (b) (4) 60 units/kg of body weight once every 2 weeks and the dosage should be adjusted individually based on each patient's therapeutic response.

Currently, two other β-glucocerebrosidases including Cerezyme® (imiglucerase, in supply shortage since 2009) and Vpriv® (velaglucerase alfa) are in the market for the same indication. The sponsor submitted the original New Drug Application for ELELYSO™ (taliglucerase alfa) (NDA 22-458) on 4/26/2010. As a result of the review in the original review cycle, the Complete Response (CR) letter was issued on 2/24/2011 due to multiple issues with product manufacturing and testing, and inspection issues identified (please refer to the reviews of the Offices of Biotechnology Products and Compliance). Along the line, one clinical pharmacology issue that needs to be resolved was conveyed in the CR letter: "*The immunogenic potential of taliglucerase alfa and its impact on pharmacokinetic and pharmacodynamic (PK and PD) parameters cannot be adequately evaluated.*"

The sponsor resubmitted NDA 22-458 on 8/1/2011 and provided a major amendment on 11/15/2011. The resubmissions contained relevant information to address the clinical pharmacology issue raised in the CR letter. The final submission included the results from a Phase 1 pharmacokinetic (PK) study P-01-2005 conducted in healthy subjects, the pivotal Phase 3 study PB-06-001 conducted in naïve Gaucher patients, the supportive Phase 3 switchover study PB-06-002 conducted in Gaucher patients currently being treated with imiglucerase, the long term extensive study PB-06-003, and an expanded access study PB-06-004.

1.1 Recommendation

From a clinical pharmacology perspective, the information submitted to support this NDA is acceptable provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert.

1.2 Phase 4 Requirements

There are no post-marketing requirements for this submission.

1.3 Phase 4 Commitments

The Clinical Pharmacology and CMC review teams recommend the following post marketing commitments (PMC):

To further develop the neutralizing antibody assays to achieve a greater sensitivity and to use the more sensitive assays for monitoring antibody responses and assessing the impact on long-term efficacy and safety in post-marketing studies.

1.4 Summary of Clinical Pharmacology Findings

Pharmacokinetics (PK)

The PK of Taliglucerase alfa was characterized in 31 treatment naïve subjects with Gaucher disease on Day 1 and Week 38 (Month 9) who received taliglucerase alfa 30 units/kg or 60 units/kg via intravenous infusion over 2 hours every other week in Study PB-06-001.

During the infusion, the taliglucerase alfa serum concentrations rose rapidly for the first 50 minutes after administration. At the end of infusion, taliglucerase alfa serum concentrations fell rapidly with a median terminal half life of 18.9 to 31.4 minutes for both dose groups at Day 1 and Week 38. The median systemic clearance (CL) values were approximately 30 L/hr and 20 L/hr for 30 and 60 units/kg, respectively, on Week 38. The median volume of distribution at steady state (V_{ss}) ranged from 9.06 to 12.1 L for both dose groups.

Consistent with the short half life and the long dosing interval (every two weeks), no significant accumulation in serum taliglucerase alfa concentrations was observed with repeated doses of 30 or 60 units/kg. Taliglucerase alfa PK did not appear to change over time (Day 1 vs. Week 38).

The median C_{max} and area under the concentration-time curve (AUC_{last} or AUC_{∞}) of taliglucerase alfa were approximately 3-fold higher in the subjects received 60 units/kg than in the subjects received 30 units/kg, which is greater than the expected 2-fold increase assuming dose proportionality. Thus, the PK of taliglucerase alfa appeared to be nonlinear with a greater than dose-proportional increase in exposure at the doses studied (the CL values were reduced by approximately 30% to 35%).

Hepatic and renal impairment and drug interaction studies were not conducted for taliglucerase alfa.

Exposure Response Relationship

In Study PB-06-001, 31 treatment-naïve patients with Gaucher disease received taliglucerase alfa 30 units/kg or 60 units/kg via intravenous infusion over 1-2 hours every other week for 9 months. Both taliglucerase alfa dose groups demonstrated a highly significant reduction in spleen volume (primary clinical endpoint) at Month 6 visit (30 units/kg, 22.2%; 60 units/kg, 29.9%; $p< 0.0001$) and Month 9 visit (30 units/kg, 26.9%; 60 units/kg, 38.0%; $p < 0.0001$). There appeared to be a trend of greater reduction in spleen volume with increasing dose. Nevertheless, the sponsor concluded there was no statistically significant difference observed in mean spleen volume change between the two dose groups at Months 6 and 9 ($p = 0.060$) based on the small sample size.

A significant reduction in liver volume (secondary clinical endpoint) was observed in both dose groups from screening to Month 6 (30 units/kg, 7.56%, $p = 0.0020$; 60 units/kg, 7.51%, p =

0.0022) and Month 9 (30 units/kg, 10.48%, p = 0.0041; 60 units/kg, 11.11%, p < 0.0001). There was no significant difference in the mean observed liver volume between two dose groups (p=0.349).

No exposure-response relationship was established for safety as no statistical differences were observed between dose groups.

Overall, the dose-response relationship indicates no statistically significant differences between two dose groups (30 and 60 Units/kg) in terms of observed efficacy and safety.

Immunogenicity Incidence

In the pivotal Phase 3 study (PB-06-001), the incidence of anti-taliglucerase alfa IgG antibody was assessed in subjects naïve to enzyme replacement therapy at baseline and throughout the 9-month treatment period. Following administration of 30 units/kg or 60 units/kg taliglucerase alfa every two weeks to 32 subjects who were tested for immunogenicity, eighteen subjects (18/32, 56%) developed positive anti-drug antibodies (ADA). One additional patient (Patient 10-003) had positive ADA before the first infusion and discontinued from the study after receiving the first infusion due to hypersensitivity reaction. It was noted that the immunogenicity incidence rate increased with dose: 40% (6/15) at 30 units/kg dose and 75% (12/16) at 60 units/kg dose. Of the 18 ADA positive subjects two subjects were positive for neutralizing antibodies based on enzymatic activity inhibition assay, but both were negative in the cell-based assay.

In the Phase 3 switchover study (PB-06-002) where subjects switched from imiglucerase to taliglucerase alfa therapy, six out of 28 patients were ADA positive – one subject (Patient 23-206) had positive ADA pre-switch and the remaining 5 subjects became ADA positive after the switch. Out of the 6 patients, one was positive for neutralizing antibodies based on enzymatic activity inhibition assay, but negative based on cell-based assay.

However, the neutralizing antibody assays were not sensitive and thus inadequate to detect neutralizing ADA. As such, the sponsor should develop the neutralizing antibody assays to achieve greater sensitivity.

Immunogenicity Impact on PK, Efficacy and Safety

The impact of immunogenicity on PK, efficacy and safety was assessed in the pivotal study (PB-06-001). There appeared to be no significant impact of ADA on the PK of taliglucerase alfa based upon the comparisons between 17 subjects with positive ADA and 12 subjects with negative ADA at Month 9. However, this result should be interpreted with caution as the study did not have sufficient power to detect the PK difference due to a small sample size.

The impact of ADA on efficacy is not conclusive. At the dose level of 60 units/kg, there appeared to be a trend of greater efficacy with respect to reduction in spleen and liver volume in the 4 subjects with negative ADA compared to 11 subjects with positive ADA. However, this trend was not observed at the lower dose level of 30 units/kg (N=6 for positive ADA and N=8 for negative ADA).

There appeared to be no consistent patterns across two dose groups in terms of ADA's impact on the safety of taliglucerase alfa such as hypersentivity, thus the sponsor concluded that the relationship between ADA and safety could not be established.

However, due to the small sample size (n=31) the aforementioned ADA's impacts should be interpreted with caution. To assure the efficacy and safety, the sponsor should monitor the patients who developed ADA with more sensitive neutralizing antibody assays and assess the impact of neutralizing antibodies on the long-term efficacy and safety in post-marketing studies (PMC).

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?

Taliglucerase alfa is a recombinant β-glucocerebrosidase (β-D-glucosyl-N-acylsphingosine glucohydrolase), which is expressed in transformed carrot plant root cells. β-Glucocerebrosidase is a lysosomal glycoprotein enzyme that catalyzes the hydrolysis of the glycolipid glucocerebroside to glucose and ceramide. Purified taliglucerase alfa is a monomeric glycoprotein comprised of (b) (4) containing 4 N-linked glycosylation sites (molecular weight, 60,800 daltons). Taliglucerase alfa differs from native human glucocerebrosidase by 2 (b) (4) amino acids at the N-terminal and 7 (b) (4) amino acids at the C-terminal. Taliglucerase alfa is a glycosylated protein with oligosaccharide chains at the glycosylation sites with terminal mannose sugars. These mannose-terminated oligosaccharide chains of taliglucerase alfa are recognized by endocytic carbohydrate receptors (i.e., mannose receptors) on macrophages, the cells that accumulate lipid in Gaucher disease.

Taliglucerase alfa is supplied as a sterile, non-pyrogenic, lyophilized product. The quantitative composition of the lyophilized drug include taliglucerase alfa 212 units, D-mannitol 206.7 mg, polysorbate 80 0.56 mg, sodium citrate 30.4 mg. After reconstitution with Sterile Water for Injection, USP, the taliglucerase alfa concentration is 40 U/mL. Reconstituted solutions have an approximate pH of 6.0.

The enzyme unit (U) is defined as the amount of enzyme that catalyzes the hydrolysis of 1 micromole of the synthetic substrate para-nitrophenyl-β-D-glucopyranoside (pNP-Glc) per minute at 37°C. (b) (4)
(see Section 2.6 Analytical).

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Taligucerase alfa catalyzes the hydrolysis of glucocerebroside to glucose and ceramide, and is indicated for the treatment of Gaucher disease. Gaucher disease is characterized by a deficiency of β-glucocerebrosidase activity, resulting in accumulation of glucocerebroside in tissue macrophages which become engorged and are typically found in the liver, spleen, and bone marrow and occasionally in lung, kidney, and intestine. Secondary hematologic sequelae include severe anemia and thrombocytopenia in addition to the characteristic progressive hepatosplenomegaly, skeletal complications, including osteonecrosis and osteopenia with secondary pathological fractures. Therefore, the symptoms in Gaucher disease include splenomegaly, hepatomegaly, anemia, thrombocytopenia and bone disease with pain.

Taliglucerase alfa exhibits an interaction with the Man/GlcNAc receptor present on specialized macrophages called Gaucher cells. In clinical trials, taligucerase alfa reduced spleen and liver size, and improved anemia and thrombocytopenia.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

Taliglucerase alfa is to be administered by intravenous infusion over 1 - 2 hours. Dosage should be individualized for each patient. Initial dosages (b) (4) 60 units/kg of body weight once every 2 weeks. Dosage adjustments should be made on an individual basis and may increase or decrease, based on achievement of therapeutic goals as assessed by routine comprehensive evaluations of the patient's clinical manifestations.

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 summary of studies providing PK, efficacy, and safety information is shown in Table 1; which included one Phase 1 study (Study P-01-2005), one pivotal phase 3 study (Study PB-06-001), and three supportive phase 3 studies (Studies PB-06-002, PB-06-003 and PB-06-004). PK was collected in the Phase 1 study and the pivotal Phase 3 study, whereas no PD markers were employed in any of the studies.

Study P-01-2005 was a Phase 1 PK and safety study conducted in 6 healthy Caucasian subjects (3 males and 3 females aged between 10 and 35 years old; mean ± SD body weight of 72.5 ± 7.7 kg). Subjects were to receive a single IV dose of vehicle at the baseline visit, followed by three escalating doses of taligucerase alfa on Day 8 (15 units/kg), Day 15 (30 units/kg), and Day 22 (60 units/kg) as a single IV infusion (135 mL) over 90 minutes (1.5 mL/min). Blood samples for PK analyses were designed to be collected prior to dosing (0) and at 5, 45, 80, and 90 minutes during the infusion of taligucerase alfa and 100, 115, 130, 150, 180, 210 minutes and 24 hours post initiation of infusion. ECG was performed at baseline prior to infusion and 8 hours following infusion.

Study PB-06-001 was a multi-center, randomized, double-blind, parallel group, dose-ranging trial to assess the safety and efficacy of taliglucerase alfa in 31 untreated patients with Gaucher disease (n = 15 in 30 units/kg and n=16 in 60 units/kg). The patients consist of 15 males and 16 females (30 Caucasians and 1 black South African) with a mean age of 36.1 years (range 19 to 74), and a mean weight of 68.0 kg (range, 50 kg to 93 kg). IV infusion of taliglucerase alfa was administered every two weeks and the duration of treatment was nine months. Blood samples for PK analysis were designed to be collected at 0, 45, 70, 110, 125, 135, 150, 175, 200, and 225 minutes after start of the first (Day 1) and last (Month 9, Week 38) infusions. Anti-taliglucerase alfa antibody status was determined at baseline and every other week until Month 9.

PB-06-002 is an ongoing multi-center, open label, switch over trial to assess the safety and efficacy of taliglucerase alfa in up to 30 patients with Gaucher disease who were treated with a stable dose of imiglucerase ERT. Patients are receiving IV infusion of taliglucerase alfa every two weeks at the same dose as their previous imiglucerase dose. The duration of the study is nine months. Enrollment in the study started in December 2008 and all patients have completed the study except for two children who are ongoing.

PB-06-003 is an ongoing trial open to patients completing PB-06-001 and PB-06-002 and continues the treatment regimens in those trials. The duration of this trial was extended by

amendment from 15 months to a maximum of 30 months or until commercial product is available at the treating centers.

PB-06-004 is a treatment protocol to provide expanded access to patients whose Cerezyme® dose was reduced or discontinued due to a shortage of Cerezyme®.

Table 1: Summary of Clinical Studies Supporting Taliglucerase alfa NDA

Study Number	Study Objective	Study Design and Type of Control	Dosage Regimen	# Subjects (ITT)	Duration of Treatment
Phase 1 PK, safety and tolerability study					
P-01-2005	Safety of three escalating doses intravenously administered once a week in healthy subjects	Phase 1, non-randomized, open label, single dose-escalation safety study	Day 1 (Vehicle) Day 8 (15 units/kg) Day 15 (30 units/kg) Day 22 (60 units/kg)	6	29 days
Pivotal Phase 3 Study					
PB-06-001	Safety and efficacy of two dose levels of taliglucerase alfa in patients with Gaucher disease	Multicenter, randomized, double blind, parallel group, dose ranging, no placebo control	30 units/kg every 2 weeks 60 units/kg every 2 weeks	N=15 N=16	38 weeks (9 months)
Supportive Phase 3 studies					
PB-06-002	Safety and efficacy in patients switching from imiglucerase ERT	Multicenter, open label	Dose equivalent to prior imiglucerase dose	28	38 weeks (9 months)
PB-06-003	Extended safety and efficacy of patients completing PB-06-001 and PB-06-002	PB-06-001 patients: Multicenter, double blind, parallel group, dose ranging PB-06-002 patients: Multicenter, open label	Continue same dose as previous study	Up to 60 anticipated	15 months (with possible further extension until marketing approval)
PB-06-004	Expanded access treatment protocol	Multicenter, open label	Continue same dose as previous imiglucerase therapy	Up to 200	9 months

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?

The primary efficacy endpoint was the measurement of organ (spleen and liver) volumes by magnetic resonance imaging (MRI) since Gaucher disease results in accumulation of glucocerebroside in tissue macrophages which are typically found in the liver and spleen. The MRIs obtained at Screening, Month 6, and Month 9 were read independently by two central MRI readers in a blinded, randomized manner (i.e., the identity of the patient, treatment group, image sequence, patient clinical history and treatment response were masked to the reader).

The major secondary efficacy endpoints were the change from baseline of hemoglobin and platelet counts because Gaucher disease results in accumulation of glucocerebroside in tissue macrophages in the bone marrow.

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

Yes, the active moiety, taliglucerase alfa, was measured by two different methods. An electrochemiluminescent (ECL) assay was used in the pivotal Study P-06-001 and an enzyme-linked immunosorbent assay (ELISA) was used in the Phase 1 Study P-01-2005. Both assays measured the plasma concentrations of taliglucerase alfa as ng/mL (not enzymatic activity units). The ECL assay was validated and the ELISA assay was not due to unacceptable accuracy and precision. Please refer to Section **2.6 Analytical** for more information about the performance of these bioanalytical assays.

There were no PD endpoints and/or characterization in this submission.

2.2.4 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy?

Spleen Volume (Primary Clinical Endpoint)

As shown in Table 2, both taliglucerase alfa dosage groups (ITT Population) in the pivotal Phase 3 study (Study PB-06-001) demonstrated a highly significant reduction in spleen volume at Month 6 visit (30 units/kg, 22.2%; 60 units/kg, 29.9%; $p < 0.0001$) and Month 9 visit (30 units/kg, 26.9%; 60 units/kg, 38.0%; $p < 0.0001$). While there appeared to be a trend of greater reduction in spleen volume with increasing dose, the sponsor concluded there was no statistically significant difference between the two dose groups either at Months 6 or 9 ($p = 0.060$).

Table 2: Changes in spleen volume after taliglucerase alfa administration to Gaucher patients (Study PB-06-001)

SPLEEN VOLUME (mL) -- Imputed Values Averaged		30 units/kg N = 15	60 units/kg N = 16
PERCENT CHANGE FROM SCREENING TO 6-MONTH	N	15	16
	MEAN	-22.21	-29.94
	SD	4.63	12.65
	MEDIAN	-22.35	-32.10
	RANGE	-30.99 to -12.49	-52.72 to 3.43
	p-value	<0.0001*	<0.0001*
PERCENT CHANGE FROM SCREENING TO 9-MONTH	N	15	16
	MEAN	-26.91	-38.01
	SD	7.79	9.38
	MEDIAN	-27.85	-37.63
	RANGE	-42.60 to -15.58	-56.30 to -20.04
	p-value	<0.0001*	<0.0001*

Liver Volume (Secondary Clinical Endpoint)

As shown in Table 3, a significant reduction in liver volume was observed in both 30 units/kg and 60 units/kg dose groups (ITT Population) from screening to Month 6 (30 units/kg, 7.56%, $p = 0.0020$; 60 units/kg, 7.51%, $p = 0.0022$) and Month 9 (30 units/kg, 10.48%, $p = 0.0041$; 60 units/kg, 11.11%, $p < 0.0001$). However, there was no significant difference observed in mean liver volume between the two dose groups at either visit.

Table 3: Changes in liver volume after taliglucerase alfa administration to Gaucher patients (Study PB-06-001)

LIVER VOLUME (mL)		30 units/kg N = 15	60 units/kg N = 16
PERCENT CHANGE FROM SCREENING TO 6-MONTH	N	15	16
	MEAN	-7.56	-7.51
	SD	7.74	8.17
	MEDIAN	-9.21	-6.94
	RANGE	-22.28 to 11.37	-25.15 to 5.53
	p-value	0.0020*	0.0022*
PERCENT CHANGE FROM SCREENING TO 9-MONTH	N	14	15
	MEAN	-10.48	-11.11
	SD	11.27	6.68
	MEDIAN	-13.87	-12.25
	RANGE	-19.11 to 25.31	-22.29 to 2.32
	p-value	0.0041*	<0.0001*

Hemoglobin Levels (Secondary Clinical Endpoint)

The mean hemoglobin values at baseline were at the lower limit of the normal range (12.2 g/dL and 11.4 g/dL for taliglucerase alfa 30 units/kg and 60 units/kg, respectively) and improved to being within normal limits (14.0 g/dL and 13.6 g/dL for taliglucerase alfa 30 units/kg and 60 units/kg, respectively) at Month 9 (ITT Population). A significant increase in mean hemoglobin level was observed between baseline and the end of study for both taliglucerase alfa 30 units/kg (1.6 g/dL, $p = 0.0010$) and 60 units/kg (2.2 g/dL, $p < 0.0001$) dosage groups. As shown in Table 4, there was no significant difference observed in mean hemoglobin values between the two dose groups at Months 9 ($p = 0.719$).

Platelet Counts (Secondary Clinical Endpoint)

A significant increase in platelet count from baseline was observed in the 60 units/kg dose group (ITT Population) at Month 9 (from 65,038 counts/mm^3 to 106,531 counts/mm^3, difference = 41,494 counts/mm^3, $p = 0.0031$). A clinically meaningful improvement in platelet count at Month 9 was also observed for the taliglucerase alfa 30 units/kg dose group (from 75,320 counts/mm^3 to 86,747 counts/mm^3, difference = 11,427 counts/mm^3, $p = 0.0460$), but did not meet the pre-specified alpha level of 0.025. Significant increases in mean platelet count from baseline were observed in taliglucerase alfa 60 units/kg treated patients compared to taliglucerase alfa 30 units/kg treated patients at Months 9 ($p = 0.042$) when determined using a mixed effect statistical model (Table 4).

Table 4: Changes in hemoglobin and platelet count from baseline on Month 9 after taliglucerase alfa administration to Gaucher patients (Study PB-06-001)

	30 units/kg N = 15	60 units/kg N = 16
CHANGE IN HEMOGLOBIN (g/dL) FROM BASELINE		
N	14	15
MEAN	1.6	2.2
SD	1.4	1.4
MEDIAN	1.3	1.6
RANGE	-0.1 to 5.8	0.5 to 5.1
p-value	0.0010*	<0.0001*
CHANGE IN PLATELET COUNT FROM BASELINE		
N	15	16
MEAN	11427	41494
SD	20214	47063
MEDIAN	10000	38000
RANGE	-25000 to 59000	-15000 to 186000
p-value	0.0460*	0.0031*

2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

Taliglucerase alfa exposure-safety response relationship was not explored in this submission. Instead, the descriptive statistical analysis was summarized. Overall, 23 of 31 taliglucerase alfa treated patients (30 units/kg, 12; 60 units/kg, 11) experienced 137 AEs (30 units/kg, 65; 60 units/kg, 72) in study PB-06-001. Eight of these 23 patients (30 units/kg, 3; 60 units/kg, 5) experienced 28 events (30 units/kg, 12; 60 units/kg, 16) that were considered treatment-related.

All AEs were mild or moderate in intensity and the majority of the events resolved by the end of the study. No deaths or SAEs occurred during the study. Two patients (10-003, taliglucerase alfa 30 units/kg; 10-002, taliglucerase alfa 60 units/kg) discontinued from the study due to a hypersensitivity reaction. Please refer to the clinical review by Dr. Carla Epps for more information.

2.2.4.3 Does this drug prolong the QT or QTc interval?

All subject had normal ECG results at all visits in Study P-01-2005. According to the conclusion in the study report, there were no clinically significant ECG changes observed from baseline throughout the study.

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?

The proposed dose regimens of (b) (4) 60 units/kg to be administered every other week as intravenous infusion over 1-2 hours are the same as what were studied in the pivotal Study PB-06-001. In addition, this was chosen based on previous efficacy and safety study results of the commercially available imiglucerase (Cerezyme®) with supporting nonclinical studies showing comparable potency and safety to that of Cerezyme® (Please refer to the nonclinical review by Dr. Tamal Chakraborti).

2.2.5 What are the pharmacokinetic characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose pharmacokinetic parameters?

Single dose PK in Healthy Subjects (Study P-01-2005)

Single dose PK parameter values of taligucerase alfa were determined in healthy volunteers in Study P-01-2005 using the non-compartmental analysis method. Six healthy Caucasian subjects (3 males and 3 females aged between 10 and 35 years old; mean ± SD body weight, 72.5 ± 7.7 kg) were enrolled in the study. Subjects received a single IV dose of vehicle at the baseline visit, followed by three escalating doses of taligucerase alfa on Day 8 (15 units/kg), Day 15 (30 units/kg) and Day 22 (60 units/kg) as a single IV infusion (135 mL) over 90 minutes (1.5 mL/min). Blood samples for PK analyses were designed to be collected prior to dosing (0) and at 5, 45, 80, and 90 minutes during the infusion of taligucerase alfa and at 100, 115, 130, 150, 180, 210 minutes and 24 hours post initiation of infusion.

The PK results are summarized in this section; however, due to the poor assay performance (described in the bioanalytical section 2.6.5) the data should be interpreted with caution.

Due to the short half-life ($t_{½}$) observed in this study (up to 32 min) relative to the dosing frequency of once weekly, each infusion was treated as a single dose for the purpose of pharmacokinetic analysis. The concentration of taligucerase alfa at time zero was set equal to zero, which might not be appropriate because β-glucocerebrosidase produced endogenously were

detected in study subjects. The sponsor didn't provide pre-dose endogenous enzyme concentrations, thus the impact of setting to zero can not be evaluated.

PK parameter values such as CL and half-life of taligucerase alfa could not be reliably determined at the dose of 15 units/kg due to an insufficient number of samples with quantifiable concentrations. The PK parameter values of taligucerase alfa determined in 30 and 60 units/kg doses are presented in Table 5. As the total number of evaluable subjects studied in each dose group was less than 6, median and the range of the PK parameter values are presented.

Table 5: Pharmacokinetic parameters (median and range) of taliglucerase alfa determined in Healthy Subjects (Study P-01-2005)

Dose Group (Units/kg)	30		60	
	Median	Range	Median	Range
Number of Patients	4 (6 for AUC_{last} and C_{max})		5 (6 for AUC_{last} and C_{max})	
C_{max} (ng/mL)	3964	1059 to 10396	16748	1619 to 23888
AUC_{last} (ng·hr/mL)	4252	1416 to 7878	14510	1756 to 34177
CL (L/hr)	12.8	4.3 to 14.3	8.0	3.4 to 11.3
V_{ss} (L)	3.9	2.8 to 6.4	5.2	2.4 to 6.6
$t_{½}$ (min)	9	8 to 10	17	13 to 32

Taliglucerase alfa was cleared from systemic circulation rapidly and had a median terminal half-life of 9 to 17 minutes. Comparing the median AUC_{last} and CL values for 30 units/kg and 60 units/kg, the PK of taliglucerase alfa appeared to be nonlinear with a greater than dose-proportional increase in exposure at the doses studied. With a doubling of the dose, the exposure (AUC) increased by approximately 4-fold, and the CL values were reduced by approximately 40%.

Reviewer's comments:

Quantitation of taliglucerase alfa in human plasma was conducted using an inadequate ELISA assay with a range of (b) (4) *. Therefore, as pointed out in Section 2.6.5, the overall performance of ELISA was not acceptable. Thus, the PK results from this study should be interpreted qualitatively rather than quantitatively.*

The plasma concentrations of taliglucerase alfa were reported as ng/mL by the analytical laboratory. The doses administered to the subjects were calculated on the basis of enzyme activity of units/kg (U/kg). Plasma concentrations in ng/mL units were used for calculation of the pharmacokinetic parameters. In estimating CL and Vss, the sponsor converted the dose in enzyme activity units to dose in mg using a fixed conversion factor (b) (4) *. The studied drug product came from two manufacture lots (#021005 and #010106) which are likely to have different specific activity, thus the fixed conversion factor may be inappropriate. The sponsor didn't provide enzyme specific activity for each individual lot, thus the magnitude of the deviation from the fixed conversion factor can not be evaluated.*

The observed nonlinear PK property could be due to the saturation of the mannose receptors. Nonclinical studies demonstrated that taliglucerase alfa, after administrated intravenously, uptake into target tissue is specifically medicated by mannose receptors on the macrophages (refer to nonclinical review). Upon saturation of the mannose receptors at a higher dose, a smaller fraction of taliglucerase alfa will be taken up into tissues and a greater portion of taliglucerase alfa will be present in the systemic circulation.

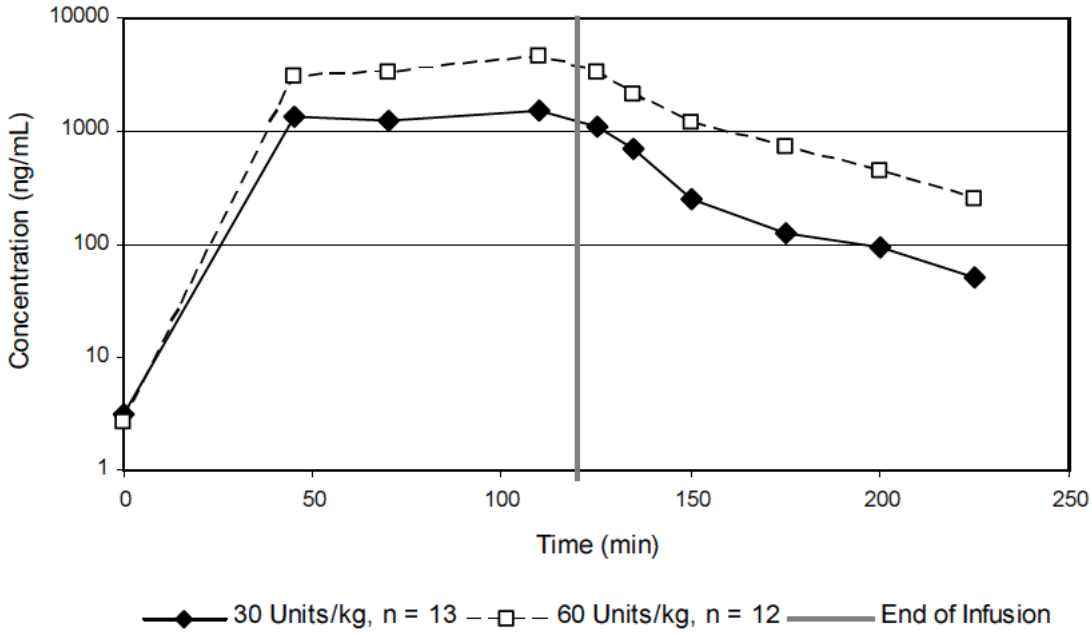
Multiple dose PK in subjects with Gaucher Disease (Study PB-06-001)

The PK parameter values determined from the Gaucher patients in Study PB-06-001 are summarized in Table 6. The PK profiles of taliglucerase alfa following 120 minutes infusion are presented in Figure 2.

Table 6: Pharmacokinetic parameters (median ± standard deviation) of taliglucerase alfa determined in Gaucher patients (Study PB-06-001)

Dose Group (Units/kg)	30		60	
Study Visit	Day 1	Week 38	Day 1	Week 38
Number of Patients	10	14	16	15
C_{max} (ng/mL)	1,504 ± 742	1,382 ± 1116	3,650 ± 2230	4,565 ± 3099
AUC_{last} (ng·hr/mL)	2,440 ± 669	1,989 ± 2,130	6,349 ± 2,200	6,751 ± 4,578
AUC_{∞} (ng·hr/mL)	2,459 ± 674	2,007 ± 2,270	6,372 ± 2,229	6,773 ± 5157
CL (L/hr)	23.2 ± 13.9	30.6 ± 14.5	19.7 ± 7.1	16.5 ± 9.6
V_{ss} (L)	11.0 ± 7.3	12.1 ± 6.0	9.06 ± 5.32	10.5 ± 4.8
$t_{½}$ (min)	23.6 ± 11.8	18.9 ± 15.5	22.0 ± 10.1	31.4 ± 22.9

Figure 2. Mean Plasma Concentrations of Taliglucerase alfa following 120-minute infusion at 30 and 60 units/kg on Week 38 (Semilog Plot)



During the infusion, the taliglucerase alfa serum concentrations rose rapidly for the first 50 minutes after administration. At the end of infusion, taliglucerase alfa serum concentrations fell rapidly with a median terminal half life of 18.9 to 31.4 minutes for both dose groups at Day 1 and Week 38. The median systemic clearance (CL) values were approximately 30 L/hr and 20 L/hr for 30 and 60 units/kg, respectively, on Week 38. The median volume of distribution at steady state (V_{ss}) ranged from 9.06 to 12.1 L for both dose groups.

Consistent with the short half life and the long dosing interval (every two weeks), no significant accumulation in serum taliglucerase alfa concentrations was observed with repeated doses of 30 or 60 units/kg. Taliglucerase alfa PK did not appear to change over time (Day 1 vs. Week 38).

The median Cmax and area under the concentration-time curve (AUC_{last} or AUC_{∞}) of taliglucerase alfa were approximately 3-fold higher in the subjects received 60 units/kg than in the subjects received 30 units/kg, which is greater than the expected 2-fold increase assuming dose proportionality. Thus, the PK of taliglucerase alfa appeared to be nonlinear with a greater than dose-proportional increase in exposure at the doses studied (the CL values were reduced by approximately 30% to 35%).

Reviewer's comment:
There were some documented protocols deviations (dose and infusion duration) in Study PB-06-001 and the impact of these deviations was evaluated by this reviewer.

The difference between the actual and nominal doses was less than 10 % except one subject with 13% difference in planned 30 units/kg dose on Day 1. Thus the deviation of dose is not expected to have significant impact on PK results.

For some patients who were included in the PK analysis, the length of infusion time were not the same as and the planned infusion time in the study protocol as shown in Table 6.

Table 7: Actual taliglucerase alfa dose administered and infusion time in in Gaucher patients (Study PB-06-001)

Dose Group (Units/kg)	Study Visit	Number of Patients (N)		Mean	SD	Median	Range
		Evaluable	No Deviation*				
				Dose (units/kg) Based on Evaluable N			
30	Day 1	10	9	31.1	1.3	30.8	29.9 - 34.0
	Week 38	14	14	30.9	1.1	31.3	28.9 - 32.9
60	Day 1	16	16	61.0	0.9	60.9	59.6 - 62.4
	Week 38	15	15	59.3	1.6	59.7	55.8 - 61.1
				Infusion Time (min) Based on Evaluable N			
30	Day 1	10	8	120	22	120	70 - 165
	Week 38	14	13	119	5	120	100 - 120
60	Day 1	16	10	114	20	120	75 - 140
	Week 38	15	12	114	17	120	60 - 120

* *Number of patients who received taliglucerase alfa with < 10% difference in dose or infusion time from that in the protocol*

There were 12 incidences that actual infusion time was deviated by more than 10% (i.e., 12 min) from the planned time in the protocol. The actual infusion time was as short as 60 minutes or as long as 165 min. Conceivably, these different infusion rates would result in different C_{max} values. In particular, for 60 units/kg group on Day 1, 6 out of 16 subjects deviated from the planned infusion time more than 10%. As a result, the comparison of C_{max} values should be interpreted with caution.

As mentioned above, the plasma concentrations of taliglucerase alfa were reported as ng/mL by the analytical laboratory while the doses administered to the patients were calculated on the basis of enzyme activity units/kg. Therefore, the dose in enzyme units was converted to dose in mg using a fixed conversion factor (b) (4) *The studied drug products came from four manufacture lots (#K-38743, K-39065, K-40306, PR2001 and PR-2002). The sponsor didn't provide the specific activity of the enzyme for each individual lot, thus the magnitude of the deviation from the fixed conversion factor can not be evaluated.*

2.2.5.2 How do the pharmacokinetics in healthy volunteers compare to those in patients?

As mentioned in Section 2.6, different bioanalytical assays were used in Study P-2005-01 with healthy subjects (ELISA) compared to Study PB-06-001 with patients (ECL). The sponsor did not present data for cross-method comparisons. Thus a direct comparison between healthy subjects and patients would not reliable and not conducted. Furthermore, the overall performance of ELISA assay in Study PB-2005-01 was not satisfactory; therefore, PK data in healthy subjects should be interpreted with caution.

2.2.5.3 What are the characteristics of drug absorption?

Not applicable to taliglucerase alfa as it is to be administered intravenously.

2.2.5.4 What are the characteristics of drug distribution?

As shown in Table 6, when determined in Gaucher patients (Study PB-06-001), The median volume of distribution at steady state (V_{ss}) ranged from 9.06 to 12.1 L for both dose groups. Taliglucerase alfa appears to be distributed to the body other than blood or taken up to the target tissues.

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

Not applicable to taliglucerase alfa, a therapeutic protein product.

2.2.5.6 What are the characteristics of drug metabolism?

Not applicable to taliglucerase alfa, a protein product that is known to be catabolized by proteolytic enzymes to amino acids.

2.2.5.7 What are the characteristics of drug excretion?

Not applicable to taliglucerase alfa, a large size protein (60,800 dalton) that is not expected to be excreted intact.

2.2.5.8 Based on pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

In subjects with Gaucher disease, the pharmacokinetics of taliglucerase alfa appears to be nonlinear with a greater than dose-proportional increase in AUC_{last} over the dose range of 30 to 60 units/kg, as shown in Table 6. When the dose was doubled, the AUC_{last} values were increased approximately 3-fold, and the CL values were reduced by approximately 30% to 35%. The observed nonlinear PK properties could be due to the saturation of the mannose receptors.

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

As shown in Table 6, following once every 2 week dosing in subjects with Gaucher disease, the AUC_{last} values on week 38 were comparable to that on day 1: AUC_{last} were slightly increased by 8% (30 units/kg dose) and 17% (60 units/kg dose) on week 38. The mean CL values were similar between Day 1 and Week 38 for both dose groups. Whereas the mean t½ values were similar between Day 1 and Week 38 at 30 units/kg dose, the value was greater on Week 38 (31.4 minutes) compared to Day 1 (22 minutes) for 60 units/kg dose.

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

Based on median AUC_{last} values shown in Table 6, the inter-subject variability was in the range of 33.8% to 72.0%. Due to the deviation on the infusion time (and different infusion rate) at 12 incidences, inter-subject variability of C_{max} is considered unreliable and thus not included here. The causes of the variability other than infusion time deviation were not evaluated.

2.2.6 What are the pharmacodynamic characteristics of the drug? *(Include PD parameters that are not addressed in 2.2.4 but important to understand the clinical pharmacology of the drug)*

Pharmacodynamics were not characterized in this application

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The applicant did not explore the impacts of intrinsic factors on taliglucerase alfa exposure-efficacy or -safety response relationships in this application.

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 Elderly

No dedicated geriatric study has been conducted for this application. No assessment was done because the pivotal study conducted in Gaucher patients (Study PB-06-001) included only one elderly (> 74 years old) patient.

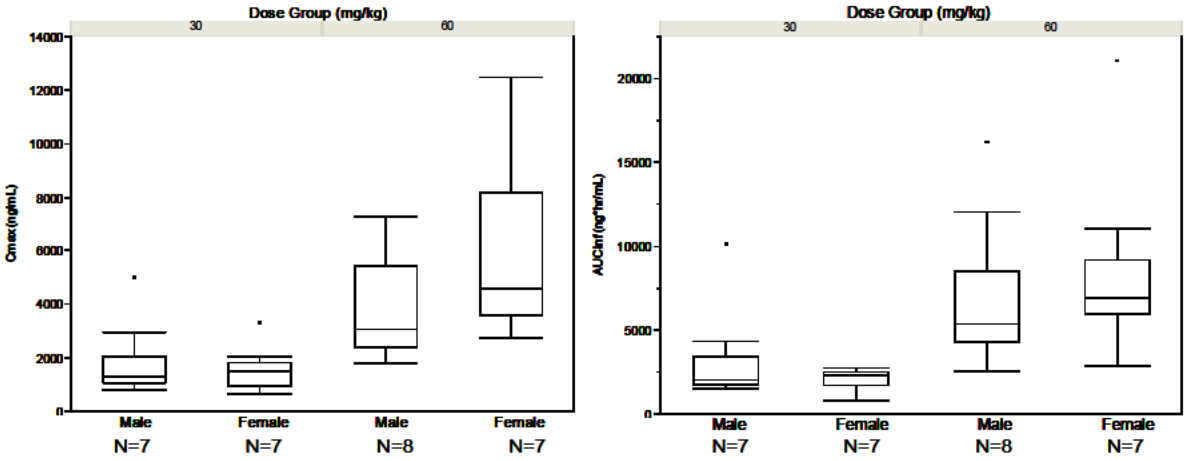
2.3.2.2 Pediatric Patients

No pediatric patients were enrolled in the pivotal clinical studies conducted for this application. According to the Pediatric Research Equity Act of 2007, products with orphan designation are exempt from the requirements of a pediatric study. Therefore, a pediatric assessment or requests for waiver or deferral are not included in this application. However, the applicant proposes to conduct a clinical trial of Gaucher disease patients aged 2 to 17 years old (Study PB-06-005).

2.3.2.3 Gender

No apparent gender differences were observed in exposure or PK parameters in healthy subjects (Study P-01-2005). However, the number of subjects (n = 3 in each gender) is not sufficient to draw a definitive conclusion whether there is gender difference in the pharmacokinetics of taliglucerase alfa or not. This reviewer conducted an analysis to explore the gender difference in Gaucher patients (Study PB-06-001). The observed C_{max} or AUC_{∞} values were generally similar between males and females (Figure 3). Thus, gender had no apparent impact on the PK of taliglucerase alfa based on 29 subjects.

Figure 3. PK Parameters C_{max} (left) and AUC_{∞} (right) Stratified by Gender at 30 and 60 units/kg Dose Levels



2.3.2.4 Race

No specific analysis was conducted to evaluate the effect of race on the clinical pharmacology of taliglucerase alfa in this application. In the pivotal Study PB-06-001, the study subjects consisted of 30 Caucasians and 1 African.

2.3.2.5 Renal impairment

No specific study was conducted to evaluate the effect of renal impairment on the clinical pharmacology of taliglucerase alfa in this application.

2.3.2.6 Hepatic impairment

No specific study was conducted to evaluate the effect of hepatic impairment on the clinical pharmacology of taliglucerase alfa in this submission.

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

Pregnancy Category B: According to the applicant's proposed labeling text, reproductive studies have been performed in rats and rabbits at doses up to 5 times the maximum human dose on a mg/m^2 basis and have revealed no evidence of impaired fertility or harm to the fetus due to taliglucerase alfa. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if the physician judges the potential benefit to justify the risk.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when taliglucerase alfa is administered to a nursing woman.

2.3.3 Immunogenicity (applicable only to therapeutic proteins)

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

In the pivotal Phase 3 study (PB-06-001), the incidence of anti-taliglucerase alfa IgG antibody was assessed in subjects naïve to enzyme replacement therapy at baseline and throughout the 9-month treatment period. Following administration of 30 or 60 units/kg taliglcerase alfa every two weeks to 32 subjects who were tested for immunogenicity, eighteen subjects (18/32, 56%) developed a positive anti-drug antibodies (ADA) based on ELISA assay. One additional subject (Patient 10-003) had positive ADA before the first infusion and discontinued from the study due to hypersensitivity reaction after receiving the first infusion. It was noted that the immunogenicity incidence rate increased with dose: 40% (6/15) at 30 units/kg dose and 75% (12/16) at 60 units/kg dose.

In the Phase 3 switchover study (PB-06-002) where subjects switched from imiglucerase to taliglucerase alfa therapy, six out of 28 patients were ADA positive. One subject (Patient 23-206) had positive ADA during the pre-switch screening and the remaining 5 subjects became ADA positive after the switch.

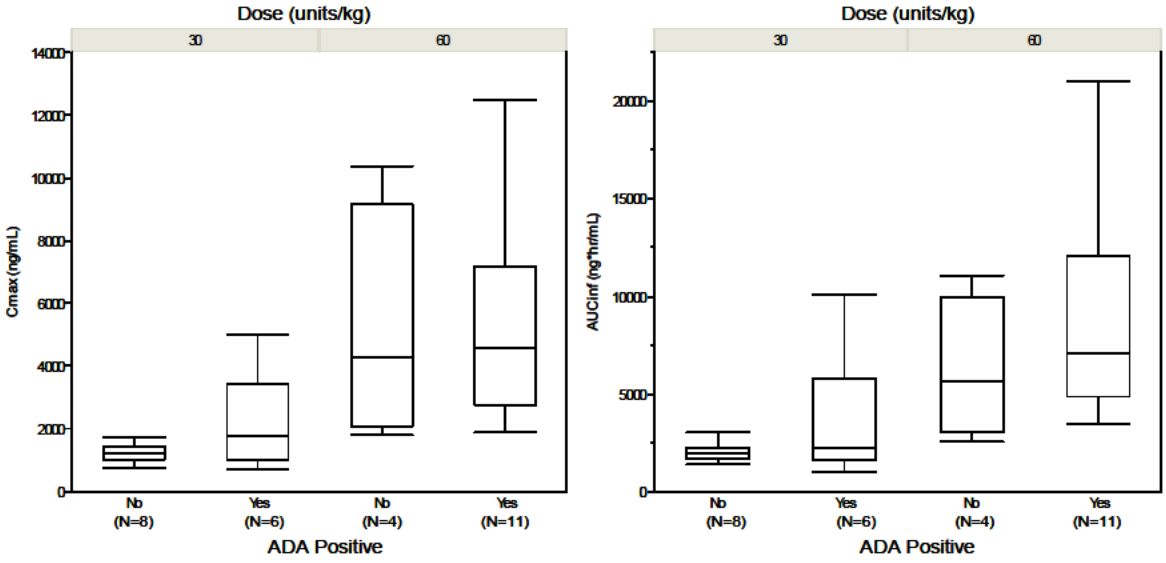
2.3.3.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

Impact on Pharmacokinetics

Overall, ADA appeared to have no significant impact on the PK of taliglucerase alfa based upon the comparisons between 17 subjects with positive ADA and 12 subjects with negative ADA at Month 9 in the pivotal study (PB-06-001). However, as Study PB-06-0001 did not have sufficient power to detect the PK difference due to a small sample size, this result should be interpreted with caution.

The boxplot in Figure 4 compared PK parameters (C_{max} and AUC_{∞}) on Week 38 for subjects with positive or negative ADA status after receiving 30 or 60 units/kg taliglucerase alfa every other week. The PK variability was generally greater in subjects with positive ADA status compared to subjects with negative ADA status, especially in the 30 units/kg dose group. The observed C_{max} or AUC_{∞} values for subjects with negative ADA status fell within the range for subjects with positive ADA status. The observed median C_{max} or AUC_{∞} values were generally similar for subjects with negative ADA status and subjects with positive ADA status; the median C_{max} values were slightly greater in subjects with positive ADA compared to that for subjects with negative ADA.

Figure 4 Boxplot Comparison of PK Parameters (C_{max} and AUC_{∞}) On Week 38 for Subjects with Positive (marked as 'Yes') or Negative (marked as 'No') ADA Status After Receiving 30 or 60 units/kg Taliglucerase alfa Every Other Week



Impact on Pharmacodynamics

The pharmacodynamics of taliglucerase alfa were not characterized in this application.

2.3.3.3 Do the anti-product antibodies have neutralizing activity?

As mentioned previously, the neutralizing antibody assays were not sensitive thus unacceptable. Please refer to CMC review by Dr. Faruk Sheikh for more details. The results from the sponsor's analysis using the inadequate assays are presented in this section to reflect the preliminary finding.

In the pivotal Phase 3 study (PB-06-001), two out of the 19 patients with positive binding ADA were positive for neutralizing antibodies based on enzymatic activity inhibition assay, but negative based on cell-based assay. In the Phase 3 switchover study (PB-06-002), one out of the 6 patients with positive binding ADA was positive for neutralizing antibodies based on enzymatic activity inhibition assay, but negative based on cell-based assay.

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

The impact of ADA on efficacy is uncertain. As shown in Table 8, at 60 units/kg the mean percentage changes in spleen and liver volume at Month 9 were 49.6% and 12.7%, respectively, for subjects with positive ADA status (n=11) while the corresponding values were 65.7% and 31.6%, respectively, for subjects with negative ADA status (n=4). There appeared to be a trend of greater spleen and liver volume reduction in the 4 subjects with negative ADA compared to 11 subjects with positive ADA. However, this trend was not observed at the lower dose level of 30 units/kg (6 subjects with positive ADA and 8 subjects with negative ADA). Taken together, the overall sample size is very small and the impact of ADA on efficacy is not conclusive.

Table 8 Summary of Percentage Change in Spleen and Liver Volume at Month 9 by Dose Group and Antibody Status in PB-06-001

		30 units/kg			60 units/kg		
		Antibody Positive			Antibody Positive		
Efficacy Endpoints		YES	NO	p value	YES	NO	p value
%Change in Spleen Volume from Baseline to Last Follow up	N	6	8	0.569	11	4	0.067
	MEAN	40.85	37.20		49.61	65.72	
	SD	10.96	11.97		14.80	9.66	
	CV	27%	32%		30%	15%	
	MEDIAN	41.14	34.81		55.90	67.90	
	MINIMUM	58.48	51.00		65.33	74.91	
	MAXIMUM	28.06	15.92		20.64	52.19	
%Change in Liver Volume from Baseline to Last Follow up	N	6	8	0.583	11	4	0.005
	MEAN	20.05	15.73		12.66	31.58	
	SD	3.98	18.22		10.23	7.37	
	CV	20%	116%		81%	23%	
	MEDIAN	18.91	17.17		15.00	29.62	
	MINIMUM	26.79	33.75		30.22	41.40	
	MAXIMUM	15.83	25.31		9.40	25.68	

P values are from one way ANOVA.

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.)?

Due to the small sample size as mentioned above, the sponsor concluded that it is difficult to establish the relationship between ADA and the safety of taliglucerase alfa such as hypersensitivity. Please refer to the clinical review by Dr. Carla Epps for more details.

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?

No specific analysis was conducted to evaluate the effect of the extrinsic factors on the clinical pharmacology of taliglucerase alfa.

2.4.2 Drug-drug interactions

No drug-drug interaction studies were conducted for this submission.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

Not available

2.5 General Biopharmaceutics

2.5.1 What is the pharmacokinetic and/or pharmacodynamic comparability of the proposed to-be-marketed formulation to the pivotal clinical trial? (Applicable to Biologics only)

Not applicable to this application. All studies were conducted using to-be-marketed formulation.

2.6 Analytical

This section should address issues related to the analytical and bioanalytical methods used to support the CPB studies. (For therapeutic protein products, see 2.6.5, 2.6.6 and 2.6.7 only. Others analytical questions are not applicable to therapeutic protein products.)

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

A validated electrochemiluminescent (ECL) assay was used in the pivotal Study P-06-001 to measure taliglucerase alfa in plasma for PK characterization. Additionally, an inadequate enzyme-linked immunosorbent assay (ELISA) was used to measure the drug for PK characterization in the Phase 1 Study P-01-2005.

ELISA assay (used in Study P-01-2005)
The bioanalytical assay method used to quantitate taliglucerase alfa in human plasma in Study P-01-2005 is based on an ELISA method using 96-well microtiter plates coated with chicken anti-plant recombinant-human glucocerebrosidase antibodies (Assay Report MBR06-102).
Pre-diluted controls and unknown samples were pipetted into the wells of the plate and incubated with shaking at room temperature, allowing any taliglucerase alfa present to bind to the anti-taliglucerase alfa antibodies. After two hours of incubation the plate was washed four times to remove any nonreactive plasma components. Rabbit anti-taliglucerase alfa antibodies were

added and the plates were incubated for 1.5 hours at room temperature to allow the rabbit anti-taliglucerase alfa to bind to taliglucerase alfa. The unbound protein and reagents were removed by another wash step and followed by the addition of an alkaline phosphatase-affinity purified goat anti-rabbit IgG conjugate. After a 60-minute incubation, the plate was washed again. In the final step, the phosphatase substrate was added to the wells to develop color as the phosphatase catalyzed the substrate. The color was allowed to develop at room temperature for 45 minutes or until the optical density (OD) of the highest standard was 1.0 or greater. The absorbance was measured at 405 nm using a plate spectrophotometer.

The calibration curves of the assay were constructed using purified recombinant taliglucerase alfa at the concentrations of 7.8, 15.6, 31.3, 62.5, 125 and 250 ng/mL diluted in a 4% human plasma matrix by fitting to a four-parameter curve equation. Calibration standards were assayed in duplicate for each sample run (plate). Because the calibration curves were constructed in duplicate, the within-run accuracy (% relative error to nominal concentrations, %RE) and precision (% coefficient of variation of back-calculated QC concentrations, %CV) could not be calculated. The performance of the assay based on the between-run accuracy and precision determined form 8 assay runs were in the range of 2% (at 250 ng/mL) to 26% (at 7.8 ng/mL) and 1.7% (250 ng/mL) to 9.4% (at 7.8 ng/mL), respectively. The lower limit of quantitation (LLOQ) after accounting for 1:25 dilution was 195 ng/mL or 6.83 mUnits/mL (b) (4)

Quality control (QC) samples were prepared at the concentration of 600 ng/mL (low control, LC) and 3000 ng/mL (high control, HC). The QC samples were assayed in duplicate and two sets of each control were assayed per sample run (plate). Because the QC samples were run in duplicate, the within-run accuracy and precision could not be calculated. The performance of the assay based on the accuracy and precision determined form 8 assay runs were in the range of -2.9 % to 33.7 % and 18.9% to 23.8%, respectively.

Reviewer's Comment:
The performance of the assay was determined using only two quality control concentrations (600 ng/mL and 3000 ng/mL for LC and HC, respectively). This reviewer reviewed and re-calculated the between-run accuracy and precision only using the values provided in the assay report MBR06-102. The performance of the assay based on the accuracy and precision determined form 8 assay runs were up to 33.7 % RE and 24.1% CV, respectively which are greater than those acceptance criteria recommended in the Guidance for Industry: Bioanalytical Method Validation
(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf).

Due to the poor quality of the assay used for PK assessment, the PK information from healthy subjects (study P-01-2005) was considered unreliable (b) (4)

ECL assay (used in Study P-06-001)
Briefly, this assay used 96-well microtiter plates coated with chicken affinity purified anti-taliglucerase alfa IgY that served as a capture antibody (Assay Report MBR08-245). Standards and quality controls containing taliglucerase alfa and unknown plasma samples were added to the wells of the microtiter plate and incubated at room temperature for 2 hours with shaking,

which allowed any taliglucerase alfa present to bind to the capture antibody. The plate was then washed to remove any non-reactive plasma components. Sulfo-tagged chicken anti- taliglucerase alfa IgY was added to bind to the captured taliglucerase alfa for detection during a one hour incubation at room temperature with gentle shaking. The plate was washed to remove any residual reagent. An ECL read buffer was then added to the wells of the plate. The plate was read using a Meso Scale Discovery (MSD) Sector PR™ 100 reader. The sulfo-tagged label on the bound antibody emitted light upon electrochemical stimulation from the electrode surface on the plate. The intensity of the light emitted was proportional to the taliglucerase alfa concentration in the sample. The taliglucerase alfa levels were quantified according to the standard curve utilizing a four-parameter curve fit equation. A summary of the in-process validation results is presented in Table 9 below.

Table 9 Summary of In-Process Validation for Study Sample Analysis (Study P-06-001)

Validation Parameter	**Validation Result**
Precision	
Intra-Assay Precision	(b) (4)
Inter-Assay Precision VLC (10 ng/mL)	
Inter-Assay Precision LC (30 ng/mL)	
Inter-Assay Precision MC (120 ng/mL)	
Inter-Assay Precision HC (750 ng/mL)	
Inter-Assay Precision DC (50,000 ng/mL)	
Accuracy	
Intra-Assay Accuracy	
Inter-Assay Accuracy VLC (10 ng/mL)	
Inter-Assay Accuracy LC (30 ng/mL)	
Inter-Assay Accuracy MC (120 ng/mL)	
Inter-Assay Accuracy HC (750 ng/mL)	
Inter-Assay Accuracy DC (50,000 ng/mL)	
Standard Curve	
Standard Curve Range (ng/mL)	
Assay Sensitivity/Lower limit of Quantification (LLOQ) (7.8 ng/mL)	
Upper limit of Quantification; ULOQ (1,000 ng/mL)	
Standard Curve Analysis Precision	
Standard Curve Analysis Accuracy	
Selectivity	
Selectivity (6 individual human plasma samples unspiked)	

Repeat Run 1: Selectivity [redacted] (b) (4)	[redacted] (b) (4) individuals had CV ≤ 30% and within ± 30% RE [1]
Repeat Run 2: Selectivity [redacted] (b) (4)	[redacted] (b) (4) individuals had CV ≤ 30% and within ± 30% RE [1]
[1] Initial selectivity run did not meet acceptance criteria and these additional runs were performed as explained in Protocol Amendment 1. VLC: Very Low Control LC: Low Control MC: Mid Control HC: High Control DC: Dilution Control	

Overall, the ECL assay used in Study P-06-001 was validated and acceptable, thus the PK information collected from this study will be used in the label.

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.

Four bioanalytical methods were used to assess the formation of ADA and neutralizing antibody. The methods were briefly summarized below. For more information, please refer to CMC review by Dr. Faruk Sheikh.

(1) Anti-taliglucerase alfa antibody ELISA assay:
The sponsor used an ELISA assay with bridging format to assess for anti-drug antibodies using microtiter plates with either prGCD or human IgG coated wells.

Two positive controls were used in the assay, *rabbit anti-prGCD antibody* (PC-1) and *human IgG* (PC-2). Briefly, PC-1 and unknown serum samples were added in to the prGCD coated wells of the micro-plate, while assay diluent (PBS containing 1.0% BSA) was added to the human IgG coated wells (for PC-2). The plate was incubated at room temperature with gentle shaking for 2 hours and then washed to remove non-reactive serum components.

A goat anti-rabbit IgG peroxidase conjugate and an anti-human IgG peroxidase conjugate was added to the corresponding wells and incubated at RT for 1 hour. After incubation the plate wells were washed and the substrate, a solution of ABTS [2,2'-azino-di (3-ethyl-benzthiazoline-6-sulphonate)] was added to produce color and the absorbance was measured at 405 nm using a plate spectrophotometer.

According to Dr. Faruk Sheikh's review, this assay is validated and acceptable. A summary of the validation results is presented in Table 10 below.

Table 10 Summary of anti-taliglucerase alfa Antibody Assay Validation Results

Validation Parameter		Validation Result
Intra-Assay Precision	PC-1	(b) (4)
	PC-2	
Inter-Assay Precision	PC-1	
	PC-2	
Freeze-Thaw Stability (12 cycles) Precision	PC-1	
Freeze-Thaw Stability (12 cycles) Mean $OD_{405\ nm}$	PC-1	
Short-Term Stability (21.5 hours at 5 ± 3 °C) Precision	PC-1	
Short-Term Stability (21.5 hours at 5 ± 3 °C) Mean $OD_{405\ nm}$	PC-1	
Short-Term Stability (4 hours on wet ice) Precision	PC-1	
Short-Term Stability (4 hours on wet ice) Mean $OD_{405\ nm}$	PC-1	
Immunodepletion	(PC-1)	
	Pooled Human Serum (PHS)	
Titer Determination (30-fold through 65,610-fold dilution including MRD): Precision PC-1		
Assay Cutpoint: Delta		
Assay Sensitivity PC-1		
Assay Sensitivity PC-2		
Drug Tolerance PC-1		
MRD: Minimum Required Dilution		

(2) Confirmatory Immunodepletion Assay:
Confirmatory immunodepletion testing was assessed by adding 10 μg/mL of prGCD to 100 individual normal human serum samples. Each sample was analyzed in duplicate wells on a single occasion. The log ratio of the response with and without prGCD was calculated for each individual and used to calculate the confirmatory cutpoint.

The outliers were excluded from the statistical analysis of cutpoint. The remaining values were used to calculate a confirmatory cutpoint of 40.33%.

(3) Neutralizing antibody Assay for detecting enzymatic activity inhibition *in vitro*:
This assay measures the change in taliglucerase alfa enzymatic activity by the presence of neutralizing antibodies in patient's serum. In this assay, pre-diluted human serum samples (1:40, MRD) and taliglucerase alfa (TGA) solution (1500 ng/mL) was pipetted into the wells of microtiter plates. The plate was then incubated for 30 min at 37^{o}C with gentle shaking. After incubation, the substrate p-nitrophenyl β-D-glucopyranoside was added to the wells and incubated for one hour at 37°C. Following incubation, stop solution (0.3 M glycine/0.2 M sodium carbonate, pH 10.7) was added. The final absorbance was measured at 405nm using a plate reader spectrophotometer.

The Controls were Normal Serum Pool (NSP) spiked with TGA and the neutralizing quality control (QC) of NSP spiked with affinity purified anti-TGA antibodies (Rb1-Nab). In addition the assay background level was measured by a blank sample that contains NSP without TGA.

A summary of the validation results provided by the sponsor is presented in Table 11 below. However, the assay had unacceptable sensitivity of 400 μg/mL (please refer to CMC review by Dr. Faruk Sheikh). The sponsor proposed to use the PK/PD model to justify the assay sensitivity. However, according to the Pharmacometrics review by Dr. Kevin Krudys, the results of the Sponsor's PK/PD model do not support an assay sensitivity of 400 μg/mL for detecting enzyme activity inhibition. Thus, the sponsor should further develop an assay with greater sensitivity (as outlined in the PMC) to assure the safety of taliglucerase alfa.

Table 11 Summary of Neutralizing anti-taliglucerase alfa Antibody Assay Validation Results

Validation Parameter		Validation Result
Specificity - Three different lots of NSP[a]	NSP[a]	(b) (4)
Intra-Assay Precision	Rb1-Nab[b]	
	NSP	
Inter-Assay Precision	Rb1-NAb	
	NSP	
Freeze-Thaw Stability (6 cycles) Precision	Rb1-NAb	
	NSP	
Freeze-Thaw Stability (6 cycles) Mean $OD_{405\ nm}$	Rb1-NAb	
	NSP	
Short-Term Stability (5 hours on wet ice) Precision	Rb1-NAb	
	NSP	
Short-Term Stability (5 hours on wet ice) Mean $OD_{405\ nm}$	Rb1-NAb	
	NSP	
Short-Term Stability (Over night at 5 ± 3°C) Precision	Rb1-NAb	
	NSP	
Short-Term Stability (Over night at 5 ± 3°C) Mean $OD_{405\ nm}$	Rb1-NAb	
	NSP	

Validation Assay Cutpoint:	(b) (4)
Assay Normalization Factor (Delta):	
Assay Sensitivity Rb1-NAb	

NSP[a]: negative control
Rb1-Nab[b] : positive control, consist of affinity purified rabbit anti-drug antibodies

(4) Cell-based neutralizing antibody Assay:

Rat alveolar macrophage cell line NR8383 was used for detecting uptake inhibition by anti-TGA (anti-taliglucerase alfa) antibodies in human serum samples which were confirmed positive for the presence of anti-TGA antibodies previously. Briefly, the neutralizing antibody (NAb) assay was based on the formation of taliglucerase alfa antibody complex (Ab-TGA complex) during a pre-incubation period, followed by applying this mixture to the macrophage cell line allowing the Ab-TGA complex to be internalized by the cells.

Two steps were used to measure TGA uptake. (1) An enzymatic activity method using p-nitrophenyl-ß-glucopyranoside as a substrate for determining the enzymatic activity of internalized TGA to the cell following the uptake step. (2) An ELISA method for determining the total amount of TGA protein taken up by the cells.

A summary of the validation results provided by the sponsor is presented in Table 12 below. As mentioned for the enzymatic activity inhibition assay, the assay had unacceptable sensitivity of

(b) (4) (please refer to CMC review by Dr. Faruk Sheikh). Similarly, the sponsor should further develop an assay with greater sensitivity as outlined in the PMC.

Table 12 Summary of Cell-Based Neutralizing anti-taliglucerase alfa Antibody Assay Validation Results

Validation Parameter		Validation Result (b) (4)
Intra- Assay Precision	Drug	
	Rb2[a]	
	Rb1-NAb[b]	
	Mannan[c]	
Inter- Assay Precision	Drug	
	Rb2[a]	
	Rb1-NAb[b]	
	Mannan[c]	
Specificity	Rb2[a]	
	Rb2[a]	
	Rb1-NAb[b]	
	Mannan[c]	
	2 Placebo lots	
	2 NSP[d] lots	
Primary Cutpoint-Ratio : multiplicative correction factor		
Secondary Cutpoint - Activity		
Assay Sensitivity (based on Rb1-NAb and Primary Assay Cutpoint)		

Rb2[a]: negative control: Anti- glucocerebrosidase antibody that does not have a neutralizing activity
Rb1-NAb[b]: positive control: Anti-glucocerebrosidase antibody with neutralizing enzymatic activity
Mannan[c]: positive control, non antibody: Mannose receptor uptake neutralizing control (reduced TGA activity and concentration)
NSP[d]: negative control: Normal uptake levels

2.6.7 Is the proposed neutralizing antibody assay sensitivity for taliglucerase alfa supported by the argument proposed in the Sponsor's PK/PD report?

No, the results of the Sponsor's argument in the PK/PD report do not support an assay sensitivity of (b) (4) for detecting enzyme activity inhibition or 283 µg/mL for the cell-based assay. There are reasonable arguments to doubt the basis for many of the assumptions on which the Sponsor's calculations relied.

The assumptions are listed below:

- Average concentration over 24 hours is an appropriate marker of C_{ave}.
- A 50% reduction in exposure represents a clinically relevant loss of efficacy.
- One to one binding of neutralizing antibody to taliglucerase alfa.
- Value of K_D.

Furthermore, even if one were to accept these assumptions, the results of the Sponsor's analysis suggest that the assay sensitivity should be less than 310 µg/mL. This analysis does not support the Sponsor's in vitro enzyme activity inhibition assay which has a sensitivity of (b) (4). Likewise, the cell-based assay sensitivity of 283 µg/mL would not be supported for K_D values less than 2000 nM. For further information, please refer to the Pharmacometrics Review (Appendix 3.2).

2.6.8 What bioanalytical methods were used to assess the pharmacodynamic effect of the therapeutic protein?

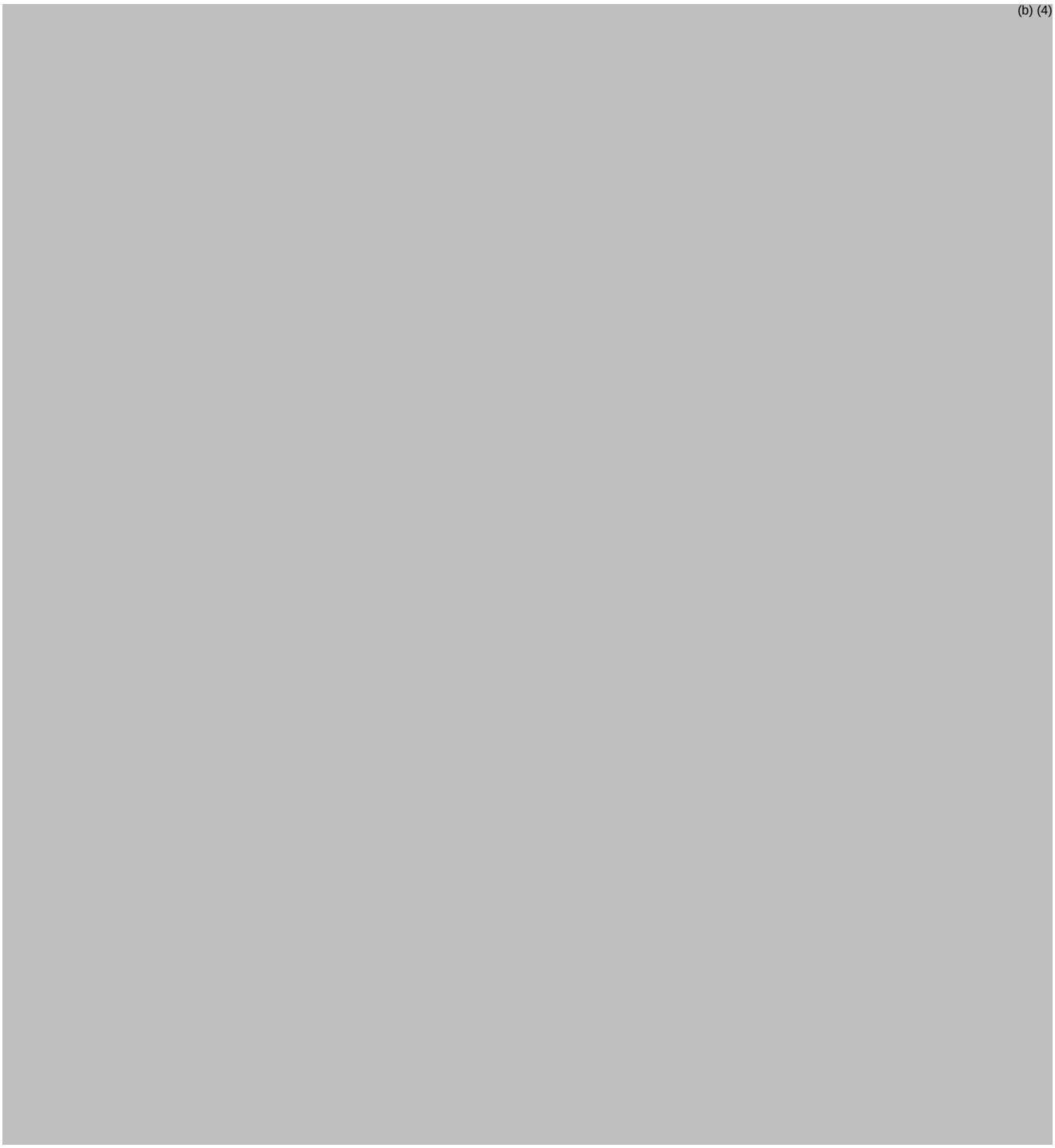
Not applicable. No pharmacodynamic (PD) markers were characterized in this submission.

3 APPENDIX

3.1 Detailed Labeling Recommendations

Product Label

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.



3.2 **Pharmacometric Review**

SUMMARY OF FINDINGS

Key Review Questions

The purpose of this review is to address the following key question.

Is the proposed neutralizing antibody assay sensitivity for taliglucerase alfa supported by the argument proposed in the Sponsor's PK/PD report?

No, the results of the Sponsor's argument in the PK/PD report do not support an assay sensitivity of (b) (4) for detecting enzyme activity inhibition or 283 µg/mL for the cell-based assay. There are reasonable arguments to doubt the basis for many of the assumptions on which the Sponsor's calculations relied.

The assumptions are listed below:

1. (b) (4)
2. (b) (4)

3. [redacted]

4. [redacted]

Furthermore, even if one were to accept these assumptions, the results of the Sponsor's analysis suggest that the assay sensitivity should be less than [redacted]. This analysis does not support the the Sponsor's in vitro enzyme activity inhibition assay which has a sensitivity of [redacted]. Likewise, the cell-based assay sensitivity of [redacted] would not be supported for K_D values less than [redacted]

Recommendations

The Sponsor should further develop the neutralizing antibody assays to achieve greater sensitivity and to use the new and more sensitive assays for monitoring antibody responses and assessing the impact on long-term efficacy and safety in post-marketing studies.

PERTINENT REGULATORY BACKGROUND

An original New Drug Application was submitted for taliglucerase alfa (NDA 22-458) on 4/26/2010 and a Complete Response was issued on 2/24/2011. One of the clinical pharmacology issues identified in the Complete Response was that the immunological potential of taliglucerase alfa and its impact of pharmacokinetic and pharmacodynamic parameters could not be adequately evaluated. The sponsor resubmitted the NDA on 8/1/2011. On 11/15/2011, the Sponsor submitted a PK/PD analysis report to support the adequacy of the sensitivity of two neutralizing antibody assays; one enzymatic activity inhibition assay and one cell-based assay.

RESULTS OF SPONSOR' S ANALYSIS

PK/PD Model

The sponsor developed a PK/PD model to explore potential relationship between taliglucerase alfa concentrations and selected efficacy endpoints. Pharmacokinetic data were obtained in Study PB-06-001 from 31 treatment naïve patients with Gaucher disease receiving taliglucerase alfa 30 units/kg or 60 units/kg via intravenous infusion over 1-2 hours every other week for 9 months. Samples for measurement of taliglucerase alfa concentration were obtained over 3 hours following the first and final infusions. Pharmacodynamic data were obtained in Study PB-06-003, which was the extension study for Study PB-06-001. PK/PD models were developed to describe the relationship between taliglucerase alfa exposure (AUC or dose) and pharmacodynamic endpoints (spleen volume and platelet count).

Reviewer's Comment: The PK/PD modeling performed by the sponsor was not relevant to answer questions regarding neutralizing antibody assay sensitivity and was therefore not reviewed or discussed in further detail.

Neutralizing Antibody Assay Sensitivity

The sponsor presented a set of mathematical functions based on pharmacological principles to illustrate the sensitivity of nAb influence on the exposure of taliglucerase alfa.

To determine the effect of neutralizing antibodies (nAbs), it was assumed that formation of nAbs would decrease the exposure of taliglucerase alfa and therefore reduce efficacy. A dose of 60 units/kg was chosen as a starting point because this is the highest dose studied and the highest dose being sought for approval. Exposure was defined as the average concentration over a 24 hour period (C_{ave}). A clinically relevant effect of nAb was defined as a reduction of the free taliglucerase alfa C_{ave} by half. The concentration of total nAbs that are required to cause this effect provides a measure of assay sensitivity. This reasoning can be understood by the following equations:

A detailed description of the mathematical model is provided below.

For a dose of 60 U/kg:

$C_{ave} = 4.04$ nM [Equation 1]

Total concentration of taliglucerase alfa is the sum of free and bound:

$C_{ave,tot} = C_{ave,bound} + C_{ave,free}$ [Equation 2]

If there are enough nAbs to reduce exposure of free taliglucerase by 50%:

$C_{ave,bound} = C_{ave,free} = 2.02$ nM [Equation 3]

If one nAb binds to one taliglucerase alfa:

$nAb_{bound} = C_{ave,bound} = 2.02$ nM [Equation 4]

Based on stoichiometry:

$nAb_{free} + C_{ave,free} <----^{KD}----> nAb_{bound}$

$$K_D = \frac{nAb_{free} \cdot C_{ave,free}}{nAb_{bound}} = \frac{nAb_{free} \cdot 2.02nM}{2.02nM} = nAb_{free}$$ [Equation 5]

And therefore, total nAb is equal to the bound and free components:

$nAb_{tot} = 2.02$ nM + K_D

The Sponsor concludes that the total neutralizing antibody concentration (nAb_{tot}) provides a measure of the sensitivity of the assay to detect neutralizing antibodies. Because the actual values of disassociation constant (K_D) for taliglucerase alfa and its nAbs are unknown, the assay sensitivity for a range of K_D values was calculated (Table 1). The Sponsor included Table 1 in this report but did not otherwise provide justification for or discussion of the sensitivity of their current assay. In separate immunogenicity reports an assay sensitivity of (b) (4) was reported for the enzymatic activity inhibition assay and a sensitivity of (b) (4) was reported for the cell-based assay.

Table 1: Required sensitivity of an assay to detect neutralizing antibodies for different values of dissociation constant (K_D)

K_D	sensitivity	
(nM)	(nM)	(µg/ml)[a]
10	12.02	1.86
20	22.02	3.41
40	42.02	6.51
50	52.02	8.06
80	82.02	12.71
200	202.02	31.31
250	252.02	39.06
400	402.02	62.31
800	802.02	124.31
1250	1252.02	194.06
2000	2002.02	310.31

[a]Mw antibody assumed to be 155 kDA

Reference: Sponsor's PK-PD Report, Table 4.3:2
Reviewer's Comment: Even if all the assumptions were to be accepted, the results in Table 1 do not appear to support the Sponsor's neutralizing antibody assay sensitivity for detecting enzymatic activity of (b) (4) *. For K_D values between* (b) (4) *, the required sensitivity values are all* (b) (4) *. Likewise, the cell-based assay sensitivity of* (b) (4) *would not be supported for K_D values less than* (b) (4)

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
03/30/2012

YOW-MING C WANG
03/31/2012

HAE YOUNG AHN
04/02/2012

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	**22-458**
Submission Dates	**Stamp (4/26/10), Amendment 0002 (12/8/09), Amendment 0003 (12/16/09)**
PDUFA Due Date	**2/26/10**
Brand Name	**To be determined**
Generic Name	**Taliglucerase alfa**
Primary Reviewer	**Jang-Ik Lee, Pharm.D., Ph.D.**
Team Leader (Acting)	**Gilbert J. Burckart, Pharm.D.**
OCP Division	**DCP 3**
OND Division	**DGIP**
Sponsor	(b) (4)
Relevant IND(s)	**69,703**
Submission Type	**NME NDA**
Formulation; Strength(s)	**Lyophilized solid for intravenous infusion; 2000 U/vial**
Proposed indication	**Treatment of Gaucher disease**
Proposed Dosage and Administration	(b) (4) **60 U/kg every 2 weeks**

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

Taliglucerase alfa (formerly prGCD) is a recombinant β-glucocerebrosidase (β-D-glucosyl-N-acylsphingosine glucohydrolase), which is expressed in transformed carrot plant root cells. β-Glucocerebrosidase is a lysosomal glycoprotein enzyme that catalyzes the hydrolysis of the glycolipid glucocerebroside to glucose and ceramide. Taliglucerase alfa is proposed for a long-term enzyme replacement therapy (ERT) for patients with Gaucher disease. Currently, other β-glucocerebrosidases including Cerezyme® (imiglucerase) and Vpriv® (velaglucerase alfa) are in the market for the same indication. This original submission includes a Phase 1 pharmacokinetic (PK) study report P-01-2005 conducted in healthy subjects and a Phase 3 PK study report PB-06-001 conducted in Gaucher patients.

Since the multiple and uncorrectable manufacturing and inspection issues within the current review cycle that would result in the complete response action (see the reviews and reports logged in DARRTS by the Offices of Compliance and Biotechnology Products), the clinical pharmacology review of this application was suspended as of January 10, 2011. According to the reviewing biologist, Dr. Richard Ledwidge' midcycle presentation held on November 16, 2010, the master and working cell banks for the production of taliglucerase alfa contain (b) (4) The impact of immunogenicity on the pharmacokinetics (PK), efficacy and safety of taliglucerase alfa remain to be reviewed based on the Applicant's responses to the reviewer's information requests conveyed to the Applicant before the suspension of this review.

1.1 Recommendation

Since the clinical pharmacology review of this application was suspended due to the expected complete response action, the reviewer has no conclusive recommendation. In case that the Applicant resubmits the application, the impact of immunogenicity on the pharmacokinetics (PK) and efficacy of taliglucerase alfa needs to be reviewed in depth. In order to address those issues, the reviewer conveyed information requests to the Applicant on November 23 and December 21, 2010 through the Clinical Division. In the event that the genomic instability of master and/or working cell banks have affected the distribution of structural variants of taliglucersase alfa significantly, the PK study may need to be repeated in the proposed patient population using the new to-be-marketed product after the genomic mutation issue is resolved.

1.2 Phase 4 Requirements

Not applicable since this application is not to be approved in this review cycle.

1.3 Summary of Clinical Pharmacology Findings

Pharmacokinetics

The PK parameter values of taligucerase alfa were determined in patients with Gaucher disease in Study PB-06-001 on Day 1 and Week 38 (Month 9) of biweekly administration of taliglucerase alfa 30 units/kg or 60 units/kg using a non-compartmental method. The PK

parameter values are summarized in Table 1. [redacted] (b) (4) [redacted] (see Section 2.6 Analytical).

Table 1: Pharmacokinetic parameters (mean ± standard deviation) of taliglucerase alfa determined in Gaucher patients (Study PB-06-001)

Dose Group (Units/kg)	30		60	
Study Visit	Day 1	Week 38	Day 1	Week 38
Number of Patients	10	14	16	15
AUC_{last} (ng·hr/mL)	2,229 ± 669	2,654 ± 2,130	6,349 ± 2,200	7,665 ± 4,578
AUC_{∞} (ng·hr/mL)	2,244 ± 674	2,706 ± 2,270	6,383 ± 2,229	8,095 ± 5,087
Extrapolation (%)	0.64 ± 0.40	0.90 ± 1.43	0.46 ± 0.39	3.25 ± 5.28
AUC_{last}/Dose (ng·hr/mL)/mg	39.1 ± 13.2	42.2 ± 30.4	54.3 ± 18.9	63.4 ± 33.9
CL (L/hr)	29.4 ± 13.9	30.7 ± 14.5	20.5 ± 7.1	19.9 ± 9.6
Vz (L)	17.5 ± 11.1	16.8 ± 12.7	11.7 ± 4.5	14.4 ± 6.6
t½ (min)	25.9 ± 11.8	25.1 ± 15.5	25.0 ± 10.1	36.3 ± 22.8

The PK parameter values listed in Table 1 include mean ± standard deviation (SD) values determined from all pharmacokinetically evaluable patients. However, the values appear to be different between anti-product antibody (APA) positive and negative patients. Such level of analyses has not been done in depth since taliglucerase alfa is not expected to be approved in the current review cycle.

Comparing the mean dose normalized AUC_{last} and CL values at the administration of 30 units/kg and 60 units /kg in Guacher, the PK of taliglucerase alfa does not appears to be dose-proportional at the doses studied. Although the dose was doubled, the AUC values were increased by 178% and 200%, and the CL values were reduced by approximately 30% and 35% on Day 1 and Week 38, respectively.

Exposure-Response Relationship

In Study PB-06-001, both taliglucerase alfa dose groups demonstrated a highly significant reduction in spleen volume used as a primary clinical endpoint from screening to Month 6 treatment visit (30 units/kg, 22.2%; 60 units/kg, 29.9%; $p< 0.0001$) and Month 9 visit (30 units/kg, 26.9%; 60 units/kg, 38.0%; $p < 0.0001$). However, There was no statistically significant difference observed in mean spleen volume values between the two dose groups ($p = 0.060$).

A significant reduction in liver volume as a co-primary clinical endpoint was observed in both dose groups from screening to Month 6 (30 units/kg, 7.56%, $p = 0.0020$); 60 units/kg, 7.51%, $p = 0.0022$) and Month 9 (30 units/kg, 10.48%, $p = 0.0041$; 60 units/kg, 11.11%, $p < 0.0001$). Similarly to the reduction in spleen volume, there was no significant difference observed in mean liver volume values between the two dose groups ($p=0.349$).

Thus, there appears to be no taliglucerase alfa exposure-response relationship in the primary clinical efficacy endpoints at the doses studied.

Immunogenicity

The incidence of the formation of APAs has not been adequately determined. According Dr. Faruk Sheik's micycle presentation on immunogenicity assays held on November 16, 2010, since the Applicant set the cut-point in the confirmatory immunogenicity assay unreasonable high, the incidence of immunogenicity was underestimated. Therefore, the impact of immunogenicity on the PK, efficacy and safety of taliglucerase alfa has not been adequately determined.

Whether the APAs have neutralizing activity or not is not conclusive. According Dr. Faruk Sheik's micycle presentation, although the Applicant developed a neutralizing antibody assay to assess for antibodies that interfere with enzymatic activity, the Applicant does not have an assay to assess for antibodies that neutralize drug uptake into the target cells.

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?

Taliglucerase alfa is a recombinant β-glucocerebrosidase (β-D-glucosyl-N-acylsphingosine glucohydrolase), which is expressed in transformed carrot plant root cells. β-Glucocerebrosidase is a lysosomal glycoprotein enzyme that catalyzes the hydrolysis of the glycolipid glucocerebroside to glucose and ceramide. Purified taliglucerase alfa is a monomeric glycoprotein comprised of (b) (4), containing 4 N-linked glycosylation sites (molecular weight, 60,800 daltons). Taliglucerase alfa differs from native human glucocerebrosidase by 2 amino acids at the N-terminal and 7 amino acids at the C-terminal. Taliglucerase alfa is a glycosylated protein with oligosaccharide chains at the glycosylation sites having terminal mannose sugars. These mannose-terminated oligosaccharide chains of taliglucerase alfa are recognized by endocytic carbohydrate receptors on macrophages, the cells that accumulate lipid in Gaucher disease.

Taliglucerase alfa is supplied as a sterile, non-pyrogenic, lyophilized product. The quantitative composition of the lyophilized drug include aliglucerase alfa 212 units, D-mannitol 206.7 mg, polysorbate 80 0.56 mg, sodium citrate 30.4 mg. After reconstitution with Sterile Water for Injection, USP, the taliglucerase alfa concentration is 40 U/mL. Reconstituted solutions have an approximate pH of 6.0.

The enzyme unit (U) is defined as the amount of enzyme that catalyzes the hydrolysis of 1 micromole of the synthetic substrate para-nitrophenyl-β-Dglucopyranoside (pNP-Glc) per minute at 37°C. (b) (4)
(see Section 2.6 Analytical).

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Gaucher disease is characterized by a deficiency of β-glucocerebrosidase activity, resulting in accumulation of glucocerebroside in tissue macrophages which become engorged and are typically found in the liver, spleen, and bone marrow and occasionally in lung, kidney, and intestine. Secondary hematologic sequelae include severe anemia and thrombocytopenia in addition to the characteristic progressive hepatosplenomegaly, skeletal complications, including osteonecrosis and osteopenia with secondary pathological fractures. Therefore, the symptoms in Gaucher disease include splenomegaly, hepatomegaly, anemia, thrombocytopenia and bone disease with pain.

Taligucerase alfa catalyzes the hydrolysis of glucocerebroside to glucose and ceramide, and indicated for the treatment of Gaucher disease. Taliglucerase alfa exhibits an interaction with the Man/GlcNAc receptor present on specialized macrophages called Gaucher cells. In clinical trials, taligucerase alfa reduced spleen and liver size, and improved anemia and thrombocytopenia.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

Taliglucerase alfa is administered by intravenous infusion over 1 - 2 hours. Dosage should be individualized to each patient. Initial dosages (b) (4) 60 units/kg of body weight once every 2 weeks. Dosage adjustments should be made on an individual basis and may increase or decrease, based on achievement of therapeutic goals as assessed by routine comprehensive evaluations of the patient's clinical manifestations.

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?

Study P-01-2005 was a Phase 1 PK and safety study conducted in 6 healthy Caucasian subjects (3 males and 3 females aged between 10 and 35 years old; mean ± SD body weight, 72.5 ± 7.7 kg). Subjects were to receive a single IV dose of vehicle at the baseline visit, followed by three escalating doses of taligucerase alfa on Day 8 (15 units/kg), Day 15 (30 units/kg) and Day 22 (60 units/kg) as a single IV infusion (135 mL) over 90 minutes (1.5 mL/min). The infusion rate could be adjusted according to subject's signs and symptoms: 1mL/min upon occurrence of an adverse effect or 2 mL/min upon lack of any signs and symptoms of adverse events. Blood samples for PK analyses were designed to be collected prior to dosing (0) and at 5, 45, 80, and 90 minutes during the infusion of taligucerase alfa and 100, 115, 130, 150, 180, 210 minutes and 24 hours post initiation of infusion. The procedures for blood samples taken were the same for all three IV infusion visits. ECG was performed at baseline prior to infusion and 8 hours following infusion.

Study PB-06-001 was a multi-center, randomized, double-blind, parallel group, dose-ranging trial to assess the safety and efficacy of taliglucerase alfa in 31 untreated patients with Gaucher disease (n = 15 in 30 units/kg and 16 in 60 units/kg). The patients consists of 15 males and 16 females, and 30 Caucasians and 1 black South African with mean age of 36.1 years old (range 19

to 74) and mean weight of 68.0 kg (range, 50 kg to 93 kg). Study patients received IV infusion of taliglucerase alfa every two weeks. There were two treatment groups, with 15 patients expected to be enrolled in each treatment group: Treatment Group I, 30 units/kg; Treatment Group II: 60 units/kg. Patients had PK data collected over 3 hours following the first and final (Month 9) infusions of taliglucerase alfa. Anti-taliglucerase alfa antibody status was determined at baseline and every other week until Month 9. Blood samples for PK analysis were designed to be collected at 0, 45, 70, 110, 125, 135, 150, 175, 200, and 225 minutes after start of the first (Day 1) and last (Month 9, Week 38) infusions.

Reviewer's Comment: Although the time length of taliglucerase alfa infusion was 90 minutes, the PK sample was not collected at or around 90 minutes post infusion. Thus, the Cmax has not been measured in Study P-01-2005.

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?

The primary efficacy endpoint was measurement of organ (spleen and liver) volumes by magnetic resonance imaging (MRI) since Gaucher disease results in accumulation of glucocerebroside in tissue macrophages which are typically found in the liver and spleen. All MRI volumetric analyses were made by central radiographic experts. The readers were radiological experts and the reading was done under the guidance and responsibility of the director of the reading center. The MRIs obtained at Screening, Month 6 and Month 9 were read independently by two central MRI readers in a blinded, randomized manner (i.e., the identity of the patient, treatment group, image sequence, patient clinical history and treatment response were masked to the reader). The major secondary efficacy endpoints were the change from baseline of hemoglobin and platelet counts because Gaucher disease results in accumulation of glucocerebroside in tissue macrophages in the bone marrow.

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

See Section **2.6 Analytical**.

2.2.4 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Spleen Volume (Primary Clinical Endpoint)

As shown in Table 2, both taliglucerase alfa dosage groups (ITT Population) demonstrated a highly significant reduction in spleen volume used as a primary clinical endpoint from screening to Month 6 treatment visit (30 units/kg, 22.2%; 60 units/kg, 29.9%; $p < 0.0001$) and Month 9 visit (30 units/kg, 26.9%; 60 units/kg, 38.0%; $p < 0.0001$). However, There was no statistically

significant difference observed in mean spleen volume between the two dose groups at Months 6 and 9 (p = 0.060).

Table 2: Changes in spleen volume after taliglucerase alfa administration to Gaucher patients (Study PB-06-001)

		____30 units/kg_____ N = 15	____60 units/kg_____ N = 16
SPLEEN VOLUME (mL) -- Imputed Values Averaged			
SCREENING	N	15	16
	MEAN	2130.94	2117.38
	SD	1154.72	1356.17
	MEDIAN	1642.11	1699.45
	RANGE	886.41 to 4901.13	913.65 to 5417.82
6-MONTH	N	15	16
	MEAN	1674.89	1544.07
	SD	958.51	1142.14
	MEDIAN	1278.97	1132.05
	RANGE	629.85 to 4117.29	522.83 to 4523.60
9-MONTH	N	15	16
	MEAN	1566.08	1376.89
	SD	900.17	1055.81
	MEDIAN	1184.78	1044.60
	RANGE	606.27 to 3893.79	483.23 to 4219.63
PERCENT CHANGE FROM SCREENING TO 6-MONTH	N	15	16
	MEAN	-22.21	-29.94
	SD	4.63	12.65
	MEDIAN	-22.35	-32.10
	RANGE	-30.99 to -12.49	-52.72 to 3.43
	p-value	<0.0001*	<0.0001*
PERCENT CHANGE FROM SCREENING TO 9-MONTH	N	15	16
	MEAN	-26.91	-38.01
	SD	7.79	9.38
	MEDIAN	-27.85	-37.63
	RANGE	-42.60 to -15.58	-56.30 to -20.04
	p-value	<0.0001*	<0.0001*

Liver Volume (Primary Clinical Endpoint)

As shown in Table 3, a significant reduction in liver volume as a primary clinical endpoint was observed in both dose groups (ITT Population) from screening to Month 6 (30 units/kg, 7.56%, p = 0.0020); 60 units/kg, 7.51%, p = 0.0022) and Month 9 (30 units/kg, 10.48%, p = 0.0041; 60 units/kg, 11.11%, p < 0.0001). However, there was no significant difference observed in mean liver volume between the two dose groups at Months 6 and 9 (p = 0.349).

Table 3: Changes in liver volume after taliglucerase alfa administration to Gaucher patients (Study PB-06-001)

LIVER VOLUME (mL)		30 units/kg N = 15	60 units/kg N = 16
SCREENING	N	15	16
	MEAN	2880.60	2481.31
	SD	736.12	452.74
	MEDIAN	2609.96	2484.68
	RANGE	2282.47 to 5095.80	1758.30 to 3297.33
6-MONTH	N	15	16
	MEAN	2655.49	2275.88
	SD	670.15	352.94
	MEDIAN	2411.35	2279.02
	RANGE	1930.02 to 4598.04	1809.33 to 2815.15
9-MONTH	N	14	15
	MEAN	2564.07	2190.99
	SD	559.57	376.70
	MEDIAN	2473.19	2098.13
	RANGE	2000.33 to 4121.94	1654.07 to 2894.12
PERCENT CHANGE FROM SCREENING TO 6-MONTH	N	15	16
	MEAN	-7.56	-7.51
	SD	7.74	8.17
	MEDIAN	-9.21	-6.94
	RANGE	-22.28 to 11.37	-25.15 to 5.53
	p-value	0.0020*	0.0022*
PERCENT CHANGE FROM SCREENING TO 9-MONTH	N	14	15
	MEAN	-10.48	-11.11
	SD	11.27	6.68
	MEDIAN	-13.87	-12.25
	RANGE	-19.11 to 25.31	-22.29 to 2.32
	p-value	0.0041*	<0.0001*

Hemoglobin Levels (Secondary Clinical Endpoint)

The mean hemoglobin values at baseline were at the lower limit of the normal range (12.2 g/dL and 11.4 g/dL for taliglucerase alfa 30 units/kg and 60 units/kg, respectively) and improved to within normal limits (14.0 g/dL and 13.6 g/dL for taliglucerase alfa 30 units/kg and 60 units/kg, respectively) at the end of study (ITT Population). A significant increase in mean hemoglobin level was observed between baseline and the end of study for both taliglucerase alfa 30 units/kg (1.6 g/dL, $p = 0.0010$) and 60 units/kg (2.2 g/dL, $p < 0.0001$) dosage groups. The increase in mean hemoglobin level was also observed at 6 months for both taliglucerase alfa 30 units/kg (1.6 g/dL, $p = 0.0002$) and 60 units/kg (1.7 g/dL, $p = 0.0002$). However, there was no significant difference observed in mean hemoglobin values between the two dose groups at Months 6 and 9 ($p = 0.719$).

Platelet Counts (Secondary Clinical Endpoint)

A significant increase in platelet count from baseline was observed in the 60 units/kg dose group (ITT Population) at Month 9 (from 65,038 counts/mm^3 to 106,531 counts/mm^3, difference = 41,494 counts/mm^3, p = 0.0031). A clinically meaningful improvement in platelet count at Month 9 was also observed for the taliglucerase alfa 30 units/kg dose group (from 75,320 counts/mm^3 to 86,747 counts/mm^3, difference = 11,427 counts/mm^3, p = 0.0460), but did not meet the prespecified alpha level of 0.025. Significant increases in mean platelet count from baseline were observed in taliglucerase alfa 60 units/kg treated patients compared to taliglucerase alfa 30 units/kg treated patients at Months 6 and 9 (p = 0.042) when determined using a mixed effect statistical model.

2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

Taliglucerase alfa exposure-safety response relationship was not explored in this submission.

2.2.4.3 Does this drug prolong the QT or QTc interval?

All subject had normal ECG results at all visits in Study P-01-2005. According to the conclusion in the study report, there were no clinically significant ECG changes observed at baseline throughout the study.

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?

The dose range of taliglucerase alfa of 30 or 60 units/kg in the pivotal Study PB-06-001 and labeling was chosen based on previous efficacy and safety study results in commercially available imiglucerase (Cerezyme®) with supporting nonclinical studies showing comparable potency and safety to that of Cerezyme®.

2.2.5 What are the pharmacokinetic characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose pharmacokinetic parameters?

In Healthy Subjects (Study P-01-2005)

The PK parameter values of taligucerase alfa were determined in healthy volunteers in Study P-01-2005 using a non-compartmental method. Due to the short half-life (t½) observed in this study (up to 30 min) relative to the dosing frequency of once weekly, each infusion was treated as a single dose for the purpose of pharmacokinetic analysis. The concentration of taligucerase alfa at time zero was set equal to zero, which might not be appropriate because there may be β-glucocerebrosidase produced endogenously in study subjects.

One subject (017) had measurable taligucerase alfa concentrations at 24 hours postdose that occurred at the lowest dose (15 uints/kg). The applicant considered this subject as an outlier. The PK parameter values of taligucerase alfa could not be reliably determined at the dose of 15

units/kg because of an insufficient number of samples having concentrations above the lower limit of quantitation (LLOQ). All AUC calculations were based on the time interval from start of infusion to the last measurable plasma concentration (AUC_{last}), which may a biased estimation of the PK parameter values because the values are dependent upon the time (T_{last}) and concentration (C_{last}) of the last measurable point. It is noted that T_{last} generally increased with increasing dose for most subjects. The PK parameter values of taligucerase alfa summarized by the applicant in Study P-01-2005 are shown in Table 4:

Table 4: Pharmacokinetic parameters of taliglucerase alfa determined in healthy subjects (Study P-01-2005)

Dose (U/kg)	Subject	Half Life (min)	Tmax (min)	Cmax (mU/mL)	Cmax/ Dose	T_{last} (min)	AUC_{last} (mU•hr/mL)	AUC_{last}/ Dose	CL (mL/ min/kg)	Vss (mL/kg)
15	1	Missing	45	10	1	90	10	1	Missing	Missing
15	4	Missing	45	61	4	45	20	1	Missing	Missing
15	8	Missing	45	49	3	100	47	3	Missing	Missing
15	9	Missing	45	77	5	80	52	3	Missing	Missing
15	16	Missing	45	77	5	90	56	4	Missing	Missing
15	17	6556	45	114	8	1440	185	12	0.1	1525.7
	Mean [a]	6556	45	65	4	308	62	4	0.1	1525.7
	Mean [b]		45	55	4	81	37	2		
30	1	Missing	80	37	1	100	50	2	Missing	Missing
30	4	8	80	130	4	115	154	5	3.2	68.6
30	8	9	80	148	5	115	144	5	3.4	91.4
30	9	Missing	45	115	4	100	114	4	Missing	Missing
30	16	9	45	181	6	115	170	6	2.9	42.9
30	17	10	90	364	12	130	276	9	1.8	40.0
	Mean [a]	9	70	162	5	113	151	5	2.8	60.7
	Mean [b]	8	66	122	4	109	126	4	3.2	67.6
60	1	Missing	90	57	1	100	61	1	Missing	Missing
60	4	13	80	713	12	150	915	15	1.1	34.3
60	8	21	80	566	9	150	512	9	1.9	74.3
60	9	16	80	277	5	150	366	6	2.7	94.3
60	16	17	80	606	10	150	504	8	1.9	82.9
60	17	32	80	836	14	210	1196	20	0.8	34.3
	Mean [a]	20	82	509	8	152	592	10	1.7	64.0
	Mean [b]	17	82	444	7	140	472	8	1.9	71.4

[a] Mean including all six subjects [b] Mean excluding outlier Subject 17
"Missing" – values could not be calculated because an insufficient number of time points had concentrations above the LLOQ after termination of the 90-min infusion

At the doses of 30 units/kg and 60 units/kg, the median clearance (CL) values of taligucerase alfa were 3.1 mL/min/kg (range, 1.8 to 3.4 mL/min/kg; n = 4) and 1.9 mL/min/kg (range, 0.8 to 2.7 mL/min/kg; n = 5) including the outlier, respectively. The median volume of distribution values at state (Vss) were 55.8 mL/kg (range, 40.0 to 91.4 mL/kg; n = 4) and 74.3 mL/kg (range, 34.3 to 94.3 mL/kg; n = 5) including the outlier, respectively, which are between the plasma and blood volume of an adult. The median t½ values were 9 hr (range, 8 to 10 hr; n = 4) and 17 hr (range, 13 to 32 hr; n = 5) including the outlier, respectively. Based on the Assay Report MBR06-102 (see Section 2.6 Analytical), (b) (4).

In Patients with Gaucher Disease (Study PB-06-001)

The PK parameter values of taligucerase alfa were determined in patients with Gaucher disease in Study PB-06-001 on Day 1 and Week 38 (Month 9) of biweekly administration of taliglucerase alfa 30 units/kg (n = 15) or 60 units/kg (n = 16) using a non-compartmental method. The plasma concentrations of taliglucerase alfa were reported as ng/mL by the analytical

laboratory although the doses administered to the patients were calculated on a basis of enzyme units/kg. Therefore, the dose in enzyme units was converted to dose in mg using the conversion factor [redacted](b) (4)

On Day 1 during the administration of 30 units/kg, infusion errors were occurred in 5 patients and those patients' data were excluded in PK analyses. Two other patients (30 units/kg on Week 38, 60 units/kg on Week 38) were also excluded from PK analysis because of unknown time of blood collection and unexplainable prominent concentration, respectively. One patient on Week 38 at the dose of 60 units/kg was included only in AUC_{last} calculation because there were no sufficient sampling points to determine t½ and AUC_{∞}. For some patients who were included in the PK analysis, the actual doses received and the length of infusion time were not the same as the nominal dose and infusion time planned in the study protocol as shown in Table 5. The difference between the actual and nominal doses were up to 13 % (Day 1, 30 units/kg dose group) with coefficients of variation in the range of 1.5% to 2.7 %. There were 11 patients out of 54 patients (20.4%) whose actual infusion time was deviated by more than 10% (i.e., 12 min) from the planned time in the protocol. The actual infusion time was as short and long as 60 min and 165 min, respectively.

Table 5: Actual taliglucerase alfa dose administered and infusion time in Study PB-06-001 conducted in Gaucher patients

Dose Group (Units/kg)	Study Visit	Number of Patients (N)		Mean	SD	Median	Range
		Evaluable	No Deviation*				
				Dose (units/kg)			
30	Day 1	10	9	31.1	1.3	30.8	29.9 - 34.0
	Week 38	14	14	30.9	1.1	31.3	28.9 - 32.9
60	Day 1	16	16	61.0	0.9	60.9	59.6 - 62.4
	Week 38	15	15	59.3	1.6	59.7	55.8 - 61.1
				Infusion Time (min)			
30	Day 1	10	8	120	22	120	70 - 165
	Week 38	14	13	119	5	120	100 - 120
60	Day 1	16	10	114	20	120	75 - 140
	Week 38	15	12	114	17	120	60 - 120

* Number of patients who received taliglucerase alfa with < 10% difference in dose or infusion time from that in the protocol

The PK parameter values determined from the Gaucher patients in Study PB-06-001 are summarized in Table 6. Cmax values are not included in the summary because the actual infusion time was not same as the planned time in the study protocol (i.e., 120 min) for many patients as shown in Table 5. The mean extrapolation to determine AUC_{∞} based on AUC_{last} and terminal t½ was in the range of 0.46% to 2.36% though there is one extreme value of 20.8% (Week 38, 60 units/kg dose group). The mean ± SD values for systemic CL, volume of distribution at terminal phase (Vz), and t½ were 20.5 ± 7.1 L/hr, 11.7 ± 4.5 L, and 25.0 ± 10.1 min, respectively.

Table 6: Pharmacokinetic parameters of taliglucerase alfa determined in Study PB-06-001 conducted in Gaucher patients

Dose Group	Units/kg	30		60	
Study Visit		Day 1	Week 38	Day 1	Week 38
Patients	N	10	14	16	15
AUC_{last} (ng·hr/mL)	Mean ± SD	2,229 ± 669	2,654 ± 2,130	6,349 ± 2,200	7,665 ± 4,578
	Median	2,441	1,989	6,350	6,751
	Range	807 - 3,082	1,002 - 9,546	2,877 - 10,077	2,545 - 20,496
AUC_{∞} (ng·hr/mL)	Mean ± SD	2,244 ± 674	2,706 ± 2,270	6,383 ± 2,229	8,095 ± 5,087
	Median	2,459	2,008	6,372	6,773
	Range	810 - 3,119	1,007 - 10,092	2,885 - 10,265	2,548 - 21,020
Extrapolation (%)	Mean ± SD	0.64 ± 0.40	0.90 ± 1.43	0.46 ± 0.39	3.25 ± 5.28
	Median	0.53	0.33	0.36	0.34
	Range	0.28 - 1.41	0.12 - 0.54	0.12 - 1.83	0.13 - 20.81
AUC_{last}/Dose (ng·hr/mL)/mg	Mean ± SD	39.1 ± 13.2	42.2 ± 30.4	54.3 ± 18.9	63.4 ± 33.9
	Median	42.8	32.7	50.9	57.8
	Range	17.7 - 59.3	14.6 - 139	28.0 - 98.0	26.3 - 156
CL (L/hr)	Mean ± SD	29.4 ± 13.9	30.7 ± 14.5	20.5 ± 7.1	19.9 ± 9.6
	Median	23.3	30.6	19.7	16.5
	Range	16.8 - 56.4	6.79 - 68.0	10.0 - 35.6	6.25 - 37.9
Vz (L)	Mean ± SD	17.5 ± 11.1	16.8 ± 12.7	11.7 ± 4.5	14.4 ± 6.6
	Median	13.8	12.8	12.6	14.5
	Range	6.19 - 45.9	6.95 - 55.3	5.69 - 20.4	3.91 - 24.8
t½ (min)	Mean ± SD	25.9 ± 11.8	25.1 ± 15.5	25.0 ± 10.1	36.3 ± 22.8
	Median	23.7	18.9	22.0	31.4
	Range	9.95 - 42.4	9.20 - 57.9	13.3 - 43.7	11.3 - 104

2.2.5.2 How do the pharmacokinetics in healthy volunteers compare to those in patients?

When determined 5 healthy subjects after the first dose of 60 units/kg (Study P-01-2005), the mean values for AUC_{last}, CL, Vss, and t½ were 592 mU·hr/mL, 1.7 mL/min/kg, 64 mL/kg, and 20 min, respectively, as shown in Table 6. When determined in 16 Gaucher patients after the first dose of 60 units/kg (Study PB-06-001), the mean ± SD values for CL, Vz, and t½ were 6,383 ± 2,229 ng·hr/mL, 20.5 ± 7.1 L/hr, 11.7 ± 4.5 L, and 25.0 ± 10.1 min, respectively. Because the metrics are different between healthy subject and patient studies, a direct comparison of PK parameters is not straight forward. Assuming that the mean body weight of the healthy subjects in Study P-01-2005 is 72.5 kg and the [redacted] (b) (4) the mean values for AUC_{last} and CL in the healthy subjects can be converted to [redacted] (b) (4). Thus, the CL of taliglucerase alfa determined in

Gaucher patients was 2.8 fold larger than the CL in healthy subject, which is consistent to 2.6 fold greater AUC_{last} in healthy subjects. The mean t½ values were slightly longer (25 min vs. 20 min) in Gaucher patients.

2.2.5.3 What are the characteristics of drug absorption?

Not applicable to taliglucerase alfa that is to be administered intravenously.

2.2.5.4 What are the characteristics of drug distribution?

As shown in Table 6, when determined in Gaucher patients (Study PB-06-001), the mean Vz values at the doses of 30 units/kg and 60 units/kg were 17.5 L and 11.7 L, respectively, which are 2 - 3 fold larger than blood volume of an adult. Thus, taliglucerase alfa appears to be distributed to the body other than blood or taken up to the target tissue.

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

Not applicable to taliglucerase alfa, a therapeutic protein product.

2.2.5.6 What are the characteristics of drug metabolism?

Not applicable to taliglucerase alfa, a protein product that is known to be not metabolized but disintegrated by proteolytic enzymes to amino acids.

2.2.5.7 What are the characteristics of drug excretion?

Not applicable to taliglucerase alfa, a large size protein (60,800 dalton) that is not to be excreted intact.

2.2.5.8 Based on pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Comparing the mean dose normalized AUC_{last} and CLvalues at the administration of 30 units/kg and 60 units /kg in Guacher patients as shown in Table 6, the pharmacokinetics of taliglucerase alfa does not appears to be dose-proportional at the dose studied. When the dose was doubled, the AUC values were increased by 178% and 200%, and the CL values were reduced by approximately 30% and 35% on Day 1 and Week 38, respectively.

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

Comparing the mean dose normalized AUC_{last} values on Day 1 and Week 38 in Guacher patients as shown in Table 6, it appears that taliglucerase alfa exposure was slightly increased by 8% (30 units/kg dose) and 17% (60 units/kg dose). The mean CL values were very similar between Day 1 and Week 38 for both dosing groups. Whereas the mean t½ values were similar at 30 units/kg dose level, the values were greater by 9.8 hr on Week 38. Similarly, whereas the mean Vz values were similar at 30 units/kg dose level, the values were greater by 23% on Week 38.

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

Based on the dose-normalized mean AUC_{last} values shown in Table 6, the inter-subject variability was in the range of 33.8% to 72.0%. The causes of the variability is not known

2.2.6 What are the pharmacodynamic characteristics of the drug? *(Include PD parameters that are not addressed in 2.2.4 but important to understand the clinical pharmacology of the drug)*

Pharmacodynamics were not characterized in this application

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The applicant did not explore the impacts of intrinsic factors on taliglucerase alfa exposure-efficacy or -safety response relationships in this application.

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 Elderly

No dedicated geriatric study has been conducted for this application. The pivotal study conducted in Gaucher patients (Study PB-06-001) included only one elderly (age, 74 years old) patient.

2.3.2.2 Pediatric Patients

No pediatric patient has been enrolled in the clinical studies conducted for this application. According to the Pediatric Research Equity Act of 2007, products with orphan designation are exempt from the requirements of a pediatric study. Therefore, a pediatric assessment or requests for waiver or deferral are not included in this application. However, the applicant proposes to conduct a clinical trial of Gaucher disease patients aged 2 to 17 years old (Study PB-06-005).

2.3.2.3 Gender

No gender differences were observed in exposure or PK parameters in healthy subjects (Study P-01-2005). However, the number of subjects (n = 3 in each gender) doe not appear to be sufficient number to draw a conclusion whether there is gender difference in the pharmacokinetics of taliglucerase alfa or not. The gender difference was not explored in Gaucher patients (Study PB-06-001). However, the study will not likely demonstrate whether

the gender difference exists in the PK of taliglucerase alfa because the coefficients of variation of PK parameters are as high as 72% (Table 6).

2.3.2.4 Race

No specific analysis was conducted to evaluate the effect of race on the clinical pharmacology of taliglucerase alfa in this application. The study patients consist of 30 Caucasians and 1 African.

2.3.2.5 Renal impairment

No specific analysis was conducted to evaluate the effect of renal impairment on the clinical pharmacology of taliglucerase alfa in this application. Considering that the molecular weight of taliglucerase alfa is 60,800 dalton, the renal impairment study does not appear to be necessary.

2.3.2.6 Hepatic impairment

No specific analysis was conducted to evaluate the effect of hepatic impairment on the clinical pharmacology of taliglucerase alfa in this submission. Because taliglucerase alfa, a protein product, is not exclusively metabolized in the liver but disintegrated to amino acids by multiple pathways, the hepatic impairment study does not appear to be necessary.

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

Pregnancy Category B: According to the applicant's proposed labeling text, reproduction studies have been performed in rats and rabbits at doses up to 5 times the maximum human dose on a mg/m^2 basis and have revealed no evidence of impaired fertility or harm to the fetus due to taliglucerase alfa. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the physician judges the potential benefit to justify the risk.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when taliglucerase alfa is administered to a nursing woman.

2.3.3 Immunogenicity (applicable only to therapeutic proteins)

2.3.3.1 What is the incidence 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?

The incidence of the formation of APA has not been adequately determined. According Dr. Faruk Sheik's micycle presentation on immunogenicity assays held on November 16, 2010, since the applicant set the cut-point for the confirmatory immunogenicity assay unreasonable high, the incidence of immunogenicity was underestimated.

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

Impact on Pharmacokinetics

The impact of immunogenicity on the PK of taliglucerase alfa has not been adequately determined. According Dr. Faruk Sheik's micycle presentation, since the applicant set the cut-point in the confirmatory immunogenicity assay unreasonable high, the incidence of immunogenicity was underestimated.

Impact on Pharmacodynamics

The pharmacodynamics of taliglucerase alfa were not characterized in this application.

2.3.3.3 Do the anti-product antibodies have neutralizing activity?

Whether the anti-product antibodies have neutralizing activity or not is not conclusive. According Dr. Faruk Sheik's micycle presentation, although the Applicant developed a neutralizing antibody assay to assess for antibodies that interfere with enzymatic activity, the Applicant does not have an assay to assess for antibodies that neutralize drug uptake into target cells.

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

The impact of immunogenicity on clinical efficacy has not been adequately determined. According Dr. Faruk Sheik's micycle presentation, since the applicant set the cut-point in the confirmatory immunogenicity assay unreasonable high, the incidence of immunogenicity was underestimated.

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 impact of immunogenicity on clinical safety has not been determined in this application.

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?

No specific analysis was conducted to evaluate the effect of the extrinsic factors on the clinical pharmacology of taliglucerase alfa.

2.4.2 Drug-drug interactions

No drug-drug interaction studies were conducted for this submission.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

This question cannot be answered until the impacts of immunogenicity on the PK an efficacy are reviewed in depth.

2.5 General Biopharmaceutics

This section should summarize the salient points about the attributes of the drug product. (For Biologics, see 2.5.10 only. Others biopharmaceutics questions are not applicable to Biologics.)

2.5.10 What is the pharmacokinetic and/or pharmacodynamic comparability of the proposed to-be-marketed formulation to the pivotal clinical trial? *(Applicable to Biologics only)*

Not applicable to this application. All studies were conducted using to-be-marketed formulation.

2.6 Analytical

This section should address issues related to the analytical and bioanalytical methods used to support the CPB studies. (For therapeutic protein products, see 2.6.5, 2.6.6 and 2.6.7 only. Others analytical questions are not applicable to therapeutic protein products.)

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

The bioanalytical assay method used to quantitate taliglucerase alfa in human plasma in Study P-01-2005 is based on an ELISA method using 96-well microtiter plates coated with chicken anti-plant recombinant-human glucocerebrosidase antibodies (Assay Report MBR06-102). Prediluted controls and unknown samples were pipetted into the wells of the plate and incubated with shaking at room temperature, allowing any taliglucerase alfa present to bind to the anti-taliglucerase alfa antibodies. After two hours of incubation the plate was washed four times to remove any nonreactive plasma components. Rabbit anti-taliglucerase alfa antibodies were added and the plates were incubated for 1.5 hours at room temperature to allow the rabbit anti-taliglucerase alfa to bind to taliglucerase alfa. The unbound protein and reagents were removed by another wash step and followed by the addition of an alkaline phosphatase-affinity purified goat anti-rabbit IgG conjugate. After a 60-minute incubation, the plate was washed again. In the final step, the phosphatase substrate was added to the wells to develop color as the phosphatase catalyzed the substrate. The color was allowed to develop at room temperature for 45 minutes or until the optical density (OD) of the highest standard was 1.0 or greater. The absorbance was measured at 405 nm using a plate spectrophotometer.

The calibration curves of the assay were constructed using purified recombinant taliglucerase alfa at the concentrations of 7.8, 15.6, 31.3, 62.5, 125 and 250 ng/mL diluted in a 4% human plasma matrix by fitting to a four-parameter curve equation. Calibration standards were assayed in duplicate for each sample run (plate). Because the calibration curves were constructed in duplicate, the within-run accuracy (% relative error to nominal concentrations, %RE) and precision (% coefficient of variation of back-calculated QC concentrations, %CV) could not be

calculated. The performance of the assay based on the between-run accuracy and precision determined form 8 assay runs were in the range of 2% (at 250 ng/mL) to 26% (at 7.8 ng/mL) and 1.7% (250 ng/mL) to 9.4% (at 7.8 ng/mL), respectively. The lower limit of quantitation (LLOQ) after accounting for 1:25 dilution was 195 ng/mL or 6.83 mUnits/mL (b) (4)

Quality control (QC) samples were prepared at the concentration of 600 ng/mL (low control, LC), 3000 ng/mL (high control, HC), and 25,000 ng/mL (dilution control, DC). Considering that the samples were diluted to the ratio of 1:25 prior to the assay, the LC and HC concentrations were 24 and 120 ng/mL. The QC samples were assayed in duplicate and two sets of each control were assayed per sample run (plate). Because the QC samples were run in duplicate, the within-run accuracy and precision could not be calculated. The performance of the assay based on the accuracy and precision determined form 8 assay runs were in the range of -2.9 % to 33.7 % and 18.9% to 21.1%, respectively, shown in the table below:

Sample Run #	Low Control (600 ng/mL)	High Control (3000 ng/mL)	Dilution Control (25,000 ng/mL)
1	(b) (4)		
2			
3			
4			
5			
6			
7			
8			
Mean	802.2	2914.4	32064.6
Relative Error (%)	33.7	-2.9	28.3
Standard Deviation	191.2	549.6	7720.7
Coefficient Variation (%)	23.8	18.9	24.1

Reviewer's Comment: The performance of the assay was determined using only two quality control concentrations (600 ng/mL and 3000 ng/mL for LC and HC, respectively). Although the assay reports included the performance of within-assay runs, it is unclear how the within-run precision was calculated using duplicated quality control and calibration curve samples. Therefore, the reviewer reviewed and re-calculated the between-run accuracy and precision only using the values provided in the assay report MBR06-102. The overall quality of the in-process assay validation and the results of assay performance were below those described in the Guidance for Industry: Bioanalytical Method Validation

(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf).

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.

The bioanalytical methods used to assess the formation of APAs are not considered to be adequate. According Dr. Faruk Sheik's micycle presentation on immunogenicity assays held on November 16, 2010, since the applicant set the cut-point in the confirmatory assay unreasonable high, the incidence of immunogenicity was underestimated.

2.6.7 What bioanalytical methods were used to assess the pharmacodynamic effect of the therapeutic protein?

Not applicable. The secondary endpoints including hemoglobin levels and platelet counts were measured in the clinical laboratory of the study sites.

3 DETAILED LABELING RECOMMENDATIONS

No labeling recommendation was made since this application is not expected to be approved in the current review cycle.

End of Document

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

/s/

JANG IK LEE
01/13/2011

GILBERT J BURCKART
01/13/2011

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	**22-458**	**Brand Name**	**TBD**
OCP Division (I, II, III, IV, V)	**DCP III**	**Generic Name**	**Taliglucerase alfa**
Medical Division	**DGIP**	**Drug Class**	**Enzyme Replacement Therapy**
OCP Reviewer	**Jang-Ik Lee, PharmD, Ph.D.**	**Indication(s)**	**Gaucher disease**
OCP Secondary Reviewer	**Hae-Young Ahn, Ph.D.**	**Dosage Form**	**Lyophilized powder for injection**
Pharmacometrics Reviewer	**N/A**	**Dosing Regimen**	**(b) (4) 60 U/kg every 2 weeks as 1-2 hr IV infusion**
Date of Submission	**12/9/2009 (Clin Pharm section)** **4/26/2010 (final piece for filing)**	**Route of Administration**	**IV infusion**
Estimated Due Date of OCP Review	**8/12/2010 (if priority review)**	**Sponsor**	(b) (4)
Medical Division Due Date	**8/26/2010 (if priority review)**	**Priority Classification**	**TBD**
PDUFA Due Date	**10/26/2010 (if priority review)**	**Dosing Strength**	**200 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.				**4 rolling submissions; difficult to locate information**
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**4**		**Assay report for study P-01-2005 may have review issues**
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**		Study P-01-2005
multiple dose:				
Patients-				
single dose:				
multiple dose:	**X**	**1**		Study PB-06-001
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**1**		Study P-01-2005
fasting / non-fasting multiple dose:	**X**	**1**		Study PB-06-001
Drug-drug interaction studies -				

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

In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
Age:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
Immunogenicity:	**X**	**4**		
PD -				
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:				
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	**X**			**Provided synopsis for a pediatric study**
Literature References	**X**			
Total Number of Studies		**8**	**6 - 8**	**Including 2 clinical studies**

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	The clinical and TBM products are the same
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			Review issues in Study P-01-2005

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

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		Many broken links but still reviewable
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		Many broken links but still reviewable
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	
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			May have many review issues
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		But still reviewable
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 only
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Provided a proposed study synopsis
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		Need extensive revision
	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			May have many review issues
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

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

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

The assay report for Study P-01-2005 omitted some important information such as adequate assessment of intra- and inter-assay accuracy and precision. The information may need to be requested to the applicant during detailed review.

Jang-Ik Lee, PharmD, Ph.D.

Primary Clinical Pharmacology Reviewer Date

Hae Young Ahn, Ph.D.

Secondary Clinical Pharmacology Reviewer Date

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

Filing Review Summary

A new molecular entity product, taliglucerase alfa (formerly prGCD, (b)(4) is a plant cell expressed, recombinant human glucocerebrosidase proposed for the treatment of Gaucher disease. This original submission includes a Phase 1 pharmacokinetic (PK) study report P-01-2005 and a Phase 3 PK study report PB-06-001.

Study P-01-2005 was a Phase 1, single-center, non-randomized, open label safety trial. Three escalating single doses of taliglucerase alfa were administered 1 week apart as an intravenous (IV) infusion to healthy volunteers. The vehicle served as control. Six eligible subjects were administered the vehicle on Day 1, followed by taliglucerase alfa on Day 8 (15 units/kg), Day 15 (30 units/kg) and Day 22 (60 units/kg). Blood samples were collected for PK analysis at 0, 5, 45, 80 and 90 minutes during the infusion and 100, 115, 130, 150, 180, 210 minutes and 24 hours post initiation of infusion. The assay report for this study omitted some important information such as intra- and inter-assay accuracy and precision because the quality control of the assay was not adequately performed. .

Study PB-06-001 was a Phase 3, multi-center, randomized, double-blind, parallel group, dose ranging trial to assess the safety and efficacy of taliglucerase alfa in 31 untreated patients with Gaucher disease. Patients received IV infusion of taliglucerase alfa every 2 weeks. The duration of treatment was 9 months. At baseline, patients were randomized to receive either 30 or 60 units/kg for the duration of the study. Blood samples for pharmacokinetic analysis were collected at 0, 45, 70, 110, 125, 135, 150, 175, 200 and 225 minutes after the start of the first infusion and the last infusion at Month 9 of the study. The assay report for this study appears to be acceptable and reviewable.

A comparison of the results of the two studies assessing PK in healthy subjects and patients with Gaucher disease is presented in the table below.

Study/ Protocol # (Country)	Product Batch #	Study Objective	Study Design	# Subjects Entered/ Completed (M/F)	HV/P[1] (Age: Mean, range)	Treatments		Mean Pharmacokinetic Parameters						
						Drug	Dose	Cmax (ng/mL)	AUC (ng*hr/mL)	$T_{1/2}$ (min)	CL (mL/ min/kg)	CL (L/hr)	V (mL/ kg)	V (L)
P-01-2005 (Israel)	021005 010106	Safety and PK	Open label, single-dose escalation	6/6 (3/3)	HV (26.3, 19-35)	taliglucerase alfa (90 minute infusion)	15 U/kg	1569	1767	-	-	-	-	-
							30 U/kg	3489	3608	8	3.2	-	67.6	-
							60 U/kg	12684	13474	17	1.9	-	71.4	-
PB-06-001 (Multicenter)	K-38743 K-39065 K-40306 PR2001 PR2002	Efficacy, Safety and PK	Double blind, randomized, parallel dose groups	32/29 (16/16)	P (36.1, 19-74)	taliglucerase alfa (120 minute infusion)	30 U/kg Day 1	1556	2229	26	-	29	-	17.5
							Week 38	1656	2654	25	-	31	-	16.8
							60 U/kg Day 1	4250	6349	25	-	21	-	11.7
							Week 38	5153	7665	35	-	20	-	14.4

[1]HV = Healthy Volunteers, P = Patients

The two studies demonstrated that taliglucerase alfa is rapidly cleared from the blood with a half life of approximately 15 minutes in healthy subjects and 25 minutes in patients. Because of the small number of subjects in Phase 1 and of patients in Phase 3, the formal analyses of intrinsic or extrinsic factors were not conducted. No adequate pharmacodynamic information and dose-response data are provided. However, this missing information is not considered to be a filing

issue since the availability of study patients is limited in Gaucher disease. The incidence of anti-product antibody development during the Phase 3 study was 6%. The to-be-marked product was used in all clinical studies.

The efficacy and safety of taliglucerase alfa were assessed in the studies presented in the table below.

Study Number	Study Objective	Study Design and Type of Control	Test Product(s)	Dosage Regimen	Number of Subjects (ITT)	Duration of Treatment
Pivotal Study						
PB-06-001	Safety and efficacy of two dose levels of taliglucerase alfa in patients with Gaucher disease	Multicenter, randomized, double blind, parallel group, dose ranging	Taliglucerase alfa	30 units/kg every 2 weeks 60 units/kg every 2 weeks	N=15 N=16	38 weeks (9 months)
Supporting Studies						
PB-06-002	Safety and efficacy in patients switching from imiglucerase ERT	Multicenter, open label	Taliglucerase alfa	Dose equivalent to prior imiglucerase dose	Up to 30 planned	38 weeks (9 months)
PB-06-003	Extended safety and efficacy of patients completing PB-06-001 and PB-06-002	PB-06-001 patients: Multicenter, double blind, parallel group, dose ranging PB-06-002 patients: Multicenter, open label	Taliglucerase alfa	Continue same dose as previous study	Up to 60 anticipated	15 months (with possible further extension until marketing approval)

During internal filing discussions, a concern was raised in the batch numbers for the drug product used in the pivotal Phase 3 clinical/pharmacokinetic study (PB-06-001); the sponsor used two different series of product batches (3 K-xxxxx and 2 PRxxxx series batches). To determine whether the 2 different batches have potential comparability and resulting filing issues, a consult was requested to the Division of Therapeutic Proteins (DTP).

According to the summary results of the consult:

1) There were five manufacturing changes during Phase 1 and 3 clinical trials that included:

(b) (4)

(b) (4)

2) Risk assessments, comparability reports and batch record analysis indicate that manufacturing changes a, b, c and d did not impact product quality..

3) The switch to (b) (4) caused a change in the proportion (not type) of different terminal mannose containing glycan structures. Glycan structure is a critical quality attribute that is highly relevant to targeting of the drug to macrophages at the site of action. (b) (4)

(b) (4)

4) The targeting of macrophages with glucocerebrosidases with different terminal mannose containing glycan structures has been reported in the scientific literature. Different glycan structures (all containing terminal mannose residues) had little effect on macrophage targeting and therefore the increase in the percentage of (b) (4) upon switching to (b) (4) is unlikely to change the pharmacokinetic properties of taliglucerase alfa.

The reviewing biologist, Dr. Richard Ledwidge in DTP concluded that manufacturing changes that occurred during Phase 1 and Phase 3 clinical trials are not expected to negatively impact pharmacokinetic properties and/or clinical performance of taliglucerase alfa.

Reviwer's Note: It is not reported in the submission why the drug product batch numbers used in Study PB-06-001 have two different series. Dr. Ledwidge could not find the information, either.

(b) (4)

Overall, there is no filing issue associated with the absence of pharmacokinetic comparability study.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22458	ORIG-1	PROTALIX LTD	PLANT CELL EXPRESSED RECOMBINANT HUMAN G

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

/s/

JANG IK LEE
06/24/2010

SUE CHIH H LEE
06/24/2010
Acting for Dr. Hae-Young Ahn