Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report [1] for taliglucerase alfa rpc

Proprietary Product Name: Elelyso

Sponsor: Pfizer Australia Pty Ltd

Date of CER 1:
First round: 25 August 2011
Second round: 30 January 2012.

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], or similar, where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
AE	Adverse Event
ALT	Alanine Aminotransferase
ANF	Anti Nuclear Factor
ATU	Autorisation Temporaire d'Utilisation
BBB	Blood-Brain Barrier
BMD	Bone Mineral Density
BMI	Body Mass Index
CBC	Complete Blood Cell
CRF	Case Report Form
CSR	Clinical Study Report
CTM	Clinical Test Materials
CUP	Compassionate Use Program
DEXA	Dual-Energy X-ray Absorptiometry
DMC	Data Monitoring Committee
EAP	Expanded Access Protocol
ECG	Electrocardiogram
ERT	Enzyme Replacement Therapy
ESR	Erythrocyte Sedimentation Rate
EWGGD	European Working Group on Gaucher Disease
FDA US	Food and Drug Administration
GCD	Glucocerebrosidase
GCP	Good Clinical Practice
GD	Gaucher Disease
HBsAg	Hepatitis B Surface Antigen

Abbreviation	Meaning
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IgG	Immunoglobulin G
ITP	Idiopathic Thrombocytopenic Purpura
ITT	Intent-To-Treat
IV	Intravenous
LOCF	Last Observation Carried Forward
LPLV	Last Patient, Last Visit
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MN	Multiples of Normal
MRI	Magnetic Resonance Imaging
NA	Not Applicable
NDA	New Drug Application
NGD	Neuronopathic Gaucher Disease
NNGD	Non Neuronopathic Gaucher Disease
PAR/CCL	Pulmonary and Activation-Regulated Chemokine
PDCO	Paediatric Committee
PFT	Pulmonary Function Test
PID	Patient Identification Number
PK	Pharmacokinetics
PP	Per Protocol
PT	Prothrombin Time
PTT	Partial Thromboplastin Time

Abbreviation	Meaning
QCSI	Quantitative Chemical Shift Imaging
rpc	Recombinant Plant Carrot
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Special Access Scheme
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SRT	Substrate Reduction Therapy
TSH	Thyroid Stimulating Hormone
U	Unit
UK	United Kingdom

1. Introduction

This is a Category 1 submission to register ELELYSO (taliglucerase alfa) for the treatment of systemic symptoms in patients with Gaucher disease. This product is a new biological entity. The medicine has been developed as an enzyme replacement therapy by Protalix Limited, and Pfizer Australia P/L is the Australian sponsor.

Taliglucerase alfa is a recombinant active form of the human lysosomal enzyme β-glucocerebrosidase. The proposed indication is:

> *"for long-term enzyme replacement therapy for the treatment of systemic symptoms in patients with a confirmed diagnosis of Gaucher disease".*
>
> **Comment:** Gaucher Disease (GD) is the most prevalent lysosomal storage disorder [Altarescu G et al; 2000]. The disease is caused by mutations in the human glucocerebrosidase gene, which has been mapped to chromosome 1 q21-q31, leading to reduced activity of the lysosomal enzyme glucocerebrosidase and resulting in the accumulation of substrate glucocerebroside in the cells of the monocyte-macrophage system. This accumulation leads to the visceral manifestations of the disease which include hepatosplenomegaly, anaemia and thrombocytopenia, as well as to skeletal deterioration and less frequently to lung involvement [Grabowski, 1998].
>
> The sponsor's proposed indication includes treatment of the systemic symptoms of GD without qualification by disease subtype (i.e. traditionally Type 1, 2, and 3). This approach differs from that adopted for the GD indications of Cerezyme (imiglucerase) and Zavesca (miglustat) which specifically refer to Type 1 GD. The submission proposes

approval of taliglucerase alfa for the treatment of systemic symptoms in adult GD patients irrespective of the classification into Types 1, 2, and 3.

GD encompasses a spectrum of clinical findings from a perinatal lethal form to an asymptomatic form. The disease can present with systemic (visceral and haematological) and neuronopathic symptoms. Traditionally, GD has been classified into Type 1, 2 or 3 according to symptoms and severity. In essence, the three clinical types are delineated by the absence (Type 1) or presence (Types 2 and 3) of primary central nervous system (CNS) involvement [Harrison, 16th Edition, 2005; Pastores and Hughes, Gaucher Disease, Pagon RA, Bird TD, Dolan CR, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-, Bookshelf ID: NBK1269 PMID: 20301446].

However, the clinical overview [Module 2.5] notes that the range of symptoms varies significantly among patients with GD and, often, a clear classification into the three traditional subtypes is difficult [Capablo et al. 2008]. Consequently, the clinical overview refers to the recent classification adopted by treating physicians and supported by the European Working Group on GD (EWGGD) [Vellodi, Tylki-Szymanska et al. 2009], in which the GD population is classified according to the absence (non-neuronopathic GD [NNGD]) or presence (neuronopathic GD [NGD]) of complex neurological symptoms.

NNGD (traditionally Type 1) accounts for 94% of GD cases. NNGD can present in childhood to adulthood with slowly to rapidly progressive visceral disease. The average age at diagnosis is about 20 years with bimodal peaks at <10 to 15 years and at about 25 years, and patients are usually asymptomatic before the age of 2. Hepatosplenomegaly occurs in virtually all symptomatic patients, and accompanying anaemia and thrombocytopaenia are variable and not linearly related to liver or spleen volume. Severe liver dysfunction is unusual, splenic infarction can occur, and pulmonary hypertension and alveolar Gaucher cell accumulation are uncommon, but can be life threatening. All patients with Gaucher disease have non uniform infiltration of bone marrow by lipid-laden macrophages (Gaucher cells), which can lead to marrow packing with subsequent bone infarction, bone ischaemia, bone necrosis, and cortical bone destruction.

NGD is subdivided into an acute group (which accounts for about 1% of GD cases), and a chronic group (which accounts for about 5% of GD cases). Acute neuronopathic GD (acute NGD traditionally Type 2) appears in newborns (≤ 1 year) with a very severe neurological presentation that results in the death of the patient generally within the first 2 years of life. In chronic neuronopathic GD (chronic NGD; traditionally Type 3), the neurological symptoms develop later and progress at a variable rate to a disease with neurological symptoms of varied severity. Chronic NGD can present in early childhood with rapidly progressive visceral disease and slowly progress to static CNS involvement, in adolescence with dementia, or in early adulthood with rapidly progressive, uncontrollable myoclonic seizures and mild visceral disease [Harrison's, 2005].

The clinical overview indicates that the sponsor is targeting the treatment of systemic symptoms (i.e. visceral and haematological) in NNGD (traditionally Type 1) and chronic NGD (traditionally Type 3). The clinical overview comments that experience with enzyme replacement therapy (ERT) for the treatment of NNGD suggests that the systemic symptoms of chronic NNGD can also be treated and alleviated with this treatment modality [Vellodi, Tylki-Szymanska et al. 2009]. However, as taliglucerase alfa is a protein it is not expected to cross the natural blood brain barrier (BBB), and therefore is not expected to be effective in treating the severe neurological symptoms exhibited by patients with NGD (either chronic or acute). To date, all attempts to arrest or reverse neurological progression with ERT in patients with acute NGD have been

unsuccessful, irrespective of whether ERT was administered intravenously at high concentrations or directly into the brain.

2. Clinical rationale

The clinical rationale for taliglucerase alfa is long-term ERT for the treatment of GD. Following intravenous infusion, taliglucerase alfa targets and penetrates macrophages through the mannose receptor delivering glucocerebrosidase to the lysosome. This allows the hydrolysis of accumulated glucocerebrosides resulting from reduced activity of the lysosomal enzyme glucocerebrosidase.

Taliglucerase alfa is an analogue of a known human enzyme glucocerebrosidase (GenBank entries M11080 and M16328). The predicted amino acid sequence of taliglucerase alfa differs from the glucocerebrosidase sequence by the addition of amino acids at the N-terminal and C-terminal of the protein, which are introduced by the plant expression cassette. Glucocerebrosidase is a peripheral lysosomal membrane protein that requires an activator molecule (saposin C) and negatively charged phospholipids for optimal activity and, probably, intracellular stability. This enzyme is naturally active in lysosomes and catalyses the hydrolysis of the glycolipid glucocerebroside into ceramide and glucose in subjects not affected by GD. There are no alternative metabolic pathways when glucocerebrosidase activity is deficient. For reasons that remain poorly understood, tissue macrophages are the predominant cell type that accumulate excessive glucocerebroside under enzyme deficient conditions. Consequently, GD is characterised by the presence of lipid-laden macrophages in the liver, spleen, bone, and lungs.

The sponsor states that GD remains a life-threatening and/or debilitating medical condition. The sponsor requested priority status for evaluation of the submission, “based on the recognised clinical need for effective treatments in Australia”. The sponsor maintains that taliglucerase alfa offers a valuable and reliable alternative therapeutic option for the treatment of patients with GD. The clinical overview states that over the past decade ERT for NNGD has been the treatment of choice for significantly affected patients with this condition [Grabowski and Hopkin 2003]. Nevertheless, the clinical overview argues that there are still unmet medical needs within the condition and refers specifically to bone disease and pulmonary hypertension not being successfully addressed by the current ERT, with some of the patients remaining unresponsive to current available therapy. In addition, the sponsor also claims that the plant cell culture system used to produce taliglucerase alfa diminishes the risk of propagation of mammalian infectious agents, associated with the production of imiglucerase in Chinese hamster ovary cells.

> **Comment:** In general, the sponsor’s clinical rationale for the development of an alternative ERT to the currently approved imiglucerase is acceptable. It is assumed that the Therapeutic Goods Administration (TGA) did not grant priority evaluation status.

2.1. Orphan drug designation

Taliglucerase alfa (Elelyso) was designated as an orphan drug for the treatment of Gaucher disease on 11 March 2011 by a Delegate of the Secretary, Department of Health and Ageing, Australian Government.

> **Comment:** The designated orphan drug indication is consistent with that proposed for registration in the current submission. The prevalence of GD in Australia has been estimated to be 1 per 57,000 live births, based on retrospective data both from patient referrals and prenatal diagnosis for the period 1 January 1980 through 31 December 1996 collected from the National Referral Laboratory, Department of Chemical Pathology, Women’s and Children’s Hospital, Adelaide, Australia, and from the Division of Chemical Pathology, Royal Brisbane Hospital, Brisbane, Australia [Miekle et al., 1999].

Based on the current Australian population of 22 million the maximum prevalence of GD of all types would be 386 people. The Life Saving Drug Program administered by the Australian Government, Department of Health and Ageing has less than 100 people diagnosed with GD.

2.1.1. Guidance

The provided data indicates that a pre-submission meeting was held on 2 February 2010 between officers of Pfizer and the TGA, and included the following information relating to some of the points raised by the TGA at that meeting:

- Some of the data requested by the TGA such as long-term data of more than 12 months, home administration data, and post-marketing data (from SAS program) were not available at the time of the submission. However, they may be provided at a later stage, if available, and if requested by the TGA.
- The TGA was concerned about the lack of control data in study PB-06-001 (i.e. direct comparison to Cerezyme) and queried whether the sponsor could match comparison to historical data (e.g. age of patients, severity of disease). In response to this concern, the sponsor included in the submission an historical comparison, as well a dose separation post-hoc analysis (for studies PB-06-001 and PB-06-003).
- The sponsor confirmed that, as part of its post-market commitment, a patient registry will be created and that this will include post-marketing data captured from Australian patients. In addition, the sponsor indicated that it is in the process of collating data from the Special Access Scheme (SAS) program and that these data can be provided to the TGA once available, possibly during day 120 queries response time. The sponsor stated that there are 8 SAS patients in Australia, and that there have been no adverse drug reactions (ADRs) reported for these patients.
- The sponsor confirmed that there are currently no drug interaction data.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

Module 5:

- 8 reports of bioanalytical and analytical methods for human studies [studies MBR05-194, MBR06-154, MBR06-102, MBR07-300, MBR07-378, MBR08-245, MBR09-153, MBR09-180].
- 1 Phase 1, non-randomised, open-label, single dose-escalation completed study of taliglucerase alfa in 6 healthy volunteers [study P-01-2005].
- 1 Phase 3, pivotal, multi-centre, randomized, double-blind completed trial to assess the safety and efficacy of two-parallel dose groups of taliglucerase alfa in 31 patients with GD [study PB-06-001]
- 1 multi-centre, double-blind, ongoing extension trial of PB-06-001 providing interim data only to assess the safety and efficacy of two-parallel dose groups of taliglucerase alfa in patients with GD [study PB-06-003].
- 1 Phase 3, multi-centre, open-label, switchover ongoing trial providing interim data only to assess the safety and efficacy of taliglucerase alfa in up to 30 patients with GD treated with imiglucerase enzyme replacement therapy [study PB-06-002].

- 2 reports of analyses of data from more than one study (Efficacy Historical Comparison and Therapeutic Goals; and Dose Separation Post hoc Analysis for studies PB-06-001 and PB-06-003).
- 1 other ongoing study [PB-06-004] to assess the safety of taliglucerase alfa in patients with GD who require ERT due to a shortage of imiglucerase.
- 91 literature references for background information.

Module 2:

- Clinical Overview, Summary of Clinical Pharmacology, Summary of Clinical Efficacy, Summary of Clinical Safety and Literature references.

3.2. Paediatric data

The submission states that the next step of the taliglucerase alfa clinical development program will be a Phase 3 multi-centre, double-blind, randomised safety and efficacy study of 2 dose levels of taliglucerase alfa (30 and 60 units/kg) in paediatric patients (aged 2 to < 18 years old) with a confirmed diagnosis of GD (excluding acute NGD). Patients will receive an iv infusion of taliglucerase alfa every 2 weeks and the total duration of treatment will be 12 months. At the end of the 12-month treatment period, eligible subjects will be offered enrollment in the open-label extension study PB-06-003, if taliglucerase alfa is not commercially available at the time of enrollment. Paediatric patients have also been included in the amended switch over study [PB-06-002]. As of October 2010, inclusion of paediatric patients in both studies has been initiated. However, no data on paediatric or adolescent patients (i.e. aged < 18 years) were included in the submission.

3.3. Good clinical practice

The global clinical development program of taliglucerase alfa has been undertaken according to International Committee on Harmonization (ICH) guidelines and EU guidelines, in consultation with Regulatory Authorities both in the USA and in Europe and in consultation with more than 20 international GD experts. The product development has been conducted in compliance with applicable regulatory guidelines, including GMP and GCP.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

The pharmacokinetics of taliglucerase alfa were assessed in healthy volunteers in one Phase 1 study [P-01-2005], and in GD patients in the pivotal Phase 3 clinical efficacy and safety study [PB-06-001]. Neither of the PK studies had deficiencies that excluded their results from consideration.

4.1.1. Study summaries

4.1.1.1. Study P-01-2005 – Healthy subjects

4.1.1.1.1. Objectives

This was an initial Phase 1, single-centre, non-randomized, open label, safety and PK study of taliglucerase alfa administered by iv infusion to 6 human volunteers. The primary objective of the study was to evaluate the safety of three escalating single iv doses of taliglucerase alfa, and the secondary objective was to determine the PK profile. The study was undertaken at the Hadassah Medical Center, Jerusalem, Israel, between 22 November 2005 and 21 March 2006.

The study was conducted in accordance with IRB approval, and in compliance with the Helsinki Declaration and FDA/European GCP guidelines.

4.1.1.1.2. Design

Healthy volunteers meeting the entry criteria were eligible to enter the study. Seven visits were scheduled: pre-screening (Day -1), Screening (Day 0), Baseline (Day 1), Visit 1 (Day 8), Visit 2 (Day 15), Visit 3 (Day 22) and follow-up visit (Day 29). The study procedures for each visit are presented in a study flow chart. The duration of the study was 29 days.

Subjects received a single iv dose of vehicle (i.e. placebo) at the baseline visit (Day 1), followed by three single escalating doses of taliglucerase alfa at one week intervals on Day 8 (15 units/kg), Day 15 (30 units/kg) and Day 22 (60 units/kg). Escalation to the next dose level was based on the results of drug toxicity of the lower level. Subjects remained at the clinic for 8 hours post initiation of infusion and were discharged if no AEs were observed. Subjects returned to the clinic 24 hours post initiation of infusion for additional safety assessment.

A urine sample was collected 24 hours prior to screening to assess renal function, and blood samples for standard clinical laboratory assessments (biochemistry and haematology) were collected prior to dosing and at 24 hours post the initiation of the infusion. Blood samples for PK assessment were collected prior to dosing (0), and then at 80 and 210 minutes and 24 hours post initiation of infusion of the vehicle. Blood samples for PK assessment were also collected prior to dosing (0) and then at 5, 45, 80 and 90 minutes during the infusion of taliglucerase alfa and then at 100, 115, 130, 150, 180, 210 minutes and 24 hours post initiation of the infusions. ECG was performed at baseline and 8 hours following infusion. Vital signs were recorded during the infusion and at PK sampling every 30 minutes (up to 3.5 hours) and 8 and 24 hours post initiation of infusion.

4.1.1.1.3. Inclusion and exclusion criteria

The study included healthy male and female adult subjects between 18 and 45 years of age. Female subjects were required to use a medically acceptable method of contraception at all times during the study, and to have negative serum pregnancy tests at baseline and during the study period. Subjects with clinical evidence of active significant disease that could potentially compromise the ability of the investigator to evaluate or interpret the safety of the study treatment were excluded. The study also included standard criteria for discontinuing subjects from treatment or assessment. All subjects prematurely discontinued from the trial, regardless of cause, were to be seen for a follow-up safety visit according to the study schedule. The inclusion and exclusion criteria are provided in the submission.

4.1.1.1.4. Treatments

The four administered treatment regimens were 1 vehicle treatment and 3 increasing dose treatments of taliglucerase alfa (15, 30 and 60 units/kg body weight). A unit was defined as the amount of enzyme that catalyses the hydrolysis of 1 micromole of the synthetic substrate para-nitrophenyl-beta-D-glucopyranoside (pNP-Glc) per minute at 37°C. Taliglucerase alfa vials are stored lyophilized at 4°C. The taliglucerase final concentration was 40 units/mL after reconstitution with water for injection (WFI) or 0.9% NaCl. The final concentration and administration volumes were supplied in a 200 unit/vial.

Taliglucerase alfa was administered as an iv infusion over 1.5 hours at a rate of 135 mL/90 minutes (1.5 mL/minute) for all three doses. The infusion rate could be adjusted according to the observed signs and symptoms. A slower rate (1 mL/min) was administered if adverse effects were observed, and a faster rate (2 mL/min) was administered if no adverse signs and symptoms were observed. Subjects weighing over 90 kg at the 60 units/kg time point had the dosing volume increased to 150 mL.

Based on pre-clinical studies, the non-toxic-effect level of taliglucerase was considered to be 55 mg/kg/day (marmosets). The maximum human dose in this study was 60 units/kg

(1.8 mg/kg), which is approximately 5 fold less than the animal maximum tested dose. The two higher doses (30 units/kg and 60 units/kg) had been used previously with different ERT preparations and shown to be safe and effective in patients with GD.

4.1.1.1.5. Pharmacokinetic endpoints

Standard PK parameters were calculated using non-compartmental methods (WinNonLin software). Blood samples were collected at pre-determined times and the plasma was analysed for taliglucerase alfa to provide a standard PK profile. Taliglucerase alfa was measured in human plasma using a validated enzyme-linked immunosorbent assay (ELISA), with a range of 7.8 to 250 ng/mL [Study MBR05-194]. The concentration of taliglucerase alfa at time zero was set to zero, and the AUC_{last} values were calculated using the linear trapezoid rule. Concentrations listed as below the lower limit of quantification were set to zero.

4.1.1.1.6. Statistical methods and sample size

In general, all the PK analyses were considered exploratory and descriptive in nature and were designed to give information on the relationship between the treatment and potential outcomes. No formal power or sample size calculations were undertaken.

4.1.1.1.7. Study subjects

Of the 17 healthy subjects screened, 6 were eligible for inclusion. The basic demographics (mean ± SD) of the 6 healthy Caucasian subjects (3 females and 3 males) were: age 26.3 ± 6.3 years; weight 72.5 ± 7.7 kg; height 173 ± 6.6 cm; and BMI 24.2 ± 2.4 kg/m^2.

After completing a single dose of the vehicle on Day 1, all 6 subjects received taliglucerase alfa 15 units/kg (Level I) on Day 8 and tolerated this dose. All 6 subjects then received taliglucerase alfa 30 units/kg (Level II) on Day 15, and 60 units/kg (Level III) on Day 22. All 6 subjects completed the study.

There were 17 reported protocol deviations in the 6 subjects. The most common deviation was missed laboratory sample assessment (5 subjects), followed by PK sampling out of the protocol-designated window (4 subjects), placebo infusion administered over a period of 2 hours instead of 90 minutes (4 subjects), and infusions at 55 units/kg over 105 minutes instead of 60 units/kg over 90 minutes (2 subjects).

4.1.1.1.8. Pharmacokinetic results

All AUC calculations were based on the time interval from start of infusion to the last measurable plasma concentration (AUC_{last}). Analyses were performed and presented in two ways, one included subject 17 and one excluded subject 17. Subject 17 had measurable taliglucerase alfa concentrations at both the period of vehicle control infusion, and between 0 to 24 hours for all three dose level post-dose timepoints 24 hours post dose. Consequently, this subject was considered an outlier and therefore the calculations were done with and without the data from this subject. The mean taliglucerase alfa PK parameters are summarised below in Table 1.

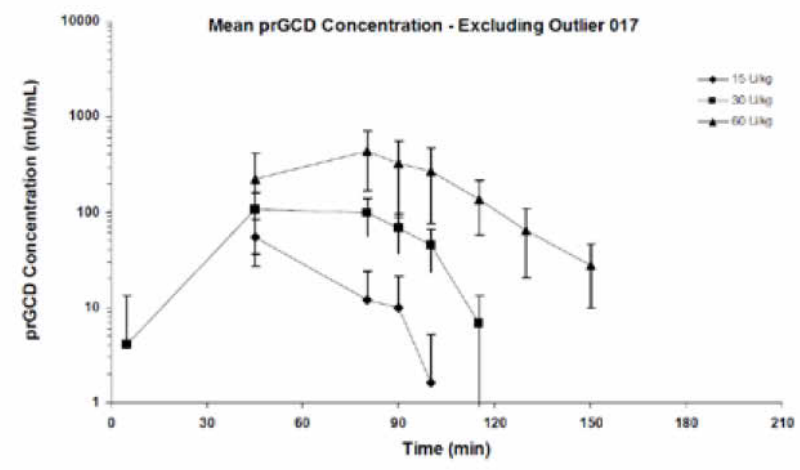
Table 1: Study P-01-2005 – Mean plasma taliglucerase alfa PK parameters (with and without subject 17).

Dose (U/kg)	Subject	Half Life (min)	Tmax (min)	Cmax (mU/mL)	Cmax/ Dose	Tlast (min)	AUClast (mU•hr/mL)	AUClast/ 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

The mean taliglucerase alfa concentration - time profiles for each of the doses (excluding outlier subject 17) are summarised below in Figure 1.

Figure 1: Study P-01-2005 – Log mean plasma taliglucerase alfa concentration – time profiles excluding outlier subject 17.



Comment: This was a first-in-humans study with taliglucerase alfa. The study was of standard design for an initial safety and PK study in healthy subjects. Safety was the primary outcome in this study and the PK parameters were secondary outcomes. The safety and PK analyses were considered exploratory and descriptive in nature and were designed to give some insight into the relationship between the treatment and potential outcomes. The elimination of taliglucerase alfa was rapid for both the 30 and 60 units/kg doses, with the mean half-life (excluding subject 17) being 8 minutes [range: 8-9] and 17 minutes [range: 13-21], respectively. The mean half-life for the two doses was about 13 minutes, which suggests that mean steady-state plasma concentration is

reached at about 65 minutes (i.e. five half-lives). Therefore, on average steady-state plasma concentration should be reached before the end of the 90 minute infusion. In the analysis without subject 17, mean AUC_{last}, mean $C_{max.last}$ and mean T_{last} increased with dose. However, the mean data for the AUC_{last} and the $C_{max.last}$ suggest that exposure is greater than dose proportional over the range 15, 30, and 60 units/kg. At 24 hours after the initiation of the infusion, plasma concentrations of taliglucerase alfa were not detectable following the 30 and 60 units/kg doses. However, subject 17 had detectable concentrations following the 15 units/kg dose at 24 hours, but not following the 30 and 60 units/kg doses.

4.1.1.2. Study PB-06-001 – Patients with gaucher disease

4.1.1.2.1. Overview

Study PB-06-001 was the pivotal Phase 3, multi-centre, randomized, double-blind, parallel group, dose-ranging trial to assess the safety and efficacy of taliglucerase alfa in 30 untreated patients with GD. Patients received iv infusion of taliglucerase alfa every two weeks and the duration of treatment was 9 months. At the end of the 9-month treatment period eligible patients were offered enrollment in a double blind extension study. In addition to the efficacy and safety data (evaluated later in this CER), the study also included PK data and these results are evaluated in this section of the CER.

The study included male and female patients 18 years or older with a diagnosis of GD (leukocyte GCD activity level ≤ 3 nM/mg.hr [≤30 % of the mean activity of the reference range]. The inclusion and exclusion criteria are provided in the submission.

4.1.1.2.2. Pharmacokinetic analysis

There were two treatment groups with different doses: Group I, 30 units/kg every 2 weeks; and Group II, 60 units/kg every 2 weeks. The initial infusion rate was 1.2 mL/min for all patients. If the initial infusion rate was well tolerated then it could be increased up to 2.25 mL/min to deliver the 135 mL volume over 1 hour for all subsequent dosing. However, at the request of the sponsor most infusions were administered over 120 minutes at a rate of 1.125 mL/min in a total volume of 135 mL.

Blood samples for plasma taliglucerase alfa concentration were obtained at Baseline and after 9 months of treatment. Samples 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.

Plasma was shipped frozen to MBR (Skokie, IL USA) for analysis. Quantitation of taliglucerase alfa in human K3EDTA plasma was conducted at MBR using a validated electrochemiluminescent (ECL) procedure [study MBR07-300], with a range of 7.8-1,000 ng/mL, a precision of 18.67% (CV), and an accuracy of 18.88% (RE).

The plasma concentrations of taliglucerase alfa were reported as ng/mL by the analytical laboratory, and the protocol specified that administered dose was calculated on basis of enzyme U/kg. In the cases where the dose was needed for a PK parameter, the dose in enzyme units was converted to dose in mg using the conversion factor 1 unit = 0.02855 mg.

4.1.1.2.3. Pharmacokinetic parameters

Plasma concentrations reported as below the limit of quantitation were assumed to be 0 ng/mL for the calculation of the mean concentrations and pharmacokinetic parameters. The following parameters were calculated for Day 1 and Week 38:

- $AUC_{0\text{-}t}$: Area under the curve from the start of the infusion to the last measurable concentration above the limit of quantitation was calculated using linear trapezoidal estimation.
- C_{max}: Maximum observed concentration.

- T_{max}: Time associated with C_{max}.
- C_{max}/Dose (NC_{max}): Calculated using the total dose of taliglucerase alfa expressed in mg. Since C_{max} depends not only on total dose, but also on the rate of infusion (100 mg) infused over 1 hr will produce a higher C_{max} than 100 mg infused over 2 hr, only those results for infusion lengths between 1.8 and 2.2 hr were included in the summary statistics.
- AUC_{0-t}/Dose ($NAUC_{0-t}$): Calculated using the total dose of taliglucerase alfa expressed in mg. This parameter provided an indication of the dose-proportionality.
- k_e and t½ : These parameters were calculated using a minimum of three post-infusion concentrations above the limit of quantitation. The results were considered reliable if the coefficient of determination, r^2, was greater than 0.8. Results not meeting this criterion were listed, but not included in the summary statistics.
- $AUC_{0-\infty}$: Calculated for those patients with reliable values for k_e. $AUC_{0-\infty}$ was considered reliable only if the percent of extrapolation from AUC_{0-t} to $AUC_{0-\infty}$ was < 25%.
- CL and Vz: These were calculated by WinNonlin using equations based on dose, AUC_{0-t}, and k_e. The number of reliable results were limited to those patients which had k_e and $AUC_{0-\infty}$ which passed the criteria of $r^2 > 0.8$ and % extrapolation < 25%.

The protocol specified that C_{min} was to be calculated. However, this parameter was not calculated as it was not considered relevant given that the half-life of taliglucerase alfa was only 15 minutes and the dose was administered as an iv infusion over 120 minutes every 2 weeks (i.e. dosing was pharmacokinetically equivalent to a series of single doses). Similarly, the volume of distribution at steady state (Vss) was not calculated, but the volume of distribution during the terminal elimination phase (Vz) was calculated.

4.1.1.2.4. Population for pharmacokinetic analysis

All patients with plasma concentration data for taliglucerase alfa on Day 1 and/or Week 38 were included in the PK analysis with the following exceptions: (1) On Day 1, the infusions were stopped and restarted for 4 patients. Consequently it was not possible to calculate the PK parameters for these patients given the short half-life of taliglucerase alfa, and the mathematics used by the WinNonlin non-compartmental model which assumes a constant infusion and balances the infusion rate with the elimination rate to calculate the PK parameters; and (2) If there were too many missing samples at crucial times for the reliable determination of C_{max} or AUC_{0-t}, the patient was excluded.

The PK population is summarised below in Table 2. There were 5 patients excluded from the 30 units/kg dose group analysis (4 due to interruption of the infusion on Day 1, and 1 due to incomplete collection of samples on Day 1). The available data from these 5 excluded patients (30 units/kg, Day 1) were analysed by the sponsor and did not alter the conclusions regarding the PKs of taliglucerase alfa derived from the 10 included patients.

None of the available patients at Week 38 in both treatment groups were excluded from the PK analysis at this time point.

Two samples from two patients were identified as “outliers” and not included in the PK analysis: 1 patient had a sample that was taken at unknown time after the start of the infusion; and 1 patient had sample with a prominent peak concentration of unknown cause 30 minutes after the end of the Week 38 infusion (i.e. at 150 minutes).

Table 2: Study PB-06-001 – Pharmacokinetic population.

Dose Group (U/kg)	Sampling Day	Total Number of Patients	Patients in Pharmacokinetic Population
30	Day 1	15	10
	Week 38	14	14
60	Day 1	16	16
	Week 38	15	15

4.1.1.2.5. Results – Plasma concentrations of taliglucerase alfa

The mean plasma taliglucerase alfa concentrations were only evaluated for patients with 120 minute infusions for consistency. For the patients with 120 minute infusions, the mean concentrations were calculated for each dose group and each sampling day. The mean plasma concentrations for patients with 120 minute infusions are summarised below in Table 3.

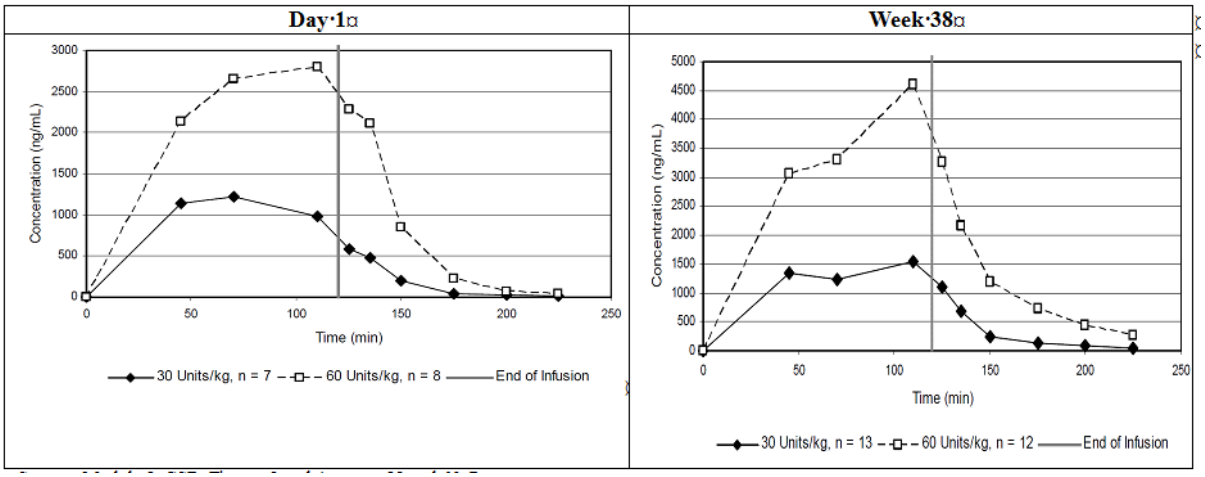
Table 3: Mean plasma concentration or taliglucerase alfa for patients with 120 minute infusions.

	Mean Concentration (ng/mL) for 30 U/kg		Mean Concentration (ng/mL) for 60 U/kg	
Time (min)	Day 1 (n = 7) Mean ± SD	Week 38 (n = 13)[a] Mean ± SD	Day 1 (n = 8) Mean ± SD	Week 38 (n = 12) Mean ± SD
0	2.77 ± 7.33	3.11 ± 7.65	1.46 ± 4.14	2.68 ± 9.30
45	1,137 ± 402	1,352 ± 1,147	2,131 ± 975	3,061 ± 1,422
70	1,217 ± 479	1,232 ± 641	2,653 ± 721	3,315 ± 1,625
110	984 ± 461	1,540 ± 1,147	2,800 ± 966	4,602 ± 3,186
125	581 ± 528	1,104 ± 903	2,277 ± 1,036	3,259 ± 2,459
135	473 ± 403	689 ± 751	2,107 ± 1,415	2,154 ± 2,211
150	203 ± 199	247 ± 422	844 ± 915[c]	1,186 ± 1,774[d]
175	46.3 ± 31.1	128 ± 301	228 ± 206	732 ± 1,029[d]
200	22.2 ± 16.0	93.5 ± 235.6[b]	68.9 ± 48.2	448 ± 649[d]
225	13.7 ± 15.4	50.4 ± 136.1	33.9 ± 24.4[e]	254 ± 460[e]

[a] Group includes one patient with a 119-minute infusion.
[b] n = 12 [c] n = 7 [d] n = 11 [e] n = 10

The mean plasma concentration taliglucerase alfa – time plots (linear) for the 120 minute infusions on Day 1 at Week 38 are summarised below in Figure 2.

Figure 2: Study PB-06-001 – Mean plasma concentrations of taliglucerase alfa for 120 minute infusions on Day 1 and at Week 38; linear plots.



4.1.1.2.6. Results – Pharmacokinetic parameters of taliglucerase alfa

The mean ± SD PK results for taliglucerase alfa for the two doses (30 and 60 units/kg) on Days 1 and at Week 38 are summarised below in Table 4.

Table 4: Study PB-06-001 – Pharmacokinetic parameters in patients with GD.

	30 U/kg, Mean ± SD (Range)		60 U/kg, Mean ± SD (Range)	
	Day 1, n = 10	Week 38, n = 14	Day 1, n = 16	Week 38, n = 15
C_{max} (ng/mL)	1,556 ± 742 (637 - 3,275)	1,656 ± 1,116 (720 - 4,989)	4,250 ± 2,230 (1,792 - 10,351)	5,153 ± 3,099 (1,834 - 12,504)
T_{max} (min)	82.5 ± 42.1 (45.0 - 175)	82.5 ± 42.1 (45.0 - 125)	86.6 ± 28.4 (45.0 - 135)	95.0 ± 28.8 (45.0 - 135)
AUC_{0-t} (ng•hr/mL)	2,229 ± 669 (807 - 3,082)	2,654 ± 2,130 (1,002 - 9,546)	6,349 ± 2,200 (2,877 - 10,077)	7,665 ± 4,578 (2,545 - 20,496)
$AUC_{0-\infty}$ (ng•hr/mL)	2,244 ± 674 (810 - 3,119)	2,706 ± 2,270 (1,007 - 10,092)	6,383 ± 2,229 (2,885 - 10,265)	7,814 ± 5,157[a] (2,548 - 21,020)
$t_{1/2}$ (min)	25.9 ± 11.8 (9.95 - 42.4)	25.1 ± 15.5 (9.20 - 57.9)	25.0 ± 10.1 (13.3 - 43.7)	34.8 ± 22.9[a] (11.3 - 104)
CL (L/hr)	29.4 ± 13.9 (16.8 - 56.4)	30.7 ± 14.5 (6.79 - 68.0)	20.5 ± 7.1 (10.0 - 35.6)	19.9 ± 9.6[a] (6.25 - 37.9)
V_z (L)	17.5 ± 11.1 (6.19 - 45.9)	16.8 ± 12.7 (6.95 - 55.3)	11.7 ± 4.5 (5.69 - 20.4)	14.4 ± 6.8[a] (3.91 - 24.8)

[a] n = 14

The dose normalised mean ± SD values for the C_{max} and AUC_{0-t} are summarised in Section 4.2.2.2.

> **Comment on PK Substudy**: This sub study provided important information on the pharmacokinetics of taliglucerase alfa in patients with GD at the clinically relevant proposed doses. Relevant comments relating to the results are provided below in the Summary of Pharmacokinetics (Section 4.2).

4.1.1.3. Comparison of PKs in healthy volunteers and patients with GD

The PKs of taliglucerase alfa in healthy subjects and patients with GD are summarised in below in Table 5.

Table 5: Summary of PK parameters in healthy volunteers (HV) and patients with GD (P).

Study/ Protocol # (Country)	Product Batch #	Study Objective	Study Design	# Subjects Entered/ Completed (M/F)	HV/P (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 DP 010106 DP	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	1,569	1,767	-	-	-	-	-
							30 U/kg	3,489	3,608	8	3.2	-	67.6	-
							60 U/kg	12,684	13,474	17	1.9	-	71.4	-
PB-06-001 (Multicentr er)	K-38743 DP K-39065 DP K-40306 DP PR2001 DP PR2002 DP	Efficacy, Safety and PK	Double blind, randomised, parallel dose groups	32/29 (16/16)	P (36.1, 19-74)	taliglucerase alfa (120 minute infusion)	30 U/kg Day 1	1,556	2,229	26	-	29	-	17.5
							Week 38	1,656	2,654	25	-	31	-	16.8
							60 U/kg Day 1	4,250	6,349	25	-	21	-	11.7
							Week 38	5,153	7,665	35	-	20	-	14.4

HV = Healthy Volunteers, P = Patients, PK: pharmacokinetics, CL: individual clearance, AUC: area under the curve, V: volume.

For batches: 021005 and 010106: Changes were made during pharmaceutical development mainly to adapt to the change in the manufacturing sites and lyophilisation. However, the analysis for release testing demonstrates that the drug product (DP) remains the same and these batches are defined as representative of commercial production.

Comment: It is considered that there is limited value in this submission in comparing the PKs of taliglucerase alfa in healthy subjects and patients with GD, given the difference in subject numbers between the two populations. The PK study in healthy volunteers was an exploratory, first in humans dose-escalating study primarily aimed at evaluating the safety and tolerability of taliglucerase alfa at the proposed doses. The results showed that systemic exposure to taliglucerase alfa, based on the C_{max} and the AUC, was notably higher in healthy subjects than in patients with GD following both 30 units/kg and 60 units/kg. In addition, the half-life was notably shorter in healthy subjects than in patients with GD. The observed difference in the PKs of taliglucerase alfa between healthy subjects and patients with GD might not indicate a true difference between the two populations, but might simply reflect the limited data in healthy subjects.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

4.2.1. Absorption

Taliglucerase alfa is administered by iv infusion. Consequently, data relating to oral absorption are not required.

4.2.1.1. Bioavailability

Taliglucerase alfa is administered by iv infusion. Consequently, data relating to bioavailability following oral administration are not required.

4.2.1.1.1. Bioequivalence of clinical trial and market formulations

The submission indicates that the "to-be-marketed" formulation of taliglucerase alfa was used in the Phase 1 and Phase 3 studies.

4.2.1.1.2. Bioequivalence of different dosage forms and strengths

The only formulation submitted for approval is a lyophilised powder for reconstitution with water for iv injection. The reconstituted solution contains 40 units of taliglucerase alfa per mL and the initial dosage range is 30 units/kg to 60 units/kg with dosage being individualised for each patient. There are no formal bioequivalence data for the 30 units/kg and 60 units/kg doses.

4.2.1.1.3. Bioequivalence to relevant registered products

There are no data assessing the bioequivalence of taliglucerase alfa to imiglucerase (the registered glucocerebrosidase). It is considered that such data are not required in this submission which includes "stand alone" clinical data supporting the approval of taliglucerase alfa.

4.2.1.1.4. Influence of food

Taliglucerase alfa is administered by iv infusion. Consequently, data relating to the influence of food on oral absorption are not required.

4.2.1.1.5. Dose proportionality

The PK study in patients with GD included dose normalised comparisons of C_{max} and AUC_{0-t} which showed that exposure to taliglucerase alfa was not dose proportional for the 30 units/kg and 60 units/kg doses, with the higher dose being associated with more than dose proportional increases in exposure (see Table 6, below).

Table 6: Study PB-06-001 – Mean (range) dose normalised C_{max} and AUC_{0-t} in patients with GD.

	30 U/kg, Mean ± SD (Range)		60 U/kg, Mean ± SD (Range)	
	Day 1, n = 10	Week 38, n = 14	Day 1, n = 16	Week 38, n = 15
NC_{max}	22.3 ± 7.6[a]	26.8 ± 16.8	28.1 ± 7.8[b]	42.4 ± 26.7[c]
(ng/mL/mg)	9.84 - 32.5	10.5 - 72.8	18.1 - 42.4	14.5 - 95.4
$NAUC_{0-t}$	39.1 ± 13.2	42.2 ± 30.4	54.3 ± 18.9	63.4 ± 33.9
(ng•hr/mL)/mg	17.7 - 59.3	14.6 - 139	28.0 - 98.0	26.3 - 156

Note: The values of NC_{max} were limited to those patients with infusions that were within 10% of 120 min.
[a] n = 8 [b] n = 10 [c] n = 13

The mean normalised AUC_{0-t} values for the 60 units/kg dose were 1.4-fold and 1.5-fold higher than for the 30 units/kg dose on Day 1 and at Week 38, respectively, with overlapping ranges at both time points for the two doses. The mean normalised C_{max} values for the 60 units/kg dose were 1.3-fold and 1.6-fold higher than for the 30 units/kg dose on Day 1 and at Week 38, respectively, with overlapping ranges at both time points for the two doses. These results suggest that the uptake of taliglucerase alfa into target cells is saturable.

As regards the raw data, the mean C_{max} on Day 1 was approximately 2.7 fold higher for the 60 units/kg dose (4,250 ng/ml) compared with the 30 units/kg dose (1,556 ng/ml), and the C_{max} at Week 38 was about 3.1-fold higher for the 60 units/kg dose (5,153 ng/mL) compared with 30 units/kg dose (1,656 ng/ml). The mean $AUC_{0-\infty}$ on Day 1 was 2.8-fold higher for the 60 units/kg dose (6,383 ng.hr/mL) compared with the 30 units/kg (2,244 ng.hr/mL), and the $AUC_{0-\infty}$ at Week 38 was about 2.9-fold higher for the 60 units/kg (7,814 ng.hr/mL) compared with the 30 units/kg dose (2,706 ng.hr/mL).

4.2.1.1.6. Bioavailability during multiple-dosing

The PK data in patients with GD indicate that exposure to taliglucerase alfa does not notably increase between Day 1 and Week 38 following dosing (iv infusion) once every 2 weeks at doses of 30 units/kg and 60 units/kg. The PK data in patients with GD indicates that exposure to taliglucerase alfa at a dose of 30 units/kg is similar on Day 1 and Week 38, as assessed by the C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. In patients with GD, exposure to taliglucerase alfa at a dose of 60 units/kg is approximately 1.2-fold higher at Week 38 compared with Day 1, as assessed by the C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.

4.2.1.1.7. Effect of administration timing

Taliglucerase alfa is administered by iv infusion over 1 to 2 hours once every 2 weeks. There are no data on whether administration at different times of the day results in different exposures to taliglucerase alfa. However, it is considered that such data are not required.

4.2.2. Distribution

4.2.2.1. Volume of distribution

In patients with GD, the mean volumes of distribution in the elimination phase (Vz) were 17.5 L [range: 6.2 to 50.0] and 16.8 L [7.0 to 55.3] at Day 1 and at Week 38, respectively, for the 30 units/kg dose, and the corresponding values for the 60 units/kg dose were 11.7 [range: 5.7 to 55.3] at Day 1 and 14.4 L [range: 3.9 to 24.8] at Week 38. In healthy volunteers, the volume of distribution (Vss) ranged from 34 to 94 mL/kg at 30 and 60 units/kg, which is consistent with the size of the human plasma compartment.

4.2.2.2. Plasma protein binding

There are no data on plasma protein binding. The sponsor considered that plasma protein binding studies were not applicable as taliglucerase alfa is a protein and not expected to significantly interact with plasma proteins. Plasma proteins are not a target of taliglucerase alfa.

4.2.2.3. Erythrocyte distribution

There were no studies in humans on erythrocyte distribution.

4.2.2.4. Tissue distribution

There were no studies in humans on tissue distribution. Cellular uptake of taliglucerase alfa is mediated by mannose receptors and distribution and uptake by tissues/target cells is receptor-driven.

4.2.3. Metabolism

There were no studies in humans on the metabolism of taliglucerase alfa. The sponsor did not perform metabolism studies for taliglucerase alfa since it is expected that the drug will be degraded to small peptides and individual amino acids that do not pose a safety concern. Therefore, in line with ICH 6, the sponsor considered that metabolism studies were not necessary.

The relevant TGA adopted guidelines on the clinical investigation of the pharmacokinetics of therapeutic proteins [CHMP/EWP/89249/2004] states that the metabolism of these products can be predicted, to a large extent, from the molecular size and specific studies may not be necessary. Catabolism of proteins usually occurs by proteolysis. Small proteins of MW < 50,000 Dalton (Da) are eliminated by renal filtration followed by tubular re-absorption and subsequent metabolic catabolism. For larger protein molecules (such as taliglucerase alfa with a MW of 60,800 Da) elimination in other tissues and/or in target cells (e.g. receptor mediated endocytosis followed by catabolism) is more important relative to renal function.

4.2.4. Excretion

There were no excretion studies in humans. The sponsor stated that clearance mechanisms are well known for proteins. The t½ of taliglucerase alfa is short with mean values ranging from 25.1 to 43.8 minutes, the mean CL ranges from 19.9 to 29.4 L/hr, and the T_{max} ranges from 82.5 to 95.0 minutes. The drug is rapidly cleared from the plasma suggesting extensive uptake into the target cells via the mannose receptors and/or rapid excretion.

4.2.4.1. Mass balance studies

There were no mass balance studies in humans. The relevant clinical guideline [CHMP/EWP/89249/2004] states that mass-balance studies are not useful for determining the excretion of pattern of therapeutic proteins and drug related material. Excreted proteins are not necessarily recovered in the urine or faeces as intact substances, but are instead metabolised and re-absorbed as amino acids and incorporated into general protein synthesis pathways.

4.2.5. Intra- and inter-individual variability of pharmacokinetics

The taliglucerase PK data in patients with GD demonstrated considerable inter-individual variability for all parameters based on the coefficients of variation and ranges. For the C_{max} values for both the 30 units/kg and the 60 units/kg dose at Day 1 and Week 38, the coefficients of variation ranged from 48% to 67%, with the corresponding values for the $AUC_{0-\infty}$ being 30% to 84%. There were no data on intra-individual variability.

4.2.6. Pharmacokinetics in the target population

The pivotal PK data in the submission related to the population with GD and were derived from patients in the pivotal Phase 3 efficacy and safety study. The PK data in healthy volunteers were exploratory and were derived from a small number of subjects exposed to taliglucerase alfa in a first-in-human Phase 1 safety study.

4.2.7. Pharmacokinetics in other special populations

4.2.7.1. Pharmacokinetics in subjects with impaired hepatic function

There were no PK studies in subjects with impaired hepatic function.

4.2.7.2. Pharmacokinetics in subjects with impaired renal function

There were no PK studies in subjects with impaired renal function.

4.2.7.3. Pharmacokinetics according to age

There were no studies investigating the effect of age on the PKs of taliglucerase alfa.

4.2.7.4. Pharmacokinetics related to genetic factors (sex, ethnicity, genetic polymorphism)

There were no studies in patients with GD investigating the effect of genetic factors on the PKs of taliglucerase alfa.

4.2.8. Pharmacokinetic interactions

The submission included no PK interaction studies. The sponsor states that no such studies have been conducted and that interactions with co-administered drugs subject to CYP3A4 metabolism are unlikely to occur.

4.3. Evaluator's overall conclusion on pharmacokinetics

The PKs of taliglucerase alfa has been studied in 6 young healthy adult subjects of both sexes (n=3 males, n=3 females) [study P-01-2005], and in 30 patients of both sexes with GD [study PB-06-001]. It is considered that the most relevant PK data relate to the patients with GD. The PK data in these subjects relate to the 30 units/kg and the 60 units/kg iv infusion doses of taliglucerase alfa proposed for approval. The basic PK parameters for both these doses were determined at Day 1 and Week 38 using standard non-compartmental methods, and plasma taliglucerase alfa concentrations were measured by a validated assay.

In patients with GD, the plasma concentration of taliglucerase alfa increased rapidly after initiation of the infusion and the T_{max} after both doses was reached prior to the conclusion of the 120 minute infusion at both Day 1 and Week 38. Following T_{max}, plasma concentrations rapidly decreased in what appears to be a bi-phasic fashion reaching baseline levels between 200 and 250 minutes after initiation of the infusion (i.e. 80 to 130 minutes after the end of the 120 minute infusion). The data indicate that taliglucerase alfa clearance is rapid and is consistent with uptake of the drug into macrophages via mannose receptors.

Exposure to taliglucerase alfa in patients with GD as assessed by the C_{max} and $AUC_{0-\infty}$ was greater after the 60 units/kg dose than after the 30 units/kg dose, but the increase in exposure was more than dose proportional. This suggests that uptake of taliglucerase alfa into target cells is saturable. The Day 1 and Week 38 exposure data were similar within the 30 units/kg group and within the 60 units/kg, suggesting that taliglucerase alfa does not accumulate with a once every 2 week treatment regimen repeated through to Week 38. Accumulation would be unusual given the mean short half-life of the drug (about 25 to 35 minutes) and the long interval between doses (2 weeks).

The mean t½ of taliglucerase alfa after 30 units/kg was 25.9 and 25.1 minutes at Day 1 and Week 38, respectively, with the corresponding values after 60 units/kg being 25.0 and 34.8 minutes. The half-life results indicate that times are similar for both doses at Day 1, but about 10 minutes longer for the higher dose at Day 38. The mean CL of taliglucerase alfa after 30 units/kg was 29.4 and 30.7 L/hr at Day 1 and Week 38, respectively, with the corresponding values after 60 units/kg being 20.5 and 19.9 L/hr. The clearance results suggest that clearance is slower following the higher dose at both Day 1 and Week 38.

The mean T_{max} of taliglucerase alfa after 30 units/kg was 82.5 minutes at both Day 1 and Week 38, with the corresponding values after 60 units/kg being 86.6 and 95.0 minutes. The T_{max} values were longer for the higher dose at both Day 1 and Week 38. The mean Vz of taliglucerase alfa after 30 units/kg was 17.5 and 16.8 L/hr at Day 1 and Week 38, respectively, with the corresponding values after 60 units/kg being 11.7 and 14.4 L/hr. The Vz values were lower for the higher dose at both Day 1 and Day 38.

Overall, there was marked inter-subject variability in the PK parameters for both doses in patients with GD, with the ranges being wide and overlapping for the two doses. However, the mean values for the t½, CL, Vz and T_{max} values differed for the two doses suggesting non-linear pharmacokinetics for 30 and 60 units/kg doses. There was no marked difference in the t½, CL, Vz and T_{max} parameters as assessed on Day 1 and at Week 38 for either the 30 or 60 units/kg doses.

The PK profile of taliglucerase alfa has not been completely characterised. This is not unusual given that the drug is an orphan with a small number of patients available for study. PK data were available for young healthy adults with the mean ± SD age 26 ± 6 years, and patients with GD of mean age of about 36 years [range: 19 to 74]. There were no PK data in paediatric, adolescent, or elderly subjects. There were no data comparing PKs in males and females with GD. In healthy volunteers it was stated that there was no difference in the PKs between males (n=3) and females (n=3), but the data confirming this statement could not be located in the CSR.

There were no PK data on metabolism or excretion of taliglucerase alfa. The relevant clinical guideline [CHMP/EWP/89249/2004] indicates that while the main elimination pathway should be identified this could be predicted for therapeutic proteins from the molecular size. Therefore, specific studies exploring the main elimination pathway may not be necessary. There are no PK data exploring potential interactions between taliglucerase alfa and other drugs. However, as with other enzyme replacement therapies, drug-drug PK interactions are not expected.

There are no PK data in subjects with hepatic impairment. The clinical overview argues that "despite the fact that all patients with GD have liver involvement most of the patients do not have functional liver impairment so that patients without hepatic dysfunction and GD were not studied due to population relevance". The argument is not unreasonable as clearance of taliglucerase alfa is unlikely to be through hepatic metabolism.

There are no PK data in subjects with renal impairment. However, the relevant clinical guideline [CHMP/EWP/89249/2004] indicates that for protein molecules with a MW larger than 50,000 Da elimination through methods other than renal filtration is of greater relative importance. Taliglucerase alfa meets this criterion as it has a MW of approximately 60,000 Da. The clinical overview argues that "renal impairment is extremely rare in patients with GD, and that when it does occur it is usually in the form of renal hyperfiltration which has no detrimental effect on patients [Becker-Cohen et al., 2005]". In a study of 161 patients with GD, Becker-Cohen et al (2005) found no patients with decreased renal function despite the multi-organ nature of the disease. Glomerular hyperfiltration was observed in a proportion of patients, particularly those with markers of more severe disease, but this did not seem to be associated with a subsequent decline in renal function.

5. Pharmacodynamics

The submission included no specific studies investigating the pharmacodynamics of taliglucerase alfa in humans. However, the mechanism of action of enzyme replacement therapy for the treatment of GD is well established. The sponsor states that comparative characterisation studies demonstrate that taliglucerase alfa and imiglucerase have similar profiles when analysed by SDS-PAGE, Western Blot, RP-HPLC, kinetic evaluation and macrophage cellular uptake, but have differences in IEF profile, AA sequence, and glycan

structural analysis. Their active sites as demonstrated by X-ray crystallography are similar. The sponsor also states that studies confirmed the structure of taliglucerase alfa and showed higher levels of terminal mannose compared with imiglucerase, which plays an important role in the targeting and uptake of taliglucerase alfa to macrophages, mediated by the Mannose/N-acetylglucosamine (Man/GlcNAc) receptor.

6. Dosage selection for the pivotal studies

The dose range of taliglucerase alfa of 30 or 60 units/kg was chosen for the pivotal study [PB-06-001] based on previous efficacy and safety study results with commercially available imiglucerase, with supporting nonclinical studies showing comparable potency and safety to that of imiglucerase.

7. Clinical efficacy

7.1. Pivotal efficacy study [PB-06-001]

7.1.1. Study design, objectives, locations and dates

The objective of this Phase 3, multi-national (9 countries), multi-centre (11 centres), randomized, double-blind, parallel-group, dose-ranging study was to assess the safety and efficacy of taliglucerase alfa in 30 untreated patients with GD. Patients received an iv infusion of taliglucerase alfa (30 units/kg or 60 units/kg) every two weeks, and the duration of the study was 9 months. At the end of the 9 month treatment period (21 visits, 20 infusions, 38 weeks) eligible patients were offered enrollment in a double blind extension study.

The study was undertaken in Israel, South Africa, UK, Spain, Italy, Canada, Serbia, Mexico, and Chile. The study was sponsored by Protalix Biotherapeutics, Israel. The co-ordinating investigator was located in the Shaare Zedeck Medical Center, Jerusalem, Israel. The first patient was enrolled on 5 August 2007 and the last patient completed on 11 September 2009. The original protocol, Informed Consent Form (ICF), and all other relevant documents were reviewed by the Institutional Review Board (IRB) or Ethics Committee (EC) associated with the study site, and approved prior to study initiation. The IRBs and the regulatory authorities were informed of, and approved, all subsequent protocol amendments prior to their implementation. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines. All patients provided written informed consent.

The study included a screening visit (Visit 0, Day -25±20) at which comprehensive medical assessment was undertaken and eligibility for inclusion was determined. The first treatment was administered at Visit 1 (Baseline, Day 1) and after taliglucerase alfa dosing patients were observed clinically for a minimum of 2 hours, vital signs were evaluated every 15 minutes for the first hour and then every 30 minutes if the patient tolerated the infusion, the injection site was evaluated, and follow-up telephone call with the patient was held the day after the infusion. Subsequent treatments with taliglucerase alfa were performed at 2 weekly intervals from Visit 2 to 20, with the last treatment being at Visit 20 (Month 9, Week 38±7 days) and outcomes being assessed at this visit.

Efficacy assessments were performed at baseline (Visit 1), Month 6 (Visit 14) and Month 9 (Visit 20, the end of study). The PK profile was assessed at baseline and the end of study (Month 9). Safety parameters (AEs and concomitant medications) were recorded at each iv infusion visit. Haematology, biochemistry, urinalysis, anti-human prGCD antibodies were determined at baseline, Weeks 2, 4, 6 and 8 and then monthly (every other visit) up to Month 9, and the ECG was performed during the efficacy assessments. Additional safety parameters (pulmonary

function tests, echocardiography, DEXA and QCSI) were performed at baseline, and the end of study (Month 9). The study schedule is provided in the dossier.

> **Comment**: The study planned to enrol 30 patients with GD. This is a small number of patients, but given the rarity of GD it is unrealistic to expect studies of this condition to enrol a large number of patients. This study had no placebo or active (i.e. imiglucerase) control. The sponsor states that a placebo control group was not considered ethical for treating this population of moderately to severely affected GD patients for 9 months. However, there appears to be no reason for not having included an imiglucerase control group. The addition of such a group would have allowed for a double-blinded comparison between taliglucerase alfa and imiglucerase. The absence of an imiglucerase control group is considered to be a deficiency in the study design as it introduces well known biases into the interpretation of the outcomes. This deficiency is mitigated, to some extent, by the fact that GD does not improve spontaneously. Therefore, the natural history of the disease suggests that if improvement occurs with taliglucerase alfa then this is likely to be causally related to treatment with the drug. The 9 month double-blind treatment duration for the two randomized doses of taliglucerase alfa is considered sufficient to provide data on the efficacy of the drug as enzyme replacement therapy.
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> The clinical overview included an extensive discussion of the study design of the pivotal study. The overview states that the design was extensively discussed with key opinion leaders (KOLs) including European GD experts. The study was designed to align with the TGA adopted CHMP guideline "Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study" [CPMP/EWP/2330/99]. In addition, the study was accepted under Special Protocol Assessment (SPA) with the FDA. The sponsor states that the comparator arm was the subject of "major discussion". Reference was made to the TGA adopted CHMP guideline on "Choice of Control Group in Clinical Trials" [CPMP/ICH/2711/99, ICH E10], which states "in cases where an available treatment is known to prevent serious harm, such as death or irreversible morbidity in the study population, it is generally inappropriate to use a placebo control". The sponsor elected for ethical reasons not to include a placebo comparator arm.
>
> Furthermore the sponsor elected not to include an active imiglucerase arm in the study. Instead it chose to investigate two different taliglucerase alfa comparator arms for "medical reasons and in the interest of patients". The sponsor noted that current clinical dosing protocols for ERT for the management of GD are still based on consensus rather than on "Level 1 scientific grounds evidence". Consequently, the sponsor considered that "it seemed most prudent to design a two arm study that looked at two different [taliglucerase alfa] dose levels". Dose selection was (i) based on experience with Cerezyme, (ii) on the currently available national guidelines for the management of GD, (iii) on the selection of a distinctly lower dose that would give well controlled information on its efficacy, and (iv) strongly supported by more than 20 KOLs worldwide including experts from the UK, The Netherlands, Italy, France and Spain.
>
> Despite the sponsor's extensive justification for including two doses of taliglucerase alfa in the study, it still remains unclear why the sponsor chose not to include a control imiglucerase comparator arm. The reason appears to be that the sponsor considered that, at the time the study was designed, there was still no consensus on the optimal imiglucerase doses for the treatment of GD, "except that 60 U/kg is considered a high but efficacious dose". However, the clinical evaluator considers that the study would have been strengthened by the inclusion of an imiglucerase comparator arm.

7.1.1.1. Inclusion and Exclusion criteria, and Discontinuation criteria

The study included males and females, 18 years or older, with a diagnosis of GD with leukocyte glucocerebrosidase (GCD) activity level ≤ 3 nM/mg.hr (≤ 30 % of the mean reference range). In

addition, patients were required to have splenomegaly defined as greater than eight times the expected volume (measured volume divided by estimated volume [0.2% of body weight]) as determined by MRI volumetric analysis, and thrombocytopaenia (defined as platelet counts <120,000 per mm^3) with or without anaemia (defined by Hb of least 1 g/dL below normal range according to sex and age). The inclusion criteria also included patients who had not received ERT in the past, patients who had not received ERT in the past 12 months and had a negative anti-glucocerebrosidase antibody test, and patients who had not received substrate reduction therapy (SRT) in the past 12 months. The exclusion criteria were satisfactory and excluded patients with severe neurological signs and symptoms characteristic of NGD. The inclusion and exclusion criteria are summarised in the dossier.

The study also included satisfactory criteria for prematurely discontinuing the study. The details of all discontinuations were collected and recorded, and thorough efforts were required to follow-up and document the outcome of discontinuations due to adverse events. If circumstances prevented the patient from completing all visits, every attempt was made to complete all procedures listed for Visit 20. The discontinuation criteria are summarised in the dossier.

7.1.1.2. Study treatments

Eligible patients were randomized centrally to one of the two treatment groups (1:1) by site using a unique randomization number which included the site and patient number. Patients were randomized to receive taliglucerase alfa iv infusions of 30 units/kg or 60 units/kg every 2 weeks. Individual doses for each randomized patient were prepared according to the patient's weight. For practical reasons, the dose in terms of total units was rounded up to avoid use of partial vials (e.g. a 65 kg patient assigned to 30 units/kg received 2000 units [i.e. 10 vials] but the calculated dose was 1950 units). Each dose was prepared by an unblinded pharmacist at each site. A dose adjustment check was performed every three months, and if a patient's weight changed ± 5% from the previous weight the dose was adjusted according to the new weight.

The human taliglucerase alfa final concentration was 40 units/mL after reconstitution with 5.1 mL of sterile water for injection. The reconstituted volume was 5.3 mL (40 units/mL) which results in a withdrawal volume of 5 mL (200 units). The solution was mixed gently until clear, and the required amount of enzyme units was adjusted with normal saline (0.9%) up to 135 mL/infusion. A unit is defined as the amount of enzyme that catalyzes the hydrolysis of 1 micromole of the synthetic substrate paranitrophenyl-beta-D-glucopyranoside (pNP-Glc) per minute at 37°C. Human taliglucerase alfa vials were stored lyophilized at 2-8°C.

As this study was the first to administer taliglucerase alfa to GD patients, the first three enrolled patients received the study drug in a staggered schedule with sufficient time between infusions to evaluate the patients for adverse experiences. For initial infusions in all patients, taliglucerase alfa was administered at a rate of 1.2 mL/min. The tolerability of the infusion was determined by signs and symptoms during the infusion, for 1 hour after the infusion in the clinic, and by telephone contact the day after the infusion. The infusion rate was adjusted according to individual patient signs and symptoms using a Protocol specified algorithm. If the rate of infusion was well tolerated it could be increased up to 2.25 mL/min to deliver the 135 mL volume over 1 hour for all subsequent dosing. However, during the study, the sponsor notified all investigators that all subsequent infusions should occur over a 2 hour period to minimize the potential for increased risk of infusion reactions due to faster infusion rates.

7.1.1.3. Blinding

Investigators and patients were blinded to the identity of the treatment. In addition, the sponsor, CROs, laboratories and the central MRI reader were also blinded to the patient's identity. Blinded interim safety data were reviewed by an independent DMC. Knowledge of the randomization code was limited to the persons responsible for the creation of the randomization code and implementation into the eCRF, preparation of the study medication

(site pharmacist), and unblinded monitors and personnel responsible for product accountability. Unblinded study personnel did not have access to the clinical data and were not involved in the management of the study. Except in specified circumstances relating to patient safety, the code was not to be broken until after data entry was complete, the validity of the data checked, all queries resolved, and the database locked. The medication code could be broken only in the event of an adverse event (AE) that the investigator felt could not be adequately treated without knowing the identity of the study drug.

7.1.2. Efficacy variables and outcomes

The primary efficacy endpoint was the percent change from baseline of spleen volume after 9 months of treatment with taliglucerase alfa.

> **Comment:** The inclusion criteria included patients with splenomegaly defined as greater than eight times the expected volume as determined by MRI volumetric analysis. Published data defines splenomegaly as a splenic mass greater than the normal 0.2% of total body weight in kilograms. It has been estimated that the pre-treatment spleen volume is greater than five times normal in about 90% of all symptomatic non-splenectomized patients with type 1 disease [Pastores et al., 2004]. Therapeutic goals for patients with splenomegaly are to reduce spleen volume to ≤ 2 – 8 x normal, alleviate discomfort due to splenic enlargement (abdominal distension, early satiety) and abdominal pain due to recurrent episodes of splenic infarction, and eliminate hypersplenism. This study was powered to detect a change from baseline in spleen volume of greater than 20%. Based on previous research, a normal spleen volume is expected to be approximately 0.12 L, and patients in this study were expected to have spleen volumes 8 times this size (i.e. approximately 0.96 L). Therefore, a 20% reduction in spleen volume in patients in this study was anticipated to be equal to an 0.192 L change in mean spleen volume, and was considered to be clinically meaningful.

The major secondary efficacy endpoints were the change from baseline at Month 9 of haemoglobin level, liver volume (percent), and platelet count. The other secondary outcome measures were biomarkers (chitotriosidase or pulmonary and activation-regulated chemokine [PARC/CCL18]), and the proportion of patients with greater than 10% reduction in spleen volume at 9 months.

> **Comment:** Haemoglobin was analysed at a central laboratory. Platelet counts were measured in local laboratories because of the instability in the measurement associated with shipment time and conditions. Thrombocytopaenia was an inclusion criteria for this study, but patients with or without anaemia could be included in the study. The mean haemoglobin level at baseline was within normal limits for both treatment groups. The generally accepted target for all GD patients with thrombocytopaenia is to increase platelet counts during the first year of treatment sufficiently to prevent surgical, obstetrical and spontaneous bleeding [Pastores et al., 2004]. In clinical practice, significant increases in haemoglobin levels are expected in patients with GD during the first 6 months of treatment even in the most severely effected patients (i.e. Hb < 8.0 g/dL) [Pastores et al., 2004].
>
> Liver volume was measured by MRI, and a 10% reduction in liver volume was considered to be a clinically relevant change. Hepatomegaly was not an inclusion criterion and not all patients enrolled in the study had significantly enlarged livers at baseline. Reduction in liver volume to 1.0 to 1.5 times normal in patients with hepatomegaly is a therapeutic goal of ERT for GD [Pastores et al., 2004].
>
> Plasma chitotriosidase biomarker levels reflect the sum of secreted enzyme by Gaucher cells [Boot et al., 2009], and is used in Australia to monitor patients receiving treatment with imiglucerase or miglustat [Life Saving Drugs Program, 2010]. Serum from patients with GD show an increase in chitotriosidase activity of up to 1000-fold compared with

individuals without the disease [Boot et al., 2009]. The biomarker PARC/CCL18 has been found to be particularly useful in those patients (about 5%) who do not express chitotriosidase.

The tertiary efficacy endpoints were quantitative chemical shift imaging (QCSI) used for long-term follow up in a small subpopulation of patients to measure bone infiltration, and dual energy X-ray absorptiometry (DEXA) to measure change in bone mineral density.

7.1.3. Statistical analyses and sample size

7.1.3.1. Primary efficacy analysis

The primary efficacy analysis was based on one-sample t-tests for each dose group. The null hypothesis was that the percent change in spleen volume was zero and the alternative hypothesis was that the percent change in spleen volume was not equal to zero. The analysis was performed on the ITT population (i.e. patients who received at least one dose of medication and had at least the screening/baseline MRI evaluation), and the PP population (i.e. all ITT patients who completed 9 months and had no major protocol violations.). The primary efficacy analysis in the ITT population used the multiple imputation (MI) method to account for missing data (ITT MI).

With 12 patients in each treatment group (taliglucerase alfa 30 and 60 units/kg), there was greater than 95% power to detect a change of 20% more in spleen volume using a one-sample t-test (alpha=0.025, 2-sided test to allow for each group to be tested separately) to evaluate the primary outcome of percent change in spleen volume after nine months. This calculation was based on the assumption that the standard deviation (SD) for the percent change in spleen volume would be 12%. However, if the actual SD was as large as 19% there would still have been a power of 83% to detect a difference of at least 20% in spleen volume between screening and Month 9. No formal statistical comparisons between treatment dose groups of 30 and 60 units/kg were proposed, but the final study report included comparison of the two groups.

7.1.3.2. Secondary efficacy analyses

Three major secondary endpoints were selected for confirmatory evidence of efficacy: mean change in haemoglobin; percent change in liver volume; and mean change in platelet count. The three secondary efficacy endpoints were examined in a sequential (step-down) approach. First, the primary efficacy analysis (spleen volume) was performed at each dose level and if shown to be significant for either one or both doses, the mean change in haemoglobin was tested for that dose (or doses) using an alpha level of 0.025 to allow each dose to be tested. Next, if the percent change in haemoglobin (major secondary efficacy endpoint) was shown to be significant for either one or both doses, then the percent change in liver volume (major secondary efficacy endpoint) was tested for that dose (or doses) using an alpha level of 0.025 to allow each dose to be tested. Finally, if percent change in liver volume was shown to be significant for either one or both doses, then mean change in platelet count (major secondary efficacy endpoint) was tested for that dose (or doses) using an alpha level of 0.025 to allow each dose to be tested.

For each of the major secondary efficacy endpoints, a one-sample t-test was examined first for each dose using the step-down approach. Next, a mixed effects model that included dose and time, with subject as a random effect, was fitted to examine whether there was a difference between dose groups, for those outcomes that were tested in the step-down approach. All secondary efficacy analyses were performed on the ITT and PP populations.

Based on previous studies, the expected SD for mean change in haemoglobin was 15%, and with 12 patients on each dose there was an 84% power to detect a mean change in haemoglobin equal to 16% of the baseline mean (or approximately 1.07 standard deviations of the mean change in haemoglobin), assuming a 2-sided test with alpha=0.025 (using a one sample t-test of whether the mean change was zero versus an alternative that it was not zero). Based on previous studies, the expected SD for the change in liver volume was 10%, and with 12 patients

on each dose there was an 86% power to detect a change in percent liver volume equal to 11%, assuming a 2-sided test with alpha=0.025 (using a one sample t-test of whether the mean percent change was zero versus an alternative that it was not zero). The expected SD for mean change in the platelet count was 46%, and with 12 patients on each dose there was an 81% power to detect a change in platelet count of 47%, assuming a 2-sided test with alpha=0.025 (using a one sample t-test of whether the mean change was zero versus an alternative that it was not zero).

7.1.3.3. Sensitivity analyses

Patients who withdrew early were analysed in several ways in order to examine the sensitivity of the study results to different assumptions concerning missing data. First, the primary efficacy analysis was performed using a multiple imputation (MI) approach to predict missing values from all observed results for both doses. The MI was undertaken using standard statistical methods performed by SAS software.

In addition to the MI primary efficacy method to impute missing data, sensitivity analyses were performed using different statistical methods to impute missing data. A no-change from baseline imputation method was used to determine efficacy for patients with SAEs and missing efficacy data. Patients with missing efficacy data and no SAEs were analysed using a last observation carried forward (LOCF) imputation method. The results from this sensitivity analysis were compared with those from the primary efficacy analysis which used the MI approach.

7.1.3.4. Interim analyses

Blinded interim safety data reviews were conducted on three occasions during the study by an independent Data Monitoring Committee (DMC). There were no interim efficacy analyses.

7.1.4. Patient disposition

The study screened 44 patients, and 33 of these patients were eligible and randomized to 30 units/kg (n=16) or 60 units/kg (n=17). Of the 33 randomized patients: 32 patients received treatment (30 units/kg [n=16], 60 units/kg [n=16]); 29 patients received treatment and completed all study visits (30 units/kg [n=14]; 60 units/kg [n=15]); 3 patients received treatment and discontinued prematurely (2 experienced AEs [1 in each treatment group], and 1 in the 30 units/kg group became pregnant [major protocol violation]; and 1 patient randomized to 60 units/kg voluntarily withdrew for personal reasons and did not receive study treatment.

The study included 24 patients with 50 protocol violations. The majority of the deviations were visits outside of scheduled window, or study procedures such as QCSI, ECG, DEXA or MRI that were not performed according to the protocol schedule. The Medical Director approved randomization of 4 patients whose laboratory values did not meet the protocol inclusion criteria: i.e. 2 patients with glucocerebrosidase activity levels that were >3 nM/mg.hr; and 2 patients with platelet counts that were >120,000/mm^3.

> **Comment:** The number of patients included in the efficacy analyses indicates that the study was satisfactorily powered to assess the primary and secondary efficacy outcomes (based on the data used to estimate the sample size). The majority of patients had one or more protocol violations. However, examination of these violations suggests that these were not sufficiently serious to invalidate the study.

7.1.4.1. Patient demographics

The patient demographics are summarised below in Table 7. Analysis for GD mutations was performed at Visit 1 and showed that 14 patients had homozygous mutations and 17 patients had heterozygous mutations.

Table 7: Study PB-06-001 – Patient demographics; ITT population.

PARAMETER		prGCD 30 units/kg N = 15	prGCD 60 units/kg N = 16	Overall N = 31
AGE (yrs) at INFORMED CONSENT	N	15	16	31
	MEAN	36.3	36.0	36.1
	SD	12.2	12.2	12.0
	MEDIAN	35.0	33.0	35.0
	RANGE	19 to 74	19 to 58	19 to 74
GENDER	N	15	16	31
	MALE	7(46.7%)	8(50.0%)	15(48.4%)
	FEMALE	8(53.3%)	8(50.0%)	16(51.6%)
RELIGION	N	15	16	31
	JEWISH - ASHKENAZI	6(40.0%)	4(25.0%)	10(32.3%)
	JEWISH - NON ASHKENAZI	0(0.0%)	0(0.0%)	0(0.0%)
	NON JEWISH	9(60.0%)	12(75.0%)	21(67.7%)
RACE/ETHNICITY	N	15	16	31
	CAUCASIAN	15(100.0%)	15(93.8%)	30(96.8%)
	AFRICAN AMERICAN	0(0.0%)	0(0.0%)	0(0.0%)
	NATIVE AMERICAN	0(0.0%)	0(0.0%)	0(0.0%)
	ASIAN/PACIFIC ISLANDER	0(0.0%)	0(0.0%)	0(0.0%)
	OTHER (South African Black)	0(0.0%)	1(6.3%)	1(3.2%)
WEIGHT (kg)	N	15	16	31
	MEAN	68.8	67.3	68.0
	SD	11.8	8.9	10.2
	MEDIAN	70.6	67.4	70.5
	RANGE	52 to 93	50 to 81	50 to 93

The most commonly used concomitant medications (30 vs 60 units/kg groups) were analgesics (31.3% vs 37.5%), antibacterials for systemic use (37.5% vs of 25.0%), and antihistamines for systemic use (25.0% vs 6.3%).

7.1.5. Primary efficacy results – Spleen volume

The primary efficacy analysis was performed on the ITT (MI) population (see Table 8, below). Both dose groups demonstrated statistically significant reductions (p<0.0001) in spleen volume from screening at Month 9 of 26.91% in the 30 units/kg dose group (n=15) and 38.01% in the 60 units/kg dose group (n=16). There was no statistically significant difference observed in mean spleen volume between the two dose groups at Months 6 and 9 (p=0.060). The change in spleen volume (mL) results are summarised in the dossier. The results for the primary efficacy analysis in the ITT (MI) population were consistent with the sensitivity analyses in the ITT (LOCF) and the PP populations.

Table 8: Study PB-06-001 – Spleen volume percent change from screening to Months 6 and 9; imputed values averaged (ITT population).

SPLEEN VOLUME (mL) -- Imputed Values Averaged		prGCD 30 units/kg N = 15	prGCD 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*

Multiple Imputation (100 times) for Missing.

*p-value is from one-sample t-test (combined) to test the null hypothesis that percent change = 0.

Comment: Reductions in spleen volume from screening at both 6 and 9 months were statistically significantly greater (p<0.0001) than 20% for both taliglucerase alfa doses. The study was powered on reduction in spleen volume of 20%. Consequently, it can be inferred that the reductions in spleen volume from baseline at both Month 6 and Month 9 observed in both dose groups are clinically significant.

7.1.6. Secondary efficacy results

7.1.6.1. Haemoglobin levels (Major secondary endpoint)

In the ITT population, the mean haemoglobin levels at baseline were at the lower limit of the normal range for both the 30 and 60 units/kg dose groups (12.2 g/dL [n=14] and 11.4 g/dL [n=16], respectively), and improved at Month 9 in both groups (14.0 g/dL [n=14] and 13.6g/dL [n=15], respectively). The change in haemoglobin level from baseline at Month 9 was statistically significant in both the 30 and 60 units/kg dose groups (1.6 g/dl [n=14], p=0.0010 and 2.2 g/dL [n=15], p<0.0001, respectively). There was no statistically significant difference observed in mean haemoglobin values between the two dose groups at Months 6 and 9 (p=0.719). The results are summarised dossier.

Comment: The mean baseline haemoglobin concentrations were within the normal range for both dosage groups suggesting that the majority of the study population were not anaemic. The increases in haemoglobin level from baseline at Month 9 were statistically significant for both doses and remained within normal limits, but at higher levels than baseline. In a non-protocol specified, ad hoc analysis, the increase in haemoglobin levels from baseline at Month 9 were 14.6% in the 30 units/kg group and 22.2% in the 60 units/kg group. The study was powered on an increase in haemoglobin level of 16%, suggesting that only the percentage increase for the 60 units/kg dose was clinically significant.

Anaemia was not an inclusion criterion and the study included patients with and without anaemia (defined by haemoglobin at least 1 g/dL below normal range according to sex and age). The majority of patients in this study were not anaemic with only 2 patients (approximately 14%) in the 30 units/kg group and 8 patients (approximately 53%) in the 60 units/kg being anaemic (< 11 g/dL for women and < 12 g/dL for men). The submission included a non-protocol specified post hoc subgroup analysis in the 10 patients with baseline anaemia irrespective of dose group. This analysis showed that haemoglobin levels increased from a baseline mean level of 9.5 g/dL [range: 5.5 to 10.7] to a Month 9 mean level of 12.7 g/dL [range: 8.6 to 15.4], and the haemoglobin level increased from baseline to Month 9 by 36.0%. The sponsor did not calculate the p-value for the post hoc subgroup analysis. However, the results indicate that the observed increase in haemoglobin levels at Month 9 was clinically significant with the mean level shifting from below normal to normal following treatment.

7.1.6.2. Liver volume (major secondary endpoint)

There was a statistically significant reduction in liver volume from screening at Months 6 and 9 for both doses of taliglucerase alfa. The reductions at Month 6 were 7.56% (p=0.0020) for the 30 units/kg dose (n=15) and 7.51% (p=0.0022) for the 60 units/kg dose (n=16), and the reductions at Month 9 were 10.48% (p=0.0041) for the 30 units/kg dose (n=14) and 11.11% (p<0.0001) for the 60 units/kg dose (n=16). There was no statistically significant difference observed in mean liver volume between the two dose groups at Months 6 and 9 (p=0.349).

Comment: There was a statistically significant reduction in liver volume from screening at Months 6 and 9 for both doses. The study was powered on a reduction in liver volume of 11%, from which it can be inferred that only the reduction in spleen volume at Month 9 in the 60 units/kg dose group was clinically significant. Increased liver volume was not an inclusion criterion for this study. However, the submission included a post hoc analysis of patients who entered the study with hepatomegaly (defined as > 1.5 times

expected liver volume calculated as 2.5% of body weight). Using this definition, there were 11 patients (approximately 79%) in the 30 units/kg group and 7 patients (approximately 44%) in the 60 units/kg dose group with hepatomegaly. The reduction in liver volume from baseline at Month 9 in patients with hepatomegaly was 14% in both the 30 units/kg group (n=10) and the 60 units/kg group (n=6). Consequently, the post hoc results in GD patients with pre-treatment hepatomegaly showed that reductions in hepatic volume from baseline at Month 9 were clinically significant for both doses.

7.1.6.3. Platelet count (major secondary endpoint)

There was an increase in mean platelet count from baseline at Month 9 of 41,494/mm^3 (p=0.0031) in the 60 units/kg dose group (n=16), and 11,427/mm^3 (p=0.0460) in the 30 units/kg dose group (n=15). The increase was statistically significant for the 60 units/kg group, but not for the 30 units/kg group as the change failed to meet the pre-specified alpha significance level of 0.025. Statistically significant increases in mean platelet count from baseline were observed in the 60 units/kg dose group compared with the 30 units/kg dose group at Months 6 and 9 (p=0.042). Platelet counts by visit and the change from baseline are presented in the dossier.

Comment: Thrombocytopenia (defined as platelet counts < 120,000 per mm^3) with or without anaemia was an inclusion criteria for this study. The mean baseline platelet counts for the 30 units/kg group and the 60 units/kg group were 75,320 [range: 27,000 – 163,000] and 65,038 [range: 53,500 – 134,000], respectively. The increase in the platelet count from baseline at Month 9 was statistically significant for the 60 units/kg group, but not for the 30 units/kg group. In a non-protocol specified, ad hoc analysis, the platelet count was shown to have increased from baseline at Month 9 by 72.1% in the 60 units/kg group and by 13.7% in the 30 units/kg group. The study was powered on a mean change from baseline in platelet count of 46%, which suggests that only the increase from baseline at Month 9 for the 60 units/kg dose was clinically significant.

7.1.6.4. Other secondary efficacy endpoints

7.1.6.4.1. Chitotriosidase

There was a statistically significant reduction in chitotriosidase activity from baseline at Month 9 in both the 30 and 60 units/kg dose groups (13,264 nM/mL/h [n=14], p<0.0001 and 12,1615 nM/mL/h [n=15], p=0.0016, respectively). The mean chitotriosidase activity (nM/mL/h) at baseline was 28,158 [range: 7,791 - 50,254] in the 30 units/kg dose group (n=15) and 24,702 [range: 4,639 - 66,628] in the 60 units/kg dose group (n=15). Chitotriosidase activity by visit and change in chitotriosidase activity from baseline at Months 3, 6, and 9 were summarised in the dossier.

Comment: The units of chitotriosidase activity were not provided in the study report, but are nM/mL/h (identified in the Historical Analysis report). The reduction in chitotriosidase activity from baseline to Month 9 was statistically significant for both doses. In a non-protocol specified, ad hoc analysis, percentage reductions in chitotriosidase activity from baseline to Months 3, 6, and 9 (30 vs 60 units/kg) were 20% vs 37%, 36% vs 50%, and 47% vs 58%, respectively.

7.1.6.4.2. Spleen volume

In the ITT population, mean reduction in spleen volume ≥10% was observed in 100% (15/15) of patients to Months 6 and 9 in the 30 units/kg dose group, and in 93.8% (15/16) and 100% (16/16) of patients at Months 6 and 9, respectively, in the 60 units/kg dose group.

7.1.6.5. Tertiary endpoints

DEXA: Lumbar spine, femoral neck and total hip DEXA scans at the screening visit and the end of study (Month 9 - Visit 20) were presented by T score, Z score and bone mineral density (BMD). In the ITT population, the majority of mean values in T score, Z score and BMD measurements for bone mass at either the screening visit or the end of study visit were within the normal range. At the screening visit, patients in the 60 units/kg dose group tended to have lower mean DEXA scores than patients in the 30 units/kg dose group. There was a trend towards improvement in mean change in T and Z score for lumbar spine and femoral neck after 9 months treatment in both dose groups.

QCSI: QCSI was an exploratory endpoint used to measure bone marrow fat fraction content, and was performed at the screening visit in 10 patients (5 in each dose group) with 8 patients (4 in each dose group) having evaluable data at Month 9. At baseline, 8 of the 10 patients had a fat fraction of ≤0.23 (i.e. "bone at risk"). Of the 8 patients with evaluable data at Month 9, 6/8 (75%) had a fat fraction of ≤0.23 at baseline and following treatment 6/8 (75%) of patients had a fat fraction > 0.23 at Month 9. All 8 patients with a 9 month measurement showed increases in fat fraction of ≥ 0.02 from baseline. Of these 8 patients, 7 showed a fraction increase of ≥ 0.03 which was considered a true response to ERT, and 4 had an increase of fat fraction of ≥ 0.10 which was considered a high response.

7.2. Other efficacy studies

7.2.1. Study PB-06-002 [Ongoing phase 3 study] – Interim analysis

7.2.1.1. Study design, objectives, locations and dates

The objective of this ongoing Phase 3, multi-centre, open-label, switchover trial is to assess the safety and efficacy of taliglucerase alfa in 30 patients, 2 years or older, with GD who have been receiving imiglucerase (Cerezyme) ERT for at least 2 years at a stable maintenance regimen (dose unchanged) for at least the last six months. Patients are currently being treated at 10 investigational centres in 8 countries (Israel, Germany, Spain, UK, USA, Canada, Serbia and Australia). The first patient was enrolled on 15 December 2008 and the study is ongoing. The release date of the interim analysis (abbreviated CSR) was 20 October 2010. The study is being conducted in accordance with the ethical principles of Good Clinical Practice (GCP) according to the ICH Guideline, and with all local regulations. The sponsor states that the interim analysis of this ongoing study was requested by the US FDA as supportive data to assist in its review of the GD NDA.

Following successful screening, eligible patients entered a 12-week baseline stability evaluation period during which treatment with imiglucerase was continued. Haemoglobin level and platelet count were measured by the local laboratory every two weeks for a total of 6 measurements. Patients with stable disease were switched from imiglucerase to taliglucerase alfa, which was then administered every two weeks for a total of 20 infusions (i.e. 9 months [38 weeks] treatment). If imiglucerase treatment had been discontinued due to drug shortage the patient could start receiving taliglucerase alfa infusions based on historical data based on disease stability relating to haemoglobin levels and platelet counts.

Stable GD during the baseline stability evaluation period was defined as:

- haemoglobin: no value more than 15% below or above the mean value;
- platelet count: no values more than 40% below or above the mean value if the mean value was > 120,000/mm^3, or more than 20% below or above the mean value if the mean value was ≤120,000/mm^3;
- no major surgery in the last year; no blood transfusion or major bleeding episode in the past year; no acute avascular necrosis event in the last year; and no evidence of spleen or liver

increasing/enlargement (palpation, ultrasound, or MRI) while being treated with ERT over the last year.

Comment: The study assessed the efficacy and safety of taliglucerase alfa in patients switched from imiglucerase. It would have been preferable to have randomised patients who had been stabilised on imiglucerase to treatment with continued imiglucerase or to taliglucerase alfa as this would have allowed a direct comparison of "maintenance effect" between the two drugs.

7.2.1.2. Inclusion and exclusion criteria.

The study includes male and female patients (2 years or older) with GD with leukocyte glucocerebrosidase (GCD) activity level ≤3 nM/mg.hr (≤ 30 % of the mean activity of the reference range). Patients were to have protocol specified stable GD and to have been receiving imiglucerase therapy for at least 2 years and on a stable maintenance regimen (dose unchanged except for situation of drug shortage) for at least the last 6 months. Details of the inclusion and exclusion criteria are provided in the dossier.

7.2.1.3. Removal of patients from therapy or assessment

Patients were to be discontinued from treatment with study drug if they showed a clinically relevant deterioration in the following parameters:

- sustained reduction of platelet count from baseline (mean of 6 measurements) for three consecutive measurements two weeks apart: > 20% for baseline value of ≤ 120,000/mm^3 and > 40% for baseline value of > 120,000/mm^3; and
- sustained reduction (> 20%) of haemoglobin from baseline (mean of 6 measurements) for three consecutive measurements two weeks apart.

Patients who met the deterioration criteria and were being treated with the highest permissible dose of 60 units/kg were reviewed by the DMC, and the committee's recommendation was provided to the Investigator and Medical Director before final discontinuation. Patients who met the deterioration criteria and were not being treated with the highest permissible dose of 60 units/kg were eligible to have their dose increased at the discretion of the Investigator and approval of the Medical Director. Subsequently, the mean of the 3 consecutive measurements taken two weeks apart described above served as the baseline for detecting further clinically relevant deterioration after the dose increase was implemented. The stopping rules are:

- sustained reduction of platelet count from the mean of 3 measurements (new baseline) for 3 additional consecutive measurements two weeks apart: > 20% for baseline of ≤ 120,000/mm^3 and > 40% for baseline of > 120,000/mm^3; and/or
- sustained reduction (> 20%) of haemoglobin from baseline of mean of 3 measurements (new baseline) for 3 additional consecutive measurements 2 weeks apart.

Patients who met the discontinuation criteria after having their dose increased were reviewed by the DMC and the committee's recommendation was provided to the Investigator and Medical Director before final discontinuation.

Other reasons for discontinuation include:

- two or more Grade 3 toxicities or one or more Grade 4 toxicity considered to be associated with taliglucerase alfa treatment by the investigator;
- the patient requests to discontinue treatment; and
- the investigator feels that it is not in the best interest of the patient to continue treatment and/or the investigator believes that the patient could no longer be compliant with the requirements of the study.

7.2.1.4. Treatments

The administered taliglucerase alfa dosage was equivalent to the imiglucerase dose at screening or before imiglucerase shortage. Taliglucerase alfa was administered every 2 weeks via iv infusion at the rate of approximately 1.3 mL/min, with a total volume of 135 mL of taliglucerase alfa plus a line flush of 20 mL of normal saline being given over a 2 hour period. The rate of infusion could be increased to up to 2.25 mL/min if the infusion was tolerated by the patient and approved by the sponsor's Medical Director.

The following medications were allowed during the study: treatment for hypersensitivity, anaphylaxis, or anaphylactoid reactions; treatment for anaemia; treatment for bone disease; and analgesics. The following medications were strictly prohibited during the study: miglustat; alglucerase; and imiglucerase (allowed after screening visit until two weeks before Day 1 of the study).

7.2.1.5. Efficacy endpoints

No primary efficacy variable was selected for analysis. The efficacy outcome of main interest was whether patients deteriorate clinically during treatment with taliglucerase alfa.

Efficacy was determined by evaluation of the following parameters for clinical deterioration: platelet count; haemoglobin; spleen volume; and liver volume. Other efficacy endpoints include biomarkers (chitotriosidase and PARC/CCL18).

The study also includes exploratory growth and development assessments for patients less than 18 years old: change in growth and development in patients less than 18 years of age; height and weight for growth evaluation; Tanner Stage for sexual development; and bone age by X-ray of left hand and wrist. However, the interim analysis did not include any patients younger than 18 years of age.

7.2.1.6. Statistical analyses and sample size

Two interim analyses were planned. The first interim analysis was based on data collected before or on 30 April 2010. The second interim analysis was based on the data from the first 15 patients who completed or prematurely withdrew from the study. The results from this second interim analysis were presented in the submitted clinical evaluation report and were based on data collected before or on 15 August 2010.

Standard descriptive statistics were presented for continuous and categorical variables for change from baseline by visit for organ volumes (spleen and liver), haemoglobin level, platelet count and biomarkers (chitotriosidase and PARC/CCL18).

The main effectiveness criteria were based on whether the clinical status of the patient achieved with imiglucerase was maintained after switching to taliglucerase alfa. Clinical disease deterioration was defined as follows:

- platelet count: a decrease of >20% from the mean of six Stability Evaluation Period values of ≤ 120,000/mm^3 or a decrease of > 40% from the mean of six Stability Evaluation Period values of > 120,000/mm^3.
- haemoglobin level: a decrease of > 20% from the mean of six Stability Evaluation Period values.
- spleen volume: a 20% increase in spleen volume by MRI from Baseline to Month 9 (or the time of premature withdrawal).
- liver volume: a 10% increase in liver volume by MRI from Baseline to Month 9 (or the time of premature withdrawal).

The arithmetic mean of the six Stability Evaluation Period values for haemoglobin or platelet count was used in the evaluation and if there were less than six values then the available values

were used to estimate the mean. If the treatment with imiglucerase was temporarily discontinued due to shortage of the drug at the time of enrolment, then historical data on haemoglobin and platelet count were used to determine clinical deterioration.

The sample size of 30 patients was considered adequate to evaluate the safety endpoints for this orphan disease, and no formal power calculations were undertaken.

7.2.1.7. Patient disposition

At the time of the database freeze on 15 August 2010, 40 patients had been screened, 28 were eligible for enrolment, 25 had received treatment, and 1 had voluntarily withdrawn before treatment. A total of 16 patients had completed the study, and data from 1 of these patients were not monitored and locked in time for inclusion in the interim efficacy analysis. Therefore, data from 15 patients were included in the efficacy analysis. At the date of the data freeze, protocol deviations were listed for 6 patients. These deviations have been examined and are considered not to have compromised the validity of the interim efficacy analysis.

> **Comment**: The study was designed to include data on 30 patients, and the reported interim analysis includes data on 15 patients.

7.2.1.8. Patient demographics

The demographics of the 25 treated patients are summarised below in Table 9. At the time of database freeze on 15 August 2010, the mean±SD taliglucerase alfa dose for the 25 treated patients was 28.1±16.1 units/kg, and the median dose [range] was 25.1 units/kg [11 to 60].

Table 9: Study PB-06-002 – Demographics and baseline characteristics.

AGE (yrs) at INFORMED CONSENT	N	25
	MEAN	47.4
	SD	13.0
	MEDIAN	50.0
	RANGE	18 to 66
GENDER	N	25
	MALE	13 (52.0%)
	FEMALE	12 (48.0%)
RELIGION	N	25
	JEWISH - ASHKENAZI	14 (56.0%)
	JEWISH - NON ASHKENAZI	0 (0.0%)
	NON JEWISH	11 (44.0%)
RACE	N	25
	CAUCASIAN	25 (100%)
	AFRICAN AMERICAN	0 (0.0%)
	NATIVE AMERICAN	0 (0.0%)
	ASIAN/PACIFIC ISLANDER	0 (0.0%)
	OTHER	0 (0.0%)

> **Comment:** The 25 treated patients in the current analysis were aged from 18 to 66 years. The protocol specified that patients 2 years or older could be included, but the interim analysis included no data on patients younger than 18 years of age.

7.2.1.9. Efficacy results

Clinically relevant deterioration as an efficacy endpoint was defined by enlargement of the liver or spleen from Baseline to Month 9, or sustained (3 consecutive visits) reductions in haemoglobin or platelets. Of the 15 patients who had completed the study at the time of database lock, all 15 patients provided MRI readings.

7.2.1.9.1. Spleen volume

In the 15 patients completing 9 months of treatment, the mean spleen volume decreased from 760.5 mL at baseline to 722.2 mL at Month 9, a mean reduction of 5.1% (see Table 10, below).

Table 10: Study PB-06-002 – Spleen volume.

VISIT 1 (DAY 1)	N	15
	MEAN	760.5
	SD	662.6
	MEDIAN	548.7
	RANGE	14.2 to 2150.7
VISIT 20 (MONTH 9)	N	15
	MEAN	722.2
	SD	628.9
	MEDIAN	518.6
	RANGE	14.5 to 2141.4

Comment: The results indicate that there has been no clinical deterioration based on change in mean spleen volume after switching from imiglucerase to taliglucerase alfa. Of the 15 patients in the efficacy analysis, spleen volume remained stable in 14. In 1 patient, the spleen volume increased by greater than 20% from baseline at Month 9 (i.e. clinical relevant deterioration in spleen volume), without clinically relevant deterioration in other efficacy end points including liver volume, platelets, haemoglobin and biomarkers.

7.2.1.9.2. Liver volume

The mean liver volume decreased from 1751.3 mL at baseline to 1724.5 mL at Month 9, a mean reduction of 1.4% (see Table 11, below).

Table 11: Study PB-06-002 – Liver volume.

VISIT 1 (DAY 1)	N	15
	MEAN	1751.3
	SD	451.1
	MEDIAN	1555.5
	RANGE	1167.0 to 2642.
VISIT 20 (MONTH 9)	N	15
	MEAN	1724.5
	SD	472.3
	MEDIAN	1509.7
	RANGE	1276.0 to 2604.

Comment: The results indicate that there has been no clinical deterioration based on change in mean liver volume after switching from imiglucerase to taliglucerase alfa.

7.2.1.9.3. Haemoglobin

The haemoglobin concentration was measured at the local laboratory for the 9 visits (0, 1, 3, 5, 7, 10, 14, 17 and 20) or for additional visits at the discretion of the investigator as clinically indicated. There was no significant change in haemoglobin concentration at Month 9 from baseline (see Table 12, below).

Table 12: Study PB-06-002 – Haemoglobin concentration.

	Baseline*	Month 3	Month 6	Month 9
N	15	15	15	15
Mean	13.5	13.3	13.3	13.2
SD	1.7	1.6	2.0	1.7
Median	13.6	13.7	13.7	13.9
Range	10.7 to 16.1	10.6 to 15.6	10.0 to 16.2	10.3 to 15.7

*Baseline = Mean of the Evaluations in the Stability Period.

Comment: The results indicate that there has been no clinical deterioration based on change in mean haemoglobin concentration after switching from imiglucerase to taliglucerase alfa.

7.2.1.9.4. Platelet count

Platelet count was measured at the local laboratory for the 9 visits (0, 1, 3, 5, 7, 10, 14, 17 and 20) or for additional visits at the discretion of the investigator as clinically indicated. There was no significant change in haemoglobin concentration at Month 9 from baseline (see Table 13, below).

Table 13: Study PB-06-002 – Platelet count.

	Baseline*	Month 3	Month 6	Month 9
N	15	15	15	15
Mean	161,666.7	152,533.3	157,466.7	162,333.3
SD	83,970.3	77,133.3	87,408.6	92,765.2
Median	180,000.0	175,000.0	180,000.0	171,000.0
Range	45,000 to 305,000	45,000 to 283,000	47,000 to 316,000	39,000 to 361,000

*Baseline = Mean of the Evaluations in the Stability Period.

Comment: The results indicate that there has been no clinical deterioration based on change in mean platelet count after switching from imiglucerase to taliglucerase alfa.

7.2.1.10. Biomarker results

Chitotriosidase and CCL8 levels were measured every 3 months during the study and the results are summarised below in Table 14.

Table 14: Study PB-06-002 – Chitotriosidase and CCL8 levels.

	Chitotriosidase			
	Baseline*	Month 3	Month 6	Month 9
N	15	15	15	15
Mean	3,927.5	3,377.6	3,230.2	3,373.8
SD	5,535.3	5,082.1	5,360.2	5,533.4
Median	1,776.0	1,235.0	1,019.0	850.0
Range	103 to 18,739	111 to 17,028	102 to 18,616	139 to 18,692
	CCL8			
	Baseline*	Month 3	Month 6	Month 9
N	15	15	15	15
Mean	215.9	207.9	200.4	194.2
SD	251.0	225.7	274.9	248.9
Median	158.0	150.0	126.0	121.0
Range	34 to 1,046	32 to 933	37 to 1,144	40 to 1,044

* Baseline = Mean of the Evaluations in the Stability Period.

Comment: There was an approximately 14% decrease in mean chitotriosidase level from baseline at Month 9, and an approximately 10% decrease in mean CCL8 level from baseline at Month 9. The results indicate that there has been no clinical deterioration as assessed by the relevant biomarkers after switching from imiglucerase to taliglucerase alfa.

7.2.2. Study PB-06-003 [Phase 3 extension trial] – Interim analysis

7.2.2.1. Study design, objectives, locations and dates

The objective of this ongoing Phase 3, multi-national, multi-centre study is to extend the assessment of safety and efficacy of taliglucerase alfa in up to 60 patients with GD who have completed 9 months of treatment in studies PB-06-001 or PB-06-002. The total duration of treatment is to be at least 15 months (64 weeks) and no more than 30 months (128 weeks) or until marketing approval has been granted by the appropriate regulatory authority, whichever is earlier.

The study is being undertaken in centres in Israel, South Africa, UK, Italy, USA, Canada, Serbia, Mexico, Chile, and Australia. The first patient was enrolled on 14 September 2008 and the study is ongoing. The study is being conducted in accordance with the ethical principles of GCP, according to the ICH Guideline. The interim analysis was not defined in the study protocol, but was provided by the sponsor as supportive data and released on 25 August 2010 (Version 2).

The study includes 3 treatment groups, with patients continuing to receive the allocated dose from PB-06-001 (Group I [30 units/kg] & Group II [60 units/kg]), or the same dose being received at the completion of PB-06-002 (Group III). Patients receive iv infusion of taliglucerase alfa every 2 weeks and have the option to receive infusions at the selected medical centre, infusion centre, or at home. Local standard of practice, the investigator and the Medical Director determine the timing and method of infusion outside the medical centre. The study schedule/flow chart is provided in the dossier.

Part A of the study consists of 33 infusions and 6 Study Visits at which time efficacy parameters and clinical laboratory safety assessments are measured. Day 1 of this study is the final visit of study PB-06-001 or study PB-06-002. Adverse events, concomitant medications, and vital signs are recorded every 2 weeks at each treatment. Spleen and liver volumes are measured at Month 3 and Month 15. Evaluation at Months 3, 6, 9, 12, and 15 include physical exam, haematology, biochemistry, urinalysis, biomarkers, antihuman taliglucerase alfa antibodies, and ECG, DEXA and QCSI for patients who participated in the PB-06-001 study are performed at Month 3 and Month 15. Chest X-Ray, X-Ray skeletal evaluation, echocardiography, and pulmonary function tests are performed at Month 15. TSH, transferrin, B12 and folic acid tests are performed at Month 15.

Part B of the study consists of up to 33 infusions and up to 5 scheduled Study Visits at which time efficacy parameters and clinical laboratory for safety assessment are measured. Adverse events, concomitant medications, body weight and vital signs are recorded every 2 weeks at each treatment. Evaluation at Months 18, 21, 24, 27, and 30 include physical exam, haematology, biochemistry, urinalysis, and biomarkers, antihuman taliglucerase alfa antibodies, and ECG. Echocardiography and pulmonary function tests are performed at Month 30. TSH, transferrin, B12 and folic acid tests are performed at Month 27. DEXA (for patients who participated in study PB-06-001 study), QCSI (when applicable) and MRI for are performed at Month 27.

MRI systems at each centre are calibrated and standardized following a standard protocol, and all MRI volumetric analyses (spleen and liver) are analysed by central reading experts.

> **Comment:** The submitted report is a non-protocol specified interim analysis provided as supportive data. The study included no concurrent control group with either placebo of imiglucerase. Randomisation was not performed in this study with all patients remaining in the group to which they were assigned in study PB-06-001 or PB-06-002. Doses (30 or 60 units/kg) remain blinded in patients from PB-06-001 for at least 15 months in order to obtain at least 24 months of dose information on blinded therapy. The investigator can then request unblinding of the patient if warranted by the clinical condition. Patients from PB-06-002 continue unblinded. The study plans to enrol up to 60 subjects who have completed 9 months treatment with taliglucerase alfa 30 units/kg or 60 units/kg administered every 2 weeks in study PB-06-001 (pivotal study) or study PB-02-002 (switchover study).

7.2.2.2. Inclusion and exclusion criteria, and criteria for discontinuation

The inclusion criteria were: successful completion of study PB-06-001 or PB-06-002; and provision of written informed consent

The exclusion criteria were: currently taking another experimental drug for any condition; presence of severe neurological signs and symptoms characteristic of NGD; and presence of any medical, emotional, behavioural or psychological condition that in the judgment of the investigator would interfere with the patient's compliance with the requirements of the study.

The discontinuation criteria were: two or more Grade 3 toxicities or one or more Grade 4 toxicity considered to be associated with taliglucerase alfa treatment by the investigator; progressive hypersensitivity or severe hypersensitivity; request to discontinue treatment; the investigator feels that it is not in the best interest of the patient to continue treatment and/or if the investigator believes that the patient can no longer be compliant with the requirements of the study; marketing authorisation is obtained in the country that has regulatory authority for the protocol; the patient (in Treatment Group III only) completes the PB-06-002 study and shows clinical deterioration defined as a sustained reduction of platelet count from the Stability Evaluation Period values for 3 consecutive measurements two weeks apart, and/or a sustained reduction of haemoglobin from the Stability Evaluation Period values of >20% for 3 consecutive measurements two weeks apart.

The investigator is required to make thorough efforts to document the outcome, and to continue to follow the patient for the full duration of the study or for at least 30 days following discontinuation. If circumstances prevent the patient from completing all visits, every attempt is made to complete all procedures of the Month 15 Visit (for patients who are discontinued during Part A) or Month 27 Visit (for patients who are discontinued during Part B).

Patients who meet the discontinuation criteria and are being treated with the highest permissible dose of taliglucerase alfa of 60 units/kg are reviewed by the DMC, and the DMC provides its recommendation to the investigator and Medical Director before final discontinuation.

Patients who meet the discontinuation criteria and are not being treated with the highest permissible dose of taliglucerase alfa of 60 units/kg are eligible to have their dose increased at the discretion of the investigator and approval of the Medical Director. Subsequently, the mean of the 3 consecutive measurements taken two weeks apart described above serve as the baseline for detecting further clinically relevant deterioration after the dose increase. The following stopping rules are applied: sustained reduction of platelet count from the mean of 3 measurements (new Baseline) for 3 additional consecutive measurements two weeks apart (>20% for Baseline of ≤ 120,000/mm^3 and > 40% for baseline of > 120,000/mm^3; and/or sustained reduction (>20%) of haemoglobin from Baseline (mean of 3 measurements – new baseline) for 3 additional consecutive measurements two weeks apart. Patients who meet these criteria are reviewed by the DMC, and the DMC provides its recommendation to the investigator and Medical Director before final discontinuation.

7.2.2.3. Treatments

The three taliglucerase alfa treatment groups are: Group 1 (patients from PB-06-001) 30 units/kg; Group II (patients from PB-06-001) 60 units/kg; and Group III (patients from PB-06-002) same dose received as at the completion of PB-06-002. The initial infusions are administered at the same rates as administered at Visit 20 of PB-06-001 or PB-06-002. The tolerability of the infusion is determined by signs and symptoms during the infusion and for one hour after the infusion in the clinic. The rate of infusion could be increased up to 2.25 mL/min to deliver the 135 mL volume over one hour with approval of the Medical Director.

In Treatment Groups I and II, the individual dose for each patient is prepared according to the randomized dose in PB-06-001. Each dose is prepared by an unblinded pharmacist at each site, unless unblinding is requested by the investigator after Month 15. The dose is not adjusted for new weight changes and remains the same as for the weight at Visit 20 of PB-06-001. For each patient who completed study PB-06-001, at the completion of two years of treatment, the blind can be opened at the investigator's discretion and with the approval of the Medical Director. If clinically indicated, patients treated with 30 units/kg can have their dose increased up to 60 units/kg.

In Treatment Group III, the individual dose for each patient is prepared according to the dose received at the completion of PB-06-002. The dose can be increased to a maximum of

60 units/kg only if the patient experiences deterioration in GD according to the previously described criteria.

The allowed and restricted prior and concomitant medications were as for studies PB-06-001 and PB-06-002.

7.2.2.4. Efficacy endpoints

Efficacy is determined by evaluation of the following parameters: spleen volume; liver volume; platelet counts; haemoglobin level; biomarkers (chitotriosidase and PARC/CCL18); QCSI in approximately 10 patients who had this test performed in study PB-06-001; and change in bone mineral density by DEXA. No primary efficacy variable was selected for analysis, and all efficacy measurements are considered to contribute to the assessment of efficacy.

7.2.2.5. Statistical methods and sample

This interim analysis for efficacy and safety was conducted at the request of the US FDA to facilitate the review of a NDA for taliglucerase alfa in support of the pivotal study PB-06-001. The interim analysis was not defined in the study protocol but was performed based on the data as of 30 April 30 2010. The sponsor indicates that data are now available in the second interim report updating the safety information as of 30 June 2010. The sponsor stated that data presented in the submitted interim report may not have included all analyses described in the Interim Statistical Analysis Plan if the scarcity of data prevented drawing meaningful conclusions.

The interim population included all enrolled subjects who received treatment with taliglucerase alfa before or on 30 April 2010. The data used for the efficacy summary tables were from the records collected before or on 30 April 2010, and for safety information the cut-off date was 30 June 30 2010. The interim efficacy population consisted of 26 patients from study PB-06-001.

Descriptive statistics were presented for spleen volume, liver volume, platelet count, haemoglobin, biomarkers [chitotriosidase and PARC/CCL18), and QCSI. Several exploratory analyses were performed to examine the efficacy difference between the treatment groups using pair-wise comparisons by two-sample t-tests. For spleen and liver volumes, the percent changes from baseline to Month 12 (Month 3 in Study PB-06-003) and Month 24 (Month 15 in Study PB-06-003) are to be compared between the treatment groups by two-sample t-tests. The baseline values are the screening measurements in Studies PB-06-001 and PB-06-002. The changes in haemoglobin and platelet counts from baseline to Month 12 (Month 3 in Study PB-06-003) and Month 24 (Month 15 in Study PB-06-003) are to be compared between treatment groups by a two-sample t-tests. The baseline values are the baseline or screening measurements in the Study PB-06-001, and the mean of the six Stability Evaluation Period measurements in Study PB-06-002.

Sample size was determined by the number of patients who completed Study PB-06-001 or PB-06-002 and who agreed to continue treatment in this extension study.

7.2.2.6. Patient disposition

At the time of database freeze on 30 June 2010, 31 patients from 12 study sites were enrolled in this study and continue treatment; 26 from the pivotal dose-comparison study PB-06-001; and 5 from the switch-over study PB-06-002. The 5 patients from PB-06-002 had insufficient efficacy data to contribute to the interim report, but are included in the safety analysis. Due to delays in obtaining IRB/IEC approval for the protocol at some centres, 7 patients from PB-06-001 had 2-4 month gaps in treatment following their last infusion in the pivotal study before their first infusion in this extension study.

7.2.2.7. Patient demographics

Information on patient demographics (safety population) in this interim analysis were provided in the dossier.

7.2.2.8. Efficacy results

Spleen volume was measured at Day 1, which corresponds to the final visit (Month 9) of the predecessor trial, and at Month 3 of treatment, representing a total of 12 months of treatment with taliglucerase alfa for patients from study PB-06-001. In the 26 patients from PB-06-001 who continued treatment in PB-06-003, 12 patients in the 30 units/kg dose group had a 28.9% reduction in spleen volume and 14 patients in the 60 units/kg dose group had a 43.5% reduction after 12 months of treatment (i.e. Month 3). The difference between the two doses on reduction in spleen volume from baseline at 12 months was statistically significant (p=0.001). The results for spleen volume are summarised in the dossier.

Liver volume was also measured at the same timepoints as spleen volume. In the 26 patients from PB-06-001 who continued treatment in PB-06-003, 12 patients in the 30 units/kg dose group had a 15.9% reduction in liver volume and 14 patients in the 60 units/kg dose group had a 13.2% reduction after 12 months of treatment (i.e. Month 3). The difference between the two doses on reduction in liver volume from baseline at 12 months was not statistically significant (p=0.352). The results for liver volume are summarised in the dossier.

Haemoglobin levels are measured every three months. In the 26 patients from PB-06-001 who continued treatment in PB-06-003, 12 patients in the 30 units/kg dose group had a 1.7 g/dL increase in haemoglobin level from baseline levels (which were within normal limits) and 14 patients in the 60 units/kg had a 2.2 g/dL increase after 12 months of treatment (i.e. Month 3). The difference between the two doses in haemoglobin levels from baseline at month 12 was not statistically significant (p=0.330). The extension study also included haemoglobin levels for 9 patients in the 30 units/kg dose group and 12 patients in the 60 units/kg group who had been treated for 15 months (i.e. at Month 6). These data showed that haemoglobin levels were similar following 12 and 15 months of treatment in both dose groups.

Platelet counts are measured every three months. In the 26 patients from PB-06-001 who continued treatment in PB-06-003, 12 patients in the 30 units/kg dose group had a 15,420/mm^3 increase in the platelet count from baseline at 12 months (i.e. Month 3), and 14 patients in the 60 units/kg had a corresponding 53,814/mm^3 increase. The difference between the two doses in platelet count from baseline at 12 months was statistically significant (p=0.024). The extension study also included platelet counts for 8 patients in the 30 units/kg dose group and 12 patients in the 60 units/kg group who had been treated for 15 months (i.e. Month 6). These data showed that platelet counts were higher at 15 months (i.e. Month 6) than at 12 months (i.e. Month 3) for both dose groups.

> **Comment:** There are limited efficacy data available from the interim analysis of study PB-06-003. The available data in the 26 patients with results at the end of study PB-01-006 (i.e. Month 9) showed that mean reductions in spleen and liver volume from baseline at this endpoint could be maintained for another 3 months (i.e. 12 months from baseline). Similarly, increases in haemoglobin levels and platelet counts from baseline observed at Month 9 in study PB-01-006 in 26 patients were maintained at Month 3 (i.e. 12 months from baseline), and there was evidence that these increases could be maintained through to Month 6 (i.e. 15 months from baseline). The available results from study PB-06-003 suggest that the higher taliglucerase alfa dose of 60 units/kg is more efficacious than the lower dose of 30 units/kg, with the difference at Month 3 (i.e. 12 months from baseline) being statistically significant for spleen volumes and platelet counts.

7.2.3. Dose separation post-hoc analyses for taliglucerase alfa

7.2.3.1. Overview

The objectives of these post-hoc analyses using data from studies PB-06-001 and PB-06-003 were to compare efficacy endpoints between the 30 and 60 unit/kg doses of taliglucerase alfa after 9 and 12 months of treatment. The primary efficacy endpoint was change from baseline in

spleen volume. The secondary efficacy endpoints were changes from baseline in liver volume, platelet count, haemoglobin level, and chitotriosidase activity (biomarker).

The analyses were performed on the intention to treat (ITT) population, which includes all patients randomized in study PB-06-001 who received at least one dose of study medication and had an evaluable baseline MRI evaluation. The changes from baseline to months 9 and 12 in each of the five efficacy endpoints were analysed using analysis of covariance models for each time point separately (chitotriosidase activity was measured at month 9 only). The statistical models included dose group and the baseline value of study PB-06-001 as a continuous covariate. The raw means and standard deviations for the changes from baseline were presented along with their differences. The least squares mean (LSM) changes for each dose group, their differences and 95% confidence intervals along with the p-values for the differences were also presented. For liver and spleen volumes, the mean changes from baseline for each dose group were also expressed as percentages relative to mean baseline, where the mean baseline is the overall mean value for both dose groups combined. Each analysis was performed at the 0.05 level of significance with no adjustments for multiplicity. Missing data were handled using the three different methods described previously for the pivotal study PB-01-006. All secondary endpoints were analysed using observed data only.

7.2.3.2. Results

7.2.3.2.1. Spleen volume (primary efficacy endpoint)

Reduction in spleen volume from baseline at Month 9 and Month 12 was demonstrated in both dose groups, with the higher dose group showing greater reductions. The LSM reductions from baseline to Month 9 were 26.42% in the 30 units/kg group (n=15) and 34.9% in the 60 units/kg group (n=16), and at Month 12 the LSM reductions were 27.19% (n=15) in the 30 units/kg group and 39.23% in the 60 units/kg (n=16) group. The difference between the two dose groups was statistically significant at both Month 9 (p=0.0212) and Month 12 (p=0.0156). The LSM difference between the two dose groups at Month 9 was 8.58% [95%CI: 1.38, 15.67], and at Month 12 was 12.03% [95%CI: 2.48, 21.58].

7.2.3.2.2. Liver volume (secondary efficacy endpoint)

Reduction in liver volume from baseline at Month 9 and Month 12 was demonstrated in both dose groups, with the higher dose group showing greater reductions. The LSM reductions from baseline to Month 9 were 10.09% (n=14) in the 30 units/kg group and 13.15% in the 60 units/kg group (n=15), and at Month 12 the LSM reductions were 15.20 in the 30 units/kg group (n=12) and 15.64% in the 60 units/kg group (n=14). The LSM difference between the two dose groups was statistically non-significant at both Month 9 (p=0.3042) and Month 12 (p=0.8760).

7.2.3.2.3. Platelet count (secondary efficacy endpoint)

Increases in platelet counts at Month 9 and Month 12 were demonstrated in both dose groups, with the higher dose group showing greater increases. The LSM increase from baseline to Month 9 was 11,113/mm^3 in the 30 units/kg group (n=15) and 41,788/mm^3 in the 60 units/kg group (n=12), and at Month 12 the LSM increase was 15,265/mm^3 in the 30 units/kg group (n=12) and 53,952/mm^3 in the 60 units/kg group (n=14). The LSM difference between the two dose groups was statistically significant at both Month 9 (p=0.0313) and Month 12 (p=0.0266). The LSM difference between the 30 and 60 units/kg groups was -30,675/mm^3 [95%CI: -58,400, -2,951] at Month 9, and -38,687/mm^3 [95%CI: -72,458, -4.915] at Month 12.

7.2.3.2.4. Haemoglobin (Secondary efficacy endpoint)

Increases in haemoglobin levels at Month 9 and Month 12 were demonstrated in both dose groups, with the higher dose group showing greater increases. The LSM increase from baseline to Month 9 was 1.80 g/dL in the 30 units/kg group (n=14) and 1.98 g/dL in the 60 units/kg group (n=15), and at Month 12 the LSM increase was 1.85 g/dL in the 30 units/kg group (n=12)

and 2.12 g/dL in the 60 units/kg group (n=14). The LSM difference between the two dose groups was statistically non-significant at both Month 9 (p=0.6861) and Month 12 (p=0.5933).

7.2.3.2.5. Chitotriosidase activity

Decreases in chitotriosidase activity were demonstrated at Month 9 in both dose groups, with similar reductions in activity being observed in both groups. The LSM reduction in activity from baseline to Month 9 was -12568 nM/mL/h in the 30 units/kg group (n=14) and -12814 nM/mL/h in the 60 units/kg (n=15). The LSM difference between the two dose groups was statistically non-significant at Month 9 (p=0.9375).

> **Comment:** This post-hoc analysis demonstrates that after 9 and 12 months of treatment with taliglucerase alfa, the 60 units/kg dose resulted in statistically significantly superior reductions in spleen volume from baseline and increases from baseline in platelet count compared with the 30 units/kg dose. However, the differences between the two doses were not statistically significant at months 9 and 12 for changes from baseline in liver volume and haemoglobin concentration, or at month 9 for chitotriosidase activity. The difference between the efficacy endpoints with regard to whether they showed a dose response might be related to patient selection differences. Patients were enrolled into study PB-06-001 with splenomegaly (> 8 times normal) and thrombocytopaenia (platelet count < 120,000/mm^3), but hepatomegaly and anaemia were not required for study entry. Based on the spleen volume and platelet count, the 60 units/kg dose provides a better clinical response than the 30 units/kg dose.

7.2.4. Historical comparison

7.2.4.1. Overview – Historical analysis

The objective of this historical data analysis was to review the publicly available data regarding the efficacy of imiglucerase and alglucerase for the treatment of GD by focusing on publications for which the clinical study population and clinical endpoints were as close as possible to those of the pivotal study PB-06-001. Relevant papers (including reviews) for the historical analysis were identified by a computerised search of the PubMed database, as well as in the websites of European Medicines Agency (EMA) and www.clinicaltrials.gov. This search retrieved 357 papers out of which 305 were written in English and were retained for evaluation. Of these 305 papers, 50 were review articles and the other 255 were original articles.

The 255 original articles were further assessed using the following criteria: aim; design (with at first level of interest the randomised and preferably blinded studies); population; duration; endpoints (primary, secondary, exploratory); methods used for the analysis; and overall quality of the reported data. All studies selected had to have retrievable data at 9 or 12 months treatment endpoints. Priority was given to studies that included adult patients with systemic symptoms of GD and intact spleen. Studies which focused only on neurological symptoms were not included, nor were studies that included only paediatric patients. The 50 literature review articles were also analysed in order to identify relevant cited original articles that may have been missed in the initial search.

As a result of this process, 18 original papers were selected and 14 of these papers, including information from over 1,000 patients, were chosen to provide summaries of historical control data for the major parameters. The other 4 papers provided information on biomarkers, for which less data is available in the literature. The selection process is summarised in the dossier.

> **Comment:** Overall, the sponsor's search strategy for the analysis appeared to be satisfactory. However, the limitations and biases associated with the historical analysis included: potential retrieval and publication bias (e.g abstracts not assessed or literature in foreign languages); comparative historical data was derived from published literature and not from original data source; variability in quality of published literature used in the analysis; patient dosing and length of treatment widely variable; formal

statistical measure of heterogeneity not performed; and lack of standardization of efficacy endpoint measurements (e.g MRI, CT or ultrasound). The identified limitations and biases are consistent with those for all historical analyses.

7.2.4.2. Results – Historical analysis vs Pivotal efficacy data

7.2.4.2.1. Spleen volume

Splenomegaly was defined as spleen enlargement greater than the normal estimated spleen size of 0.2% of total body weight in kilograms. At diagnosis, about 90% of all symptomatic non-splenectomised patients with GD have a spleen volume exceeding five times the normal size (i.e. 5 multiples of normal [MN]) [ICGG, 2008; Pastores et al., 2004]. Spleen volumes at baseline in pivotal study PB-06-001 were 8 to 54 MN, and in the papers included in the historical analysis nearly all patients had enlarged spleens (>5 MN) with a baseline range of means between 10 MN and 28.5 MN and a total range of from 3.5 to 62 MN. Spleen size in the pivotal study was determined by MRI, and in the identified published articles MRI, CT and ultrasound were used to determine spleen size. The reductions in spleen volume at Month 9 and Month 12 in patients from the pivotal study, and at Month 12 from the historical analysis are summarised below in Table 15.

Table 15: Historical analysis vs Patients from pivotal study – Change in spleen volume from baseline.

Data	Treatment	Mean % Change	Range %
Study PB-06-001[1]	Taliglucerase 60 units/kg [n=16]	-38.01% [p<0.0001]	-56.3% to -20.0%
	Taliglucerase 30 units/kg [n=15]	-26.91% [p<0.0001]	-42.6% to -15.6%
PB-06-001 EXT to PB-06-003[2]	Taliglucerase 60 units/kg [n=14]	-43.5% [p not calculated]	-64.2% to -17.8%
	Taliglucerase 30 unit/kg [n=12]	-28.9% [p not calculated]	-44.3% to -11.6%
Historical[3]	ERT 15-60 units/kg up to 12 months	-38.0% to -17.4% range of means -84% to -8% total range	

1: Reduction from baseline at Month 9.

2: Reduction from baseline at Month 12 [i.e. Month 3 of PB-06-003]

3: Reduction from baseline at approximately Month 12.

7.2.4.2.2. Liver volume

Normal liver volume was defined as 2.5% of the total body weight in kilograms. Hepatomegaly has been defined as a liver mass greater than 1.25 times the normal volume [Grabowski et al., 1995; Pastores et al., 2004]. In patients with GD, reduction in liver volume to less than 1.5 MN has been considered to be clinically relevant (or "normalisation") with ERT treatment [Pastores et al., 2004]. About 65% of GD patients have hepatomegaly [ICGG, 2008] up to 4 multiples of normal size. In the historical data, the baseline range of means was 1.6 to 3.4 MN [total range 0.9 to 4.5 MN] for liver volume. The reductions in liver volume at Month 9 and 12 in patients from the pivotal study and at Month 12 from the historical analysis are summarised below in Table 16.

Table 16: Historical analysis vs Patients from pivotal study – Change in liver volume from baseline.

Data	Treatment	Mean % Reduction	Range %
Study PB-01-001[1]	Taliglucerase 60 units/kg [n=15]	-11.11% [p<0.0001]	-22.29% to +2.32%
	Taliglucerase 30 units/kg [n=14]	-10.48% [p=0.0041]	-19.11% to +25.31
PB-06-001 EXT to PB-06-003[2]	Taliglucerase 60 units/kg [n=14]	-13.2%	-32.7% to -2.3%
	Taliglucerase 30 units/kg [n=12]	-15.9%	-25.5% to -4.5%
Historical[3]	ERT 15-60 units/kg up to 12 months	-27% to -5.8% range of means -34% to +9.5% total range	

1 Reduction from baseline at Month 9.

2 Reduction from baseline at Month 12 [i.e. Month 3 of PB-06-003]

3 Reduction from baseline at approximately Month 12.

Hepatomegaly was not an inclusion criterion for study PB-06-001. In a post-hoc subgroup analysis in this study in 16 patients (both dose groups combined) with hepatomegaly (> 1.5 MN volume) the mean reduction in hepatic volume was 14% at Month 9.

7.2.4.2.3. Haemoglobin level

Anaemia is found in about 30% of GD patients [Charrow et al., 2000; ICGG, 2008]. Reduction in haemoglobin level from baseline to month 9 was a secondary efficacy endpoint in study PB-06-001. The results for change in haemoglobin levels from study PB-06-001 and the historical analysis are summarised below in Table 17.

Table 17: Historical analysis vs Patients from pivotal study - Summary of haemoglobin results.

Study	Mean Values [range]				Change from Baseline %	
PB-06-001[1]	Baseline	n	Month 9	n	% change [range]	n
T 60 units/kg	11.4 g/dL [5.5-16.0]	16	13.6 g/dL [8.6-16.5]	15	22.2% [3.1-56.4]	15
T 30 units/kg	12.2 g/dL [7.9-14.6]	14	14.0 g/dL [12.2-16.9]	14	14.6% [-0.7-73.4]	14
Historical[2] ERT 15-60 units/kg	8.8 to 2.6 g/dL range of means		6 to 15.7 g/dL range of means		10 to 24% range of means [-15.8% to +30%] total range	

1 Reduction from baseline at Month 9.
2 Reduction from baseline at approximately Month 12, data from 14 studies.

Anaemia was not an inclusion criterion for GD patients in study PB-06-001. The mean haemoglobin values at baseline in the total population studied in PB-06-001 were 12.2 g/dL for

the group treated with 30 units/kg dose and 11.4 g/dL for the group treated with 60 units/kg. These values were at the lower limit of the normal range (12-16 g/dL) and the increases from baseline to Month 9 for both doses were not statistically significant. Consequently, a post-hoc subgroup analysis in patients with baseline anaemic was undertaken in study PB-06-001. Of the 31 patients, 10 were anaemic at baseline (haemoglobin levels 5.5 to 10.7 g/dL). The mean [range] haemoglobin level for these 10 patients was 9.5 g/dL [5.5-10.7] at baseline and 12.7 g/dL [8.6-14.4] at Month 9, and the mean percentage change [range] from baseline was 36.0% [12.6-73.4]

7.2.4.2.4. Platelet counts

The platelet response to GD therapy may depend on the initial magnitude of thrombocytopaenia, with patients with moderate severity (platelet counts 60,000/mm^3 to 120,000/mm^3) being more likely to achieve a higher platelet count (>120,000/mm^3) than those with more pronounced thrombocytopenia (<60,000/mm^3) [Connock et al., 2006; Weinreb et al., 2002]. In the Gaucher Registry, 45% of GD patients had platelet counts below 120,000/mm^3 and 15% had platelet counts below 60,000/mm^3 [ICGG, 2008]. In study PB-06-001, thrombocytopaenia was an inclusion criteria (platelet counts < 120,000/mm^3) and change in platelet count from baseline to Month 9 was a secondary efficacy endpoint. The results for change in platelet counts from study PB-06-001 and the historical analysis are summarised below in Table 18.

Table 18: Historical analysis vs Patients from pivotal study - Summary of platelet count results

Study	Mean Values [range] & Change [range]		Change [range] from Baseline %
PB-06-001[1]	**Baseline**	**Month 9**	
T 60 units/kg [n=16]	65,038 [28,000 to 134,000]	106,531 [27,000 to 163,000]	72.1% [-37.5 to +338.2]
	Change = 41,949 [-15,000 to 186,000]		
T 30 units/kg [n=15]	75,320 [25,000 to 241,000]	86,747 [20,000 to 168,000]	13.7% [-31.4 to +55.1]
	Change = 11,427 [-25,000 to 69,000]		
Historical[2] ERT 15-60 units/kg	45,000 to 147,000 range of means	79,000 to 199,000 range of means	9.9% to 91% range of means

1 Reduction from baseline at Month 9.
2 Reduction from baseline at approximately Month 12, data from 14 studies.

Comment: The results for the main efficacy endpoints assessed for taliglucerase alfa from baseline to 9 months in study PB-06-001 (splenomegaly, hepatomegaly, platelet counts and haemoglobin levels), supplemented by the additional 3 months data from PB-06-003 (to achieve a total of 12 months), are within the ranges derived from the historical analysis. This suggests that taliglucerase alfa and alglucerase/imiglucerase are likely to have similar efficacies in patients with GD.

7.2.4.2.5. Evaluation of efficacy respective to therapeutic goals

The Historical Analysis include an evaluation of the success of taliglucerase alfa at 12 months in meeting therapeutic goals for GD. Consensus therapeutic goals for the treatment of GD have

been proposed by an international panel of physicians with extensive clinical experience in GD [Pastores et al., 2004], and reflect cumulative data derived mostly from the ICGG Gaucher Registry. The consensus therapeutic goals are defined for ERT of a duration of at least 12 months and are not dose specific. A total of 26 patients from study PB-06-001 had 12 month efficacy data for comparison with consensus therapeutic goals for the four parameters of splenomegaly, hepatomegaly, haemoglobin level, and platelet count.

Splenomegaly: The therapeutic goal for splenomegaly was: "To reduce the spleen volume by 30% to 50% within 1 year of imiglucerase treatment and by 50% to 60% by years 2 to 5 of treatment and to achieve a spleen volume of 2 to 8 times normal"[Pastores et al., 2004]. Achievement of the therapeutic goal was assessed for each taliglucerase alfa dose separately, and for both doses combined, in three ways (see Table 19, below):

- spleen volume at month 12: ≤ 8 multiples of normal (MN);
- spleen volume at month 12: ≥ 30% decrease from baseline; and
- spleen volume at month 12: ≤ 8 multiples of normal (MN) and/or ≥30% decrease from baseline.

Table 19: Therapeutic goals based on spleen volume at Month 12.

	≤ 8MN at month 12		≥ 30% decrease from B/L		≤ 8 MN at month 12 and/or ≥ 30% decrease from B/L	
Dose	**N**	**% [95% CI]**	**N**	**% [95% CI]**	**N**	**% [95% CI]**
60 units/kg	11/14	78.6% [49.2, 95.3]	13/14	92.9% [66.1, 99.8]	13/14	92.9% [66.1, 99.8]
30 units/kg	6/12	50.0% [21.1, 78.9]	5/12	41.7% [15.2, 72.3]	8/12	66.7% [34.9, 90.1]
Overall	17/26	65.4% [44.3, 82.8]	18/26	69.2% [48.2, 85.7]	18/26	80.8% [60.6, 93.4]

Hepatomegaly: The therapeutic goal for hepatomegaly was: "To reduce liver volume by 20% to 30% within year 1 to 2 and by 30% to 40% by years 3 to 5 and achieve a liver volume of 1 to 1.5 times normal" [Pastores et al., 2004]. Achievement of the therapeutic goal was assessed for each taliglucerase alfa dose separately and for both doses combined, in three ways (see Table 20, below):

- Liver volume at month 12: ≤ 1.5 MN,
- Liver volume at month 12: ≥ 20% decrease from baseline; and
- Liver volume at month 12: ≤ 1.5 MN and/or ≥ 20% decrease from baseline.

Table 20: Therapeutic goals based on liver volume at Month 12.

	≤ 1.5 MN at month 12		≥ 20% decrease from B/L		≤ 1.5 MN month 12 and/or ≥ 20% decrease from B/L	
Dose	**N**	**% [95% CI]**	**N**	**% [95% CI]**	**N**	**% [95% CI]**
60 units/kg	13/14	92.9% [66.1, 99.8]	3/14	21.4% [4.7, 50.8]	14/14	100.0% [76.8, 100.0]

	≤ 1.5 MN at month 12		≥ 20% decrease from B/L		≤ 1.5 MN month 12 and/or ≥ 20% decrease from B/L	
Dose	**N**	**% [95% CI]**	**N**	**% [95% CI]**	**N**	**% [95% CI]**
30 units/kg	11/12	91.7% [61.5, 99.8]	2/12	16.7% [2.1, 48.4]	11/12	91.7% [61.5, 99.8]
Overall	24/26	92.3% [74.9, 99.1]	5/26	19.2% [6.6, 39.4]	25/26	96.2% [80.4, 99.9]

Haemoglobin: The therapeutic goal for anaemia was: "To increase haemoglobin levels within 12 to 24 months to at least 11 g/dl for women and children and 12 g/dl for men" [Pastores et al., 2004]. Achievement of the therapeutic goal for haemoglobin was assessed for each taliglucerase alfa dose separately and for both doses combined: i.e. haemoglobin at month 12 ≥ 12 g/dl for male subjects ≥ 12 years old and ≥ 11 g/dl for others (see Table 21, below).

Table 21: Haemoglobin level ≥ 12 g/dL male subjects ≥ 12 years old and ≥ 11 g/dL for others.

Dose	N	% [95% CI]
60 units/kg	12/14	85.7% [57.2, 98.2]
30 units/kg	12/12	100.0% [73.5, 100.0]
Overall	24/26	92.3% [74.9, 99.1]

Platelet Counts The therapeutic goal for thrombocytopenia was as: "For all patients: to achieve a sufficient increase in platelets to prevent spontaneous bleeding; for splenectomised patients: to achieve normalisation of platelet counts; and for patients with an intact spleen: to achieve an increase of at least 1.5 fold in the first year of treatment" [Pastores et al., 2004]. Achievement of the therapeutic goal for platelet counts was assessed for each taliglucerase alfa dose separately and for both doses combined: i.e. platelet count at month 12 ≥ 50% increase from the baseline value (see Table 22, below).

Table 22: Platelet counts at Month 12 (≥ 50% increase from baseline).

Dose	N	% [95% CI]
60 units/kg	9/14	64.3% [35.1, 87.2]
30 units/kg	2/12	16.7% [2.1, 48.4]
Overall	11/26	42.3% [23.4, 63.1]

Comment: In this post-hoc analysis, the efficacy outcomes in 26 patients with GD after 12 months of treatment with taliglucerase alfa showed that the drug can achieve consensus therapeutic goals [Pastores et al, 2004]. Taliglucerase alfa was particularly effective in achieving therapeutic goals relating to reduction in spleen and liver volumes, with the 60 units/kg dose being more effective than the 30 units/kg dose. However, hepatomegaly was not a requirement for inclusion in the pivotal study. Both taliglucerase alfa doses were effective in achieving haemoglobin level goals, but most subjects in these two treatment groups in the pivotal study were not anaemic at

baseline. The 60 units/kg dose of taliglucerase alfa was notably more effective than the 30 units/kg dose of taliglucerase alfa at achieving the therapeutic goal relating to increases in platelet count.

7.3. Analyses performed across trials

In this submission, there were no analyses pooled across trials.

7.4. Evaluator's conclusions on clinical efficacy

The efficacy of taliglucerase alfa for the treatment of GD is based primarily on the data (ITT population) from one pivotal Phase 3 study in 31 adult patients not previously treated with ERT [PB-06-001]. Inclusion criteria included splenomegaly greater than 8 times the expected volume and thrombocytopaenia defined as platelet count < 120,000/mm^3, but baseline hepatomegaly and anaemia were not required for inclusion in this study. The pivotal study included two double-blinded doses of taliglucerase alfa, but no placebo or active control. Consequently, it is subject to the well known biases of uncontrolled studies. The sponsor justified the absence of a placebo control on ethical grounds, and this is considered to be acceptable. However, there appeared to be no reason why the study could not have included an active control imiglucerase comparator. The inclusion of a third treatment group would have provided valuable comparative efficacy data for taliglucerase alfa and imiglucerase and assisted in interpretation of the data.

The lack of a control group is mitigated to some extent by the progressive natural history of GD. While the clinical course and life expectancy of patients with NNGD are variable, most often the disease is progressive and symptomatic patients may die prematurely due to sequelae of severe skeletal disease, bleeding complications, infection, liver failure, and severe pulmonary disease [Pastores et al., 2004].Consequently, it is not unreasonable to infer that the observed improvements in the pivotal study are likely to be causally related to treatment with taliglucerase alfa rather than chance occurrences. Furthermore, the efficacy data from the historical analysis in patients with GD treated with ERT (alglucerase, imiglucerase) are consistent with the taliglucerase alfa data from the pivotal study at 9 months (31 patients) and 12 months (26 patients). In addition, the 12 month efficacy data on 26 patients from the pivotal study are consistent with consensus therapeutic goals in patients with GD.

In the pivotal study [PB-06-001], both doses of taliglucerase alfa (30 and 60 units/kg), infused iv over 2 hours every 2 weeks for a period of 9 months, statistically significantly reduced spleen volume (primary efficacy outcome) from screening in the ITT population (multiple imputation method for missing data). In the 30 units/kg group (n=15) the reduction in spleen volume from screening at 9 months was 26.91% ($p<0.0001$), and in the 60 units/kg group (n=16) the corresponding reduction was 38.01 % ($p<0.0001$). The study was powered on a reduction in spleen volume of 20%, suggesting that the reductions at Month 9 were clinically significant for both dose groups.

In the pivotal study [PB-06-001], reductions in liver volume (major secondary endpoint) from screening at Month 9 were statistically significant for both the 30 units/kg dose (10.48% [n=14], $p=0.0041$) and the 60 units/kg dose (11.11% [n=16], $p<0.0001$), but the reductions were of doubtful clinical significance. However, baseline hepatomegaly was not an inclusion criterion for the pivotal study. In a post hoc analysis of patients with hepatomegaly in the pivotal study, reductions in liver volume from baseline at Month 9 were 14% in both the 30 units/kg group (n=10) and the 60 units/kg group (n=6). The study was powered on a reduction in liver volume of 11%, which suggests that the reductions in liver volume at Month 9 in patients with baseline hepatomegaly in both dose groups were clinically meaningful.

In the pivotal study [PB-06-001], mean baseline haemoglobin levels (major secondary efficacy endpoint) were within normal limits for both dose groups and increased in both groups over 9 months. The change in haemoglobin level from baseline to Month 9 was statistically significant for both the 30 and 60 units/kg dose groups (1.6 g/dl [n=14], p=0.0010 and 2.2 g/dL [n=15], p<0.0001), respectively). However, baseline anaemia was not an inclusion criterion for the pivotal study. In a post hoc subgroup analysis in all patients with baseline anaemia (n=10) in the pivotal study, the percentage increase in baseline haemoglobin level at Month 9 was 36.0%. The study was powered on an increase in haemoglobin level of 16%, which suggests that the increase in patients with baseline anaemia was clinically meaningful.

In the pivotal study [PB-06-001], the platelet count (major secondary efficacy endpoint) increased from baseline at Month 9 by 41,494/mm^3 (p<0.0031) in the 60 units/kg (n=16) and by 11,427/mm^3 (p=0.0460) in 30 units/kg (n=15). The result for the 30 units/kg group was not statistically significant as the increase from baseline failed to meet the pre-specified alpha significance level of 0.025. In an ad hoc analysis, the increase in platelet count from baseline at Month 9 was 72.1% in the 60 units/kg group and 13.7% in the 30 units/kg group. The study was powered on an increase in platelet count of 46%, which suggests the increases in platelet count at Month 9 were clinically meaningful for the 60 units/kg dose but not for the 30 units/kg dose.

In a post hoc dose separation analysis of the efficacy data from the pivotal study [PB-06-001], the 60 unit/kg dose was statistically significantly superior to the 30 units/kg dose at Month 9 and Month 12 as regards the primary efficacy endpoint of reduction in spleen volume from baseline. Similarly, the higher dose was statistically significantly superior to the lower dose at Month 9 and Month 12 as regards the secondary efficacy endpoint of increase in platelet count from baseline. However, there were no statistically significant differences between the two doses from baseline at Month 9 or Month 12 as regards changes in liver volume (reduction) and haemoglobin level (increase).

Supportive efficacy data for taliglucerase alfa was provided from an interim analysis in 15 (60%) of 25 patients enrolled in an ongoing Phase 3 switchover study [PB-06-002]. In this study, patients with stable GD who have been treated with imiglucerase for at least 2 years, and have been on a stable dose for at least six months prior to enrollment, are switched-over to taliglucerase alfa administered at a starting dose equivalent to their stable imiglucerase before the switch. The total duration of treatment with taliglucerase alfa is 9 months and the maximum dose is 60 units/kg. No primary efficacy endpoint was defined in this study. The efficacy outcome of main interest was whether patients deteriorated clinically during treatment with taliglucerase alfa as assessed by protocol specified changes in platelet count, haemoglobin level, spleen volume and liver volume. The control is the patient's historical status while on imiglucerase therapy. The data showed that in 15 adult patients with GD, there was no clinically significant deterioration after 9 months of treatment with taliglucerase alfa after switching from imiglucerase. The mean reductions from baseline (stable) to Month 9 in spleen and liver volumes were 5.1% and 1.4%, respectively, while haemoglobin levels and platelet counts also remained stable.

Supportive efficacy data for taliglucerase alfa was also provided from an interim analysis in 26 patients from the pivotal Phase 3 study [PB-06-001] enrolled in the ongoing Phase 3 extension study [PB-06-003]. No patients from study PB-06-003 were included in the interim efficacy analysis. The extension study plans to enrol up to 60 patients with GD who have completed 9 months treatment with taliglucerase alfa in studies PB-06-001 or PB-06-002. The total duration of treatment in the extension study is planned to be at least 15 months (64 weeks) and no more than 30 months (128 weeks) or until marketing approval has been granted by the appropriate regulatory authority, whichever is earlier. The interim analysis was not defined in the study protocol, but was provided by the sponsor as supportive data for marketing applications at the request of the US FDA. The taliglucerase alfa doses were the same as allocated in study PB-06-

001 (30 or 60 units/kg), or the same dose received at the completion of study PB-06-003. The spleen and liver volumes were measured at Day 1, which corresponds to the final visit (Month 9) of the predecessor trial, and at Month 3 of treatment, representing a total of 12 months treatment with taliglucerase alfa for patients from study PB-06-001. The results from this study showed that patients who improved following 9 months treatment in the pivotal study [PB-06-001] maintained this improvement for a further 3 months in the extension study [PB-06-003]. The extension study also suggested that patients in the 60 units/kg dose group did better than patients in the 30 units/kg dose group.

The submission included a historical analysis which compared efficacy data for imiglucerase/alglucerase from published articles with efficacy data from the pivotal study [PB-06-001]. This analysis showed that changes from baseline at 12 months in the historical data for imiglucerase/alglucerase at doses of 15 to 60 units/kg were similar to changes from baseline at 9 months in the pivotal study (n=31) for both the 30 and 60 units/kg doses. This similarity was shown for the efficacy outcomes of percentage reductions in spleen and liver volume, and percentage increases in platelet count and haemoglobin level. This comparison for these outcomes was supported by that between the historical efficacy data at 12 months and the 12 month efficacy data (i.e. additional 3 months of treatment) from 26 patients from the pivotal study who were included in extension study PB-06-003. In addition, the sponsor also undertook a comparison between the 12 month efficacy data on the 26 patients from the pivotal study who were included in extension study PB-03-006 and consensus therapeutic goals at 12 months [Pastores et al., 2004]. In general, this comparison showed that treatment with taliglucerase alfa (particularly at the 60 units/kg dose) satisfied the consensus therapeutic goals.

In summary, it is considered that the efficacy results for taliglucerase alfa for the treatment of non-neuronopathic GD in adults are promising. However, the submission included pivotal efficacy data following 9 months treatment with taliglucerase alfa on only 31 patients [PB-01-001]. Supportive efficacy data on 26 of these patients were available following a further 3 months of treatment from the interim analysis of extension study [PB-06-003] giving a total of 12 months treatment for these patients. However, the extension study aims to provide efficacy data in up to 60 patients from studies PB-06-001 and PB-06-002 following at least 15 months treatment (i.e. a total of 64 weeks) and up to 30 months treatment (i.e. a total of 128 weeks), depending on whether marketing approval by the appropriate regulatory authorities is granted prior to the planned treatment durations being reached. Consequently, the interim analysis of the extension study only includes limited and preliminary data from the planned study. Further supportive efficacy data from the interim analysis of the switchover study [PB-02-001] were available on 15 patients who had been treated with taliglucerase alfa for 9 months following switchover from imiglucerase. However, the switchover study aims to provide efficacy data on 30 patients treated with taliglucerase alfa for 9 months after being switched from imiglucerase. Consequently, the interim analysis of the switchover study only includes data on about half of the total number of patients planned for the final analysis.

The small number of patients with efficacy data in the submission is a function not only of the limited number of patients available for study due to the rarity of GD, but also of the results of two interim rather than final analyses being presented for evaluation. Taken together, the two interim analyses include data on about half of the total number of patients planned for the final analyses of the extension and switchover studies. In the absence of a controlled efficacy study with imiglucerase, and because total patient numbers for efficacy evaluation are so small, it is considered that the final data from the extension and switchover studies should be evaluated in order to confirm the promising results observed with taliglucerase alfa.

8. Clinical safety

8.1. Studies providing evaluable safety data

The studies providing safety data in support of taliglucerase alfa for the treatment of GD, as of 30 June 2010, is summarised below in Table 23. The data includes 89 subjects (6 healthy volunteers from one PK study and 83 GD patients from four clinical trials). The safety data from the 6 healthy subjects in the PK study included adverse events, general infusion related toxicities, physical examination including changes in vital signs and body weight, and laboratory tests. In general, the safety data for the 6 healthy subjects are consistent with that for patients with GD, and examination of the small amount of safety data in 6 healthy subjects does not give rise to additional safety concerns beyond those observed for patients with GD. Consequently, the safety data from the 6 healthy subjects will not be discussed in the evaluation of safety in this clinical evaluation report. The focus will be on the 83 predominantly Caucasian patients (n=79) with GD treated with taliglucerase alfa, of whom 77 were aged 18 to 65 years and 6 were aged > 65 years.

Table 23: Studies providing safety information for taliglucerase alfa.

Study ID (Phase)	Design Control Type	Study Objective	Study and Control Drug Dose, Route and Regimen	Subjects by Arm Completed/ Entered	Duration of Treatment	Study Population Inclusion Criteria
Completed Studies						
P-01-2005 (Phase 1)	Non-randomised, open-label, single-dose escalation	Safety and PK	Day 1: vehicle Day 8: 15 U/kg taliglucerase alfa Day 15: 30 U/kg taliglucerase alfa Day 22: 60 U/kg taliglucerase alfa IV	6/6	3 single dose; 1 week apart	Healthy subjects
PB-06-001 (Phase 3)	Randomised, double-blind, parallel group trial 2 parallel dose groups	Safety and efficacy and PK	Group 1: 30 U/kg Group 2: 60 U/kg IV Every 2 weeks	29/32 LPLV: September 2009	9 months	Untreated patients with Gaucher disease Age 18 or older Leukocyte glucocerebrosidase activity level ≤3 nmol/mg*hr Splenomegaly eight times the expected volume Thrombocytopenia No ERT in past 12 months
Ongoing Studies						
PB-06-002 (Phase 3) *[safety cut-off date: 15 August 2010]*	Open-label, Switchover trial	Safety and efficacy	Same dose as imiglucerase dose	16/25	9 months	Patients with stable Gaucher disease currently treated with Cerezyme under a stable maintenance regimen
PB-06-003 (Phase 3)	Double-blind* extension study	Safety and efficacy	Same dose as received during PB-06-001 or PB-06-002	26 + 5 =31	15 months	Eligible patients from PB-06-001 and PB-06-002
PB-06-004 EAP	Open-label, expanded access trial	Safety	Same dose as imiglucerase before reduction or discontinuation due to drug shortage	26	38 weeks	Age 18 years or older Diagnosis of GD treated historically with imiglucerase

Source: Module 2, Summary of Clinical Safety [2.7.4], Table 2.7.4-1, page 10.
Abbreviations: U= unit; NA= not applicable; GD: Gaucher disease; LPLV: last patient, last visit; ERT: enzyme replacement therapy; EAP: expanded access program; CUP: compassionate use programs; MA: marketing authorization.
* This study will be modified as an open-label extension when PB-06-001 will be unblinded.

The Medical Dictionary for Regulatory Activities (MedDRA) version 10.1 was used to encode all AEs in studies PB-06-001, PB-06-002, PB-06-003 and PB-06-004. All adverse events occurring after randomization or which were present prior to randomization but worsened after treatment were presented by MedDRA System Organ Class [SOC] / preferred term [PT]. The protocol definitions for causal relationship and degree of intensity for the AEs from these four

studies were derived from WHO Common Toxicity Criteria. All volunteered, elicited and observed AEs were documented. Hypersensitivity reactions were analysed as AEs of special interest using descriptive statistics. Hypersensitivity reactions were evaluated in the context of antibody formation. Laboratory test results were tabulated for each visit, and compared with baseline measurements.

The exposure data in GD patients from the four clinical trials who received treatment with taliglucerase alfa iv are summarised below in Table 24.

Table 24: Total taliglucerase alfa exposure in GD patients from the completed pivotal clinical study [PB-06-001], ongoing supportive clinical studies [PB-06-002, PB-06-003], and expanded access program [PB-06-004].

		Months of treatment											
Study	#*	3	6	9	12	15	18	21	24	27	30	33	36
PB-06-001	32	31	29	29									
PB-06-002	25	25	24	16									
PB-06-003	31					30	27	23	15	3	2	1	
PB-06-004	26	16	6										
Total	83	72	59	45	30	27	23	15	9	3	2	1	

*Number of subjects enrolled and treated as of June 30, 2010 for all studies except PB-06-002, which is August 30, 2010.

- In the pivotal study [PB-06-001], 33 patients were randomised to 30 (n=16) or 60 units/kg (n=17), with 1 withdrawing from the study before being treated. Therefore, 32 patients (30 units/kg [n=16]; 60 units/kg [n=16]) were administered study medication at least once during the study. Of these 32 patients, 1 received only one single part dose of 60 units/kg (4.5 mL), 1 developed hypersensitivity and withdrew at Week 22, and 1 became pregnant and withdrew at Week 18. Therefore, 29 of the 32 treated patients completed the 9 months of treatment.
- In the switchover study [PB-06-002], 25 patients have received treatment as of 15 August 2010 and 16 have completed the study to date and no subjects have been withdrawn prematurely.
- In the extension study [PB-06-003], 31 patients were enrolled as of 30 June 2010 (26 from study PB-06-001 and 5 from Study PB-06-002), and 9 from study PB-06-001 have completed 24 months treatment. Thirty-one (31) patients are continuing treatment on taliglucerase alfa; 12 with 30 units/kg and 14 with 60 units/kg from study PB-06-001. Five (5) patients from Study PB-06-002 are receiving total doses ranging from 1000 to 2000 units every 2 weeks. One (1) patient has completed a total of 33 months of continuous treatment in studies PB-06-001 and PB-06-003.
- In the EAP [PB-06-004], 26 patients from the USA and Israel have been enrolled (with patient accrual continuing) and 5 have voluntarily withdrawn from the study (none because of safety reasons). Patients enrolled in study PB-06-004 were treated with the same taliglucerase alfa dose as the imiglucerase dose the patient was receiving before reduction or discontinuation due to imiglucerase shortage. The submission included an interim analysis of the safety data from this study at the cut-off date of 30 June 2010. The mean age of the 26 patients (14:15 males:females) was 50 years [range: 25 to 85 years] and the population was predominantly Caucasian (88.5%, n=23).

8.2. Adverse events

8.2.1. All adverse events (irrespective of relationship to study treatment)

8.2.1.1. Overview

Overall, there were 83 GD patients treated with taliglucerase alfa in the relevant safety population, and the number of patients experiencing AEs are summarised below in Table 25.

Table 25: Summary GD patient numbers experiencing AE; safety population.

Patients from:		PB-06-001 and PB-06-003				PB-06-002 and PB-06-003		PB-06-004		Overall	
		30 U/kg N=16		60 U/kg N=16		12-60U/kg N=25		N=26		N=83	
		N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
With at least one AE	Yes	16	(100.0)	15	(93.8)	23	(92.0)	18	(69.2)	**72**	**(86.7)**
	No	0	(0.0)	1	(6.3)	2	(8.0)	8	(30.8)	**11**	**(13.3)**
With at least one mild or moderate AE	Yes	16	(100.0)	15	(93.8)	23	(92.0)	18	(69.2)	**72**	**(86.7)**
	No	0	(0.0)	1	(6.3)	2	(8.0)	8	(30.8)	**11**	**(13.3)**
With at least one severe or very severe AE	Yes	0	(0.0)	2	(12.5)	2	(8.0)	1	(3.8)	**4**	**(4.8)**
	No	16	(100.0)	14	(87.5)	23	(92.0)	25	(96.2)	**79**	**(95.2)**
With at least one serious AE	Yes	0	(0.0)	1	(6.3)	3	(12.0)	1*	(3.8)*	**4***	**(4.8)***
	No	16	(100.0)	15	(93.8)	22	(88.0)	25	(96.2)	**79**	**(95.2)**
With at least one probably or definitely not treatment-related AE	Yes	15	(93.8)	14	(87.5)	23	(92.0)	14	(53.8)	**66**	**(79.5)**
	No	1	(6.3)	2	(12.5)	2	(8.0)	12	(46.2)	**17**	**(20.5)**
With at least one definitely, probably or possibly or definitely not treatment - related AE	Yes	6	(37.5)	8	(50.0)	7	(28.0)	10	(38.5)	**31**	**(37.3)**
	No	10	(62.5)	8	(50.0)	18	(72.0)	16	(61.5)	**52**	**(62.7)**

AE: adverse event; N: number of patients

* A severe adverse event was marked as serious at the time of data cut-off for this analysis, but has since been corrected.

Overall, the 83 GD patients treated with taliglucerase alfa experienced 526 AEs of which 134 were considered by the investigator to be at least possibly treatment related. The majority of AEs were mild or moderate in intensity. The AEs are summarised below in Table 26, and the cut-off date was 30 June 2010 (unless otherwise stated).

Table 26: Summary of number of AEs in GD patients; safety population.

Parameter	PB-06-001		PB-06-002 (August 15, 2010)	PB-06-003 (June 30, 2010)			PB-06-004 (June 30, 2010)	Overall
				Derived from PB-06-001		Derived from PB-06-002		
	30 U/kg N=16	60 U/kg N=16	11-60U/kg N=25	30 U/kg N=12	60 U/kg N=14	12-29 U/kg N=5	13-65 U/kg N=26	N=83
AE	65	72	135	64	85	1	104	526
Mild or moderate AE	65	72	132	64	81	1	103	518
Severe or very severe AE	0	0	3	0	4	0	1	12
Serious AE	0	0	3	0	1	0	1*	5
AE probably or definitely not related to treatment	53	56	115	50	75	1	42	392
AE definitely, probably or possibly related to treatment	12	16	20	14	10	0	62	134

AE: adverse event; N: number of patients
* A severe adverse event was marked as serious at the time of data cut-off for this analysis, but has since been corrected.

8.2.1.2. Common AEs irrespective of relationship to treatment

8.2.1.2.1. Pivotal Study – PB-06-001

Overall, 23 (71.9%) treated patients experienced 137 AEs over the 9 months duration of the study. In the 30 units/kg group, 12 (75.0%) patients experienced 65 AEs and in the 60 units/kg group, 11 (68.8%) patients experienced 72 AEs. All AEs were mild or moderate in intensity, and the majority of the events resolved by the end of the study. However, 4 patients experienced 6 AEs that were ongoing at the end of study, but which did not prevent continuing study drug treatment and were considered by the investigators to be not treatment related.

The safety profile was similar for the two dose groups. The most commonly experienced AE in both dose groups was headache, which occurred in 6 patients (1 [6.3%] in the 30 units/kg group and 5 [31.3%] in the 60 units/kg group). The only other AEs occurring in 5 or more patients were pharyngitis and upper respiratory tract infection, each of which occurred in 3 patients (18.8%) in the 30 units/kg group and 2 patients (12.5%) in the 60 units/kg group. There were no other AEs reported in a total of 5 or more patients. The number of patients with AEs are summarised below in Table 27 (data on AEs by SOC and preferred term are provided in the dossier).

Table 27: Study PB-06-001 - Patients with adverse events in the pivotal clinical study.

		PB-06-001 (Safety Population)			
		30 U/kg N=16		60 U/kg N=16	
		N	(%)	N	(%)
With at least one AE	Yes	12	(75.0)	11	(68.8)
	No	4	(25.0)	5	(31.3)
With at least one mild or moderate AE	Yes	12	(75.0)	11	(68.8)
	No	4	(25.0)	5	(31.3)
With at least one severe or very severe AE	Yes	0	(0.0)	0	(0.0)
	No	16	(100.0)	16	(100.0)
With at least one serious AE	Yes	0	(0.0)	0	(0.0)
	No	16	(100.0)	16	(100.0)
With at least one probably or definitely not treatment-related AE	Yes	11	(68.8)	11	(68.8)
	No	5	(31.3)	5	(31.3)
With at least one definitely, probably or possibly or definitely not treatment -related AE	Yes	3	(18.8)	5	(31.3)
	No	13	(81.3)	11	(68.8)

AE: adverse event; N: number of patients

8.2.1.2.2. Other supportive studies

· Study PB-06-003

At the date of the database freeze, of the 31 patients in the safety population, 24 (77.4%) had experienced at least 1 AE. Of the 26 patients enrolled from study PB-06-001, 23 (88.5%) had experienced at least 1 AE, and of the 5 patients enrolled from study PB-06-002, 1 (20.0%) patient had experienced at least 1 AEs. The 23 patients enrolled from study PB-06-001 had experienced 149 AEs (i.e. 11 [91.7%] patients in the 30 units/kg group experienced 64 AEs, and 12 [85.7%] patients in the 60 units/kg groups experienced 85 AEs).

The most commonly experienced AEs were arthralgia, which occurred in 6 patients (3 in each of the 30 and 60 units/kg groups), headache in 5 patients (3 in the 30 units/kg group, and 2 in the 60 units/kg group), and nasopharyngitis in 4 patients (2 in each of the 30 and 60 units/kg groups).

All AEs were mild or moderate in intensity except for 2 patients in the 60 units/kg treatment group enrolled from study PB-06-001: 1 patient experienced a severe SAE Grade 4 immune thrombocytopenia not considered to be treatment related; and 1 patient developed diabetes mellitus requiring treatment with insulin not considered to be treatment related.

· Study PB-06-002

At the date of the database freeze, 23 (92.0%) of the 25 patients in the safety population had experienced 135 AEs. The most commonly experienced AEs were nasopharyngitis, which occurred in 5 (20%) patients, and infusion related reactions, which occurred in 4 (16%) patients. All other AEs occurred in ≤ 3 patients. All AEs were mild or moderate in intensity, except for 3 AEs in 2 patients that were reported as severe (haematuria, renal stone, prolapsed rectum bladder and cervix).

· Study PB-06-004 [EAP Study]

At the data cut-off date, 18 (69.2%) patients had experienced 104 AEs. The most commonly occurring AEs (≥ 10% of patients) were headache (19.2%, n=5), fatigue (15.4%, n=4), nausea (11.5%, n=3), arthralgia (11.5%, n=3), and back pain (11.5%, n=3). All other AEs occurred in ≤ 2 patients. Only one event was considered severe (Back Pain), but was not considered related to treatment with taliglucerase alfa.

8.2.1.2.3. Overall

In the total safety population in patients with GD (n=83), 72 (86.7%) patients were reported to have experienced one or more AE. The most common AEs (occurring in ≥ 3 % of patients) were headache (20.5%, n=17), arthralgia (16.9%, n=14), fatigue (12.0%, n=10), nasopharyngitis

(12.0%, n=10), upper respiratory tract infection (10.8%, n=9), back pain (9.6%, n=8), influenzae (8.4%, n=7), nausea (7.2%, n=6), infusion related reactions (7.2%, n=6), pharyngitis (7.2%, n=6), pharyngolaryngeal pain (7.2%, n=6), pain (6.0%, n=5), pyrexia (6.0%, n=5), gastroenteritis (6.0%, n=5), urinary tract infection (6.0%, n=5), cough (6.0%, n=5), erythema (6.0%, n=5), pruritus (6.0%, n=5), abdominal pain (4.8%, n=4), constipation (4.8%, n=4), diarrhoea (4.8%, n=4), asthenia (4.8%, n=4), lymphadenopathy (3.6%, n=3), and spleen disorder (3.6%, n=3).

8.2.2. Infusion reactions

8.2.2.1. Pivotal Study PB-06-001

During the infusions, 10 patients (6 in the 30 units/kg group; 4 in the 60 units/kg group) experienced 22 AEs (10 and 12, respectively) which were considered to be treatment related. The most common AEs reported during the infusion in both treatment groups were headache (10 events [1 in the 30 units/kg group; 9 in the 60 units/kg group]). Hypersensitivity reactions were reported in 2 patients during the infusion (1 in each dose group).

8.2.2.2. Other (Supportive) Studies

· Study PB-06-003

During the infusions, 9 patients experienced 22 AEs. Of these 9 patients, 1 patient experienced the same treated related AE (fixed drug eruption on left cheek) on 11 separate occasions.

· Study PB-06-002

During the infusions, 9 patients experienced 26 AEs. One (1) patient experienced itching between the thumb and index finger on the left hand on 12 separate occasions. Two (2) patients were reported to have experienced an AE during the infusions, but there was no reported AE associated with the infusion visit by date (to be clarified in the final analysis of the study).

· PB-06-004

No data provided

8.2.2.3. Overall

In the total safety population in patients with GD (n=83), 38 (45.8%) patients experienced 111 AEs during or after 98 infusions, and most of these were considered to be treatment related. The most common infusion related AEs were headache, asthenia or fatigue, dizziness, infusion related reaction, and pruritus. The experience to date is insufficient to assess whether there is a dose relationship with any of these events.

8.2.3. Hypersensitivity reactions

8.2.3.1. Pivotal Study PB-01-006

Two (2) patients discontinued from the study due to a hypersensitivity reaction (1 in each of the 30 and 60 units/kg dose groups).

One (1) female patient in the 60 units/kg group during the 11th infusion developed mild, grade 1 symptoms consistent with a hypersensitivity reaction (feeling of warmth, palpitation, tightness in chest, nausea and facial flushing). The infusion was temporarily discontinued and after the symptoms resolved was resumed at a lower rate without further symptoms. The symptoms were attributed to other causes and not considered to be related to taliglucerase alfa. However, during the 12th infusion, the patient again experienced symptoms consistent with a hypersensitivity reaction (facial flushing, nausea, tightness in the chest, urticaria, inspiratory and expiratory wheezing, and feeling of prickling in the hands). The infusion was permanently discontinued and a corticosteroid and antihistamine were administered. IgG and IgE antibody tests were both found to be negative. This event was considered as probably related to study drug.

One (1) male patient in the 30 units/kg group experienced an immediate reaction (moderate, grade 2) within minutes of the start of his 1st infusion. The symptoms were rash with itching, redness, urticaria, whole body chills and tremor, and swelling of the right eyelid. A corticosteroid and antihistamine were administered. The patient was withdrawn from the study. The pre-dose antibody sample was positive for anti-taliglucerase alfa IgE. The patient had an extensive allergy workup which was negative, including a history of prior exposure to glucocerebrosidase enzyme. This event was considered definitely related to study drug. The patient subsequently had a similar hypersensitivity reaction (pruritis and urticaria) to Cerezyme.

8.2.3.2. Other (supportive) studies

· Study PB-06-003

At the data of the database freeze, 2 patients had been reported as having developed hypersensitivity to taliglucerase alfa.

One (1) patient with a history of hypertension (being treated) experienced a grade 2 hypersensitivity reaction with dizziness, nausea, vomiting, urticaria and hypotension after 70 minutes of the 3rd infusion of the extension study and the 23rd infusion in total. The patient had been treated with taliglucerase alfa over the previous 10 months without AEs. The infusion was discontinued and the patient was treated with adrenaline, methylprednisolone and chloropiramine. The patient quickly recovered and was released from the clinic. Taliglucerase alfa infusions were resumed two weeks later with dose reduction (0.65 mL/min [4 hour infusion] and premedication with loratidine 10 mg and ranitidine 150 mg administered 12 hours and 2 hours before each infusion. The patient is reported to be tolerating further infusions.

One (1) patient experienced a fixed drug eruption on his left cheek during his 12th infusion (24 weeks) in study PB-06-003. The infusion was completed without any changes in vital signs or symptoms of hypersensitivity. He had not experienced any previous treatment related AEs during his first 20 infusions received in study PB-06-001. The same eruption occurred during or after some (but apparently not all) subsequent infusions. The eruptions were not associated with other hypersensitivity symptoms and resolved without treatment or change in the infusion. The patient was found to be positive for IgG anti-taliglucerase alfa antibodies in study PB-06-001. The sponsor considered that this was probably not related to the development of the fixed drug eruption as this condition is a delayed hypersensitivity reaction mediated by T cells.

· Study PB-06-002

At the time of database freeze no events of hypersensitivity reactions were reported in patients in the safety population. This is unusual as 1 patient developed itching at the same site on the hand with repeated infusions.

· Study PB-04-004

At the data cut-off date, 1 patient experienced a hypersensitivity reaction and continues taliglucerase alfa treatment receiving premedication for prevention of hypersensitivity symptoms.

8.2.3.3. Overall

See Section 8.5 of this clinical evaluation report.

8.2.4. Treatment-related adverse events (adverse drug reactions)

8.2.4.1. Pivotal Study PB-01-006

In this study, 8 patients experienced 28 AEs considered by the investigator to be treatment related: 3 patients/12 events in the 30 units/kg group; 5 patients/16 events in the 60 units/kg

group. The most commonly reported treatment related AE was headache, with most of these events being reported in one patient. Two (2) patients (1 in each treatment group) experienced hypersensitivity reactions during the infusion which were considered to be related to treatment and resulted in discontinuation.

8.2.4.2. Other (supportive) studies

· Study PB-06-003

Of the 26 patients enrolled from study PB-06-001, 7 patients experienced 24 events considered treatment related by the investigators: n=3 (25.0%), 14 events in the 30 units/kg group; n=4 (28.6%), 10 events in the 60 units/kg group. Of the 5 patients enrolled from study PB-06-002, no (0%) patients experienced an AE considered to be treatment related by the investigators.

· Study PB-06-002

Of the 25 patients, 7 (28.0%) experienced 20 AEs considered to be treatment related by the investigators.

· Study PB-06-004 (EAP Study)

Of the 25 patients, 14 (56.0%) experienced 62 AEs considered to be treatment related.

8.2.4.3. Overall

In the pivotal study and the three supportive studies there were 31 (37.3%) patients with one or more treatment related AEs, and a total of 134 events. The most commonly reported treatment related AEs occurring in ≥ 5% of patients in the total GD safety population (n=83) were infusion related reactions (6%, n=5) and headache (6%, n=5). All other treatment related AEs occurred in ≤ 3 patients. The treatment related AEs in the pivotal study and the three supportive studies are summarised in the dossier.

8.2.5. Deaths and other serious adverse events

8.2.5.1. Pivotal Study PB-06-001

No deaths or SAEs occurred during the study.

8.2.5.2. Other (supportive) studies

· Study PB-03-001

No deaths occurred during the study up to the database freeze date. One (1) patient experienced a SAE reported as immune thrombocytopaenia (not treatment related).

· Study PB-06-002

No deaths occurred during the study up to the database freeze date. Three (3) patients each experienced a SAE (epistaxis, renal stone and prolapsed rectum bladder and cervix), all three events were reported as resolved or resolving,

· Study PB-06-004 (EAP Study)

No deaths or SAEs have been reported.

8.2.6. Discontinuation due to adverse events

8.2.6.1. Pivotal Study PB-06-001

Two (2) patients (1 in each of the 30 and 60 units/kg dose groups) discontinued due to a hypersensitivity reaction (see description above).

8.2.6.2. Other (supportive) studies

· Study PB-06-003

No patients discontinued prematurely up to the database freeze date.

· Study PB-06-002

No patients discontinued prematurely up to the database freeze date

8.3. Laboratory tests

8.3.1. Liver function

8.3.1.1. Pivotal Study PB-06-001

Alanine Aminotransferase (ALT): All patients in both treatment groups had normal ALT levels at screening (0/16 in both groups). At Month 9 (last visit), high levels were reported in 2/14 (14.3%) patients in the 30 units/kg group and 4/15 (26.7%) patients in the 60 units/kg group.

Aspartate Aminotransferase (AST): All patients in both treatment groups had normal ALT levels at screening (0/16 in both groups). At Month 9 (last visit), high levels were reported in 1/14 (7.1%) patients in the 30 units/kg group and 2/15 (13.3%) patients in the 60 units/kg group.

Bilirubin, Total: At screening, high total bilirubin levels were reported in 6/16 (37.5%) patients in both treatment groups. At Month 9 (last visit), high levels were reported in 6/14 (42.0%) patients in the 30 units/kg group and 4/15 (26.7%) patients in the 60 units/kg group.

8.3.1.2. Other studies

· Study PB-06-003

No clinically significant abnormalities reported.

· Study PB-06-002

Two (2) patients had normal ALT values at screening which shifted to above ULN at Visits 1 and 5, respectively and one (1) patient had normal ALT and AST values at screening which shifted to above ULN at Visits 1, 5 and 10; none of these levels were >3X ULN. Four (4) patients had normal bilirubin values at screening which shifted to > ULN. No patients had sustained elevations of ALT, AST, or bilirubin after screening for three consecutive visits 2 weeks apart.

· Study PB-06-004 (EAP Study)

No data provided.

8.3.2. Kidney function

8.3.2.1. Pivotal Study PB-06-001

Creatinine: At screening, low/normal levels were reported in all patients (16/16) patients in both treatment groups. At Month 9 (last visit), normal levels were reported all patients (14/14 in the 30 units/kg group and 15/15 in the 60 units/kg group).

8.3.2.2. Other studies

· Study PB-06-003

No clinically significant abnormalities reported.

· Study PB-06-002

No clinically significant abnormalities reported.

· Study PB-06-004 (EAP Study)

No data provided.

8.3.3. Other clinical chemistry

8.3.3.1. Pivotal Study PB-06-001

Examination of other standard clinical chemistry results does not give rise to concern.

8.3.3.2. Other studies

· Study PB-06-003

No other clinically significant abnormalities reported.

· Study PB-06-002

No other clinically significant abnormalities reported.

· Study PB-06-004 (EAP Study)

No data provided.

8.3.4. Haematology

8.3.4.1. Pivotal Study PB-01-006

Changes in haemoglobin levels and platelet counts were efficacy endpoints and have been discussed previously in this clinical evaluation report. There were no clinically significant effects of treatment on the white cell count (total and differential), partial thromboplastin time, prothrombin time or ESR.

8.3.4.2. Other studies

· Study PB-06-003

No clinically significant abnormalities reported in WCC (total and differential).

· Study PB-06-002

No clinically significant abnormalities reported in WCC (total and differential). One (1) of the 25 treated patients experienced a clinically significant deterioration in platelet count after 22 weeks of treatment of taliglucerase alfa dose. This patient entered the study on a very low dose of Cerezyme (equivalent to taliglucerase alfa 800 units, or 9.5 units/kg, every 2 weeks). The dose was doubled (approximately 20 units/kg) and the platelet counts have been reported to have increased to baseline level. The patient had completed 34 weeks treatment at the time of the database freeze.

· Study PB-06-004 (EAP Study)

No data provided.

8.3.5. Anti-human taliglucerase alfa antibodies

8.3.5.1. Pivotal Study PB-06-001

Of the 32 patients who were tested for immunogenicity to taliglucerase alfa, 2 (1 in each dose group) developed a positive IgG antibody reaction to human taliglucerase alfa at the end of the study. Neutralizing antibody test results were negative for both patients. Both patients were enrolled in the extension study PB-06-003. One (1) patient experienced five AEs at various visits (vomiting, facial flushing, fever/flu, submandibular lymph nodes slightly enlarged, hypertension) during the study but did not develop a hypersensitivity reaction and completed the study. One (1) experienced two AEs (glucosuria and influenza) at two different visits during the study, but did not develop a hypersensitivity reaction and completed the study.

As discussed previously, 1 patient in 30 units/kg groups had a positive IgE antibody pre-dose, and an immediate hypersensitivity reaction occurred within minutes of starting the first infusion.

8.3.5.2. Other studies

· Study PB-06-003

No results provided.

· Study PB-06-002

Analysis has been performed in 15 patients who have completed 9 months treatment. Fourteen (14) patients (93.3%) were negative for anti-taliglucerase alfa IgG antibodies, and 1 patient was positive (with negative neutralizing activity). The one IgG positive patient did not experience any AEs during the study.

· Study PB-06-004 (EAP Study)

No data provided.

8.3.6. Electrocardiograph

8.3.6.1. Pivotal Study PB-06-001

There were no clinically significant ECG changes from baseline reported at Visits 7 (Week 12), 14 (Week 26) and 20 (Week 38).

8.3.6.2. Other studies

· Study PB-06-003

There were no clinically significant ECG changes observed at three monthly intervals from Month 3 to Month 21. However, patient numbers were small, with only 2 patients being available for assessment at months 18 and 21.

· Study PB-006-002

There were no clinically significant changes from baseline observed at months 3, 6, and 9.

Study PB-06-004 (EAP Study)

· No data provided.

8.3.7. Echocardiography

8.3.7.1. Pivotal Study PB-06-001

Echocardiograph abnormalities were reported in 9 (28.1%) of 32 patients at screening (the majority involving tricuspid or mitral valve insufficiency). Of these 9 patients, the ECHO was considered normal in 6 patients at the end of the study (Visit 20, Week 38) and remained abnormal in 3 patients.

8.3.7.2. Other (supportive) studies

· PB-06-003

At Month 15, echocardiographs were reported as normal in the 6 patients with available data.

· PB-06-002

There was no difference in the percentage of patients with echocardiograph abnormalities at screening (40%, 10/25) and Month 9 (40%, 6/15).

· Study PB-06-004 (EAP Study)

No data provided.

8.3.8. Vital signs

8.3.8.1. Pivotal Study PB-06-001

Vital signs (systolic blood pressure, diastolic blood pressure, respiratory rate, temperature) were monitored at each infusion visit for 210 minutes, every 15 minutes during the infusion up to the first 2 hour time period, with continued monitoring for three additional 30 minute periods. The same time schedule was also performed at the pre-dose screening visit. Changes in vital signs during taliglucerase alfa infusions were not analysed, but no AEs events were reported for significant vital sign changes not related to hypersensitivity reactions.

The overall mean vital signs values from screening to Visit 20 (Week 38) are summarised as follows: diastolic blood pressure 75.4 to 72.3 mmHg [range: 71.1 - 75.3 mmHg]; systolic blood pressure 125 to 121 mmHg [range: 118 - 123 mmHg]; pulse rate 71.9 to 74.8 bpm [range 72.1 - 77.5 bpm], respiratory rate 17.0 to 17.8/min [range: 16.9 - 18.6/min); temperature 36.3 to 36.2°C [range: 36.2 – 36.5°C]. Two (2) cases of hypertension (new or worsening) were reported during the study. No other AEs were reported for significant changes in vital signs except for those occurring during hypersensitivity reactions.

8.3.8.2. Other studies

· Study PB-06-002

Vital signs were measured at screening and each visit before each dose and during the infusion for each individual subject. There were 2 reports of increased temperature (pyrexia and body temperature increased) not considered to be treatment related. There were no other important changes in vital signs observed from the screening visit. No hypersensitivity reactions occurred in these patients and no infusion related reactions were associated with change in vital signs.

· Study PB-06-003

Vital signs were measured at each infusion visit prior to dosing and during the infusion for each individual subject. There were 2 cases of hypertension (one new and one worsening) reported during the study, and 3 cases of fever not associated with treatment or infusions. There were no other important changes in vital signs observed during the study. No AEs due to changes in vital signs were reported in the study, except for those occurring during hypersensitivity reactions. No infusion related reactions were associated with change in vital signs.

· Study PB-06-004 (EAP Study)

No data provided.

8.3.9. Pulmonary Function Tests (PFTs)

8.3.9.1. Pivotal Study PB-06-001

Pulmonary function tests [PFTs] (FVC, FEV1, TLC, FRC, RV, DLCO, DLCO/VA) were assessed at screening and Visit 20 (Week 38). Review of the mean, median and range of values for each of the parameters did not reveal clinically significant differences between the screening and end of treatment time-points. Not all patients completed both screening and end of study evaluations. No AEs were reported based on pulmonary function testing.

8.3.9.2. Other studies

· Study PB-06-003

PFTs at Month 15 were available on 3 patients in each of the 30 and 60 units/kg groups, and no notable clinically significant abnormalities were noted.

· Study PB-06-002

No clinically significant mean changes occurred from baseline to Visit 20 (Month 9) in PFTs in 15 of the 24 patients with data at both time points. No AEs were reported based on pulmonary function testing.

· Study PB-06-004 (EAP Study)

No data provided.

8.3.10. Bone disease

8.3.10.1. Pivotal Study PB-06-001

No patients experienced bone pain or fractures during the study. Evaluation of DEXA (tertiary efficacy outcome) showed stable to slightly improved bone density, and QCSI (tertiary efficacy outcome) showed improvement in bone marrow fat fraction.

8.4. Post-marketing experience

No post-marketing data are available on taliglucerase as the drug has not been approved for marketing in any country

8.5. Specific safety issues of regulatory importance

8.5.1. Liver toxicity

There was no evidence of liver toxicity associated with taliglucerase alfa in the submitted safety data.

8.5.2. Haematological toxicity

There was no evidence of haematological toxicity associated with taliglucerase alfa in the submitted safety data.

8.5.3. Serious skin reactions

There was no evidence of serious skin reactions associated with taliglucerase alfa in the submitted safety data.

8.5.4. Cardiovascular safety

There was no evidence of cardiovascular toxicity associated with taliglucerase alfa in the submitted safety data.

8.5.5. Unwanted immunological events

Overall, in the total safety population (n=83), 4 (4.8%) patients experienced a hypersensitivity reaction and 1 (1.2%) developed a fixed drug eruption during the taliglucerase alfa infusion. In addition, 1 (1.2%) patient developed oesophageal pain and delayed erythema under the eyes and blepharitis, symptoms which the sponsor considered not to be typical of a Type 1 sensitivity reaction, but which responded to pre-treatment with diphenhydramine 50 mg iv. Overall, 3 (6.4%) of 47 patients tested positive for anti-taliglucerase alfa IgG.

8.5.6. Pregnancy

Although pregnancy was an inclusion criterion in all studies, one female patient in the pivotal study became pregnant at Week 18 of the study and was withdrawn from the study. The patient delivered a normal baby girl. The spouse of a male patient in this study became pregnant while he was being treated and also went on to deliver a normal baby girl.

8.6. Other safety issues

8.6.1. Safety in special populations

No specific clinical studies were conducted in patients with pre-existing renal, hepatic, or cardiac disease. No specific clinical studies were carried out in patients aged > 65 years (but there were only 6/83 patients in this subpopulation), or in patients aged < 18 years (no patients in this subpopulation). There were no specific clinical studies in male and female subgroups. There were no specific studies based on race, but the study population was almost exclusively Caucasia (i.e. 95.2%, n=79).

8.6.2. Safety related to drug-drug interactions and other interactions

No data.

8.7. Evaluator's overall conclusions on clinical safety

The submission included safety data at the cut-off date of 30 June 2010 on 83 adult patients with GD who have been exposed to taliglucerase alfa, including safety data on 59 patients exposed for 6 months and 30 patients exposed for 12 months. The "rule of threes" suggests that 30 patients exposed to taliglucerase alfa for 12 months will identify treatment related AEs occurring with an incidence of 10% (with 95% confidence) [Jovanovic and Levy, 1997]. Consequently, the 12 month safety population is too small to allow identification of AEs occurring with an incidence of < 10% with taliglucerase alfa over this time interval. The "rule of threes" suggests that the overall safety data in 83 patients exposed to taliglucerase alfa will identify AEs occurring with an incidence of about 3.5% (with 95% confidence). Consequently, the total population exposed to taliglucerase alfa at any dose and for any duration is too small to allow identification of AEs occurring with an incidence of < 3.5%.

The TGA adopted guidelines relating to the extent of population exposure to assess clinical safety for medicines intended for long term treatment of non life-threatening conditions [ICH E1] anticipates that the total number of patients treated with an investigational drug will be 1500, with 300 to 600 exposed for 6 months and a minimum of 100 exposed for 1 year. The number of patients exposed to taliglucerase alfa in the current submission is well below the ICH specified target figures. However, the guideline also states that "[I]n some cases, a smaller number of patients may be acceptable, for example, where the intended treatment population is small." Consequently, the guidelines appear to accommodate applications to register orphan drugs where the intended treatment population is small. Furthermore, the ICH E1 guidelines are not strictly applicable to the current submission as NNGD can be considered to be a life-threatening condition.

In the overall safety population, 83 patients with GD treated with taliglucerase alfa experienced a total of 526 AEs (518 mild or moderate, 12 severe or very severe, 5 SAEs, 392 treatment related, 134 not treatment related). Of the 83 patients, there were 72 (86.7%) with at least 1 AE irrespective of relationship to treatment. The most common AEs reported in taliglucerase alfa treated patients (occurring in ≥ 3 % of patients) were headache (20.5%, n=17), arthralgia (16.9%, n=14), fatigue (12.0%, n=10), nasopharyngitis (12.0%, n=10), upper respiratory tract infection (10.8%, n=9), back pain (9.6%, n=8), influenzae (8.4%, n=7), nausea (7.2%, n=6), infusion related reactions (7.2%, n=6), pharyngitis (7.2%, n=6), pharyngolaryngeal pain (7.2%, n=6), pain (6.0%, n=5), pyrexia (6.0%, n=5), gastroenteritis (6.0%, n=5), urinary tract infection (6.0%, n=5), cough (6.0%, n=5), erythema (6.0%, n=5), pruritus (6.0%, n=5), abdominal pain (4.8%, n=4), constipation (4.8%, n=4), diarrhoea (4.8%, n=4), asthenia (4.8%, n=4), lymphadenopathy (3.6%, n=3), and spleen disorder (3.6%, n=3). Of the 83 patients, 31 (37.3%) experienced at least one treatment related AE. The most common treatment related AEs in patients treated with taliglucerase alfa (occurring in ≥ 5% of patients) were infusion related reactions (6%, n=5) and headache (6%, n=5).

Hypersensitivity reactions during the taliglucerase alfa infusion occurred in 4.8% (n=4) of the 83 patients in the safety population, and 1 patient developed a fixed drug eruption during the infusion. None of the patients with hypersensitivity reactions were reported to have developed anti-taliglucerase alfa IgG antibodies. The 2 patients with hypersensitivity reactions in study PB-06-001 were discontinued from treatment. The 2 other patients with hypersensitivity reactions (1 from study PB-06-003 and 1 from study PB-06-004) were reported have continued to receive treatment with taliglucerase alfa but with appropriate pre-infusion anti-allergy medication, while the 1 patient with the fixed-drug eruption was reported to have continued treatment with taliglucerase alfa without modification.

Anti-taliglucerase alfa IgG antibodies were detected in 6.3% (2/32) of patients tested at the end of pivotal study PB-06-001, and neutralizing antibodies were negative in both IgG antibody positive patients. In study PB-06-002, 6.7% (1/15) of patients were anti-taliglucerase alfa IgG antibody positive, and neutralizing antibodies were negative in this patient. None of the 3 patients identified in the submission who were IgG antibody positive were reported to have experienced a hypersensitivity reaction. In the data to date, the presence of anti-taliglucerase alfa IgG antibodies has not been found to predict the development of hypersensitivity reactions.

There were no deaths reported in the 83 patients, while SAEs were reported in 4 (4.8%) patients (i.e. immune thrombocytopaenia; epistaxis; renal stone; prolapsed rectum, bladder and cervix). Discontinuations occurred in 2 patients in study PB-06-001 due to hypersensitivity reactions, and no patients in studies PB-06-002 and PB-06-003. There was no evidence in the submission of a causal association between significant biochemical or haematological toxicities and taliglucerase alfa. Similarly, there was no evidence in the submission of causal association between taliglucerase alfa and hepatic toxicity, renal toxicity or cardiovascular toxicity.

The data from the pivotal study suggests that there is no clinically significant difference in the safety profiles of the 30 units/kg and the 60 units/kg doses of taliglucerase alfa. The most commonly experienced AE in both dose groups was headache, which occurred in 6 patients (1 in the 30 units/kg group; and 5 in the 60 units/kg group), and 5 patients each had pharyngitis and upper respiratory tract infection (taliglucerase alfa 30 U/kg, 3 in the 30 units/kg group; 2 in the 60 units/kg group), all the AEs resolved without sequelae by the end of the study

There are no specific safety data relating to drug-drug interactions and special groups such as the elderly (aged ≥ 65 years), and patients with hepatic, renal, or cardiovascular disease. While patients with newly diagnosed GD are unlikely to be elderly, it is possible that younger patients in whom successful treatment is initiated will continue treatment to 65 years or beyond. Furthermore, despite there being no specific safety data relating to drug-drug interactions and special groups it is considered that the absence of such data should not preclude approval.

9. First round benefit-risk assessment

9.1. Preliminary assessment of benefits

The single pivotal study showed in adult patients with NNGD treated with taliglucerase alfa statistically significant improvements from baseline at 9 months in spleen volume, liver volume, haemoglobin level, and platelet count. The primary efficacy outcome was the percentage change in spleen volume from baseline at month 9, and the major secondary efficacy endpoints were the changes from baseline at month 9 in percentage liver volume, haemoglobin level and platelet count. In addition, reductions in chitotriosidase activity from baseline at month 9 were also statistically significant following treatment with taliglucerase alfa, while exploratory efficacy endpoints relating to bone mineral density and QCSI showed numerical trends towards improvement. Although the pivotal study indicated that both the 30 units/kg and the 60 units/kg doses of taliglucerase alfa are efficacious, the post-hoc dose separation analysis

suggests that the higher dose is more effective than the lower dose following 9 and 12 months of treatment.

In the pivotal study [PB-06-001], treatment of NNGD in adult patients with taliglucerase alfa for 9 months was associated with statistically and clinically significant reductions from screening in the primary efficacy endpoint of spleen volume of 26.91% (p<0.0001) in the 30 units/kg group (n=15) and 38.01% (p<0.0001) in the 60 units/kg group (n=16).

In the pivotal study, mean baseline haemoglobin levels were within normal limits for patients in both treatment groups. The baseline levels statistically significantly increased following 9 months treatment by 1.6 g/dL (p=0.0010) in the 30 units/kg group (n=14) and 2.2 g/dL (p<0.0001) in the 60 units/kg group (n=15). In an ad hoc analysis, the increases in haemoglobin levels from baseline to Month 9 were 14.6% in the 30 units/kg group and 22.2% in the 60 units/kg group. Although the percentage increase from baseline in patients treated with the 60 units/kg dose was greater than the pre-specified clinically significant percentage increase of 16%, both baseline and post-treatment haemoglobin levels in the treatment group were within normal limits. Consequently, the statistically significant increases in haemoglobin levels from baseline at Month 9 for both doses are of doubtful clinical significance. However, in a post hoc subgroup analysis of all patients who were anaemic at baseline (n=10), mean haemoglobin levels increased from baseline of 9.5 g/dL [range: 5.5 to 10.7] to Month 9 of 12.7 g/dL [range: 8.6 to 15.4], while the haemoglobin level increased from baseline to Month 9 by 36.0%.

In the pivotal study, reductions in liver volume from screening at Month 9 were statistically significant for both the 30 units/kg dose (10.48% [n=14], p=0.0041) and the 60 units/kg dose (11.11% [n=16], p<0.0001), but the observed reductions were of doubtful clinical significance. However, in a post hoc subgroup analysis of patients with hepatomegaly at screening the reductions in liver volume from baseline at Month 9 were 14% in both the 30 units/kg group (n=10) and the 60 units/kg group (n=6).

In the pivotal study, the platelet count increased from baseline at Month 9 by 41,494/mm^3 (p<0.0031) in the 60 units/kg (n=16) and by 11,427/mm^3 (p=0.0460) in 30 units/kg (n=15). The result for the 30 units/kg group was not statistically significant as the increase from baseline failed to meet the meet the pre-specified alpha significance level of 0.025. In an ad hoc analysis, the increase in platelet count from baseline at Month 9 was 72.1% (clinically significant) in the 60 units/kg group, and 13.7% (not clinically significant) in the 30 units/kg group

The efficacy results observed in the pivotal study were supported by the interim results of the switchover from imiglucerase study [PB-06-002], and the extension study [PB-06-003]. In addition, the data from the historical analysis suggests that taliglucerase alfa and alglucerase/imiglucerase have similar efficacies as regards reductions in spleen and liver volumes, and increases in haemoglobin levels and platelet counts. Furthermore, a post-hoc analysis of the efficacy outcomes at 12 months in 26 patients from the pivotal study showed that taliglucerase alfa can achieve consensus therapeutic goals.

9.2. First round (preliminary) assessment of risks

The submission included safety data at the cut-off date of 30 June 2010 on 83 adult patients with NNGD who have been exposed to taliglucerase alfa, including safety data on 59 patients exposed for 6 months and 30 patients exposed for 12 months. Of the 83 patients, there were 72 (86.7%) patients with at least 1 AE irrespective of relationship to treatment. The most common AEs reported in taliglucerase alfa treated patients (occurring in ≥ 3 % of patients) were headache (20.5%, n=17), arthralgia (16.9%, n=14), fatigue (12.0%, n=10), nasopharyngitis (12.0%, n=10), upper respiratory tract infection (10.8%, n=9), back pain (9.6%, n=8), influenzae (8.4%, n=7), nausea (7.2%, n=6), infusion related reactions (7.2%, n=6), pharyngitis (7.2%, n=6), pharyngolaryngeal pain (7.2%, n=6), pain (6.0%, n=5), pyrexia (6.0%, n=5),

gastroenteritis (6.0%, n=5), urinary tract infection (6.0%, n=5), cough (6.0%, n=5), erythema (6.0%, n=5), pruritus (6.0%, n=5), abdominal pain (4.8%, n=4), constipation (4.8%, n=4), diarrhoea (4.8%, n=4), asthenia (4.8%, n=4), lymphadenopathy (3.6%, n=3), and spleen disorder (3.6%, n=3). Of the 83 patients, 31 (37.3%) patients experienced at least one treatment related AE. The most common treatment related AEs on patients treated with taliglucerase alfa (occurring in ≥ 5% of patients) were infusion related reactions (6%, n=5) and headache (6%, n=5).

There were no deaths reported in the 83 patients, while SAEs were reported in 4 (4.8%) patients (i.e. immune thrombocytopaenia; epistaxis; renal stone; prolapsed rectum, bladder and cervix). Discontinuations occurred in 2 patients in study PB-06-001 due to hypersensitivity reactions, and no patients in studies PB-06-002 and PB-06-003. There was no evidence in the submission of a causal association between significant biochemical or haematological toxicities and taliglucerase alfa. Similarly, there was no evidence in the submission of causal association between taliglucerase alfa and hepatic toxicity, renal toxicity or cardiovascular toxicity.

Infusion reactions occurring during or after the taliglucerase alfa infusion were reported in 45.8% (n=38) of the 83 treated patients. The most common infusion reaction AEs were headache, asthenia, fatigue, dizziness, and pruritus. The experience to date is insufficient to assess whether there is a dose relationship with any of these events.

Hypersensitivity reactions during the taliglucerase alfa infusion occurred in 4.8% (n=4) of the 83 patients in the safety population, and 1 patient developed a fixed drug eruption during the infusion. None of the patients with hypersensitivity reactions were reported to have developed anti-taliglucerase alfa IgG antibodies. Two (2) of the 4 patients with hypersensitivity reactions discontinued prematurely due to the AE.

Anti-taliglucerase alfa IgG antibodies were detected in 6.3% (2/32) of patients tested at the end of pivotal study PB-06-001, and neutralizing antibodies were negative in both of IgG antibody positive patients. In study PB-06-002, 6.7% (1/15) of patients were anti-taliglucerase alfa IgG antibody positive, and neutralizing antibodies were negative in the single IgG antibody positive patient. None of the 3 patients identified in the submission who were IgG antibody positive were reported to have experienced a hypersensitivity reaction. In the data to date, the presence anti-taliglucerase alfa IgG antibodies has not been found to predict the development of hypersensitivity reactions.

9.3. First round (preliminary) assessment of benefit-risk balance

The submitted data suggest that the benefit-risk balance of taliglucerase alfa is favourable given the proposed usage, but it is considered that this should be confirmed by evaluation of the final efficacy and safety data from pivotal study PB-01-001 and supportive study PB-02-001.

10. First round recommendation regarding authorisation

It is recommended that the application to register taliglucerase alfa should be rejected due to the absence of final efficacy and safety data from pivotal study PB-01-001 and supportive study PB-02-001. It is considered that the efficacy and safety of the drug for the treatment of GD can only be satisfactorily established by evaluation of the final data from these two studies.

The submission included interim pivotal efficacy data following 9 months treatment with taliglucerase alfa on only 31 patients, and there was no active control group to assist interpretation of the data [study PB-01-001]. Supportive interim efficacy data on 26 of the 31 patients who successfully completed 9 months treatment in the pivotal study were available following a further 3 months of treatment from the extension study [PB-06-003]. Further supportive interim efficacy data from switchover study [PB-02-001] were available on 15

patients who had been treated with taliglucerase alfa for 9 months following switchover from imiglucerase. The small number of patients with efficacy data in the submission is a function not only of the limited number of patients available due to the rarity of NNGD, but also of interim rather than final data from the two supportive studies being presented for evaluation. The interim analyses appear to include data on about half the number of patients planned for the final analyses. In the absence of a controlled efficacy study with imiglucerase, and because total patient numbers for efficacy evaluation are so small, it is considered that the final data from the extension and switchover studies should be evaluated in order to confirm the promising results observed with taliglucerase alfa.

The submitted interim safety data showed that taliglucerase alfa was generally well tolerated at the doses proposed for approval. The interim data from the pivotal study suggested that there was no clinically significant difference in the safety profiles of the 30 and 60 units/kg doses. However, the safety data are limited by the small number of patients with NNGD who have been exposed to the drug. The total number of patients exposed to the drug for 12 months is insufficient to satisfactorily identify AEs occurring with an incidence of less than 10% at 12 months. In addition, the total number of patients exposed to taliglucerase alfa is insufficient to satisfactorily identify AEs occurring at an incidence of less than 3.5%. It is considered that the promising safety data identified in the interim analyses of the submitted studies should be confirmed by analyses of the final safety data from these studies before approval is granted.

In the event of the application to register taliglucerase alfa being approved on the basis of the submitted data, it is recommended that it should be a condition of registration that the sponsor submit the final study reports for the pivotal and supportive studies to the TGA, as evaluable data within the context of a category 1 submission, as soon as these reports become available.

11. Clinical questions

11.1. Pharmacokinetics

What were the reasons for the anomalous PK results in one subject (outlier) in the pilot study in normal healthy subjects [P-01-2005]?

11.2. Pharmacodynamics

No questions.

11.3. Efficacy

No questions.

11.4. Safety

No questions.

11.5. Other relevant clinical matters

1. When will the analyses of the final efficacy and safety data from the pivotal and supportive studies be available?
2. What was the nature of the clinical deficiencies in the US NDA submission identified in the FDA's CRL to Protalix?

3. What actions have been undertaken by the sponsor to address the clinical deficiencies in the US NDA identified by the FDA in its CRL to Protalix?

12. Second round evaluation of clinical data submitted in response to questions

12.1. Introduction

The sponsor submitted a consolidated response to the questions raised by the TGA following the first round assessment of this application to register taliglucerase alfa for the treatment of Gaucher Disease (GD). The consolidated response included updated clinical efficacy and safety reports from two ongoing supportive studies (PB-06-002; PB-06-003), and updated immunogenicity data from studies PB-06-001, PB-06-002, and PB-06-003 based on new IgG assay cut-points.

Subsequent to the consolidated response the sponsor was requested by TGA to provide additional clinical information relating to the response. This additional information was provided in the sponsor's clinical follow-up response. This additional clinical information included an updated Summary of Clinical Safety (Module 2.7.4), and additional information relating to the updated immunogenicity data.

This second round CER reviews the clinical aspects of sponsor's consolidated response, and the sponsor's clinical follow-up response. In this second round CER, the prefix PB-06 used to identify the sponsor's studies will be replaced by a hash (#) sign (i.e., study PB0-06-001 will become study #001).

> **Comment:** Pfizer is the Australian sponsor of the taliglucerase alfa application, while in the US the application had been submitted to the FDA by Protalix. In this second round CER, reference to the "sponsor" should be interpreted as Pfizer unless specifically stated to be otherwise or the context indicates that the word "sponsor" refers to Protalix.
>
> The results of the pivotal study (#001) have now been published; Ziman A, Brill-Almon E, Chertkoff R et al. Pivotal trial with plant-cell expressed recombinant glucocerebrosidase taliglucerase alfa, a novel replacement therapy for Gaucher disease. Blood. 2011;188(22):5767-5773.

12.2. Pharmacokinetics

12.2.1. TGA Question

What were the reasons for the anomalous PK results in one subject (outlier) in the pilot study in normal healthy subjects [P-01-2005]?

12.2.2. Sponsor's response

The applicant has reviewed available data on the subject (outlier) in the pilot study in normal healthy subjects, and found no apparent reasons to explain the anomalous PK results. The between subject variability values for C_{max} and AUC_{last} following single doses of 30 U/kg and 60 U/kg taliglucerase in healthy subjects were 49 to 68% (n=6, including the outlier subject) in this study P-01-2005; this variability appears to approximate between subject variability (CV: 30 to 52%, n = 10-16) observed for C_{max} and AUC_{last} after IV infusion of 30 U/kg and 60 U/kg Taliglucerase on day 1 in patients (Clinical Study PB-06-001).

> **Comment**: The sponsor's response is satisfactory. The pharmacokinetics of taliglucerase are highly variable in both healthy volunteers and patients with GD as demonstrated by the high CV% values for both the C_{max} and the AUC_{last}.

12.2.3. Other relevant clinical matters

12.2.3.1. TGA question - Study availability

When will the analyses of the final efficacy and safety data from the pivotal and supportive efficacy and safety studies be available?

12.2.3.2. Sponsor's response

Pivotal trial #001 assessed the efficacy and safety of taliglucerase alfa in naïve patients treated during 9 months. A Clinical study report for this study was previously submitted to TGA as part of the initial dossier submission.

Trial #002 assesses the efficacy and safety of taliglucerase alfa in adult patients who were receiving imiglucerase before starting on the trial. In January 2010, this protocol was amended to allow for enrolment of children aged 2 years or older, upon EMA request. To date, all adult patients and two children have completed this trial. Upon FDA request, an interim study report was established based on data collected until 1 May 2011, this report is provided as part of the response. Final report depends on further enrolment of children in this study. If no additional child is enrolled, final report will be available in March 2012. If additional children are enrolled, final report will be available in December 2012.

Trial #003 is an extension study to assess safety and efficacy in patients who successfully completed 9 months of treatment with taliglucerase alfa in trials #001 and #002. This trial is ongoing. Upon FDA request, an interim study report was issued with data collected up to 1 May 2011. The report is provided as part of the response. Final report will be available in August 2012.

Trial #004 is an expanded access trial for patients in Israel and US who require Enzyme Replacement Therapy. An interim study report was submitted to TGA as part of the initial dossier submission to the TGA. The study is ongoing, completion date depends on approval in the US and Israel, as patients are eligible to stay on in the trial until taliglucerase is available in their country, per protocol.

Trial #005 assesses efficacy and safety of taliglucerase alfa in children naïve from previous treatment. This study is ongoing. The final study report will be available in March 2012.

> **Comment:** The sponsor's response is satisfactory. The response included Abbreviated Clinical Study Reports (Interim Analyses) of ongoing studies #002 and #003. The updated efficacy and safety data from these two studies are consistent with the data from these studies provided in the original submission (apart from the immunogenicity data). The updated results from these two studies are reviewed in Sections 12.2.2 (study #002) and 12.2.3 (study #003) of this second round CER and should be read together with the original results of these two studies evaluated in the first round CER (above).

12.2.3.3. TGA question - FDA's Complete Response Letter [CRL] to Protalix

What was the nature of the clinical deficiencies in the US NDA submission identified in the FDA's CRL to Protalix? What actions have been undertaken by the sponsor to address the clinical deficiencies in the US NDA identified by the FDA in its CRL to Protalix?

12.2.3.4. Sponsor's response

12.2.3.4.1. Protalix' [US sponsor's] overall response

Protalix received a Complete Response Letter (CRL) from the US Food and Drug Administration (FDA) on 24 February 2011. Questions 1, 2, and 3 of this CRL outlined the FDA's perspective on the clinical deficiencies of the taliglucerase alfa New Drug Application (NDA). Protalix outlined actions taken to address the clinical issues raised by the FDA, and provided copies of relevant documents. The clinical deficiencies identified by the FDA were:

1. The immunogenic potential of taliglucerase alfa and its impact on efficacy and safety cannot be adequately evaluated.
    a. Propose an acceptable cut-point for your confirmatory anti-product IgG antibody assay and submit a re-analysis of the impact of anti-product antibody development on the efficacy and safety of taliglucerase alfa.
    b. Develop an acceptable neutralizing antibody assay and submit a re-analysis of the impact of neutralizing antibodies development on the efficacy and safety of taliglucerase alfa.
2. There are insufficient data provided to assess the efficacy and safety of taliglucerase alfa in patients switched from other enzyme replacement therapies. Submit the final study report from PB-06-002, and a minimum of 12 months of efficacy and safety data from PB-06-003 for patients switched from other enzyme replacement therapies to taliglucerase alfa.
3. Longer-term safety data were insufficient to evaluate the chronic immune-mediated adverse events that are typically associated with enzyme replacement therapies, and Gaucher disease-specific bone events. Provide additional long-term safety data from PB-06-003.

    Comment: Information on the clinical issues raised by the FDA and Protalix' actions taken to address these issues was provided by the sponsor in the consolidated response to the TGA request for information and in the follow-up response. The sponsor's response is considered to be satisfactory.

12.2.3.4.2. Protalix' response to FDA (CRL) clinical Q1

FDA Q1. The immunogenic potential of taliglucerase alfa and its impact on efficacy and safety cannot be adequately evaluated.

a. Propose an acceptable cut-point for your confirmatory anti-product IgG antibody assay and submit a re-analysis of the impact of anti-product antibody development on the efficacy and safety of taliglucerase alfa.

b. Develop an acceptable neutralizing antibody assay and submit a re-analysis of the impact of neutralizing antibodies development on the efficacy and safety of taliglucerase alfa.

(a) Assay sensitivity

[Details of the sponsor's response to this question have been redacted from this CER Extract]

Comment: In response to the FDA's CRL Protalix provided a re-analysis of the immunogenicity of taliglucerase based on a new confirmatory cut-point of 52.87% for the anti-taliglucerase alfa IgG antibody assay. This resulted in more patients being categorized as IgG antibody positive than in the original data. However, the FDA considered that the confirmatory endpoint is "very high". Consequently, Protalix revised the confirmatory cut-point to 40.33%, and in a submission to the FDA dated 31 October 2011, stated that in those patients newly identified as anti-taliglucerase alfa IgG positive using the 40.33% alternate cut-off no new patients having antibodies with neutralizing activity were identified. In addition, the sponsor stated that "reassessment of the relationship of antibody positivity with safety, efficacy and pharmacokinetic parameters did not result in different conclusions from those provided in the material previously submitted to the agency as part of the NDA resubmission August 1, 2011" (i.e.,

information based on the cut-point of 52.87%). On 15 November 2011, Protalix submitted information to the FDA outlining a proposed PK/PD analysis to support the IgG and neutralizing sensitivities, and the dataset identifying all patients defined as anti-taliglucerase IgG positive based on the 40.33% cut-point. The PK/PD modelling study was submitted with the sponsor's consolidated response of 20 December 2011, and is briefly reviewed in Section 11.4.5 of this second round CER.

Data provided in the consolidated response to TGA questions to quality Question CQI-21 (Module 3) indicates that application of the alternate cut-point (40.33%) "identified 6 additional patients meeting the definition of antibody positivity, in addition to 19 patients [identified by the 52.87% cut-point] who met the criteria prior to application of the alternate cut-point. Three of the 6 new positive patients had positive baseline samples and no significant increase in titres following taliglucerase alfa treatment and therefore are considered negative for induction of anti-taliglucerase alfa antibodies". In the follow-up response to TGA questions, the sponsor provided additional clinical data on patients identified as anti-taliglucerase IgG antibody positive using the 40.33% and 53.87% cut-points for the IgG assay. The immunogenicity data are reviewed in the updated Summary of Safety (Module 2.7.4) in Section 11.4.1 of this second round CER.

(b) Neutralizing antibodies

[Details of the sponsor's response to this question have been redacted from this CER Extract]

Comment: Neutralizing antibodies appear to be relatively uncommon in patients who are anti-taliglucerase IgG positive. Neutralizing antibodies based on the in vivo assay have been identified in 3 patients, but all 3 patients were found to be negative in the cell based assay. The sponsor submitted the PK/PD analysis and this has been briefly reviewed in Section 11.4.5 of this second round CER.

(c) Effect of immunogenicity on safety

On 31 July 2011, Protalix responded to the FDA that there has been no demonstrated association between the development of the antibody response and hypersensitivity reactions and referred to the detailed discussion of immunogenicity and safety presented in the Summary of Safety (i.e., original submission). Two treatment naïve patients and one patient switched from imiglucerase were determined to be positive for neutralizing activity in an in vitro assay and were negative in a cell based assay. Both validated assays have similar sensitivity, however determination of a specific patient as positive or negative may differ depending on the method used, as the mechanism in the cellular macrophage cell uptake system represents different output. There has been no demonstrated association between antibody response and therapeutic response. The significance of these findings is undetermined at this time.

Comment: In the follow-up response to TGA questions, the sponsor provided comprehensive data relating to patients testing positive for anti-taliglucerase IgG antibodies using assays with the 40.33% and 52.87% cut-points. In addition, the sponsor investigated the association between anti-taliglucerase IgG positivity and hypersensitivity adverse events. Furthermore, the sponsor provided an updated Summary of Clinical Safety (Module 2.7.4) that included an assessment of the effect of immunogenicity status on safety. The provided data has been reviewed in the Summary of Safety (Module 2.7.4) in Section 12.3 of this CER.

It is noted that Protalix states that there has been no demonstrated association between the development of the antibody response and hypersensitivity reactions. However, it is considered that the safety data demonstrate an increased rate of hypersensitivity type I

reactions in antibody positive patients compared with antibody negative patients. This association is reflected in the PI provided with the sponsor's consolidated response to TGA questions where it is stated in the Precautions section (antibody response) that, "[a]lthough numbers were small, more hypersensitivity events have been observed in association with a positive antibody response than in the absence of an antibody response".

(d) Effect of immunogenicity on efficacy

On 31 July 2011, Protalix provided the FDA with updated efficacy and safety data from study #001 by dose group and immunogenicity status according to the new established cut-point for the IgG confirmatory assay (i.e., 52.8%). In addition, it also provided the FDA with 9 month efficacy data on 3 patients out of 28 patients from study #002 (switch from imiglucerase to taliglucerase alfa study) who became antibody positive in the study and compared these data with the overall data (n=28).

Comment: In the follow-up response to TGA questions, the sponsor provided an updated summary of the primary and secondary efficacy endpoints from study #001 comparing the results in patients with and without anti-taliglucerase alfa IgG antibodies based on the assay cut-point of 40.33%. This data updated that provided in the consolidated response which provided a similar assessment of patients in study #001 but with an assay cut-point of 52.8%. The effect of antibody status on efficacy is reviewed in Section 12.3 of this CER.

(e) Protalix' overall conclusions relating to antibody status and efficacy and safety

On 31 July 2011, Protalix informed the FDA that in its opinion "a correlative relationship between immunogenicity status and clinical parameters of taliglucerase alfa efficacy and pharmacokinetics was not noted in these analyses. To date, three patients were found to have neutralizing antibodies in the in vitro assay, but all three were found to be negative in the cell based assay. The efficacy response did not appear to be decreased in the two treatment naïve patients. A switchover patient who had neutralizing antibody activity maintained efficacy response compared to baseline at Month 9. The patient showed decreases in haemoglobin and platelet count at 15 months of treatment in the extension study, but treatment is unchanged and additional follow up information is required to determine the clinical relevance. Based on the clinical data reviewed in the Summary of Safety (Module 2.7.4), taliglucerase alfa has the potential for inducing suspected immune mediated adverse events in Gaucher disease patients. However, a clear association between the development of antibodies to taliglucerase alfa and the risk of hypersensitivity reaction has not been demonstrated."

Comment: In the consolidated response to TGA questions and in the follow-up clinical response, the sponsor provided comprehensive updated data on the effect of antibody status on the safety, efficacy and pharmacokinetics of taliglucerase alfa. The data have been reviewed in Section 12.3, below.

12.2.3.4.3. Protalix' response to FDA (CRL) clinical Q2

FDA Q2: There are insufficient data provided to assess the efficacy and safety of taliglucerase alfa in patients switched from other enzyme replacement therapies. Submit the final study report from PB-06-002, and a minimum of 12 months of efficacy and safety data from PB-06-003 for patients switched from other enzyme replacement therapies to taliglucerase alfa.

In the resubmission of the NDA to the FDA, Protalix included an interim report from study #002 that included efficacy data on 25 adult patients previously treated with imiglucerase who switched to taliglucerase alfa and completed 9 months of treatment, and safety data on 28 patients, including two patients under 18 years of age. The sponsor also included an interim report from study #003 that included efficacy data on 18 adult patients from study #002 who

had completed a total of 12 months of treatment after switching from imiglucerase. In addition, Protalix submitted all available safety data with a data cut off of 01 May 2011.

> **Comment**: The sponsor provided copies of the two updated interim study reports (#002 and #003) in the consolidated response to TGA questions. In addition, in the follow-up response the sponsor provided an updated Summary of Clinical Safety (Module 2.7.4). Both interim updated study reports and the updated Summary of Clinical Safety (Module 2.7.4) have been reviewed in Section 12.3 of this CER.

12.2.3.4.4. Protalix' response to FDA (CRL) clinical Q3

FDA Q3: Longer-term safety data were insufficient to evaluate the chronic immune-mediated adverse events that are typically associated with enzyme replacement therapies, and Gaucher disease-specific bone events. Provide additional long-term safety data from PB-06-003.

In the resubmission of the NDA to the FDA, Protalix included an interim report of safety data from study #003 for all treated patients (i.e., treatment naïve patients continuing from study #001 and switchover patients continuing from study #002). Protalix also submitted a revised Summary of Clinical Safety (Module 2.7.4) with analysis of all patients enrolled in clinical trials. In addition to the routine assessment of adverse events and other safety parameters, special attention in the Summary of Clinical Safety was given to assessment of infusion related reactions, and Type I (acute) and Type II-IV (chronic) hypersensitivity reactions. The Summary of Clinical Safety also included an evaluation of bone events reported in patients with GD.

> **Comment**: The sponsor has provided the data referred to in Protalix' response and the new data have been reviewed in Section 12.3, below.

12.3. Review of new clinical data

12.3.1. Summary of Clinical Safety (SCS) - updated module 2.7.4

12.3.1.1. Background

In the follow-up response to TGA questions the sponsor provided an updated SCS (Module 2.7.4) relating to taliglucerase alfa for the treatment of GD.

12.3.1.2. Studies containing safety data

The safety data provided in support of the submission to register taliglucerase alfa for the treatment of GD are primarily based on 1 completed Phase 3 pivotal study (#001), and 4 ongoing Phase 3 supportive studies (#002, #003, #004, #005) (see Table 28). Unless otherwise stated, the cut-off date for the safety data from the 4 ongoing clinical studies was 1 May 2011. In addition to the data from the studies in the Phase 3 clinical study program, safety data from patients treated in ongoing multi-national Compassionate Use Programs were provided, and safety data from a small Phase 1 study (PB-01-2005) in healthy subjects were also available. Overall, the safety population for the SCS was any patient treated at least once in a Phase 3 study.

Table 28: SCS (updated) – Summary of studies providing safety information.

Study Number	Study Objective	Study Design and Type of Control	Test Product(s)	Dosage Regimen	Number of Subjects (Safety)	Duration of Treatment
Pivotal Study						
PB-06-001	Safety and efficacy of two dose levels of taliglucerase in subjects 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=16 N=16	38 weeks (9 months)
Supporting Studies						
PB-06-002	Safety and efficacy in subjects switching from imiglucerase ERT	Multicenter, open label	Taliglucerase alfa	Dose equivalent to prior imiglucerase dose every 2 weeks	28	38 weeks (9 months)
PB-06-003	Extended safety and efficacy of subjects completing PB-06-001 and PB-06-002	PB-06-001 subjects: Multicenter, double blind, parallel group, dose ranging PB-06-002 subjects: Multicenter, open label	Taliglucerase alfa	Continue same dose as previous study	44 (26 from 001 and 18 from 002)	15 months (with possible further extension to 30 months until marketing approval)
PB-06-004	Expanded access treatment protocol	Multicenter, open label	Taliglucerase alfa	Continue same dose as previous imiglucerase therapy	50	9 months (with possible further extension to 24 months or until marketing approval)
PB-06-005	Safety and efficacy of two dose levels of taliglucerase in untreated pediatric subjects with Gaucher disease	Multicenter, randomized, double blind	Taliglucerase alfa	30 units/kg every 2 weeks 60 units/kg every 2 weeks	11 (blinded)	12 Months
Phase 1 Safety Study						
P-01-2005	Safety and pharmacokinetics of ascending dose range in healthy subjects	Open label, single-dose escalation	Taliglucerase alfa	Single escalating doses of 15, 30 and 60 units/kg	6	3 single doses 1 week apart

12.3.1.3. Exposure

As of 1 May 2011, 121 patients have been treated with taliglucerase alfa in the Phase 3 clinical studies (see Table 29, below).

Table 29: SCS (update) – Total subject exposure studies #001, #002, #004, and #005.

		Months of Clinical Trial Exposure												
	N*	3	6	9	12	15	18	21	24	27	30	33	36	39
PB-06-001	32	31	29	27	26	26	26	26	24	23	11	7	3	1
PB-06-002	28	27	27	19	18	17	7	1	0	0	0	0	0	0
PB-06-004	50	47	38	23	15	11	0	0	0	0	0	0	0	0
PB-06-005	11	7	2	0	0	0	0	0	0	0	0	0	0	0
Overall	121	112	96	69	59	54	33	24	24	23	11	7	3	1

Note: Data from study #003 is not identified separately in the above table; data in this study consisted of patients from studies #001 and #002 treated for more than 9 months.

In the completed pivotal study (#001), 33 ERT naïve patients were randomized and 32 were treated with taliglucerase alfa 30 units/kg or 60 units/kg, with the primary efficacy analysis being at Month 9. After completing study #001, patients could continue treatment with taliglucerase alfa in extension study #003 at the same dose received in study #001.

In the ongoing supportive switchover study (#002), 28 subjects previously stabilized on imiglucerase have been treated with taliglucerase alfa at the same dose as their previous imiglucerase dose. The primary efficacy analysis for this study is at Month 9. The study planned to enrol 30 patients and all subjects have completed the study except for 2 children who are ongoing. After completing study #002, patients could continue treatment with taliglucerase alfa in extension study #003.

In the ongoing supportive extension study (#003), 44 patients (26 from study #001 and 18 from study #002) are being treated, and are currently receiving an average taliglucerase alfa dose of 41.3 units/kg (range: 12-62 units/kg). The duration of the extension study was planned for 15 months, but was extended by protocol amendment to a maximum of 30 months or until commercial product becomes available at the treating centres. Of the 26 ERT naïve patients from study #001, all have completed 15 months treatment in the extension study (i.e., a total of 24 months treatment). Of the 18 ERT experienced patients from the switchover study (#002), all have completed 3 months treatment in the extension study (i.e., a total of 12 months treatment) while 17 have completed 6 months treatment (i.e., a total of 15 months treatment) and 7 have completed 9 months treatment (i.e., a total of 18 months treatment). As of 1 May 2011, 37 subjects (21 from #001; 16 from #002) are continuing treatment on taliglucerase alfa in extension study #003.

In the ongoing expanded access treatment protocol (study #004), safety data are available on 50 patients treated with taliglucerase alfa as of 1 May 2011.

In the ongoing paediatric treatment protocol (study #005), 11 patients aged 2 to < 18 years have enrolled and have received taliglucerase alfa treatment as of 1 May 2011.

Overall, the 121 patients have been exposed to taliglucerase alfa for a total of 1734.4 months (see Table 30, below).

Table 30: SCS (update) – Duration of exposure person-time (months).

INDICATION (or TOTAL)		
Duration of exposure	**Persons**	**Person time (months)**
Cumulative < 1 month	8	3.2
Cumulative Up to 1 m	113	1734.2
Cumulative Up to 3 m	112	1732.3
Cumulative Up to 6 m	96	1663.4
Cumulative Up to 12 m	59	1355.9
Cumulative to 24 months	24	753.2

The demographic data from the 121 patients enrolling in studies #001, #002, #004, and #005, are summarized in the dossier. Of the 121 patients, 67 (55.4%) were male and 54 (44.6%) were female, and the mean±SD age of the total population was 39.9±17.7 years. The age distribution of the 121 patients was 13 (10.7%) aged < 18 years, 101 (83.5%) aged 18 to 65 years, and 7 (5.8%) aged > 65 years (see Table 31, below). Nearly all patients have been Caucasian (96.7%, n=117), with the remainder being Native American (n=1) or Other (n=3).

Table 31: SCS (update) - Exposure by age group and gender.

INDICATION (or TOTAL)				
Age group	**Persons**		**Person time (months)**	
	M	**F**	**M**	**F**
Paediatric (<18 years)	9	4	37.8	11.6
Adult (18 to 65 years	54	47	889.6	718.6
Geriatric (> 65 years)	4	3	31.0	48.8

12.3.1.4. Dosing

Dosing in studies #001, #002, #004 and #006 is summarized below in Table 32.

Table 32: SCS (update) – Dosing in studies #001, #002, #004, and #005.

Parameter		PB-06-001 30 U/kg N=16	PB-06-001 60 U/kg N=16	PB-06-002 N=28	PB-06-004 N=50	PB-06-005 N=11	Overall N=121
Average of All Dose Infusions (Units/kg)	Mean	32.8	63.4	29.2	33.5	48.7	37.7
	SD	2.2	2.2	15.9	16.9	16.8	18.0
	Median	33.2	62.9	25.5	30.4	44.8	32.7
	Range	30-37	60-67	11-60	13-64	30-73	11-73

In study #001, 32 patients were randomized to either 30 units/kg (n=16) or 60 units/kg (n=16) and 26 continued to receive these doses in extension study #003 (30 units/kg, n=12; 60 units/kg, n=14). In study #003, after unblinding at Month 15 (i.e., after a total of 24 months treatment), 3 patients in the 30 units/kg group had their dose increased in an attempt to improve the clinical response (2 patients to 60 units/kg; 1 patient to 45 units/kg).

In study #002, 28 patients were enrolled and treated with the same dose of taliglucerase alfa as the imiglucerase dose they had been receiving before switching. Of the 18 patients from this study continuing treatment in the extension study (#003), 17 patients continued to receive the dose they had been treated with in study #002 and 1 patient had an increase in dose from 400 to 800 units every two weeks. Patients (n=50) enrolled in the extended treatment protocol (#004) received the same taliglucerase alfa dose as the imiglucerase dose they had previously received. Paediatric subjects (n=11) enrolled in study #005 were randomized to taliglucerase alfa 30 units/kg or 60 units/kg.

The distribution of exposed patients by dose is: ≤15 units/kg, n=11, 123.6 person-time months; > 15 to ≤ 30 units/kg, n=33, 374.1 person-time months; > 30 to ≤ 60 units/kg, n=51, 752.5 person-time months; and > 60 units/kg, n=25, 487.2 months person-time months.

12.3.1.5. Adverse events

12.3.1.5.1. Overview

In each study, adverse event (AE) severity was defined by WHO Toxicity Criteria as Mild, Moderate, Severe, and Very Severe. The study investigator was responsible for determining whether an AE was treatment related (definitely, probably, or possibly). Overall, 104 of the 121 (86.0%) taliglucerase alfa treated patients experienced at least one AE (see Table 33, below). AEs did not appear to be more likely to occur in patients switching from imiglucerase in studies #002 and #004 compared with patients who were naïve to ERT in studies #001 and #005.

Table 33: SCS (update) – Number (%) of patients with an adverse event; safety population.

Parameter		PB-06-001 30 U/kg N=16	PB-06-001 60 U/kg N=16	PB-06-002 N=28	PB-06-004 N=50	PB-06-005 N=11	Overall N=121
With at least 1 AE	Yes	16 (100)	15(93.8)	27(96.4)	40(80.0)	6(54.5)	104(86.0)
	No	0	1(6.3)	1(3.6)	10(20.0)	5(45.5)	17(14.0)
With at least 1 mild/moderate AE	Yes	16 (100)	15(93.8)	27(96.4)	40(80.0)	6(54.5)	104(86.0)
	No	0	1(6.3)	1(3.6)	10(20.0)	5(45.5)	17(14.0)
With at least 1 severe/very severe AE	Yes	1(6.3)	2(12.5)	3(10.7)	5(10.0)	1(9.1)	12(9.9)
	No	15(93.8)	14(87.5)	25(89.3)	45(90.0)	10(90.9)	109(90.1)
With at least 1 SAE	Yes	2(12.5)	2(12.5)	5(17.9)	0	1(9.1)	10(8.3)
	No	14(87.5)	14(87.5)	23(82.1)	50(100.0)	10(90.9)	111(91.7)
With at least 1 probably or definitely not related AE	Yes	15(93.8)	15(93.8)	26(92.9)	36(72.0)	6(54.5)	98(81.0)
	No	1(6.3)	1(6.3)	2(7.1)	14(28.0)	5(45.5)	23(19.0)
With at least 1 definitely, probably, or possibly related AE	Yes	8(50.0)	9(56.3)	11(39.3)	22(44.0)	2(18.2)	52(43.0)
	No	8(50.0)	7(43.8)	17(60.7)	28(56.0)	9(81.8)	69(57.0)

AE=Adverse event SAE=Serious adverse event Note: Adverse events occurring during treatment in the extension study (PB-06-003) are reported under the subjects' original protocol and treatment group.

12.3.1.5.2. Most commonly occurring adverse events

All AEs reported in treated patients with an incidence of ≥1%, regardless of causality, are shown in the dossier by MedDRA (Version 10.1), System Organ Class (SOC) and Preferred Term (PT).

The most commonly reported AEs occurring with an incidence of ≥ 5% were nasopharyngitis (21.5%), arthralgia (18.2%), headache (18.2%), upper respiratory tract infection (15.7%), pain in extremity (11.6%), cough (10.7%), fatigue (9.9%), back pain (9.9%), vomiting (8.3%), pain (7.4%), pharyngolaryngeal pain (7.4%), pruritus (7.4%), diarrhoea (6.6%), pyrexia (6.6%), influenzae (6.6%), pharyngitis (6.6%), sinusitis (6.6%), nausea (5.8%), dizziness (5.8%), epistaxis (5.8%), gastroenteritis (5.8%), bone pain (5.0%), and hypertension (5.0%)

12.3.1.5.3. Intensity of adverse events

There were a total of 910 AEs reported in 121 patients, and 230 of these events reported in 52 patients were considered by the investigator to be at least possibly related to study treatment. The majority of the 910 reported AEs were considered to be mild/moderate in intensity, while 15 of the reported AEs in 12 (9.9%) patients were reported as severe/very severe. Of the 15 severe/very severe AEs, only 1 event was reported in 2 patients (pain in extremity) and all other events were each reported in 1 patient. Of the 15 severe/very severe AEs, only 1 was reported as being treatment related (gastroenteritis).

In the extension study (#003), 3 patients from study #001 experienced 4 severe AEs: 1 patient in the 30 units/kg dose group experienced Grade 3 pain due to haemangioma in left knee and a Grade 4 pulmonary embolism and both were considered serious; 1 patient in the 60 units/kg dose group was subsequently diagnosed with autoimmune thrombocytopenia while being treated with taliglucerase alfa and this event was reported as a SAE; and 1 patient in the 60 units/kg dose group developed Type 1 diabetes mellitus requiring treatment with insulin.

In study #002, 2 patients experienced 3 severe AEs (haematuria and nephrolithiasis, and pelvic prolapse) and all were reported as SAEs. In study #004, 5 patients experienced 6 severe AEs (1 with a history of left hip pain which worsened; 1 with a history of bone infarct and torn anterior cruciate ligament (ACL) of left knee experienced left calf stabbing pain; 1 with a history of bone disease associated with GD developed severe back pain; 1 had worsening migraine headache

that resolved after taking ibuprofen; 1 had swelling and pain of the left leg, deep vein thrombosis (DVT) was ruled out by ultrasound, and the patient recovered in one day.

12.3.1.6. Deaths, serious adverse events, and discontinuations

· Deaths

No deaths had occurred in any of the 5 clinical studies as of 1 May 2011. One non-treatment-related death occurred in the Compassionate Use Program (tuberculosis/pneumonia in a Brazilian patient).

· SAES

As of 1 May 2011, SAEs had been reported in 10 patients (11 events) in the 5 clinical studies. In only 1 of these patients (study #005) was the SAE assessed by the investigator as treatment related. No SAEs were reported in study #001. However, 4 subjects from study #001 experienced 5 SAEs during the extension study #003: head trauma; autoimmune thrombocytopenia; pain due to haemangioma in left knee and pulmonary embolism; and multiple tooth extraction.

In study #002, 3 SAEs were reported: epistaxis; nephrolithiasis; prolapsed rectum bladder and cervix. Three subjects from study #002 experienced SAEs during the extension study #003: traumatic fracture of four ribs and pneumothorax; percutaneous renal stone removal; and 1 subject was hospitalized for a pre-planned knee replacement for management of gonarthrosis, a condition present prior to the study.

No SAEs were reported in study #004. In study #005, severe (grade 3) gastroenteritis in 1 paediatric patient was considered by the investigator to be a treatment related SAE.

· Discontinuations

Through to 21 September 2011, a total of 24 patients have withdrawn from the taliglucerase alfa Phase 3 clinical program. In study #001, 2 patients (1 treated with 30 units/kg and 1 treated with 60 units/kg) discontinued due to an AE (hypersensitivity reaction). In addition, 4 patients (1 from study #002, and 3 from study #004) withdrew voluntarily or for "other reasons". However, available patient details for these 4 patients include mention of infusion associated events in 3 patients, and generalized body stiffness in 1 patient. In 1 additional patient, the investigator recommended discontinuation in order to assess a possible allergic reaction after 38 infusions. Among the other patients discontinuing, reasons included travel or scheduling problems (7 patients), pregnancy (1 patient), and other reasons (9 patients).

12.3.1.7. Other significant adverse events

· Hypersensitivity events

Hypersensitivity type I (acute) events and hypersensitivity type II-IV (chronic) events were investigated in the Phase 3 clinical studies. Hypersensitivity type I events were assessed using Narrow terms in Standardized MedDRA Queries (SMQs) for MedDRA version 10.1 and preferred MedDRA terms, and hypersensitivity type II-IV events were assessed by preferred MedDRA term. Description of terms:

Hypersensitivity type I-IV events – SMQ (narrow) and MedDRA PTs.

Type I Hypersensitivity (acute events)

- **SMQ (narrow):** Anaphylactic reaction, Anaphylactic shock, Angioedema, Toxic septic shock, Asthma and bronchitis.
- **MedDRA PTs:** Application site hypersensitivity, Documented hypersensitivity to administered drug, Drug hypersensitivity, Hypersensitivity, Infusion site hypersensitivity, Injection site hypersensitivity, Type I hypersensitivity, and Pruritus.

Type II, III, and IV Hypersensitivity (Chronic events)

- **MedDRA PTs:** Anaemia haemolytic autoimmune, Anti-glomerular basement membrane antibody, Application site induration, Arthritis, Arthritis allergic, Arthritis reactive, Autoimmune thrombocytopenia, Dermatitis allergic, Dermatitis contact, Drug eruption, Drug rash with eosinophilia and systemic symptoms, Dyshidrotic eczema, Eczema, Erythema induratum, Fixed eruption, Glomerulonephritis, Goodpasture's syndrome, Granulocytopenia, Granuloma, Haemolytic anaemia, Immunoglobulins increased, Induration, Infusion site induration, Infusion site mass, Injection site induration, Injection site nodule, Lupus vasculitis, Monarthritis, Pemphigoid, Pemphigus, Polyarteritis nodosa, Polyarthritis, Pulmonary vasculitis, Rash maculo-papular, Rash papular, Reaction to drug excipients, Renal arteritis, Seronegative arthritis, Serum sickness, Skin induration, Skin reaction, SLE arthritis, Systemic lupus erythematosus, Systemic lupus erythematosus rash, Thrombocytopenia, Toxic epidermal necrolysis, Toxic skin eruption, Type II hypersensitivity, Type III immune complex mediated reaction, Type IV hypersensitivity reaction, Urticaria popular.

Hypersensitivity type I (acute) events were identified in 18 (14.9%) patients (73 all causality events). In 15 (12.4%) of the 18 patients the events were judged by investigators to be treatment related (56 treatment related AEs). Of the MedDRA all causality preferred term hypersensitivity type 1 events, the most commonly reported AE was pruritus (9 patients; 7.4%) followed by “hypersensitivity” (5 patients; 4.1%) and pruritus generalized (2 patients; 1.7%), and each of the following events were reported in 1 patient (eye swelling, lip swelling, face oedema, periorbital oedema). In study #001, 4/16 patients in the 60 units/kg group reported 15 AEs (all causality) consistent with hypersensitivity type I events compared with 2/16 patients in the 30 units/kg group reporting 5 AEs.

Of the 15 patients reported as having treatment-related hypersensitivity type I events, 9 required no intervention or only temporary intervention with interruption of the infusion and/or medication to manage the event (6 pruritus, 1 generalized pruritus, 1 face oedema, 1 lip swelling), 4 required discontinuation of the infusions (3 hypersensitivity, 1 eye swelling), and 2 continued infusions with pre-treatment medications (2 hypersensitivity). Of the 4 patients discontinuing, 3 discontinued because of hypersensitivity events (in 2 patients these events occurred with the first infusion), and 1 patient experienced multiple repeated events of eye swelling not responding to pre-treatment medication and chose to discontinue taliglucerase alfa and return to imiglucerase.

Hypersensitivity type II-IV (chronic) events were reported in 5 (4.1%) patients. Of these 5 patients, 4 (12.5%) came from study #001 (2 in each of the 30 and 60 units/kg groups) and 1 (3.6%) came from study #002. Hypersensitivity type II-IV (chronic) events were reported as mild or moderate in intensity, except for 1 patient in the 60 units/kg dose group in study #001 who experienced a very severe autoimmune thrombocytopaenia considered to be not treatment related. Contact dermatitis was reported in 2 patients in study #001 (1 in each of the 30 units/kg and 60 units/kg dose groups), but neither case was considered to be treatment related. The 1 patient in study #002 with a hypersensitivity type II-IV event was reported to have actually experienced arthritis (knee inflammation) associated with gonarthrosis not considered to be treatment related.

- Infusion related reactions

The clinical studies were designed to identify AEs associated with taliglucerase alfa infusions by asking the investigator to mark in the case report form at each infusion whether an AE had occurred “during or after an infusion”. However, the protocols did not define a time window during which the investigator should consider that an event occurred “after an infusion”, but all events identified occurred on the same date as an infusion. These events represent a

prospective assessment of AEs that, in the opinion of the investigator, occurred in temporal association with an infusion. To further define the temporal relationship between time of infusion and associated infusion related events, a retrospective analysis of AEs was performed using the following time categories: during the infusion or within 2 hours after completion of the infusion; 2 to 24 hours after completion of the infusion; and greater than 24 hours after completion of the infusion. An event may have been reported more than once for an individual patient if the event occurred in different time windows during different infusions. This time based analysis of infusion reactions appears to have been requested by the FDA.

The number of AEs occurring within the three specified time windows is summarized below in Table 34. A total of 45 (37.2%) patients experienced 168 AEs during or within 2 hours after the infusion, 134 of which were considered at least possibly related to taliglucerase alfa. AEs occurring between 2 hours and 24 hours after completion of the infusion occurred in 64 (52.9%) patients, and AEs occurring at least 24 hours after completion of the infusion occurred in 91 (75.2%) of patients. Most AEs reported for the three time windows were mild or moderate in intensity. A greater proportion of AEs reported as occurring during or within 2 hours after completion of the infusion were considered by investigators to be related to drug treatment (79.8%), than AEs reported as occurring between 2 and 24 hours after completion of the infusion (33.3%), and AEs reported as occurring at least 24 hours after completion of the infusion (5.7%).

Table 34: SCS (update) - Number of adverse events according to specified time-windows.

Parameter	Occurring during the infusion or within 2 hours after completion of the infusion	Occurring between 2 hours and 24 hours after completion of the infusion	Occurring at least 24 hours after completion of the infusion
Number of Subjects with an Event	**N=45**	**N=64**	**N=91**
AEs	168	192	546
Mild/Moderate AEs	167	190	534
Severe/Very Severe AEs	1	2	12
SAEs	1	1	9
AEs Probably or Definitely Not Related to Treatment	34	128	514
AEs Definitely, Probably, or Possibly Related to Treatment	134	64	32

The most common AEs (≥ 3 in any group) occurring during or within the first 2 hours after completion of the infusion and between 2 hours and 24 hours after the completion of the infusion compared with events reported by the investigator to have occurred during or after an infusion are summarized below in Table 35. Investigator identified AEs associated with infusions appear to most closely reflect events occurring during or within 2 hours after the completion of an infusion.

Table 35: SCS (update) - Comparison of the number (%) of the most common AEs occurring in specified time-windows and investigator designation of whether the event was during or after an infusion.

MedDRA PT	Occurring during the infusion or within 2 hours after the completion of the infusion N=121	Occurring between 2 hours and 24 hours after the completion on the infusion N=121	Investigator Indicated Event was During or After an Infusion N=121
Nausea	4(3.3)	1(0.8)	5(4.1)
Vomiting	4(3.3)	1(0.8)	4(3.3)
Chest discomfort	3(2.5)	0	3(2.5)
Fatigue	0	4(3.3)	1(0.8)
Infusion related reaction	3(2.5)	4(3.3)	5(4.1)
Infusion site pain	1(0.8)	2(1.7)	3(2.5)
Hypersensitivity	5(4.1)	0	5(4.1)
Arthralgia	2(1.7)	7(5.8)	2(1.7)
Headache	6(5.0)	7(5.8)	10(8.3)
Insomnia	0	3(2.5)	0
Haematuria	0	4(3.3)	0
Throat irritation	3(2.5)	1(0.8)	3(2.5)
Pruritus	4(3.3)	5(4.1)	5(4.1)
Flushing	4(3.3)	1(0.8)	5(4.1)

· Bone events

Bone events were analyzed because bone co-morbidities are common in patients with GD. Bone events by MedDRA SOC/PT are summarized below in Table 36. Overall, 10 (8.3%) patients experienced 15 bone events, none rated as severe or very severe. The most commonly occurring bone event was bone pain reported in 6 (5.0%) patients, followed by musculoskeletal pain in 3 (2.5%) patients and bone infarction in 1 (0.8%) patient. There were 3 patients with 4 bone events considered by the investigator to be at least possibly related to treatment: 2 patients from study #001 each experienced bone pain, and 1 patient from study #004 experienced 2 events of moderate musculoskeletal pain.

Table 36: SCS (update) - number (%) of subjects with AEs by MedDRA system organ class/ preferred term (bone events).

	PB-06-001					
	30 U/kg	60 U/kg	PB-06-002	PB-06-004	PB-06-005	Overall
MedDRA PT	N=16	N=16	N=28	N=50	N=11	N=121
Bone infarction	0	1 (6.3)	0	0	0	1 (0.8)
Bone pain	1 (6.3)	2 (12.5)	1 (3.6)	2 (4.0)	0	6 (5.0)
Musculoskeletal pain	0	1 (6.3)	0	2 (4.0)	0	3 (2.5)

· Compassionate Use Program

In addition to the patients participating in the clinical study program, taliglucerase alfa is also currently being administered in various Compassionate Use Programs in Europe, Brazil, Australia, Mexico and Israel. In these programs, taliglucerase alfa is supplied to individual patients upon physician request. While procedures are in place to facilitate reporting of AEs/SAEs to the sponsor, IECs/IRBs, and national health authorities in those countries in which the programs are being conducted, the sponsor acknowledges that it is possible that not all events will be reported. Consequently, the safety dataset from the programs is limited and not complete.

As of 1 May 2011, there were 212 patients enrolled in Compassionate Use Programs, and the SCS summarized safety data from 18 of these patients. In these 18 patients there have been 49 reported AEs. Examination of the AEs suggests that nearly all can be characterized as hypersensitivity reactions. Of the AEs, 8 were reported as SAEs occurring in 4 patients, and 4 of these events were considered to be hypersensitivity related. Discontinuations occurred in 12 patients due to AEs, and hypersensitivity reactions were reported in 10 of these patients. As

previously noted, there was 1 reported death in a Brazilian patient (pneumonia/tuberculosis) considered definitely not related to treatment with taliglucerase alfa.

12.3.1.8. Anti-taliglucerase alfa antibody results

· Background

The immunogenicity data discussed in this section are derived from the SCS update (52.87% assay cut-point), and the sponsor's follow-up response to TGA questions (40.33% and 52.87% assay cut-points). Anti-taliglucerase alfa IgG antibody was measured in subjects from studies #001, #002, and #003.

Using the IgG assay cut-point of 52.87%, the number of patients who were antibody positive at any time point (including those positive at baseline only or positive at baseline and without significant increase in titre) for studies #001, #002 and #003 were 28.1% (9/32), 11.5% (3/26) and 33.3% (15/45), respectively.

Using the IgG assay cut-point of 40.33%, the number of patients who were positive at any time point (including those positive at baseline only or positive at baseline and without significant increase in titre) for studies #001, #002 and #003 were 59.4% (19/32), 19.2% (5/26) and 35.6% (16/45), respectively. The results from studies #001/#003 and studies #002/#003 using both IgG assay cut-points were summarized for naïve patients and switchover patients.

In the analysis using the assay cut-point of 40.33%, of the 26 ERT naïve patients from pivotal study #001 who entered extension study #003 and received at least 24 months treatment, 13 (50%) patients were found to have positive test results for IgG antibodies at least at one visit. Of these 13 patients, 1 was found to have IgG antibodies with a very low titre present at baseline (i.e., before exposure) that did not change during treatment. This patient was scored by the sponsor as antibody negative in further analyses. The analyses using the cut-points of 40.33% and 52.87% identified the same 13 antibody positive patients from study #001 who entered extension study #003 and were treated for a total of at least 24 months.

In the analysis using the assay cut-point of 40.33%, of the 18 ERT experienced patients from switchover study #002 entering the extension study #003, 3 (16.7%) patients were found to have positive test results for IgG antibodies at Month 3 (i.e., after 12 months treatment). Out of the 18 patients from study #002 continuing in study #003, the analysis using the cut-point of 52.87% identified 2 antibody positive patients compared with 3 antibody positive patients identified with the 40.33% cut-point.

· Effect of antibody status on safety

The anti-taliglucerase alfa antibody results based on the assay cut-point of 40.33%, and the adverse events considered by the sponsor to be treatment related for patients from studies #001 and #002 continuing in extension study #003 are summarized for ERT naïve and ERT experienced patients. The results for the effect of antibody status on immune mediated adverse events discussed below are from the SCS update (cut-point 52.87%) unless otherwise stated. The safety results using cut-point 52.87% are unlikely to significantly differ from the safety results using cut-point 40.33%.

Previous ERT status did not appear to affect the incidence of hypersensitivity type I (acute) reactions (all causality). Irrespective of antibody status, the overall incidence of hypersensitivity type I (acute) reactions in the ERT naïve population (28%, 9/32) was very similar to the incidence in the ERT population (27%, 7/26). However, the presence of anti-taliglucerase antibodies was associated with an increased rate of hypersensitivity type I (acute) reactions (all causality), with the overall incidence in the antibody positive population being 44% (8/18) compared with 20% (8/40) in the antibody negative population. The sponsor stated that "[g]iven the small number of subjects and the different duration of treatment for individuals, potentially affecting event frequency, these observations need to be interpreted with caution".

Nevertheless, it is considered that the results suggest that positive antibody status is associated with a higher risk of hypersensitivity type I (acute) events.

The SCS update included an analysis of the treatment received for hypersensitivity type I (acute) and infusion related AEs in 21 antibody positive patients. Of the 21 patients, 13 continued treatment with no intervention, 3 discontinued treatment follow "hypersensitivity" events, 2 continued treatment with use of antihistamines for rash or pruritus, 2 subjects experiencing infusion related reactions continued treatment with OTC medication for headaches, and 1 subject who experienced "hypersensitivity" continued treatment with pre-treatment regimens.

Two independent assays measuring neutralizing antibody activity were performed, an in vitro assay based on enzyme activity and a cell-based assay that combines both cellular uptake and intracellular enzymatic activity using the same positive control. Assay validation studies of both the in vitro and cell-based assays show similar sensitivity for the detection of anti-taliglucerase alfa neutralizing antibodies. Based on the in vivo assay, neutralizing antibodies were identified in 3 subjects (irrespective of IgG status using the 55.87% or 40.33% cut-points), but the cell based assay was negative in all 3 subjects. The sponsor states that the clinical relevance of these discrepant assay results needs to be further monitored and studied.

12.3.1.9. Clinical laboratory results

No evidence of an adverse effect of taliglucerase alfa on laboratory test parameters (haematology or biochemistry) was observed, and the majority of parameters remained at normal levels or improved to normal levels by the end of the studies. Clinical laboratory results from the updated interim reports for studies #002 and #003 are considered in more detail in Sections 12.3.2 and 12.3.3, respectively, of this second round CER.

12.3.1.10. Other safety related observations

Vital signs: In the clinical study program, 6 (5.0%) events of hypertension, 1 (0.8%) event of blood pressure increased and 1 (0.8%) event of blood pressure decreased were reported. None of these events were considered to be related to treatment with taliglucerase alfa. Changes in vital signs occurring during taliglucerase alfa infusions were not analysed separately from hypersensitivity and infusion reactions.

Electrocardiogram: There is no evidence in the submitted data that treatment with taliglucerase alfa is associated with significant changes in ECG findings. There were 2 patients with significant changes from baseline (1 x supraventricular tachycardia and 1 x occasional supraventricular ectopic beats). Both events were considered unrelated to treatment, and both events resolved and the patients continued treatment with taliglucerase alfa. ECG results from the updated interim reports for studies #002 and #003 are discussed in Sections 12.3.2 and 12.3.3, respectively, of this CER.

Echocardiogram: ECHO results showed that 41/60 (68.3%) patients had a normal evaluation at screening and 40/51 (78.4%) patients had a normal echocardiography after 9 months of treatment. There were 4 patients in study #003 (3 x ERT naïve and 1 x ERT experienced) with abnormal ECH0 findings developing while on treatment with taliglucerase. These patients are discussed in more detail in Section 12.3.3 (study #003) of this CER.

Pulmonary function tests (PFTs): The PFTs are discussed in Section 12.2.3 (study #003) of this CER. No marked changes in PFTs occurred with taliglucerase alfa. and there is no evidence from the available data that the enzyme adversely affects pulmonary function.

12.3.1.11. Safety in special groups

Sex: In the 121 subjects included in this safety summary, 67 were male and 54 were female. There were no marked differences between the sexes in the percentages reported with AEs (males, 82.1%; females, 90.7%), or in the number of reported AEs (males 440; females 470).

SAEs occurred in 92.5% of males and 90.7% of females, and treatment related AEs were reported in 41.8% of males and 44.4% of females. The AE profiles (MedDRA SOC/PT) for males and females did not appear to significantly differ.

Patients aged < 18 years: Taliglucerase alfa has been administered to 13 patients younger than 18 years of age (2 to < 18 years). At the time of the database lock for the updated Summary of Clinical Safety (1 May 2011), there were 2 children enrolled in the switchover study (#002) with a total of 15 infusions completed for each child, and treatment was ongoing. These 2 children had two mild AEs each, none of which were considered serious (iron deficiency and epistaxis in 1 child; arthralgia and vomiting in 1 child). There are 11 children enrolled in the treatment naïve paediatric study (#005). In this study, 1 SAE (gastroenteritis) considered treatment related was reported in 1 paediatric patient. No unusual AEs have been observed specifically in paediatric subjects. However, the sample size in paediatric patients is too small to conclude that there are no significant differences in the safety profile of taliglucerase alfa in paediatric and adult patients.

Race: No conclusions can be drawn regarding safety differences according to race as almost all patients were Caucasian.

12.3.2. Study PB-06-002 (Ongoing Phase III Study) – updated report

The objective of this ongoing Phase 3, multi-centre, open-label, switchover study is to assess the safety and efficacy of taliglucerase alfa in 30 patients, 2 years or older, with GD who have been treated with imiglucerase. In order to be eligible for this study, patients were required to have been treated with imiglucerase (Cerezyme) as ERT for GD for at least 2 years and at a stable maintenance regimen (dose unchanged) for at least six months immediately before switching over to taliglucerase alfa. At the end of the 9 month taliglucerase alfa treatment period (20 visits, week 38), eligible patients are offered enrollment and continued taliglucerase alfa treatment in extension study #003.

The updated study report included information on 28 treated patients (mean±age 44.7±15,1 years; range 13 to 66 years; m/f = 15/13; Jewish-Ashkenazi / Non-Jewish = 14/12; 100% Caucasian). The report included 2 patients aged less than 18 years of age and both of these patients are continuing treatment. At the time of the database lock (1 May 2011), the mean±SD taliglucerase alfa dose for the 28 treated patients was 29.2±15.8 units/kg, and the median dose (range) was 25.5 units/kg (11 to 60 units/kg).

12.3.2.1. Efficacy results

Of the 28 patients included in the efficacy analysis, 25 had completed 9 months of treatment. No primary efficacy outcome was specified in this study. The efficacy outcome of interest was whether patients deteriorate clinically during treatment with taliglucerase alfa after switching from imiglucerase. Clinical deterioration was assessed by changes in spleen volume, liver volume, haemoglobin level, platelet count, and chitotriosidase activity after 9 months treatment with taliglucerase alfa after switching from imiglucerase. Clinical deterioration was defined as follows:

- Spleen volume – a 20% increase in spleen volume by MRI from Baseline to Month 9 (or the time of premature withdrawal).
- Liver volume – a 10% increase in liver volume by MRI from Baseline to Month 9 (or the time of premature withdrawal).
- Haemoglobin – a decrease of > 20% from the mean of six Stability Evaluation Period values.
- Platelet counts – a decrease of > 20% from the mean of six Stability Evaluation Period values of ≤120,000 or a decrease of >40% from the mean of six Stability Evaluation Period values of >120,000.

12.3.2.1.1. Spleen volume (efficacy)

In the 25 patients completing 9 months of treatment, 3 patients had no spleen volume results due to splenectomy and 2 patients were evaluated by ultrasound and were not included in the analysis. The mean±SD spleen volume (n=20) decreased from 822.4±603.7 mL at Baseline to 749.3±559.7 mL at Month 9. The mean±SD percent reduction from baseline was 7.6±13.3% (range: -33% to +21.6%). The mean spleen volume was 5.5 times normal spleen volume at Baseline and 5.1 times normal spleen volume at Month 9. The results for change in spleen volume indicate that no clinical deterioration had occurred 9 months after switching from imiglucerase to taliglucerase alfa.

12.3.2.1.2. Liver volume (efficacy)

In the 25 patients who completed 9 months of treatment, 2 patients were evaluated by ultrasound and were not included in the liver volume analysis. The mean±SD liver volume (n=23) decreased from 1857.4±440.0 mL at Baseline to 1785.8±423.7 mL at Month 9. The mean±SD percent reduction from baseline in liver volume was 3.5±8.1% (range: -16% to +22.2%). The results for change in liver volume indicate that no clinical deterioration had occurred 9 months after switching from imiglucerase to taliglucerase alfa.

12.3.2.1.3. Haemoglobin (efficacy)

Haemoglobin was measured at the local laboratory for the 9 visits (0, 1, 3, 5, 7, 10, 14, 17 and 20) or for additional visits at the discretion of the investigator as clinically indicated. Haemoglobin at Baseline, Month 3, Month 6 and Month 9 are summarized in the dossier. The results showed no significant change in mean haemoglobin level from baseline to Month 3, 6, and 9. The haemoglobin level remained stable over the 9 month period after switching from imiglucerase to taliglucerase.

12.3.2.1.4. Platelet count (efficacy)

Platelet count was measured at the local laboratory for the 9 visits (0, 1, 3, 5, 7, 10, 14, 17 and 20) or for additional visits at the discretion of the investigator as clinically indicated. Platelet counts at Baseline, Month 3, Month 6 and Month 9 are summarized in the dossier. The mean±SD changes in the platelet count from baseline to months 3, 6 and 9 were -5.4±23.6%, -4.4±18.1%, and -1.0±21.1%, respectively. The platelet count remained relatively stable over the 9 month period after switching from imiglucerase to taliglucerase alfa.

12.3.2.1.5. Biomarker results - chitotriosidase and CCL18 (efficacy)

The biomarkers chitotriosidase and CCL18 are being measured every 3 months during the study. There were no additional data in the updated report relating to CCL18 levels, but the report included updated data on chitotriosidase levels. In the updated report, a 12.5% mean decrease in mean chitotriosidase level from Baseline (n=23) was observed at Month 3 (n=25), and a 16.6% mean decrease was observed at Months 6 (n=25) and 9 (n=25). The mean chitotriosidase levels in the updated report at Day 1 and Months 3, 6, and 9 are summarized in the dossier. Mean chitotriosidase levels were lower at Months 3, 6 and 9 compared with baseline in patients switching from imiglucerase to taliglucerase alfa.

12.3.2.2. Safety Results

12.3.2.2.1. Overall AE experience

At the time of the database freeze (1 May 2011), 28 patients had received taliglucerase alfa and 25 of these patients had completed the study after receiving 9 months of taliglucerase alfa. Overall, 28 patients received an average dose of 29.2 units/kg of taliglucerase alfa, ranging from 11.3 to 59.5 units/kg.

Of the 28 taliglucerase alfa treated patients, 27 (96.4%) experienced at least 1 adverse event (AE), and there was a total of 143 AEs in these 27 patients. There were 10 (35.7%) patients who

experienced at least 1 AE considered treatment related by the investigator, and there was a total of 24 treatment related AEs in these 10 patients. In the 27 patients experiencing at least 1 AE, all events were reported as mild or moderate in intensity except in 2 patients who experienced 3 AEs which were reported as severe (haematuria and renal stone in 1 patient; and prolapsed rectum, bladder and cervix in 1 patient). The majority of AEs had resolved by the end of the study.

12.3.2.2.2. Most commonly occurring AEs

The most commonly experienced AEs were nasopharyngitis (5 patients, 17.9%), arthralgia (4 patients, 14.3%), infusion related reaction, urinary tract infection, pain in extremity and headache, each of which occurred in 3 (10.7%) patients, and diarrhoea, asthenia, pain, upper respiratory tract infection, cough, epistaxis, pruritus, and flushing, each of which occurred in 2 (7.1%) patients. All other AEs occurred in 1 (3.6%) patient.

12.3.2.2.3. Infusion related adverse events

There were 12 patients who experienced a total of 27 infusion related AEs. Of the 27 AEs occurring in the infusion, 17 were considered related to study treatment. However, a time window after the infusion for reporting an AE as associated with the infusion was not predefined.

12.3.2.2.4. Deaths, other serious adverse events, and other significant adverse events

No deaths occurred during the study, and no patients had discontinued from the study due to an AE at the time of database lock. One patient voluntarily withdrew from the study after experiencing a hypersensitivity reaction during the first infusion, and declined to continue infusions under pre-treatment medication. Three patients each experienced a single serious adverse event (SAE) during the study (epistaxis in 1 patient; prolapsed rectum, bladder and cervix in 1 patient; and renal stone in 1 patient). These SAEs were considered to be unrelated to treatment and were reported as resolved or resolving by the end of the study.

12.3.2.2.5. Hypersensitivity to taliglucerase alfa

One patient experienced a hypersensitivity reaction to taliglucerase alfa characterised by urticaria, diffuse rash and pruritus during the first infusion. This patient voluntarily withdrew from the study and declined continued infusion under pre-treatment medication. This patient appears to have been treated with numerous previous infusions of imiglucerase over a number of years without infusions reactions.

12.3.2.2.6. Anti-taliglucerase alfa antibodies

Antibody testing (assay using 52.87% cut-point) was undertaken in 26 patients treated with taliglucerase alfa, and 3 (11.5%) were found to be positive for taliglucerase alfa IgG antibodies while 23 (88.5%) patients were found to be negative. One of the patients found to be positive to IgG antibodies also showed neutralizing activity on the in vitro assay, but not on the cell based assay. None of the 3 patients who were IgG antibody positive experienced any treatment related AEs during the study, and 2 of the 3 patients (including the patient with neutralizing activity) continued treatment in extension study #003.

12.3.2.2.7. Clinical laboratory tests

Clinical haematology and biochemistry laboratory tests were assessed for most parameters at screening, day 1, week 4, week 8, month 3, week 18, month 6, week 32, and Month 9, and all parameters were assessed at screening at Month 9. The parameters were summarized by descriptive statistics (mean, median, and range), low/high/normal values, and shift values from screening.

There were no marked changes in the haematology or biochemistry parameters assessed for safety over the duration of the study. The descriptive statistics at screening and Month 9, and

shifts from screening to Month 9 for the assessed haematology parameters, and the corresponding results for the assessed biochemistry parameters are provided in the study report.

There were 2 patients with normal ALT values at Screening that shifted to above the ULN during the treatment: one patient (Visit 5; 44 IU/L); and another patient (Visit 1; 41 IU/L). There was 1 patient with abnormal ALT values at screening (45 IU/L), and at Visits 1, 5, 7, 10, 14, 17 and 20 the ALT ranged from 41 to 89 IU/L. There were 2 patients with normal AST values at Screening that shifted to above ULN during treatment: one patient (Visit 1; 53 IU/L); and another patient at Visits 1, 5, 10, 17 the AST ranged from 45 to 52 IU/L. Therefore, there were 4 (14.3%) patients with transaminase levels (ALT or AST) that increased from screening during treatment with taliglucerase alfa, however, the increases appeared to be transient and no increases were > 3 x ULN.

There were 4 (14.3%) patients with normal total bilirubin values at Screening that shifted to above ULN during treatment: one patient (Visit 20; 1.3 mg/dL); another patient (Visits 3 and 14; 1.3 mg/dL at each visit); another patient (Visit 1; 1.5 mg/dL); and another patient at Visits 3, 7, 10, 14 and 17 the total bilirubin ranged from 1.3 to 1.9 mg/dL. No patients had persistent elevations in total bilirubin. Two patients appear to have Gilbert disease and this condition probably explains the elevated total bilirubin and ALT and AST in these two patients. No patients had laboratory evidence fulfilling Hy's criteria for hepatotoxicity.

Elevations in non-fasting serum glucose from normal values at baseline were observed in 13 (46.4%) patients. Most of these patients were reported as showing sporadic and transient elevations in serum glucose which did not require further diagnostic work up or change in clinical care. There was 1 patient with several high serum glucose values, but the HbA1c results did not indicate a new diagnosis of diabetes mellitus. There were 2 patients with a history of Type 2 diabetes mellitus. There was 1 patient with an elevation of HbA1c at Visit 20, but no history of diabetes mellitus.

There was 1 (3.6%) patient who experienced a clinically relevant deterioration in platelet count after 22 weeks of treatment with taliglucerase alfa. This patient entered the study on a very low dose of imiglucerase (equivalent to taliglucerase alfa 800 units, or 9.5 units/kg, every 2 weeks). The patient's taliglucerase alfa dose was subsequently doubled to 20 units/kg and his platelet count responded and increased to baseline level. The day after the Week 24 visit, the patient experienced haematuria due to a large renal stone which was removed after several interventions by the Week 32 visit. Haematuria may have contributed to the patient's haemoglobin reduction from 15.6 g/dL at baseline to 12.9 g/dL at Week 32. The patient continued in the study and completed 9 months of treatment.

12.3.2.2.8. Other observations related to safety

There were no other significant safety issues involving vital signs, electrocardiographic (ECG) changes, and pulmonary function tests. There was no meaningful difference between the percentage of patients with abnormal ECG results at Screening (35.7%) and at Month 9 (33.3%). There was 1 patient with a clinically significant change in ECG from Baseline observed at Visit 14, which was reported as an AE, sinus tachycardia (supraventricular on ECG). This event resolved and was considered probably not related to treatment. The patient completed the study and subsequently continued treatment in extension study #003.

12.3.3. Study PB-06-003 (Ongoing Phase III Study) – updated report

The objective of this ongoing Phase 3, multi-national, multi-centre study is to extend the assessment of safety and efficacy of taliglucerase alfa in up to 60 patients with GD who have successfully completed 9 months of treatment in study #001 or study #002. The total treatment duration is to be at least 15 months (64 weeks) and no more than 30 months (128 weeks), or until marketing approval has been granted by the appropriate regulatory authority, whichever is earlier. The study includes 3 treatment groups with patients continuing to receive the

allocated dose from study #001 (Group I [30 units/kg] and Group II [60 units/kg]), or the same dose being received at the completion of study #002 (Group III). Patients receive iv infusion of taliglucerase alfa every 2 weeks and have the option to receive infusions at the selected medical centre, infusion centre, or at home. Local standard of practice, the investigator and the study Medical Director determine the timing and method of infusion outside the medical centre.

At the time of the database lock for the updated report (1 May 2011), 44 patients (26 from study #001; 18 from #study 002) from 14 study sites were enrolled in the study. The demographic data for the three treatment groups are summarized in Table 37. The updated report included no data in patients aged less than 18 years, and the age range of the total population was 19 to 74 years.

Table 37: Study PB-06-003 (updated report) – demographic information; study population.

		PB-06-001		
PARAMETER		30_units/kg N = 12	60_units/kg N = 14	PB-06-002_prGCD N =18
AGE (yrs) at INFORMED CONSENT	N	12	14	18
	MEAN	38.9	35.6	45.4
	SD	12.1	12.0	13.5
	MEDIAN	35.0	33.0	46.5
	RANGE	24 to 74	19 to 58	18 to 66
GENGER	N	12	14	18
	MALE	7 (58.3%)	8 (57.1%)	9 (50.0%)
	FEMALE	5 (41.7%)	6 (42.9%)	9 (50.0%)
RELIGION	N	12	14	18
	JEWISH-ASHKENAZI	4 (33.3%)	2 (14.3%)	11 (61.1%)
	JEWISH-NON ASHKENAZI	0 (0.0%)	0 (0.0%)	0 (0.0%)
	NON JEWISH	8 (66.7%)	12 (85.7%)	7 (38.9%)
RACE	N	12	14	18
	CAUCASIAN	12 (100.0%)	13 (92.9%)	18 (100.0%)
	AFRICAN AMERICAN	0 (0.0%)	0 (0.0%)	0 (0.0%)
	NATIVE AMERICAN	0 (0.0%)	0 (0.0%)	0 (0.0%)
	ASIAN/PACIFIC ISLANDER	0 (0.0%)	0 (0.0%)	0 (0.0%)
	OTHER	0 (0.0%)	1 (7.1%)	0 (0.0%)

Of the 26 ERT naïve patients enrolled from study #001, 2 patients discontinued (1 was discontinued following the investigator's recommendation in order to assess a possible allergic reaction after 38 infusions, and 1 was unable to adjust her time for infusions after 33 infusions). Of the 18 ERT experienced patients enrolled from study #002, 2 patients voluntarily withdrew (1 was not satisfied with the results of treatment after 16 infusions, and 1 wanted to pursue another research medication after 25 infusions). As of 1 May 2011, 21 patients from study #001 and 16 from study #002 are continuing treatment.

12.3.3.1. Efficacy results

There was no primary efficacy outcome specified in this study. The efficacy outcome of main interest was whether patients deteriorate clinically during continued long-term treatment with taliglucerase alfa. The efficacy outcomes of interest are spleen volume, liver volume, platelet counts, haemoglobin, biomarkers (chitotriosidase and pulmonary and activation-regulated chemokine [PARC/CCL18], Quantitative Chemical Shift Imaging (QCSI), and change in bone mineral density by DEXA .

12.3.3.1.1. Spleen volume (efficacy)

Spleen volume was measured at Day 1 of the extension study, which corresponds to the final visit (Month 9) of the predecessor study, and was scheduled for assessment in the extension study at Month 3 (12 months of treatment) and Month 15 (24 months treatment). Blinded spleen volume data were available at both the Month 3 and Month 15 timepoints for all 26 patients who continued from study #001, and open-label data were available at Month 3 for 17 patients who continued from study #002. The results for changes in spleen volume from the updated report are summarized in the study report.

In the patients from study #001 who continued treatment in the extension study, the mean±SD reduction in spleen volume from baseline in the 30 units/kg group (n=12) was 28.9±8.2% at Month 3 (12 months of treatment) and 40.5±9.6% at Month 15 (24 months of treatment), and the corresponding reductions in the 60 units/kg group (n=14) were 43.5±11.4% at Month 3 and 54.9±12.8% at Month 15. The greater reductions in spleen volume observed in the 60 units/kg group compared with the 30 units/kg group at Month 3 and Month 15 were statistically significant at both time points ($p<0.001$). There were 2 patients with Month 27 data (36 months treatment) in whom mean reductions in spleen volume from baseline were 44.7% (30 units/kg) and 56.1% (60 units/kg).

Of the patients from study #002 who continued treatment in extension study #003, 8 patients had MRIs at Month 3 (12 months of treatment). Of these 8 patients, 1 patient was splenectomized and the mean±SD reduction in spleen volume from baseline in the remaining 7 patients was 10.7±12.4%. There were 2 patients who were MRI phobic and their spleen volumes were evaluated by ultrasound and were not included in the analysis. There were 7 patients without MRIs at Month 3 due to delays in obtaining site approval of the extension protocol.

The updated report included an analysis of change in spleen volume from Screening until last follow-up visit based on MRI results (see Table 38, below). In patients from study #001, the mean±SD reduction in spleen volume in the 30 units/kg group (n=12) was 41.3±9.5% after a mean duration of 26.5 months of follow-up, and in the 60 units/kg group (n=14) the mean±SD reduction in spleen volume was 55.8±12.3% after a mean duration of follow-up of 25.6 months. In the patients from study #002 with relevant data (n=15), the mean±SD reduction in spleen volume from baseline was 8.0±12.6% after a mean of 16.1 months of follow-up. The difference between mean reductions in spleen volume for the two studies reflects the fact that in study #001 patients were naïve to ERT at baseline, while in study #002 baseline volumes represented the effect of previous treatment with imiglucerase prior to patients switching to taliglucerase alfa.

Table 38: Study #003 (updated report) – Spleen volume change and total duration of follow up.

		PB-05-001		
		30_units/kg N = 12	60_units/kg N = 14	PB-06-002_prGCD N = 18
FOLLOW UP DURATION (MONTHS)*	N	12	14	15
	MEAN	26.5	25.6	16.1
	SD	4.5	4.8	4.2
	MEDIAN	24.3	24.1	17.4
	RANGE	23.8 to 39.3	23.6 to 38.4	9.2 to 23.2
PERCENT CHANGE IN SPLEEN VOLUME**	N	12	14	15
	MEAN	-41.3	-55.8	-8.0
	SD	9.5	12.3	12.6
	MEDIAN	-41.1	-56.4	-7.2
	RANGE	-58.5 to -28.1	-74.9 to -30.5	-27.8 to 22.1

* Follow up duration is in months between first study drug infusion and last MRI.
** % change is calculated based on the results of baseline MRI to last MRI.

12.3.3.1.2. Liver volume (efficacy)

Liver volume was also measured at Day 1 of the extension study, which corresponds to the final visit (Month 9) of the preceding trial, and at Month 3 and Month 15 of treatment, representing a total of 12 and 24 months of treatment with taliglucerase alfa for 26 patients continued from study #001 and 12 months for 17 patients continued from study #002. The results for changes in liver volume from the updated report are summarized in the study report.

Of the patients from study #001 who continued treatment in extension study #003, the mean±SD reduction in the liver volume from baseline in the 30 units/kg group (n=12) was 15.9±5.2% at Month 3 and 20.6±6.9% at Month 15, and the corresponding reductions in liver volume in the 60 units/kg group (n=14) were 13.2±8.9% at Month 3 and 17.5±13.3% at Month 15. There were no statistically significant differences between the two treatment groups in

reduction in liver volume from baseline at the Month 3 and Month 15 time points (p=0.352 and p=0.473, respectively). There were 2 patients with Month 27 data (36 months treatment) in whom mean reductions in liver volume were 22.3% (30 units/kg) and 14.4% (60 units/kg). In the patients from study #002 who continued treatment in extension study #002 and with relevant data (n=8), the mean reduction in liver volume from baseline was 4.2±5.8% at Month 3.

The updated report included an analysis of change in liver volume from screening until last follow-up visit based on MRI results (see Table 39, below). In patients from study #001, the mean±SD reduction in liver volume from screening in the 30 units/kg group (n=12) was 21.5±6.3% after a mean duration of follow-up of 26.5 months, and the mean±SD reduction in liver volume from screening in the 60 units/kg group was 17.9±13.2% after a mean duration of follow-up of 25.9 months. In patients from study #002 with relevant data (n=16), the mean±SD reduction in spleen volume was 2.0±7.5% after a mean duration of follow-up of 15.9 months.

Table 39: Study PB-06-003 (updated report) – Liver volume change and total duration of follow up.

		PB-06-001		
		30_units/kg N = 12	60_units/kg N = 14	PB-06-002_prGCD N =18
FOLLOW UP DURATION (MONTHS)*	N	12	14	16
	MEAN	26.5	25.9	15.9
	SD	4.5	4.0	4.1
	MEDIAN	24.3	24.1	17.1
	RANGE	23.8 to 39.3	23.6 to 38.4	9.2 to 23.2
PERCENT CHANGE IN LIVER VOLUME**	N	12	14	16
	MEAN	-21.5	-17.9	-2.0
	SD	6.3	13.2	7.5
	MEDIAN	-19.2	-16.8	-1.6
	RANGE	-33.7 to -13.9	-41.4 to 9.4	-12.8 to 18.8

* Follow up duration is in months between first study drug infusion and last MRI.
** % change is calculated based on the results of baseline MRI to last MRI.

12.3.3.1.3. Haemoglobin changes (efficacy)

Haemoglobin level was measured every 3 months. The changes from baseline in haemoglobin levels in the updated report are summarized in the dossier. In patients (n=26) from study #001 who continued treatment in extension study #003, mean haemoglobin levels showed an improvement from baseline at Month 3 (12 months of treatment), Month 9 (18 months treatment) and Month 15 (24 months of treatment). In the 30 units/kg group (n=11) the mean±SD increase in haemoglobin level from baseline at Month 15 was 1.3±1.7 g/dL, and the corresponding increase in haemoglobin level in the 60 units/kg group (n=14) was 2.4±2.3 g/dL; p=0.207. In patients from study #002 who continued treatment in the extension study, there were no meaningful changes in haemoglobin levels at Month 3 (n=12) or Month 9 (n=10).

12.3.3.1.4. Platelet count (efficacy)

Platelet count was measured every 3 months. The changes from baseline in platelet count in the updated report are summarized in the study report. The patients (n=26) from study #001 who continued treatment in extension study #003 showed an improvement in mean platelet counts at Month 3 (12 months of treatment), Month 9 (18 months treatment) and Month 15 (24 months of treatment). In patients from study #001 in the 30 units/kg group (n=12), the mean±SD increases in the platelet count from baseline at Month 3 and Month 15 were 15,425±20,003/mm^3 and 28,433±31,996/mm^3, respectively, and the corresponding results for the 60 units/kg group (n=14) were 53,814±51,270 /mm^3 and 72,029±68.156/mm^3. The increase in platelet count at Month 3 was statistically significantly higher (p=0.024) in the 60 units/kg group compared with the 30 units/kg group, while the difference between the two treatment groups at Month 15 was not statistically significant (p=0.054). In patients from study #002 who continued treatment in extension study #003, the mean±SD platelet count increased from baseline by 10,889±24.473/mm^3 at Month 3 (n=12), while the mean±SD platelet count decreased from baseline by 130±37,706/mm^3 at Month 15 (n=9).

12.3.3.1.5. Biomarker chitotriosidase levels (secondary efficacy measure)

The biomarker chitotriosidase was measured every 3 months during studies #001 and #002. In study #003, samples for biomarkers were obtained every three months. At the time of database lock (1 May 2011), 26 patients from study #001 had entered the extension study and were treated for a total of 24 months, 1 patient (60 units/kg) was found to have no chitotriosidase activity. Consequently, chitotriosidase activity was analyzed for 25 patients. In the 30 units/kg group (n=12), at Month 15 the mean±SD chitotriosidase activity was reduced by 60.6±19.3% from baseline, and in 60 units/kg group (n=15) the corresponding reduction in activity was 76.2±22.6%.

12.3.3.1.6. DEXA (exploratory efficacy)

Lumbar spine, femoral neck and total hip DEXA scans were obtained in patients from study #001 at Month 3 (n=23-25), Month 15 (n=21-26) and Month 27 (n=2-3) and were summarized by T score, Z score and Dexa scores. There was a general trend towards improvement in BMD over the course of treatment.

12.3.3.1.7. QCSI (Quantitative Chemical Shift Imaging) (exploratory efficacy)

QCSI was used to measure bone marrow fat fraction content as an exploratory endpoint. The sponsor states that QCSI is a well accepted methodology to quantify bone marrow response to enzyme replacement therapy in GD. The optional exploratory lumbar spine QCSI assessment was performed at baseline in study #001 (n=8) and following treatment in extension study #003 at Month 3 (n=8) and Month 15 (n=8).

The sponsor compared the QCSI study results with the QCSI results from the literature in the Dutch GD population published by the Academic Medical Center, University of Amsterdam. The mean fat fraction value in healthy population is approximately 0.37 (normalization value), and a fat fraction of ≤ 0.23 is considered to be an indication of bone complications and bone at risk. At baseline, 25% (2/8) of the patients had a fat fraction > 0.23, and after 24 months of treatment 75% (6/8) of the patients showed a fat fraction > 0.23. Two patients had bone events of bone pain, and these events occurred after 12 months (1 patient) and 30 months (1 patient) of treatment.

12.3.3.2. Safety Results

At the time of database freeze (1 May 2011), 44 patients were enrolled into extension study #003 and had received a mean±SD taliglucerase alfa dose of 43.0±18.8 units/kg (range: 12 - 70 units/kg) (see Table 40, below).

Table 40: Study #003 (updated report) – dose summary estimated using baseline body weight.

		PB-06-001			
PARAMETER		30_units/kg N = 12	60_units/kg N = 14	PB-06-002_prGCD N = 18	OVERALL N = 44
AVERAGE OF ALL DOSE INFUSIONS (UNITS/KG)	N	12	14	18	44
	MEAN	34.1	64.9	31.9	43.0
	SD	2.7	3.3	17.4	18.8
	MEDIAN	33.7	63.6	28.7	36.6
	RANGE	(31 to 40)	(61 to 70)	(12 to 60)	(12 to 70)

Of the 26 ERT naïve patients from study #001, all have completed 15 months of extension study #003 treatment (i.e., total treatment of 24 months). Two patients have completed a total of 39 (9+30) months and one patient has completed a total of 24 (9+15) months of continuous treatment in studies #001 and #003, respectively. Two patients discontinued the study after receiving 33 and 38 infusions. There are 21 patients from study #001 continuing taliglucerase alfa treatment in extension study #003.

Of the 18 ERT experienced patients from study #002, all have competed 6 months of extension study #003 treatment (i.e., total treatment of 15 months). Two patients discontinued the study

after receiving 16 and 25 infusions, and the remaining 16 patients are continuing taliglucerase alfa treatment in extension study #003.

12.3.3.2.1. Overall AE experience

The updated study report include AE data on a total of 44 patients, 26 patients from study #001 (30 units/kg, n=12; 60 units/kg, n=14), and 18 patients from study #002.

Of the 26 patients from study #001, 24 (92.3%) experienced at least 1 AE and a total of 230 AEs were reported in these patients: 30 units/kg, 12/12 (100%) experienced at least 1 AE and a total of 105 events were reported in these 12 patients; 60 units/kg, 12/14 (85.7%) experienced at least 1 AE and a total of 125 events were reported in these 12 patients.

There were 11 patients (30 units/kg, n=5; 60 units/kg, n=6) reported as experiencing 34 AEs considered to be treatment related by the investigator (30 units/kg, 18 events; 60 units/kg, 16 event). All 230 AEs in the 24 patients were reported as being mild or moderate in intensity, except for 1 patient in the 30 units/kg group who experienced 2 severe AEs (pain due to haemangioma in left knee and pulmonary embolism), and 2 patients in the 60 units/kg group who each experienced 1 severe AE (immune thrombocytopenia x 1 patient, and diabetes mellitus requiring treatment with insulin x 1 patient). None of the four AEs rated as severe were considered to be associated with taliglucerase alfa treatment.

Of the 18 patients from study #002, 17 (94.4%) experienced at least 1 AE, and a total of 43 AEs were reported in these patients. All AEs were mild or moderate in intensity except for 1 patient who had percutaneous renal stone removal which was rated severe. There was 1 (5.6%) patient who experienced 3 AEs which were considered treatment related by the investigator (facial flushing, facial tightness and feeling discomfort).

12.3.3.2.2. Commonly occurring AEs

The most commonly experienced AEs were: nasopharyngitis in 10 (22.7%) patients (study #001 30 units/kg, n=2 & 60 units/kg, n=3; study #002, n=5); arthralgia in 8 (18.2%) patients (study #001 30 units/kg, n=4 & 60 units/kg, n=3; study #002, n=1); headache in 8 (18.2%) patients (study # 001 30 units/kg, n=4 & 60 units/kg, n=4); and upper respiratory tract infection in 7 (15.6%) patients (study #001 30 units/kg, n=3 & 60 units/kg, n=3; study #002, n=1).

12.3.3.2.3. Infusion related reactions

The frequency of infusion related reactions are based on best practice coding of events in MedDRA where the verbatim term in the eCRF indicated that an event occurred during an infusion. There were 12 (27.2%) patients who experienced 36 AEs during 32 infusions. Of these 12 patients, 11 (42.3%) came from study #001 and 1 (5.6%) came from study #002. Of the 36 events, 27 were possibly, probably or definitely related to treatment

12.3.3.2.4. Deaths, other SAEs, and other significant AEs

No deaths occurred during study #003. Overall, 7/44 (15.9%) patients experienced at least 1 SAE and a total of 8 SAEs were experienced by these 7 patients. No patient had discontinued from the study due to an AE at the time of database freeze. One patient withdrew from the study on the recommendation of the investigator after Month 15 “to assess possible allergic reaction” of mild itching and rash intermittently associated with the taliglucerase alfa infusions.

Of the 26 patients from study #001, 4 (15.3%) experienced a total of 5 SAEs (head injury x 1 patient; autoimmune thrombocytopenia x 1 patient; pain due to haemangioma in left knee and pulmonary embolism x 1 patient; and multiple tooth extraction x 1 patient). There were 2 patients in the 30 units/kg group who experienced 3 SAES, and 2 patients in the 60 units/kg group who experienced 2 SAEs. All SAEs recovered/resolved with no change in dose and none of the events were considered to be treatment related. There was 1 additional patient in the 60

units/kg group who experienced 2 severe non treatment related AEs (right femoral head avascular necrosis and acetabular necrosis), both events were considered SAEs.

Of the 18 patients from study #002, there were 3 patients who experienced 3 SAEs (osteoarthritis x 1 patient; traumatic fracture of 4 ribs and pneumothorax x 1 patient; and percutaneous renal stone removal x 1 patient). All 3 SAEs recovered/resolved with no change in dose and none of the events were treatment related.

12.3.3.2.5. Hypersensitivity to taliglucerase alfa

There were 2 patients from study #003 with hypersensitivity reactions to taliglucerase alfa (both patients came from study #001). Narratives for these two patients were provided in the first round CER.

12.3.3.2.6. Anti-taliglucerase alfa antibodies

Of the 26 patients from study #001 who entered extension study #003 and received a total of 24 months treatment, 13 (50.0%) were found to have had a positive test result for IgG antibody (assay cut-point 52.87%) at one visit at least. In 1 of the 13 patients, IgG antibody to taliglucerase alfa was present with a very low titre present at baseline (before exposure) and did not change during treatment. Of the 13 patients with anti-taliglucerase alfa antibodies, 6 were reported to have experienced treatment related AEs and in 4 of the patients the events were consistent with hypersensitivity reactions. Of the 13 patients without anti-human taliglucerase alfa antibodies, 3 were reported to have experienced treatment related AEs and none of these events appeared to be consistent with hypersensitivity reactions.

Of the 18 patients from study #002 who entered extension study #003, 2 (11.1%) were found to be antibody positive (assay cut-point 52.87%) at Month 3. Of the 18 tested patients, treatment related AEs consistent with hypersensitivity reactions were reported in 1 of the 2 patients with anti-taliglucerase alfa antibodies, and none of the 16 patients who were antibody negative.

12.3.3.2.7. Clinical laboratory tests

Clinical haematology and biochemistry laboratory tests were assessed at screening and then at months 3, 6, and 9 for patients from studies #001 and #002, and months 12, 15, 18, 21, 24, and 27 for patients from study #001. Patient numbers assessed after month 15 from study #001 were smaller than patient numbers assessed up to and including month 15. The clinical laboratory parameters were summarized by descriptive statistics (mean, median, and range), low/high/normal values, and shift values from screening. The descriptive statistics and shift from screening results at Month 15 for patients included in the extension study from #001 are summarized (haematology and biochemistry) in the study report.

There were no marked changes in the haematology parameters over the course of the study. There were no marked changes in the biochemistry parameters over the course of the study. There were upwards shifts in ALT and AST levels at a number of visits over the course of the study (e.g., at month 15 there were 2/16 patients with normal ALT levels at baseline who had shifted to high levels, and 1/16 patients with normal ALT levels at baseline who had shifted to a high level [patients from study #001]). However, none of the abnormal ALT or AST values reported in the study were > 3X the ULN. In 1 (7.1%) patient treated with 60 units/kg, an increased ALT level was reported as an AE. There were 3 patients from study #001 with total bilirubin levels above the ULN for all 3 month evaluations after Month 3 (12 months treatment). However, 1 of the 3 patients had an elevated total bilirubin level before treatment at the screening visit. None of the 3 patients with high total bilirubin levels had associated high ALT or AST levels. None of the reported elevations in total bilirubin levels were considered by the investigators to be clinically significant, and none were reported as an AE.

An elevation in non-fasting serum glucose from normal value at Baseline was observed in a few patients at random visits and was not considered to be clinically significant and was not reported as an adverse event. There was 1 patient with an elevated glucose level of 330 mg/dL,

greater than 2X normal level of 65-99 mg/dL, which occurred at the Month 6 visit. This patient was diagnosed as having type 1 diabetes mellitus and glucose levels normalized after insulin treatment.

Local laboratory urinalysis results for blood, glucose, leucocytes, nitrite, and protein were unremarkable over the course of the study.

12.3.3.2.8. Other observations related to safety

ECG: There were no marked ECG changes over the course of the study. ECGs were assessed at screening and then at months 3, 6, and 9 for patients from studies #001 and #002, and months 12, 15, 18, 21, 24, 27, and 38 for patients from study #001. One patient from study #002 had a clinically significant change from previous ECG results observed at Month 3 in study #003, which was reported as an AE (supraventricular premature beats occasional). This event resolved with no action taken and was considered definitely not related to treatment. This patient is continuing in the study and had received 15 infusions at the time of database freeze.

Echocardiography: ECHO was undertaken at screening and months 15 and 27. Two patients from the 60 units/kg study group of study #001 had new abnormal ECHO findings at the Month 15 visit: 1 patient had a congenital abnormality of the bicuspid valve, mild tricuspid valve regurgitation and mild pulmonary hypertension; and 1 patient had a mild left atrial dilatation. Two patients had abnormal ECHO findings at the Month 27 visit (1 in the 60 units/kg group from study #001 had mild MR and TR; 1 from study #002 had impaired relaxation pattern of LV diastolic filling, mild aortic valve insufficiency, and trace mitral valve regurgitation). No clinically significant deterioration was observed in patients with abnormal ECHO findings.

Pulmonary function tests (PFTs): There were no marked abnormalities in PFTs in patients assessed at 15 months (n=20, all from study #001) and 27 months (n=3 [study #001, n=2; study #002, n=1). The pulmonary function tests included FVC, FEV1, TLC, FRC, RV, DLCO, and DLCO/VA.

12.3.4. Efficacy and anti-taliglucerase antibody status

In the follow-up response to TGA questions, the sponsor provided an updated efficacy report for pivotal study #001 in ERT naïve patients based on antibody status (IgG assay cut-point 40.33%). The results from this study summarizing the primary and secondary efficacy endpoints by dose group and antibody status were provided. The results showed no statistically significant difference between antibody positive and negative patients in the 30 units/kg group for any of the 4 efficacy endpoints assessed (i.e., % change in spleen volume from baseline to last follow up visit; % change in liver volume from baseline to last follow up visit; change in haemoglobin level from baseline to last follow up [g/dL]]; and change in platelet count from baseline to last follow-up [/mm^3]). However, in the 60 units/kg group, antibody negative patients had statistically significantly greater reductions in mean liver volume from baseline to last follow up than antibody positive patients (-31.58% vs 12.6%, p=0.005). In addition, the results for each of the other 3 efficacy endpoints in the 60 units/kg group favoured antibody negative patients compared with antibody positive patients, but the differences were not statistically significant. There was an imbalance in patient numbers in the 60 units/kg group between antibody positive (n=11) and antibody negative patients (n=4), and it is possible that this might have contributed, at least in part, to the observed efficacy differences between the two patient groups.

In the follow-up response to TGA questions, the sponsor provided efficacy data on 5 patients out of 28 who had switched from imiglucerase therapy and were found to have a least one antibody sample during the study (cut-point 40.33%). The descriptive results showed high variability among the 5 patients for each of the 4 efficacy endpoints tested, with the results being generally consistent with the mean results for each of the endpoints from the total 28 patients.

In the follow-up response to TGA questions the sponsor provided an analysis of the correlation (Pearson correlation coefficient) between efficacy outcomes and dose and dose normalized C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for antibody positive and antibody negative patients from study #001. The correlations were inconsistent. No meaningful conclusions can be drawn from this analysis.

In the follow-up response to TGA questions, the sponsor provided an analysis of change from Day 1 to Week 38 in dose normalized pharmacokinetic parameters and antibody status in patients in study #011. The descriptive statistics showed that at Day 1 there were no notable differences in mean dose normalized pharmacokinetic parameters between antibody positive and negative patients. However, at Week 38, the mean dose normalized pharmacokinetic parameters for C_{max}, AUC_{0-t}, and AUC_{0-inf} were lower in the antibody negative group than in the antibody positive group. There was no evidence from this descriptive analysis that antibody positive status reduces exposure to taliglucerase alfa at Week 38 compared with antibody negative status.

12.3.5. Population PK-PD analysis

12.3.5.1. Overview

The sponsor's response to the TGA consolidated request for information included an Executive Summary Report (dated 14 November 2011) of a "Population pharmacokinetic-pharmacodynamic analysis of Taliglucerase alfa to assess the required sensitivity of assays detecting neutralizing antibodies [nAbs]".

In general, immunogenicity can be a significant problem in the clinical use of therapeutic proteins. The development of an immune response against a therapeutic protein can affect PKs by increasing clearance, and/or impairing efficacy due to reduced or abnormal binding to the pharmacological target. There is a concern that taliglucerase alfa nAbs might block either enzymatic activity or target cell uptake by binding to taliglucerase alfa and affecting the efficacy of the drug.

PK data were collected from ERT naïve patients from study #001 and individual concentration – time profiles were used to develop a PK model for taliglucerase alfa. The study included 15 patients from group I and 16 patients from group II who received 30 units/kg and 60 units/kg of taliglucerase alfa, respectively, as an IV infusion every two weeks for 9 months. PK data were calculated from blood samples collected following the first and final doses.

PD data were derived from ERT naïve patients at 2 different dose levels (30 units and 60 units/kg) from studies #001 and #003. Clinical efficacy was assessed by the evaluation of multiple parameters, such as changes in spleen volume, haemoglobin level, platelet counts and liver volume. Other efficacy endpoints included biomarkers (chitotriosidase or PARC/CCL18) and exploratory endpoints of bone mineral density (DEXA) and Quantitative Chemical Shift Imaging (QCSI).

Population PK/PD models to describe the possible relationship between taliglucerase alfa exposure and PD endpoints were developed and fitted to the data by means of non-linear mixed-effects modelling using NONMEM software package (version 7), and analysed using the statistical software package S-Plus (version 8). The first-order conditional estimates (FOCE) approximation method was used for parameter estimation and the INTERACTION item was used in NONMEM, which takes the presence of an interaction between the two levels of random-effects into account. The description of the PK-PD methods was comprehensive and consistent with the TGA adopted guidelines relating to the reporting of population PK analyses (CHMP/EWP/185990/06).

12.3.5.2. Results

A two-compartment disposition model with zero order infusion as input and first-order elimination process was developed to describe the concentration-time profile of taliglucerase alfa. No dose or time-variant pharmacokinetics were observed. Using the formulae from

receptor-binding theory, the total nAb concentration necessary to reduce exposure following a dose of 60 units/kg to that following a dose of 30 units/kg (i.e., 50% reduction in exposure) was calculated for a range of dissociation constants (KD) assessing the affinity of nAb for taliglucerase alfa. The total neutralizing antibody concentration calculated in this way was stated by the authors of the analysis to provide a measure of the required sensitivity of an assay to detect neutralizing antibodies. Representative results from the model indicated that the 60 units/kg dose would be reduced in efficacy to that of a 30 units/kg dose by 1.86 μg/mL of nAb of 10 nM affinity (KD), 8.06 μg/mL of nAb of 50 nM affinity (KD), 39.06 μg/mL of nAb of 250 nM affinity (KD), or 310.31 μg/mL of nAb of 2000 nM affinity (KD).

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

It is considered that the totality of the efficacy data provided in the original submission, the sponsor's response to the TGA consolidated request for further information and the follow-up response to TGA questions have satisfactorily established the benefits of taliglucerase alfa for the treatment of Gaucher Disease (GD).

The clinical study program (studies #001, #002, #003, #004, #005) includes efficacy data following treatment with taliglucerase alfa from about 57 patients at 9 months, 31 patients at 12 months, and 26 patients at 24 months. These patient numbers are small, but are considered adequate for this particular orphan drug (i.e., taliglucerase alfa). The efficacy data show that taliglucerase alfa can achieve and maintain meaningful clinical benefits in patients naïve to ERT treatment, and maintain clinical benefits in patients treated with imiglucerase (approved for the treatment of GD) after switching to taliglucerase alfa.

The original data from completed pivotal study #001 in 31 ERT naïve patients showed that treatment with taliglucerase alfa at doses of 30 units/kg (n=15) and 60 (n=16) units/kg achieved meaningful clinical benefits following 9 months treatment. Furthermore, the updated efficacy data from ongoing extension study #003 demonstrated that the benefits in ERT naïve patients achieved after 9 months treatment with taliglucerase alfa were maintained for at least 24 months in 26 patients continuing from study #001 (30 units/kg, n=12; 60 units/kg, n=14).

In addition, the updated efficacy data from supportive study #002, showed that the clinical benefits achieved in patients following imiglucerase treatment for at least 2 years could be maintained for 9 months after switching to taliglucerase alfa (n=25). Furthermore, the updated efficacy data from ongoing extension study #003 showed that the benefits observed after 9 months treatment with taliglucerase alfa after switching from imiglucerase could be maintained for at least another 3 months (i.e., a total of 12 months) in 7 patients.

In the original submission, the single pivotal study (#001) showed that adult patients (n=31) with GD treated with taliglucerase alfa had statistically significant improvements from baseline at 9 months in spleen volume, liver volume, haemoglobin level, and platelet count. The efficacy results observed in the pivotal study were supported by the efficacy data from the ongoing switch-over study (#002), and the ongoing extension study (#003). In addition, the data from the historical analysis suggested that taliglucerase alfa and alglucerase/imiglucerase had similar efficacies as regards reductions in spleen and liver volumes, and increases in haemoglobin levels and platelet counts. Furthermore, a post-hoc analysis of the efficacy outcomes at 12 months in 26 patients from the pivotal study #001 showed that taliglucerase alfa achieved consensus therapeutic goals. The updated efficacy data for ongoing supportive studies #002 and #003 included in the sponsor's consolidated response of 20 December 2011 are considered to provide satisfactory support to the efficacy findings observed in the pivotal study (#001).

The updated report for ongoing supportive study #002 included efficacy data on patients treated with taliglucerase alfa for 9 months after switching from imiglucerase and showed that there was no clinical deterioration over this period of time in the efficacy parameters of spleen and liver volume, haemoglobin level, platelet count and chitotriosidase activity. The updated report included information on 28 treated patients (2 of whom were aged less than 18 years), and provided 9 month efficacy data on 25 of these patients. At the time of the database freeze (1 May 2011), the mean±SD taliglucerase dose for the 28 treated patients was 29.2±15.8 units/kg, and the median dose was 25.5 units/kg (range: 11 to 60 units/kg). Study #002 plans to enrol 30 patients and there are now 9 month efficacy data on 83.3% (n=25) of the planned number.

No primary efficacy variable was selected for analysis in study #002. The efficacy outcome of interest was whether patients stabilized on imiglucerase deteriorate clinically during treatment after switching to taliglucerase alfa. Clinical deterioration was primarily assessed 9 months after switching by changes in spleen volume, liver volume, haemoglobin level, and platelet count. The efficacy outcomes of taliglucerase alfa following switching from imiglucerase were:

- The mean±SD spleen volume (n=20) decreased from 822.4±603.7 mL at Baseline to 749.3±559.7 mL at Month 9. This represented a reduction in mean±SD spleen volume of 7.6±13.3%. The mean±SD spleen volume was 5.5±4.8 times normal at Baseline and 5.1±5.1 times normal at Month 9. No clinical deterioration as assessed by change in spleen volume at 9 months was observed in 19 (95%) patients, while clinical deterioration was reported in 1 (5%) patient.
- The mean±SD liver volume (n=23) decreased from 1857.4±440.0 mL at Baseline to 1785.8±423.7 mL at Month 9. This represented a mean±SD reduction in liver volume of 3.5±8.1%. No clinical deterioration as assessed by change in liver volume at 9 months was observed in 22 (95.7%) patients, while clinical deterioration was reported in 1 (4.3%) patient. The mean±SD liver volume as multiples of normal liver volume was 1.0±0.2 at baseline and 0.9±0.2 at Month 9.
- The mean haemoglobin level remained stable over the 9 months of treatment and the mean level at Month 9 (n=26) was consistent with the mean level at baseline (n=28). No patients (n=26) were reported to have experienced clinical deterioration at Month 9 based on haemoglobin changes.
- The mean platelet count remained relatively stable over the 9 months of treatment, and the mean±SD count at Month 9 (n=26) was 1.0±21.3% lower than at baseline. No clinical deterioration based on platelet counts at 9 months was observed in 24 patients (92.3%), while clinical deterioration was reported in 2 (7.7%) patients.

The updated report for the extension study #003 included a total of 44 patients aged 19 to 74 years, consisting of 26 patients who continued from study #001 and 18 patients who continued from study #002. In the updated report, there were efficacy data on 31 patients (study #001, n=26; study #002, n=10) at Month 3 (i.e., after 12 months treatment), and on 26 patients (all from #001) at Month 15 (i.e., after 24 months treatment). In study #003, treatment with taliglucerase treatment is planned to continue for at least 15 months, but for no more than 30 months, or until marketing approval has been granted by the appropriate regulatory authority (presumably the FDA or EMEA), whichever is earlier.

No primary efficacy outcome was specified in study #003. The efficacy outcome of interest was whether patients deteriorate clinically during treatment with taliglucerase alfa as assessed by changes in spleen volume, liver volume, haemoglobin level, and platelet count.

- In patients from study #001 who continued blinded treatment in the extension study, the mean±SD reduction in spleen volume from baseline at Month 15 was 40.5±9.6% in the 30 units/kg group (n=12), and 54.9±12.8% in the 60 units/kg group (n=14); p<0.001. There were 2 patients with Month 27 data (36 months treatment) in whom mean reductions from

baseline in spleen volume were 44.7% (30 units/kg) and 56.1% (60 units/kg). In patients with relevant data (n=7) from study #002 who continued in the extension study, the mean±SD reduction in spleen volume from baseline was 10.7±12.4% at Month 3.

- The updated study report also included an analysis of change in spleen volume from screening until last follow-up visit based on MRI results. In patients from study #001 who continued in the extension study, the mean±SD reduction in spleen volume was 41.3±9.5% in the 30 units/kg group (n=12) after a mean±SD duration of 26.5±4.5 months of follow-up, and 55.8±12.3% in the 60 units/kg group (n=14) after a mean±SD duration of follow-up of 25.6±4.0 months. In patients from study #002 who continued treatment in the extension study and had relevant data (n=15), the mean±SD reduction in spleen volume was 8.0±12.6% after a mean±SD duration of follow-up of 16.1±4.2 months.
- In patients from study #001 who continued treatment in the extension study, the mean±SD reduction in liver volume from baseline at Month 15 was 20.6±6.9% in the 30 units/kg group (n=12) and 17.5±13.3% in the 60 units/kg group (n=14); p=0.473. There were 2 patients with Month 27 data (36 months treatment) in whom mean reductions in liver volume from baseline were 22.3% (30 units/kg) and 14.4% (60 units/kg). In patients from study #002 who continued in the extension study and had relevant data (n=8), the mean±SD reduction in spleen volume from baseline was 4.2±5.8% at Month 3.
- The updated report also included an analysis of change in liver volume from baseline screening until last follow-up visit based on MRI results. In patients from study #001 who continued in the extension study, the mean±SD reduction in liver volume from baseline was 21.5±6.3% in the 30 units/kg (n=12) group after a mean±SD duration of 26.5±4.5 months of follow-up, and 17.9±13.2% in the 60 units/kg group (n=14) after a mean±SD duration of follow-up of 25.9±4.0 months. In patients from study #002 who continued in the extension study and had relevant data (n=16), the mean±SD reduction in spleen volume was 2.0±7.5% after a mean±SD duration of follow-up of 15.9±4.1 months.
- Patients from study #001 who continued treatment in the extension study showed mean increases in haemoglobin levels from baseline at Months 3, 9 and 15. At Month 15, the mean±SD increase in haemoglobin level from baseline was 1.3±1.7 g/dL in the 30 units/kg group (n=11), and 2.4±2.3 g/dL in the 60 units/kg group (n=14); p=0.207. In patients from study #002 who continued treatment in the extension study and who had relevant data, there were no meaningful changes in haemoglobin levels from baseline at Month 3 (n=12) or Month 9 (n=10).
- Patients from study #001 who continued treatment in the extension protocol showed mean increases in platelet counts from baseline at Months 3, 9, and 15. At Month 15, mean±SD increases in platelet counts from baseline were 28,433±31,996 /mm^3 in the 30 units/kg group (n=12), and 72,029±68,157/mm^3 in the 60 units/kg group (n=14); p=0.054. In patients from study #002 who continued treatment in the extension study and who had relevant data, there were no meaningful changes in platelet counts at Month 3 (n=12) or Month 9 (n=9).

The effect of anti-taliglucerase antibodies on efficacy was investigated in study #001. In the 30 units/kg group there were no statistically significant differences between antibody positive and antibody negative patients for the primary and secondary efficacy outcome measures. However, in the 60 units/kg group, antibody negative patients had statistically significantly greater reductions in mean liver volume from baseline to last follow up than antibody positive patients (approximately 32% vs 13%, p=0.005). Furthermore, the mean reduction in liver volume in the antibody positive group was < 20% and, consequently, is unlikely to be clinically significant. The results for each of the 3 other efficacy endpoints in the 60 units/kg group favoured antibody negative patients compared with antibody positive patients, but the differences were not statistically significant. Interpretation of the results in the 60 units/kg are complicated by small

patient numbers, and an imbalance in patient numbers between the antibody positive group (n=11) and the antibody negative group (n=4). In addition, the results for the 60 units/kg group are inconsistent with the results for the 30 units/kg group. Overall, the limited available data suggest that efficacy is unlikely to significantly differ between antibody positive and negative patients. However, this matter warrants further investigation.

13.2. Second round assessment of risks

It is considered that the safety data provided in the original submission, the sponsor's response to the TGA consolidated request for further information and the follow-up response to TGA questions have satisfactorily established the safety of taliglucerase alfa for the treatment of GD. The safety data are based on 1 completed Phase 3 pivotal study (#001), and 4 ongoing Phase 3 supportive studies (#002, #003, #004, #005). In addition, safety data were available on patients from multinational ongoing Compassionate Use Programs, and a small Phase 1 study in healthy volunteers.

The safety dataset from the Phase 3 clinical studies includes 121 patients treated with taliglucerase alfa for GD as of 1 May 2011. Of these 121 patients, 96 have been treated for 6 months, 59 for 12 months, 33 for 18 months, and 24 for 12 months. These patient numbers are small, but are considered adequate for the safety assessment of this particular orphan drug (i.e., taliglucerase alfa).

Of the 121 patients, 67 (55.4%) were male and 54 (44.6%) were female, and nearly all were Caucasian (96.7%, n=117), with the remainder being Native American (n=1) or Other (n=3). Of the 121 patients, 13 (10.7%) were aged < 18 years, 101 (83.5%) were aged 18 to 65 years, and 7 (5.8%).

Of the 121 patients, 104 (86.0%) experienced at least 1 all causality AE and the majority of these events were classified as mild/moderate in intensity. There were 52 (43.0%) patients reported by the investigators as experiencing at least one AE considered to be related to treatment. There were no deaths reported in the 121 patients, and at least one SAE was reported in 10 (8.3%) patients.

13.2.1. Commonly reported adverse events

The most commonly reported AEs (≥ 5%) in the 121 patients were nasopharyngitis (21.5%), arthralgia (18.2%), headache (18.2%), upper respiratory tract infection (15.7%), pain in extremity (11.6%), cough (10.7%), fatigue (9.9%), back pain (9.9%), vomiting (8.3%), pain (7.4%), pharyngolaryngeal pain (7.4%), pruritus (7.4%), diarrhoea (6.6%), pyrexia (6.6%), influenzae (6.6%), pharyngitis (6.6%), sinusitis (6.6%), nausea (5.8%), dizziness (5.8%), epistaxis (5.8%), gastroenteritis (5.8%), bone pain (5.0%), and hypertension (5.0%)

13.2.2. Serious adverse events

SAEs (11 events) were reported in 10 (8.3%) patients. No pattern of SAEs was observed. The reported SAEs were: head trauma (1 patient); autoimmune thrombocytopenia (1 patient); pain due to haemangioma in left knee and pulmonary embolism (1 patient); multiple tooth extraction (1 patient); epistaxis (1 patient); nephrolithiasis (1 patient); prolapsed rectum bladder and cervix (1 patient); traumatic fracture of four ribs and pneumothorax (1 patient); percutaneous stone removal (1 patient); pre-planned right knee replacement for management of right gonarthrosis (1 patient); gastroenteritis (1 patient). The only SAE considered by the investigator to be treatment related was gastroenteritis in the paediatric study (#005).

13.2.3. Treatment discontinuations

Treatment discontinuation had occurred in 24 (19.8%) patients as of 21 September 2011. In study #001, 2 patients discontinued due to an AE (hypersensitivity reaction): 1 treated with 30 units/kg and 1 treated with 60 units/kg. In addition, 4 patients (1 from study #002, and 3 from

study #004) withdrew voluntarily or for "other reasons", but details of the discontinuations include mention of infusion associated events in 3 cases and generalized body stiffness in 1 case. In 1 additional patient (study #003 from study #001), the investigator recommended discontinuation after 38 infusions in order to assess a possible allergic reaction. Among the other patients, reasons included travel or scheduling problems (7 patients), pregnancy (1 patient), and "other" (9 patients).

13.2.4. Hypersensitivity adverse events

AEs of particular interest relate to disorders mediated by the immune system (i.e., hypersensitivity reactions and infusion related reactions). Hypersensitivity type I (acute) events were identified in 18 (14.9%) patients (73 all causality events), and in 15 (12.4%) of the 18 patients the events were judged by investigators to be treatment related (56 treatment related AEs). The most commonly reported hypersensitivity type I AE was pruritus (9 patients; 7.4%), followed by "hypersensitivity" (5 patients; 4.1%) and pruritus generalized (2 patients; 1.7%). Each of the following hypersensitivity type I AEs were reported in 1 patient (eye swelling, lip swelling, face oedema, periorbital oedema). In study #001, 4/16 patients in the 60 units/kg group reported 15 AEs related to hypersensitivity compared with 2/16 patients in the 30 units/kg group reporting 5 hypersensitivity type I AEs.

Of the 15 (12.4%) patients reported by investigators as having treatment related hypersensitivity type I events, 9 patients required no intervention or only temporary intervention with interruption of the infusion and/or medication to manage the event (6 pruritus, 1 generalized pruritus, 1 face oedema, 1 lip swelling), 4 patients required discontinuation of the infusions (3 hypersensitivity, 1 eye swelling), and 2 patients continued infusions with pre-treatment medications (2 hypersensitivity). Of the 4 patients discontinuing, 3 discontinued because of hypersensitivity events (in 2 patients these events occurred with the first infusion), and 1 patient experienced multiple repeated events of eye swelling not responding to pre-treatment and chose to discontinue taliglucerase alfa and return to imiglucerase.

Hypersensitivity type II-IV (chronic) events were reported in 5 (4.1%) patients. Of these 5 patients, 4 (12.5%) patients came from study #001 (2 in each of the 30 units/kg and 60 units/kg groups) and 1 (3.6%) patient came from study #002. The hypersensitivity type II-IV (chronic) events were reported as mild or moderate in intensity, except for 1 patient in the 60 units/kg dose group (study #001) who experienced a very severe autoimmune thrombocytopaenia (reported as a non-treatment related SAE). Non treatment related contact dermatitis was reported in 2 patients in study #001 (1 in each of the 30 units/kg and 60 units/kg dose groups). The 1 patient in study #002 was reported to have experienced non treatment related arthritis (knee inflammation) associated with gonarthrosis.

13.2.5. Infusion reactions

Infusion reactions occurring during the infusion or within 2 hours after the completion of the infusion occurred commonly with 45 (37.2%) patients experiencing 168 AEs of which 134 were considered treatment related. The infusion reactions occurring during the infusion or within 2 hours of completion of the infusion in ≥ 2% of patients were headache (5.0%), hypersensitivity (4.1%), nausea (3.3%), vomiting (3.3%), pruritus (3.3%), flushing (3.3%), chest discomfort (2.5%), infusion related reaction (2.5%), and throat irritation (2.5%).

13.2.6. Bone events

Bone events were of particular interest. A total of 10 (8.3%) patients experienced 15 bone events, the most common of which were bone pain (6 patients), followed by musculoskeletal pain, and bone infarction (1 patient).

13.2.7. Prolonged activated partial thromboplastin time (aPPT)

Prolonged aPPT is a feature of GD. In the clinical studies, aPPT reported as an AE occurred in 1 patient with an onset between 2 to 24 hours post-infusion. The AE was considered to be mild (Grade 1) and did not require treatment. The taliglucerase alfa dose was not changed and the patient recovered from the event. Additionally, in the ERT naive study (#001) 6 patients in the 30 units/kg group and 4 patients in the 60 units/kg group experienced prolonged aPTTs that were not reported as AEs. In the switchover study (#002), 9 subjects experienced prolonged aPTTs that were not reported as AEs.

13.2.8. Anti-taliglucerase antibodies

The most significant difference between the original and updated safety data relate to the markedly greater proportion of patients reported with anti-taliglucerase alfa antibodies in the updated safety data. The difference appears to be due to the use of more sensitivity assays for detecting anti-taliglucerase alfa IgG antibodies in the updated safety data.

The incidence of anti-taliglucerase alfa IgG antibodies was investigated in studies #001, #002, and #003. Using the IgG assay cut-point of 40.33%, the number of patients who were positive at any time point (including those positive at baseline only or positive at baseline and without significant increase in titre) for studies #001, #002 and #003 were 59.4% (19/32), 19.2% (5/26) and 35.6% (16/45), respectively. Of the 26 patients entering extension study #003 from study #001 and receiving a total of 24 months treatment, 13 (50%) patients were found to have positive test results for IgG antibody at least at one visit. Of the 18 patients entering extension study #003 from study #002 and receiving 12 months treatment, 3 (16.6%) patients were IgG positive at least at one visit.

The proportion of patients with antibodies was notably higher in study #001 in ERT naïve patients (59.4%) compared with study #002 in ERT experienced patients (19.2%). It is likely that ERT experienced patients treated in study #002 were relatively resistant to developing anti-taliglucerase antibodies compared with ERT naïve patients treated in study #001. In study #002, patients were switched from imiglucerase to taliglucerase alfa, but patients with infusion reactions suspected to be allergic in nature to Cerezyme or Ceredase [alglucerase] or receiving premedication to prevent infusion reactions were excluded from the study.

Irrespective of antibody status, the overall incidence of hypersensitivity type I (acute) events in the ERT naïve population (28%, 9/32) was similar to that in the ERT experienced population (27%, 7/26). However, based on data using the IgG assay cut-point of 52.97%, the overall incidence of hypersensitivity type I (acute) events in the antibody positive population was 44% (8/18) compared with 20% (8/40) in the antibody negative population. This suggests that patients who develop anti-taliglucerase antibodies are likely to be at a greater risk for hypersensitivity type I (acute) reactions compared with patients who remain antibody negative.

In 21 antibody positive patients (52.97% cut-point) experiencing hypersensitivity type I (acute) AEs (all causality) and infusion related AEs (all causality), 13 continued treatment with no intervention, 3 discontinued treatment follow “hypersensitivity” events, 2 continued treatment with use of antihistamines for rash or pruritus, 2 subjects experiencing infusion related reactions continued treatment with OTC medication for headaches, and 1 subject who experienced “hypersensitivity” continued treatment with pre-treatment regimens.

In the available safety data, neutralizing antibodies have been found in 3 (5.2%) patients using the in vivo assay, but all 3 patients were found to be negative for neutralizing antibodies using the cell based assay.

13.2.9. Other safety issues

It is known that intermittent elevations of liver enzymes can occur in patients with GD without co-existing morbidities. Review of the available data has shown that the elevations in ALT or AST observed in the current dataset are mild and explainable, either due to concomitant

medication or illness. All patients with liver function test abnormalities showed either clinical improvement or clinical stability while on taliglucerase treatment. Increased alanine aminotransferase was reported as an AE in 3/121 (2.5%) patients.

There were 4 (3.3%) patients who developed abnormal ECHO findings during treatment with taliglucerase alfa, none of which were associated with deterioration in cardiac function. The significance of these abnormal ECHO finding are unknown. There were no notable changes in vital signs, ECG findings or pulmonary function tests during treatment with taliglucerase.

13.2.10. Safety issues of general regulatory concern

There were no safety signals in the available data suggesting that taliglucerase alfa is hepatotoxic or has significant adverse effects on the renal, cardiovascular, or haematological systems.

13.2.11. Risks in special patient groups

Taliglucerase alfa has been administered to 13 (10.7%) patients younger than 18 years of age (2 to < 18 years) in the clinical study program. No unusual AEs have been observed specifically in paediatric subjects. However, the sample size in paediatric patients is too small to conclude that there are no significant differences in the safety profile of taliglucerase alfa in paediatric and adult patients. Paediatric patients are dosed on a unit/kg basis in the same way as adults using the standard iv formulation, and there are no plans to develop a specific paediatric formulation.

No conclusions can be drawn about safety in patients aged > 65 years: the 121 patients in the clinical safety population included only 7 (5.8%) in this age group. There are no apparent differences in the AE profiles between male and female patients. No conclusions can be drawn about safety in different racial groups as almost all patients in the clinical study program have been Caucasian.

13.2.12. Safety data from the Compassionate Use Program

As of 1 May 2011, there were 212 patients enrolled in Compassionate Use Programs, and safety data were available on 18 of these patients. In these 18 patients there have been 49 AEs reported, and 16 of the patients have experienced hypersensitivity reactions. There has been 1 reported death (pneumonia, lung disorder, tuberculosis) considered to be unrelated to treatment, and other SAEs have been reported in 3 patients including hypersensitivity in 1, anaphylactoid reaction in 1, and anaphylactic shock, dyspnoea, and cyanosis in 1. Treatment has been discontinued in 12 patients, and in all of these patients the reported AEs could be characterized as hypersensitivity reactions.

13.2.13. Unresolved safety issues

There is an unresolved safety issue associated with the potential for taliglucerase alfa to induce antibodies to plant sugars (the sponsor reports that almost all commercial batches contain xylose and some contain fructose). The sponsor acknowledges that “issues of pre-existing antibody and immunogenicity of plant glycans were not sufficiently discussed in the application” and has undertaken to evaluate this matter. The sponsor expects to complete the evaluation of anti-taliglucerase antibodies generated in patients in an attempt to determine whether these have specificity for the plant-derived glycans on taliglucerase alfa or are primarily against the protein core of the molecule by the end of July 2012. In any event, even if specific antibodies to plant sugars are found in patients treated with taliglucerase alfa it is unlikely that these will result in significant new safety issues. The incidences of hypersensitivity and infusion reactions have now been reasonably well characterized in studies #001, #002, and #003 in antibody positive and negative patients. Consequently, if anti-plant sugar antibodies are found in antibody positive or negative patients it is unlikely that this will change the known safety profiles of the two patient groups.

There are no safety data on the use of taliglucerase alfa in patients with pre-existing liver, renal or cardiovascular disease. There are no safety data relating to potential drug-drug interactions involving taliglucerase alfa. There are limited safety data in patients aged < 18 years, and no safety data on patients aged > 65 years.

13.3. Second round assessment of benefit-risk balance

It is considered that benefit-risk balance of taliglucerase alfa for the treatment of GD is acceptable. The submitted data demonstrate that clinically meaningful benefits in ERT naïve patients are achieved after 9 months treatment with taliglucerase alfa and that these benefits can be maintained with treatment for at least a further 15 months. In addition, the submitted data demonstrate that patients stabilized on imiglucerase and switched to taliglucerase can maintain clinical benefits obtained with imiglucerase for at least 12 months with taliglucerase treatment.

The main risks associated with taliglucerase alfa relate to the high incidence of infusion related reactions with 37.2% of patients experiencing a reaction during or within 2 hours after completion of the infusion. Hypersensitivity type I (acute) reactions (all causality) occurred in 14.9% of patients, and in 12.4% of patients the reactions were considered by the investigators to be treatment related. The available data suggests that hypersensitivity type I (acute) reactions occur more frequently in antibody positive patients (44%) than in antibody negative patients (20%). The submitted data indicate that infusion and hypersensitivity type 1 (acute) reactions occurring in both antibody positive and antibody negative patients can be satisfactorily managed in the majority of cases by standard treatment methods rather than treatment discontinuation. No deaths have been reported due to hypersensitivity reactions, although safety data from the Compassionate Use Programs indicates that there has been 1 report of anaphylactic shock.

14. Second round recommendation regarding authorisation

It is recommended that taliglucerase alfa be approved:

> *"for long-term enzyme replacement therapy for the treatment of systemic symptoms in patients with a confirmed diagnosis of Gaucher disease".*

It is recommended that the following should be conditions of registration:

- submission of the final clinical study reports from studies #002, #003, #004, and #005 on completion of these studies; and
- submission of the results relating to the sponsor's attempt to evaluate anti-taliglucerase antibodies generated in patients to determine whether these have specificity for the plant-derived glycans on taliglucerase alfa or are primarily against the protein core of the molecule.

15. References

15.1. Submitted Studies

- Study P-01-2005: A Phase I, Non-Randomised, Open Label, Single Dose-Escalation Safety Study of Recombinant Human Glucocerebrosidase (prGCD) in Healthy Volunteers.

- Study PB-06-001: A Phase III Multicenter, Randomized, Double-Blind Trial to Assess the Safety and Efficacy of Two Parallel Dose Groups of Plant Cell Expressed Recombinant Human Glucocerebrosidase (prGCD) in Patients with Gaucher Disease.
- Study PB-06-003: A Multicenter, Double-Blind, Extension Trial of Two Parallel Dose Groups of Plant Cell Expressed Recombinant Human Glucocerebrosidase (prGCD) in Patients with Gaucher Disease.
- Study PB-06-002 A Phase 3 Multicenter, Open-label, Switchover Trial to Assess the Safety and Efficacy of Plant Cell Expressed Recombinant Human Glucocerebrosidase (prGCD) in Patients with Gaucher Disease Treated with imiglucerase Enzyme Replacement Therapy.
- Efficacy Historical Comparison and Therapeutic Goals.
- Dose Separation Post-hoc Analysis.
- PB 06-004 Ad Hoc Safety Analysis Report

15.2. Literature References

- Altareseu G, Schiffmann R, CC, Parker CC, et al. Comparative efficacy of dose regimens in enzyme replacement therapy of type I Gaucher Disease. Blood Cells, Molecules, and Disease 2000; 26(4): 285-290.
- Capablo JL, Saenz de Cabezo A, Fraile J et al. on behalf of the Spanish Group on Gaucher Disease Neurological evaluation of patients with Gaucher disease diagnosed as type 1. J Neurol Neurosurg Psychiatry 2008;79:219–222.
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