Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 3

Extract from the Clinical Evaluation Report [2] for taliglucerase alfa rpc

Proprietary Product Name: Elelyso

Sponsor: Pfizer Australia Pty Ltd

Date of CER 2:
First round: 22 July 2013
Second round: 2 January 2014

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
ADA	Antidrug Antibodies
AE	Adverse event
AEM	Adverse Event Monitoring
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CCL 18	Chemokine (C-C motif) Ligand 18 (Pulmonary and Activation-regulated)
CER	Clinical Evaluation Report
CHQ	Child Health Questionnaire
CRF	Case Report Form
CRO	Clinical Research Organization
CSR	Clinical Study Report
DEXA	Dual energy x-ray absorptiometry
ECG	Electrocardiogram
ERT	Enzyme replacement therapy
GD	Gaucher disease
HEENT	Head, Ears, Eyes, Nose, and Throat
HRP	Horse Radish Protein
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MN	Multiples of Normal
PT (MedDRA)	Preferred Term
PFT	Pulmonary function test
SAEs	Serious adverse events
SCS	Summary of Clinical Safety

Abbreviation	Meaning
SOC (MedDRA)	System Organ Class
SRT	Substrate Reduction Therapy
TI	Tricuspid incompetence
U/kg	Units/kilogram

1. Introduction

This is a category 1 application from Pfizer Australia P/L to register a new medicine (taliglucerase alfa rpc) with the trade name ELELYSO for the treatment of Gaucher disease (GD).

Taliglucerase alfa rpc is a recombinant active form of the human lysosomal enzyme, β-glucocerebrosidase, expressed in genetically modified carrot plant root cells. β-Glucocerebrosidase is a lysosomal glycoprotein enzyme that catalyses the hydrolysis of the glycolipid glucocerebroside to glucose and ceramide.

The proposed indication is:

> *ELELYSO is indicated for long-term enzyme replacement therapy for patients with a confirmed diagnosis of Gaucher disease. The manifestations of Gaucher disease may include one or more of the following: splenomegaly, hepatomegaly, anaemia, thrombocytopenia, bone disease.*

1.1. Previous application to register Elelyso

The sponsor's application letter outlines the application history for Elelyso:

> "A Category 1 application for ELELYSO was submitted to the TGA on 4 May 2011 (Submission Number: PM-2011-00478-3-3). The non-clinical and clinical Evaluators recommended approval based on the respective data sets submitted for Module 4 and Module 5. A number of quality related deficiencies were identified by the Biochemistry evaluator, in relation to the Module 3 data set. Pfizer sought to address the quality concerns during the evaluation period; nonetheless, these could not be resolved at that time. Consequently, Pfizer reached a decision to withdraw the application without prejudice on 23 April 2012.
>
> In accordance with pre-submission meeting discussion held between Pfizer and TGA representatives on 8 June 2012, an agreement was reached on the content of a resubmission dossier. During the pre-submission meeting all of the quality concerns were discussed and Pfizer informed the TGA that a dossier with a complete Module 3 to address all of the issues raised would be prepared and submitted. TGA confirmed the resubmission dossier was to contain new and updated data only; no previously data evaluated by the TGA was required".

The re-submission dossier is stated to contain new data to address the deficiencies identified in the initial Module 3 (quality) dossier. In addition, the re-submission dossier includes a new clinical study in paediatric patients located in Module 5. Module 2 (summaries) has been modified to include only those sections relevant to the new data in the re-submission dossier. No Module 4 (nonclinical) was provided in the re-submission dossier, as the sponsor states that the Module 4 content remains unchanged from that initially submitted. No previously submitted or evaluated clinical studies were included in the re-submission dossier.

Only the clinical data in the re-submission are evaluated in this clinical evaluation report; however data from the previous application and presented in clinical evaluation report 1 (CER 1) remain applicable to this application.

2. Clinical rationale

Gaucher disease (GD) is caused by mutations in the glucocerebrosidase hGCD gene. The mutations result in a less active endogenous b-glucocerebrosidase lysosomal enzyme leading to the accumulation of glucocerebroside in the lysosomes of macrophages. The clinical rationale for taliglucerase alfa (rpc) as b-glucocerebrosidase enzyme replacement therapy (ERT) is acceptable.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The re-submission contained the following clinical information:

Module 5

- 3 bioanalytical and analytical validation biopharmaceutical studies.
- 1 clinical efficacy and safety study in paediatric patients with GD.
- Literature references.

Module 1

- Application letter; application forms; proposed Australian Product Information (PI) and package insert; proposed Australian Consumer Medicine Information (CMI); information about the sponsor's experts; orphan drug designation; details of compliance with meetings and pre-submission processes; overseas regulatory status including US prescribing information; statement regarding paediatric development program; Risk Management Plan (RMP), including Australian Specific Annex.

Module 2

- Clinical Overview; 2.7.1.3 Addendum, Immunogenicity Overview; Summary of Clinical Safety (including 5 appendices).

  Comment: The minutes of the Pre-submission meeting between Pfizer and TGA representatives indicates that the main clinical issue relates to the characterization of the potential immunogenicity of the plant-derived glycans (mannose with a1-3 fucose and b1-2 xylose) on taliglucerase alfa. The re-submission includes three biopharmaceutical validation studies for Enzyme-Linked Immunosorbent Assays (ELISAs) relating to assessment of the immunogenicity of the plant-derived glycans. However, none of the assays directly determined the immunogenicity of the glycans on taliglucerase alfa in patients with GD treated with the medicine. The re-submission includes a report prepared by Pfizer assessing the immunogenicity risk of the plant-derived glycans in taliglucerase alfa. This report is identified as "Addendum, Immunogenicity Overview", and is located in the dossier (Module 2 (section 2.7.1.3)). The three biopharmaceutical validation studies have been reviewed, and the "Addendum, Immunogenicity Review" has been examined and relevant information from the review has been incorporated in the evaluation report. The new clinical efficacy and safety study in children (PB-06-005) has been fully evaluated, as has the updated Summary of Clinical Safety (SCS).

3.2. Paediatric data

The re-submission included a decision from the European Medicines Agency (EMA) dated 9 April 2010 agreeing to the sponsor's paediatric investigation plan. The EMA granted the following waivers:

- For GD except acute neuronopathic form: a product-specific waiver for children from birth to less than 2 years on the grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies are not feasible.
- For acute neuronopathic GD: a product-specific waiver for all subsets of the paediatric population (from birth to less than 18 years of age) on the grounds that specific medicinal product is likely to be ineffective.

In addition, the conduct of the following clinical study in patients with GD (except acute neuronopathic) aged 2 years (included) to less than 18 years of age was granted:

- Paediatric study PB-06-005 (double-blind, randomised study): evaluation of the efficacy and safety of 2 doses (30 and 60 U/kg) of taliglucerase alfa in paediatric patients aged from 2 to less than 18 years of age with systemic symptoms and clinical manifestations of Gaucher disease is now complete.

Inclusion of paediatric patients in clinical studies, with protocols for the inclusion of paediatric patients:

- Study PB-06-002 (open-label, switch-over trial) as amended: evaluation of the safety and efficacy of taliglucerase alfa in paediatric patients from 2 years of age with GD (except neuronopathic form) previously treated with imiglucerase is now complete.
- Study PB-06-006 (extension trial) as amended: assessment of the long-term safety and efficacy of taliglucerase alfa in paediatric patients with GD (except neuronopathic form), to be completed by June 2014. This was a de novo study to accommodate children after studies PB-06-002 and PB-06-005.
- Study PB-06-006 (extension trial): assessment of the long-term safety and efficacy of taliglucerase alfa in paediatric patients with GD (except neuronopathic form), to be completed by June 2014.

  Comment: The re-submission included data on 11 patients from the paediatric clinical efficacy and safety study PB-06-005, and the SCS included data on 16 children (11 from study PB-06-005 plus 5 from study PB-06-001).

3.3. Good clinical practice

The sponsor stated that clinical study PB-06-005 in paediatric patients was "conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline".

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

The re-submission included no additional clinical pharmacokinetic studies. However, the re-submission included three biopharmaceutical reports grouped under (clinical) Section 5.3.1.4 of Module 5 (Reports of Bioanalytical Analytical Methods for Human Studies).

4.2. Biopharmaceutical reports

The three biopharmaceutical reports were:

- Report 70-66-027R: ELISA for the detection of antibodies to plant-specific glycans in taliglucerase alfa in human serum.
- Study PCL-11-020: ELISA to compare the binding of anti-taliglucerase alfa antibodies taliglucerase alfa with their binding to imiglucerase.
- Document PCL-12-101(1): Summary of development activities for study #PCL-11-010.

4.2.1. Study PCL-11-020

To support a determination of whether anti-taliglucerase alfa antibodies bind to the protein backbone or to the glycan moieties of taliglucerase alfa the sponsor developed an ELISA-based assay to compare the binding of these antibodies to taliglucerase alfa with their binding to imiglucerase.

[Details of the evaluation of the assay have been redacted from this CER Extract]

Comment: The sponsor states that the study results show that the ELISA can be used for the comparison of anti-taliglucerase IgG antibodies binding to taliglucerase alfa and imiglucerase in human serum samples. Furthermore, the sponsor concluded "[m]ost samples … that bound taliglucerase alfa also bound imiglucerase, suggesting that the samples contain antibodies specific to epitopes common to both taliglucerase alfa and imiglucerase. Because of the high primary and three dimensional structure similarity between these therapeutics, these antibodies are, most likely binding to the protein backbone".

The results showed binding to both taliglucerase alfa and imiglucerase occurred in samples from subjects who had not been exposed to the products (i.e., healthy subjects and ERT-naïve GD patients tested prior to treatment), but was more prominent for taliglucerase alfa. However, binding was similar for the two products in patients with GD who had been previously treated with imiglucerase but not with taliglucerase alfa. Binding was more prominent to taliglucerase alfa than to imiglucerase in ERT-naïve GD patents following treatment with taliglucerase alfa, but similar for the two products in patients who had switched from imiglucerase to taliglucerase alfa. The results suggest that taliglucerase alfa is likely to be more immunogenic than imiglucerase in ERT-naïve patients with GD, while the immunogenicity of the two products is likely to be similar in ERT-experienced patients. The results of this study can not exclude the possibility that the difference in antibody binding between taliglucerase alfa and imiglucerase is due, at least in part, to binding to plant-specific glycans on taliglucerase alfa or to binding to shared epitopes that are more highly expressed or exposed on taliglucerase alfa compared with imiglucerase.

4.2.2. Document #PCL-12-010(1)

The objective of this study was to provide supporting data for experiments conducted during the development of the assay described in validation report 70-66-027R. The glycan analysis results described in this study confirmed that horse-radish protein (HRP) is appropriate for use as the competitor in the assay in order to demonstrate antibody specificity to the plant glycan structures on taliglucerase alfa.

[Details of the evaluation of the assay have been redacted from this CER Extract]

Comment: The results show that anti-taliglucerase alfa antibodies are not reactive with the plant glycan structures on HRP. Consequently, the sponsor infers that anti-taliglucerase alfa antibodies are not reactive with the plant glycan structures in taliglucerase alfa due to the structural similarities between the plant glycans in taliglucerase alfa and HRP. The study provided indirect evidence that anti- taliglucerase alfa might not react with the plant glycans in taliglucerase alfa.

4.2.3. Report 70-66-0272R

The objective of this study was to validate the performance of an ELISA for the detection of antibodies to plant-specific glycans that are present on taliglucerase alfa in human serum.

[Details of the evaluation of the assay have been redacted from this CER Extract]

Comment: The report concluded that "data obtained during this validation study were considered acceptable and indicate that this procedure can be used for the detection of antibodies specific to plant glycans on taliglucerase alfa in human serum". Of particular note is the relatively high prevalence of antibodies to plant glycans on taliglucerase alfa in the serum of healthy subjects. However, there were no data in the report relating to antibodies to plant glycans on taliglucerase alfa in serum from patients with GD treated with the product. The sponsor should explain why patients with GD were not tested.

4.2.4. Evaluator's comments on the three validation reports

None of the three reports included data on antibodies specific to plant glycans on taliglucerase alfa in patients with GD treated with the product. Study report PCL-11-021 suggests that the majority of anti-taliglucerase alfa antibody activity is likely to be specific for the protein backbone of taliglucerase alfa, with the minority of the reactivity being specific for epitopes that are either unique to taliglucerase alfa (e.g., plant glycan structures) or are more highly expressed or exposed on taliglucerase alfa compared with imiglucerase. Study report PCL-12-010(1) showed that anti-taliglucerase alfa antibodies are highly cross-reactive with imiglucerase, which has extensive structural and sequence homology to taliglucerase alfa but lacks the plant glycan structures. Study report 70-66-027 suggests that a notable number of

healthy human serum samples test "positive" for antibodies specific to plant glycans on taliglucerase alfa (8.4% [12/143] excluding outliers; and 15.4% [24/156] including outliers]). This suggests that healthy subjects can develop antibodies to naturally occurring plant glycans (presumably in food) identical or similar in structure to those on taliglucerase alfa.

5. Pharmacodynamics

No new data.

6. Dosage selection for the pivotal studies

The dose of taliglucerase alfa (30 or 60 units/kg) for paediatric patients aged 2 to <18 years (study PB-06-005), was selected based on the safety data from the pivotal, Phase III study (PB-06-001) in adult patients with Gaucher disease who received either 30 or 60 units/kg.

7. Clinical efficacy

7.1. Study PB-06-005 (paediatric population)

7.1.1. Study design, objectives, locations and dates

Study PB-06-005 was a Phase IIIb, multi-national, multi-centre, double-blind, clinical study designed to assess the efficacy and safety of taliglucerase alfa in previously untreated patients with Gaucher disease aged 2 to <18 years. Patients were randomized to taliglucerase alfa (30 or 60 units/kg) administered by intravenous (IV) infusion every 2 weeks for 12 months, with an option to continue beyond 12 months. The study design and schedule of assessments are summarized in the clinical study report (CSR).

The study was undertaken in 3 centres from 3 countries (Israel, South Africa, and Paraguay). The first patient was enrolled on 11 October 2010 and the last patient completed on 10 April 2012. The clinical study report was released on 30 August 2012, and the date of the modified report included in the re-submission was 27 September 2012. The study was conducted in accordance with the ethical principles of Good Clinical Practice (GCP), according to the International Conference on Harmonization (ICH) Guideline. The study was sponsored by Protalix Biotherapeutics, Israel.

The efficacy objectives were to assess the efficacy of taliglucerase alfa in patients between 2 to <18 years of age with GD, as measured by the primary, secondary and exploratory efficacy variables (see Section 7.1.4, below).

7.1.2. Inclusion and exclusion criteria

Inclusion criteria (all of the following):

1. Males and females, between 2 years and <18 years of age.
2. Diagnosis of Gaucher disease with leukocyte acid β-glucosidase activity level ≤30% of the mean activity of the reference range for healthy patients.
3. Patients who have not received ERT in the past or who have not received ERT in the past 12 months and had a negative anti-glucocerebrosidase assay assessment.
4. Patients who have not received SRT in the past 12 months.
5. Patients whose clinical condition, in the opinion of the investigator, required treatment with ERT.

Exclusion criteria (any of the following):

1. Currently taking another investigational drug for any condition.
2. Presence of neurological signs and symptoms characteristic of Gaucher disease with complex neuronopathic features other than long standing oculomotor gaze palsy.
3. Presence of unresolved anaemia due to iron, folic acid or vitamin B12 deficiency.
4. Previous hypersensitivity reaction to Cerezyme® (imiglucerase) or Ceredase (alglucerase)
5. History of allergy to carrots.
6. Presence of HIV and/or HBsAg and/or hepatitis C infections.
7. The patient's parent(s) or legal guardian(s) are unable to understand the nature, scope and possible consequences of the study.
8. 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.

Removal of patients from therapy or assessment (any of the following):

1. patients experiencing two or more Grade 3 or one or more Grade 4 toxicities considered by the investigator to be associated with taliglucerase alfa treatment (WHO Common Toxicity Criteria);
2. patients who experienced progressive hypersensitivity or severe hypersensitivity were treated appropriately and withdrawn from the study;
3. patients who requested treatment discontinuation; and
4. investigator felt that it was not in the best interest of the patient to continue treatment and/or if investigator believed the patient could no longer comply with the requirements of the study.

If circumstances prevented the patient from completing all visits, every attempt was made to complete all procedures listed for Visit 27. The protocol specified that withdrawn patients were not to be replaced.

7.1.3. Study treatments

Patients were randomized to treatment with taliglucerase alfa 30 or 60 units/kg, and received an intravenous (IV) infusion of taliglucerase alfa every two weeks for 12 months. Treatment was initiated in the clinic and patients who tolerated the infusions well for 3 months were eligible for home therapy. At the end of the 12 month treatment period, eligible patients were offered enrollment in an extension study if taliglucerase alfa was not commercially available.

For initial IV infusions, taliglucerase alfa was administered at a rate of 1.0 mL/minute over 2 hours (the total volume to be prepared and infused was 100 mL + 20 mL saline flush). Tolerability was determined clinically during the infusion and for 1 hour post-infusion in the clinic, with follow-up by telephone the day after the first infusion. If the initial rate of infusion was well tolerated the infusion rate could be increased up to 2.0 mL/minute (120 mL/hour) to deliver the 100 mL volume of reconstituted enzyme plus 20 mL saline flush over 1 hour for all subsequent dosing.

The study protocol allowed certain medications to be used during the study. These included treatments for hypersensitivity/anaphylaxis; anaemia; bone disease; and pain. Medications with the potential to interfere with the evaluation of efficacy were excluded throughout the trial. Other ERT medicines and SRT medicines were strictly prohibited during the study.

Comment: The dosing regimen used in the study is the same as that specified in the proposed PI for the initial treatment of GD.

7.1.4. Efficacy variables and outcomes

7.1.4.1. Primary efficacy variable

The primary efficacy variable was median percent change in haemoglobin levels from baseline, and the interquartile range of median percent change in haemoglobin levels from baseline. Haemoglobin levels were obtained from the local laboratory, rather than from a centralized laboratory.

7.1.4.2. Secondary efficacy variables

- Percent change from baseline in chitotriosidase or CCL18 (centralized assessment).
- Percent change from baseline in spleen and liver volume (centralized MRI readings).
- Percent change from baseline in platelet count (from local laboratory).

7.1.4.3. Exploratory variables

There were a number of exploratory variables: change from baseline in height and weight; change from baseline in Tanner Stage; change from baseline in bone age by X-ray of left hand and wrist; change from baseline in bone density by DEXA; occurrence of bone crises; and Quality of Life using the Child Health Questionnaire (CHQ) PF-28 (valid for patients aged 5 to 18 years).

7.1.5. Randomization and blinding methods

All patients were assigned to treatment with taliglucerase alfa 30 or 60 units/kg based on a centralized computer-generated randomization code. A total of 10 eligible patients (2 to <18 years of age) untreated with ERT or not treated with ERT in the last 12 months were to be randomly assigned 1:1 to treatment with one of two doses of taliglucerase alfa.

The study was double-blinded, the investigators and patients were blinded to the identity of the treatment. In addition, the sponsor, Clinical Research Organizations (CROs), laboratories and the central MRI reader were also blinded to the patient's identity and treatment dose. The randomization code was limited to the persons responsible for creation and implementation of the randomization code, the site pharmacist who prepared the study medication, and unblinded monitors responsible for product accountability. Unblinded study personnel did not have access to the clinical data. The randomization code was not to be broken until the database was locked. However, the medication code could be broken in the case of an adverse event (AE) that the investigator felt could not be adequately treated without knowing the identity of the study drug.

7.1.6. Analysis populations

The analysis population consisted of all patients who received at least one complete dose of study medication.

7.1.7. Sample size

The sample size was determined pragmatically due to the limited number of paediatric patients that could be recruited in a reasonable period of time with this rare disease. The sample size of 10 paediatric patients (5 patients per treatment group) was considered adequate to evaluate the safety endpoints for this rare disease. There were no formal sample size or power calculations.

7.1.8. Statistical methods

7.1.8.1. Primary efficacy endpoint

The primary efficacy endpoint was the median percent change from baseline (Visit 1) in haemoglobin level. All haemoglobin parameters were summarized descriptively.

The percent change in haemoglobin from baseline by treatment group was also summarized post hoc in patients who were anaemic at baseline. Anaemia was defined as a haemoglobin level < 11 g/dL for subjects 6 months to 4 years old, <11.5 g/dL for subjects 5 to <12 years old, <12.0 g/dL for subjects 12 to <15 years old, <12.0 g/dL for females (< 11.0 g/dL if pregnant) and <13.0 g/dL for males 15 years or older (WHO criteria, 2008). The percent change from baseline in haemoglobin by visit was also presented graphically.

7.1.8.2. Secondary efficacy endpoints

The secondary efficacy endpoints were summarized descriptively and included:

- Percent change from baseline (Visit 1) in biomarkers (chitotriosidase or CCL18).
- Percent change from baseline (Visit 1) in spleen and liver volume.
- Percent change from baseline (Visit 1) in platelet count.

Additionally, the percent and absolute changes in platelets from baseline by treatment was summarized post-hoc in patients thrombocytopenic at baseline. Thrombocytopenia was defined as a platelet count ≤ 120,000/mm^3. The percent change and absolute change in platelet count from baseline by visit were also presented graphically.

7.1.8.3. Exploratory endpoints

The changes from baseline for the exploratory endpoints were summarized descriptively. There were also a number of post-hoc analyses assessing changes in height and weight based on chronological and bone age.

7.1.9. Participant flow

Eleven (11) patients were screened and all were eligible and randomized into the study. Six (6) patients were randomized to taliglucerase alfa 30 units/kg, and 5 patients were randomized to taliglucerase alfa 60 units/kg. All patients completed the study.

7.1.10. Major protocol violations/deviations

Three (3) patients from one site had 42 protocol deviations recorded in the eCRF. The majority of these deviations were visits outside of the scheduled window, or study procedures that were either not performed according to the protocol schedule or were not done at all. None of the protocol deviations are considered to significantly affect data analysis.

7.1.11. Baseline data

Baseline demographics: The mean (SD) age in the taliglucerase alfa 30 units/kg (n=6) and 60 units/kg (n=5) treatment groups was 9.5 (4.0) years (range: 3, 14 years) and 6.6 (3.1) years (range: 2, 10 years), respectively. In the 30 units/kg group there were 4 males and 2 females, and in the 60 units/kg group there were 4 males and 1 female. All 6 patients were Caucasian in the 30 units/kg group, and there were 4 Caucasian patients and 1 black patient in the 60 units/kg group. All 6 patients in the 30 units/kg group were non-Jewish, while 3 patients were non-Jewish and 2 patients were Jewish (Ashkenazi) in the 60 units/kg group.

Gaucher disease history: The 11 enrolled patients had glucocerebrosidase activity ranging between 0.2 to 2.6 nmol/mg/hr (≤ 30% of the mean activity of the reference range for healthy patients). The date of diagnosis for the 11 patients ranged from 27 July 2006 to 16 September 2010. None of the patients had undergone previous treatment with ERT or SRT. All patients were analysed for relevant genetic mutations at Visit 1 (Day 1), and GD was confirmed in all

patients. Mutational analysis was consistent with GD type 3 in one patient, and with GD Type 3c in one patient.

Medical history: The most common medical histories were gastrointestinal in 8 patients (n=4, 30 units/kg; n=4, 60 units/kg); head, ears, eyes, nose and throat (HEENT) in 7 patients (n=5, 30 units/kg; n=2, 60 units/kg) and haematologic in 6 patients (n=3, 30 units/kg; n=3, 60 units/kg).

Physical examination: The most commonly observed abnormal physical examination findings at the screening visit were: enlarged spleen in all 11 patients; enlarged liver in 9 patients (n=5, 30 units/kg; n=4, 60 units/kg); and skin body system in 8 patients (n=5, 30 units/kg; n=3, 60 units/kg). Two (2) patients in the taliglucerase alfa 30 units/kg treatment group had abnormal neurological physical examination findings, consistent with the diagnosis of GD Type 3: one (1) patient had supranuclear horizontal gaze palsy and mild opisthotonus; and one (1) patient had oculomotor apraxia accompanied with 3/6 systolic murmur, consistent with the diagnosis of Gaucher disease Type 3c, and abnormal ECHO findings. Of the 11 treated patients (screening visit), the systolic blood pressure ranged between 80-133 mmHg, diastolic blood pressure 50-87 mmHg; pulse 72-156 beats/minute; temperature 35.8-37.7°C and respiratory rate 20-24/minute.

Echocardiography (ECHO) at screening showed an abnormal ECHO in one (1) patient in the taliglucerase alfa 30 units/kg group (atrioventricular [AV] valves thickened, poorly opening mitral valve (MV) with thickened papillary muscles; mild mitral stenosis [MS] at peak gradient 14 mmHg and mean gradient 6 mmHg; moderate to severe mitral regurgitation [MR] with left atrial [LA] enlargement 0-2D area). No ECHO findings were considered to be abnormal in the other 10 patients at Day 1 (Visit 1) or Week 52 (Visit 27).

Other medications: Six patients (6) patients were taking at least one medication at the screening visit (n=3, 30 units/kg; n=3, 60 units/kg). The most commonly used baseline medications were anti-anaemic preparations (n=3, 30 units/kg; n=3, 60 units/kg) and vitamin supplements (n=1, 30 units/kg; n=1, 60 units/kg). Nine (9) patients took concomitant medications during the study (n=5, 30 units/kg; n=4, 60 units/kg). The most commonly used concomitant medications were systemic antibacterials (n=3, 30 units/kg; n=1, 60 units/kg), systemic antihistamines (n=1, 30 units/kg; n=3, 60 units/kg), anti-anaemic preparations (n=1, 30 units/kg; n=2, 60 units/kg), and analgesics (n=1, 30 units/kg; n=2, 60 units/kg).

7.1.12. Results for the primary efficacy outcome

The baseline and Month 12 haemoglobin parameters (mean, median, range) for patients in the taliglucerase alfa 30 units/kg and 60 units/kg groups are summarized below in Table 1, and the percent (%) and absolute changes from baseline to Month 12 are summarized below in Table 2.

Table 1: PB-06-005 – Baseline and Month 12 haemoglobin concentration (g/dL).

	Taliglucerase 30 units/kg (n=6)		Taliglucerase 60 units/kg (n=5)		Overall (n=11)	
	Baseline	Month 12	Baseline	Month 12	Baseline	Month 12
Mean (SD)	11.3 (1.7)	12.7 (1.2.)	10.6 (1.4)	12.2 (1.1)	11.0 (1.5)	12.5 (1.1)
Median	11.5	12.6	11.1	11.7	11.3	11.9
Range	(8, 13)	(11, 14)	(9, 12)	(11, 14)	(8, 13)	(11, 14)

Table 2: PB-06-005 – Change (%) from baseline and absolute change from baseline to month 12 in haemoglobin concentration (g/dL).

	Percent (%) change from Baseline to Month 12			Absolute change from Baseline to Month 12		
	30 units/kg (n=6)	60 units/kg (n=5)	Overall (n=11)	30 units/kg (n=6)	60 units/kg (n=5)	Overall (n=11)
Mean (SD)	13.8 (14.5)%	15.8 (8.3)%	14.7 (11.6)%	1.4 (1.3) g/dL	1.6 (0.7) g/dL	1.5 (1.0) g/dL
Median	12.2 %	14.2%	14.2%	1.4 g/dL	1.6 g/dL	1.6 g/dL
Range	(-2 %, 37%)	(5%, 26%)	(-2%, 37%)	(-0.3, 3) g/dL	(1, 2) g/dL	(0, 3) g/dL
1st – 3rd Q	1.7%, 22.3%	11.4%, 21.7%	5.4%, 22.3%	(0.2, 2.5) g/dL	(1.4, 2.0) g/dL	(0.6. 2.4) g/dL
Inter Q range	20.6%	10.4%	16.9%	2.3 g/dL	0.6 g/dL	1.8 g/dL

The results for the taliglucerase alfa 30 units/kg and 60 units/kg groups for percent (%) change from baseline in haemoglobin levels from baseline to Week 4, Month 6, and Month 9 are summarized below in Table 3.

Table 3: PB-06-005 – Percent change from baseline in haemoglobin concentration (g/dL).

	Taliglucerase alfa 30 units/kg (n=6)			Taliglucerase alfa 60 units/kg (n=5)		
	Percent (%) change from Baseline			Percent (%) change from Baseline		
	Week 4	Month 6	Month 9	Week 4	Month 6	Month 9
Mean (SD)	7.4 (9.7)%	13.0 (12.0)%	9.3 (10.0)%	-0.1 (9.2)%	10.5 (10.8)%	13.1 (7.9)%
Median	10.6%	9.6%	7.8%	3.5%	13.8%	14.2%
Range	(-10%, 18%)	(2%, 28%)	(-4%, 23%)	(-13%, 10%)	(-7%, 21%)	(1%, 23%)
1st – 3rd Q	4.4%, 12.9%	2.3%, 26.5%	3.8%, 17.7%	-5.4%, 4.9%	8.8%, 16.5%	12.2%, 15.4%
Inter Q range	8.5%	24.3%	13.9%	10.3%	7.6%	3.2%

In the post-hoc analysis in anaemic patients, 8 patients (4 in each treatment group) were anaemic at the baseline visit by WHO (2008) defined criteria. Of the 8 patients with baseline anaemia, median increase in haemoglobin from baseline was observed at the end of study for both the 30 units/kg group (19.6%; interquartile range 20.2%) and the 60 units/kg group (17.9%; interquartile range 14.3%). At the end of study, 2 patients in the 30 units/kg group remained anaemic and none of the patients in the 60 units/kg group were anaemic. In the two

(2) patients in the 30 units/kg group who remained anaemic at Month 12, in one patient the haemoglobin level at baseline was 8.2 g/dL and increased by 3 g/dL to reach 11.2 g/dL at Month 12 (normal 11.5 g/dL), and in the other patient the haemoglobin level was 11.8 g/dL (normal 12.0 g/dL) at Month 12. Of the 4 patients in the 60 units/kg who were anaemic at baseline, 1 was on iron replacement due to low saturation observed at screening and one 1 was given vitamin B12.

Comment: The haemoglobin levels at baseline were not equally distributed between the two treatment groups, as shown by the differences in the means, medians and ranges. However, a median increase in haemoglobin from baseline to Month 12 was observed in both the taliglucerase alfa 30 units/kg group (12.2%; interquartile range 20.6%) and the 60 units/kg group (14.2%; interquartile range 10.4%). In both treatment groups, the median percent change from baseline in haemoglobin level increased from Week 4 through to Month 12, and the median percent increase from baseline occurred earlier in the 30 units/kg group (Week 4) than in the 60 units/kg group (Month 6). However, the median percent increase in haemoglobin level from baseline to Month 12 was greater in the 60 units/kg group compared with the 30 units/kg group (14.2% vs 12.2%, respectively), and the interquartile range was narrower indicating closer clustering of the values around the median (i.e., less variability in response).

7.1.13. Results for the secondary efficacy outcomes

7.1.13.1. Biomarkers

Disease severity and response to treatment was monitored by measurement of chitotriosidase and CCL18 activity prior to administration of study medication and at Month 3, 6, 9 and 12. The mean (SE) results for both biomarkers at baseline and Month 12 are summarized below in Table 4.

Table 4: PB-06-005 – Biomarkers mean (SE) levels at baseline and Month 12, and mean (SE) change from baseline to month 12 (absolute and percent) in the taliglucerase alfa 30 units/kg and 60 units/kg groups.

	Mean (SE) Baseline	Mean (SE) Month 12	Change (absolute)	Change (%)	Change % (Range)
Chitotriosidase (nmol/mL.h)					
30 units/kg (n=6)	24820 (7308.3)	11610 (4864.8)	-13210 (4005.6)	-58.5 (7.1)%	(-75%, -32%)
60 units/kg (n=5)	34961 (11040)	14433 (7267.1)	-20528 (4357.7)	-66.1 (10.0)%	(-93%, -45%)
CCL18 (ng/mL)					
30 units/kg (n=6)	1139.3 (319.0)	641.2 (284.9)	-498.2 (133.5)	-50.6 (7.9)	(-70%, -15%)
60 units/kg (n=5)	1339.4 (276.3)	702.4 (222.9)	-637.0 (141.1)	-52.6 (10.1)	(-80%, -18%)

Comment: The mean percent reduction in chitotriosidase activity from baseline to Month 12 was similar in both treatment groups, as was the mean percent reduction from baseline in CCL18 concentration. The results indicate that both doses of taliglucerase alfa were active in patients with GD.

7.1.13.2. Spleen and liver volume

The results for the changes in mean (SE) organ volume from baseline to Month 12 are summarized below in Table 5.

Table 5: PB-06-005 – Spleen and liver volumes (mean [SE]) at baseline and Month 12, and mean (SE) change from baseline to month 12 (absolute and percent) in the taliglucerase alfa 30 units/kg and 60 units/kg groups.

	Mean (SE) Baseline	Mean (SE) Month 12	Change (absolute)	Change (%)	Change % (Range)
Spleen volume (mL)					
30 units/kg (n=6)	1218 (260.6)	811.6 (167.2)	-407 (152.2)	-28.6 (8.8)%	(-52%, -1%)
60 units/kg (n=5)	1023 (336.9)	524.0 (125.7) 680.9	-499 (220.6)	-41.1 (6.2)%	(-61%, -30%)
Liver volume (mL)					
30 units/kg (n=6)	1214 (173.4)	1116 (149.8)	-98.7 (30.6)	-6.3 (3.5)%	(-12%, 11%)
60 units/kg (n=5)	991.7 (134.7)	849.1 (121.6)	-143 (46.0)	-14.0 (4.0)%	(-27%, -5%)

In order to account for changes in organ growth during the treatment period changes in organ volume were also described in terms of multiples of normal (MN).

At the end of the study, a mean reduction was observed in spleen volume in MN for both taliglucerase alfa treatment groups. In patients treated with 30 units/kg, spleen volume decreased from 22.2 MN at baseline to 14.0 MN at Month 12, and in patients treated with 60 units/kg spleen volume decreased from 29.4 MN at baseline to 12.9 MN at Month 12. Overall, reductions from baseline to Month 12 in MN spleen volume were 34.1% in the 30 units/kg group and 48.5% in the 60 units/kg group.

At the end of the study, a mean reduction in liver volume in MN was observed for both the taliglucerase alfa treatment groups. In patients treated with 30 units/kg, liver volume decreased from 1.8 MN at baseline to 1.5 MN at Month 12, and in patients treated with 60 units/kg liver volume decreased from 2.2 MN at baseline to 1.7 MN at Month 12. Overall, reductions from baseline to Month 12 in MN liver volume were 14.5% in the 30 units/kg group and 25.0% in the 60 units/kg group.

> **Comment**: Mean percent reductions from baseline to Month 12 were observed in both treatment groups, with the reductions in volume in both organs being greater in the 60 units/kg group than in the 30 units/kg group. In addition, volume reductions in both organs from baseline to Month 12 were also observed when volume was measured as MN in order to account for organ growth during the 12 month treatment period.

7.1.13.3. Platelets

The results for the changes in mean (SE) platelet counts from baseline to Month 12 are summarized below in Table 6.

Table 6: PB-06-005 – Platelet counts (mean [SE]) at baseline and Month 12, and mean (SE) change from baseline to month 12 (absolute and percent) in the taliglucerase alfa 30 units/kg and 60 units/kg groups.

	Mean (SE) Baseline	Mean (SE) Month 12	Change (absolute)	Change (%)	Change % (Range)
30 units/kg (n=6)	162667 (29328)	208167 (37047)	45500 (21590)	30.9 (14.3)%	(-8%, 85%)
60 units/kg (n=5)	99600 (19185)	172200 (39932)	72600 (26474)	73.7 (27.7)%	(1%, 172%)

Comment: Mean platelet count increased from baseline to Month 12 in both treatment groups, with the percent mean increase being greater in the 60 units/kg group compared with the 30 units/kg group. In a post-hoc analysis, both treatment groups showed similar absolute mean increase in platelets (56,500/mm3 and 57,750/mm3; respectively) at Month 12 for patients who were thrombocytopenic at baseline (i.e., platelet count ≤ 120,000 mm3).

7.1.14. Exploratory endpoints

Increases in height and weight were observed at the end of study in all patients treated with taliglucerase alfa. The mean (SD) percent increase in height (cm) from baseline to Month 12 was 4.2% (2.2%) in the 30 units/kg group and 7.6% (2.1%) in the 60 units/kg group. The mean (SD) percent increase in weight was 9.6% (7.0%) in the 30 units/kg group and 14.7% (5.7%) in the 60 units/kg group. In the post-hoc analysis, after 12 months treatment patients in the 30 units/kg group had a mean growth rate of 5.1 cm/year, and patients in the 60 units/kg group had a mean growth rate of 8.0 cm/year. In the 60 units/kg group, both height and weight improved for chronological ages, while in the 30 units/kg group both parameters remained stable.

The Tanner stage results showed that pubertal status remained unchanged through 12 months of treatment. In the 30 units/kg group, 2 patients (1 aged 14; 1 aged 11) changed from Tanner stage I to Tanner stage II. As expected, the mean bone age determined by X-ray of the left hand and wrist advanced in both treatment groups after 12 months of treatment compared with the baseline measurement (1.9 year, 30 units/kg; 1.4 year, 60 units/kg). Of the 9 patients with evaluable data, 4 showed approximately 1 year of bone age advancement, 4 showed 1.5 to 1.75 year bone growth and 1 showed 4 year bone growth.

Lumbar spine and femoral neck DEXA scans were undertaken at the screening visit and the end of the study (Month 12). The majority of mean T and Z scores at either the screening visit or the end of the study were below the normal range (lower than -1). Z scores at the end of the study showed a slight mean decrease at both lumbar spine and femoral neck in the 30 units/kg dose group (lumbar spine, -0.20; femoral neck, -0.30), and a slight mean increase in the 60 units/kg dose group at the two locations (lumbar spine, 0.27; femoral neck 0.20).

The Child Health Questionnaire (CHQ) scores for Quality of Life assessment at Month 12 showed that more parents/guardians rated their children' global health as very good or excellent, and that most thought that their children were in better health at Month 12 than at baseline. In addition, the parents/guardians reported less emotional worry or concern about their child's physical health and less limitation on their time because of their child's physical health during the 4 weeks preceding completion of the questionnaire.

7.2. Evaluator's conclusions on clinical efficacy in study PB-06-005

The re-submission included one small efficacy and safety study in 11 paediatric patients, ranging in age from 3 to 14 years, with a definitive diagnosis of GD and who were ERT-naïve. The patients were randomized to taliglucerase alfa 30 units/kg (n=6) or 60 units/kg (n=5) administered by IV infusion every 2 weeks for 12 months. Interpretation of the efficacy results of this study is limited due to the absence of an active treatment control group. The changes from baseline through to Month 12 in the efficacy parameters were summarized descriptively with no statistical analyses of the results being undertaken. The sample size was determined pragmatically due to the limited number of paediatric patients with this rare disease available for study.

The primary efficacy endpoint was the median change from baseline (Visit 1) and the interquartile range of the median percent change in haemoglobin. In both treatment groups, a median increase in haemoglobin level from baseline to Month 12 was observed (12.2%, interquartile range 20.6%, 30 units/kg group; 14.2%, interquartile range 10.4%, 60 units/kg). In both treatment groups, each of the secondary efficacy endpoint outcomes showed improvement from baseline to Month 12, with results for the 60 units/kg group being numerically superior compared with the results for the 30 units/kg group.

Overall, it is considered that this small, uncontrolled, open-label study suggests that taliglucerase alfa 30 units/kg and 60 units/kg administered by IV infusion every second week for 12 months is efficacious for the treatment of GD in ERT-naïve children and adolescents. Improvements from baseline to Month 12 included increases in haemoglobin levels and platelet counts, reduction in spleen and liver volumes, and reductions in chitotriosidase activity and CCL18 concentration. The results are consistent with those observed in adult patients evaluated in the original submission.

8. Clinical safety

8.1. Study PB-06-005 (paediatric population)

8.1.1. Extent of exposure

In study PB-06-005, 11 children and adolescents completed 52 weeks of treatment with taliglucerase alfa and were included in the safety evaluation. The mean (SD) taliglucerase alfa doses were 34.7 (5.4) units/kg (range: 30, 45) in the 30 units/kg group (n=6) and 63.7 (3.5) units/kg (range: 61, 69) in the 60 units/kg (n=5) group.

8.1.2. Adverse events

8.1.2.1. Overview of adverse events

An adverse event (AE) was defined as any untoward medical occurrence in a subject participating in the clinical trial. AEs could be any unfavourable and unintended sign, symptom or disease temporally associated with the use of the study medication, whether or not considered related to the study medication. AEs were collected from the start of treatment until 30 days following the final dose. Each AE was classified by the investigator as serious (SAE) or non-serious (non-SAE). The SAE criteria were: death; life-threatening (i.e., an immediate risk of death); requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; associated with a congenital anomaly/birth defect; or an important medical event. The investigator determined the causality relationship between AEs and the study drug, with events being rated as related or unrelated to treatment with taliglucerase alfa. The overview of AEs occurring during the study for the two treatment groups are summarized below in Table 7.

Table 7: PB-06-005 – Overview of adverse events; patients (at least one with the event of interest) and number of events (N).

	30 units/kg (n=6)		60 units/kg (n=5)	
	Patients (%)	**Events (N)**	**Patients (%)**	**Events (N)**
Adverse events (AEs)	5 (83.3)	22	5 (100.0)	31
Mild or moderate AEs	4 (66.7)	21	5 (100.0)	30
Severe or very severe AEs	1 (16.7)	1	1 (20.0)	1
AEs probably not or definitely not related to study drug	5 (83.3)	22	5 (100.0)	23
AEs possibly, probably or definitely related to study drug	0 (0.0)	0	2 (40.0)	8
Serious adverse events (SAEs)	0 (0.0)	0	1 (20.0)	1
SAEs probably not or definitely not related to study drug	0 (0.0)	0	0 (0.0)	0
SAEs possibly, probably or definitely related to study drug	0 (0.0)	0	1 (20.0)	1

8.1.2.2. Commonly occurring adverse events

The AE profile for the two treatment groups was comparable, with 5 (83.3%) patients reporting at least one AE in the 30 units/kg group compared with 5 (100%) patients reporting at least one AE in the 60 units/kg group. However, the number of subjects in the two treatment groups was too small to definitively conclude that there was no relationship between dose and the incidence of AEs.

There were a total of 53 AEs reported in the study (29 unique MedDRA preferred terms), which included multiple reports of the same event in individual subjects. Of the 53 AEs, 2 were reported as severe: 1x gastroenteritis in one child in the 60 units/kg group; and 1x pulmonary hypertension reported in one child with GD type 3c in the 30 units/kg group, with worsening tricuspid valve incompetence demonstrated by ECHO at Month 12 considered to be clinically significant progression of underlying cardiac disease unrelated to taliglucerase alfa.

AEs occurring in patients in both treatment groups are summarised below in Table 8. The most commonly experienced AE (30 vs 60 units/kg) was vomiting reported in 4 patients (2 vs 2), while the following AEs (30 vs 60 units/kg) each occurred in 2 patients, abdominal pain (0 vs 2), diarrhoea (0 vs 2), nasopharyngitis (0 vs 2) and tooth extraction (2 vs 0).

Two (2) patients in the 60 units/kg group experienced 8 AEs considered probably or definitely related to study drug treatment (one patient: itchy throat x 3 and chest discomfort; one patient: gastroenteritis and vomiting x 3).

One (1) patient, a 13 year old male, presented 2 days before infusion 21 with an AE of “sun burn” and “facial angioedema” due to an extended exposure to sun, which completely recovered after three days with treatment, and was reported as not related to treatment.

Table 8: PB-06-005 – Number of patients with AEs; MedDRA SOC/PT.

SYSTEM ORGAN CLASS / PREFERRED TERM	taliglucerase alfa 30 units/kg (N = 6)	taliglucerase alfa 60 units/kg (N = 5)
GASTROINTESTINAL DISORDERS		
ABDOMINAL PAIN	0 (0.0%)	2 (40.0%)
DIARRHOEA	0 (0.0%)	2 (40.0%)
GASTROINTESTINAL INFLAMMATION	0 (0.0%)	1 (20.0%)
GINGIVAL BLEEDING	1 (16.7%)	0 (0.0%)
GINGIVAL PAIN	0 (0.0%)	1 (20.0%)
VOMITING	2 (33.3%)	2 (40.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
CHEST DISCOMFORT	0 (0.0%)	1 (20.0%)
INFUSION SITE EXTRAVASATION	1 (16.7%)	0 (0.0%)
PYREXIA	1 (16.7%)	0 (0.0%)
INFECTIONS AND INFESTATIONS		
GASTROENTERITIS	0 (0.0%)	1 (20.0%)
INFLUENZA	0 (0.0%)	1 (20.0%)
NASOPHARYNGITIS	0 (0.0%)	2 (40.0%)
OTITIS MEDIA	0 (0.0%)	1 (20.0%)
TONSILLITIS	1 (16.7%)	0 (0.0%)
UPPER RESPIRATORY TRACT INFECTION	1 (16.7%)	0 (0.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
HEAD INJURY	1 (16.7%)	0 (0.0%)
SUNBURN	1 (16.7%)	0 (0.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
BONE PAIN	1 (16.7%)	0 (0.0%)
PAIN IN EXTREMITY	1 (16.7%)	1 (20.0%)
NERVOUS SYSTEM DISORDERS		
HEADACHE	1 (16.7%)	1 (20.0%)
SYNCOPE VASOVAGAL	1 (16.7%)	0 (0.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
COUGH	0 (0.0%)	1 (20.0%)
EPISTAXIS	0 (0.0%)	1 (20.0%)
PULMONARY HYPERTENSION	1 (16.7%)	0 (0.0%)
RHINITIS ALLERGIC	0 (0.0%)	1 (20.0%)
THROAT IRRITATION	0 (0.0%)	1 (20.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
ANGIOEDEMA	1 (16.7%)	0 (0.0%)
RASH	1 (16.7%)	0 (0.0%)
SURGICAL AND MEDICAL PROCEDURES		
TOOTH EXTRACTION	2 (33.3%)	0 (0.0%)

8.1.2.3. Infusion related adverse events

Five (5) patients experienced 13 AEs during the infusion or within 2 hours after completion of the infusion (3 patients, 4 AEs, 30 units/kg; 2 patients, 9 AEs, 60 units/kg). The results are summarized below in Table 9.

Table 9: PB-06-005 – Adverse events during the infusion or within 2 hours after the infusion

	PID	Visit	Adverse Events	Treatment Relationship
taliglucerase alfa 30 units/kg	10-5002	3	Infusion site extravasation	Definitely not
	11-5006	14	Vomiting, Syncope Vasovagal	Definitely not
	91-5009	2	Vomiting	Definitely not
taliglucerase alfa 60 units/kg	11-5004	1	Throat irritation, Chest Discomfort	Probably
		2	Throat irritation	Probably
		3	Throat irritation	Definitely
	11-5005	1	Gastrointestinal inflammation	Definitely
		2	Vomiting	Definitely
		3	Vomiting	Definitely
		4	Vomiting	Definitely
		25	Abdominal Pain	Probably not

Five (5) patients experienced 7 AEs between 2 to < 24 hours after completion of the infusion, and 9 patients experienced 33 AEs at least 24 hours after the completion of infusion. All AEs that occurred >2 hours after the completion of infusion were considered to be unrelated to treatment.

8.1.3. Deaths and other serious adverse events (SAEs)

No deaths occurred during the study. One patient in the 60 units/kg group experienced a treatment related SAE of gastroenteritis (preferred term of gastrointestinal inflammation) during the first infusion visit resulting in hospitalization (severe AE, Grade 3). The SAE was treated with ondansetron 2 mg and resolved the day after treatment.

8.1.4. Discontinuation due to adverse events

No patient discontinued from the study due to an AE.

8.1.5. Laboratory tests

There were no clinically significant changes from baseline observed at the end of study in the laboratory parameters. The majority of the laboratory haematology and biochemistry parameters remained at normal levels throughout the study.

The laboratory test data included the number of patients with shifts from screening to end of study relative to reference limits (low, normal, high). Two (2) patients in the 30 units/kg group reported elevated glucose levels after normal baseline levels (65-99 mg/dL): 1 patient had 93 mg/dL at baseline, 124 mg/dL at Week 8 116 mg/dL at Month 3, 149 mg/dL at Month 9 and 124 mg/dL at Month 12; 1 patient had 67 mg/dL at baseline, 101 mg/dL at Month 3, and 106 mg/dL at Month 6. One (1) patient in the 60 units/kg group reported elevated ALT levels, after a normal (baseline level (26 IU/L [reference: 0-55 IU/L]), of 66 IU/L at Visit 5 (Week 8) and 67 IU/L at Visit 7 (Month 3). None of the changes from baseline in the laboratory parameters were considered clinically significant by the investigator.

8.1.6. Other safety related observations

8.1.6.1. Vital signs

Vital signs were monitored at each infusion visit for 210 minutes, including 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 used at the pre-dose screening visit. The majority of vital sign measurements (mean systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature) were within normal limits, and none of the changes or measurements outside of the limits were considered to be clinically significant. The only reported vital sign AE was fever (39˚C) occurring in one (1) patient in the 30 units/kg group 5 days after Visit 16 infusion, with recovery in 2 days, and considered to be unrelated to treatment.

8.1.6.2. Hypersensitivity

Two (2) patients in the 60 units/kg group experienced AEs related to hypersensitivity reactions: 1 patient experienced itchy throat and chest discomfort during the first infusion visit, and itchy throat during the following two infusion visits; 1 patient experienced gastrointestinal inflammation during the first infusion visit and vomiting during the following three infusion visits.

8.1.6.3. Bone crisis

No patients reported GD bone crises during the clinical trial. One (1) patient in the 30 units/kg group experienced bone pain and pain in extremity, and one (1) patient in the 60 units/kg group experienced pain in extremity during the study. The AEs in these two patients were considered to be unrelated to treatment.

8.1.6.4. Anti-human taliglucerase alfa antibody results

Of the 11 patients tested for the presence of IgG anti-taliglucerase alfa antibodies, 3 were reported antibody positive (n=1, 30 units/kg; n=2, 60 units/kg).

The patient given 30 units/kg had a positive IgG antibody response with a titre of 369 at Visit 14, 524 at Visit 20 and 166 at the end of study. This patient experienced four AEs at various visits during the study (vomiting, exodontia and facial angioedema/sunburn), but these events were not considered to be hypersensitivity reactions and were reported as being unrelated to study drug.

One of the patients given 60 units/kg had a positive IgG antibody response with a titre of 213 at Visit 1 (pre-dose), 207 at Visit 3 and 233 at Visit 5 and also had a positive IgE antibody subtype present pre-dose and at Visit 5. This patient experienced 8 AEs at various visits during the study (chest discomfort, itchy throat x3, common cold, otitis media, gastroenteritis and painful gums). Itchy throat and chest discomfort during the first infusion visit and itchy throat during the following two infusions visits were considered hypersensitivity reactions and reported as related to the study treatment.

The other patient given 60 units/kg had a positive IgG antibody response with a titre of 189 at Visit 7. This patient experienced 13 AEs at various visits during the study (gastroenteritis, flu, cough, vomiting x3, diarrhoea, influenza x5, abdominal pain). Gastroenteritis during the first infusion visit and vomiting during the following three infusion visits were considered hypersensitivity reactions and reported as related to study treatment.

Neutralizing antibody tests were negative in all three IgG anti-taliglucerase alfa antibody positive patients. All three IgG anti-taliglucerase alfa antibody positive patients completed the study.

8.1.6.5. Echocardiography

Two (2) patients had abnormal ECHO results at Month 12 considered to be unrelated to treatment: one (1) patient in the 60 units/kg group had mild tricuspid regurgitation with normal baseline tricuspid incompetence (TI) gradient (12 mmHg) which elevated to 20 mmHg at the end of study; and one (1) patient in the 30 units/kg with GD Type 3c showed worsening TI gradient (pulmonary hypertension) at the end of study with an abnormal TI gradient of 74 mmHg, which was considered a clinically significant deterioration.

8.1.7. Clinical evaluator's conclusions on clinical safety study PB-06-005

The safety profile of taliglucerase alfa in paediatric patients with GD is consistent with the safety data for the medicine obtained from previous clinical trials in adult patients. No new safety findings or signals were identified in study PB-06-005.

Of 11 taliglucerase alfa treated patients, 10 patients experienced 53 AEs (5 patients, 22 AEs, 30 units/kg; 5 patients, 31 AEs, 60 units/kg). The AEs were all reported as mild or moderate in intensity, except for worsening of pulmonary hypertension (severe) detected by ECHO in 1 patient with GD type 3c in the 30 units/kg group, and 1 patient with gastroenteritis (severe) in the 60 units/kg group. The severe gastroenteritis in the patient in the 60 units/kg group was also considered to be a SAE as it resulted in hospitalization, and there were no other SAEs reported in the study. All reported AEs resolved, except for the one case of pulmonary hypertension, unrelated to treatment, which had an unknown recovery date. The patient with pulmonary hypertension is a candidate for cardiac valve replacement surgery. No patient discontinued from the study due to an AE.

Five (5) patients had 13 AEs that occurred during the infusion or within 2 hours after the completion of the infusion. Two (2) patients in the 30 units/kg group had infusion site extravasation, vomiting (2 events) and vasovagal syncope, and three (3) patients in the 60 units/kg group had throat irritation (3 events), chest discomfort, gastrointestinal inflammation,

vomiting (3 events) and abdominal pain. In the 2 patients in the 60 units/kg group with infusion related AEs, the events of itchy throat, chest discomfort, gastrointestinal inflammation and vomiting were considered to be hypersensitivity reactions.

The majority of laboratory test results (haematology, biochemistry, urinary) remained at normal levels throughout the study. There were no clinically significant changes in laboratory test results associated with taliglucerase alfa in the study. Two (2) patients had abnormal ECHOs at Month 12 considered to be unrelated to treatment.

Of the 11 patients who were tested for the presence of IgG anti-taliglucerase alfa antibodies, 3 developed a positive reaction (n=1, 30 units/kg; n=2, 60 units/kg). One (1) of the two patients in the 60 units/kg also had IgE antibody to taliglucerase alfa. Both of the patients in the 60 units/kg group had hypersensitivity reactions to the taliglucerase alfa infusion considered to be treatment related. None of the patients testing positive for IgG anti-taliglucerase alfa antibodies tested positive for neutralizing antibodies. All 3 patients testing positive for IgG anti-taliglucerase alfa antibodies completed the study.

8.2. Summary of clinical safety (Module 2.7.4, re-submission)

8.2.1. Overview

8.2.1.1. Patient numbers

The safety data provided in the Summary of Clinical Safety (SCS) was based on 132 patients (116 adults, 16 children) who had accrued 2,761.0 patient-months of exposure to taliglucerase alfa as of 1 May 2012 (Module 2.7.4, re-submission)

In the original submission, the safety data provided in the SCS was based on 121 patients (110 adults, 11 children) who had accrued 1,734.4 patient-months of exposure to taliglucerase alfa as of 1 May 2011(see CER 1, Table 30).

Total subject exposures to taliglucerase alfa as of 1 May 2012 (re-submission) and 1 May 2011 (original submission) are summarized below in Table 10.

Table 10: Summary of patient numbers in the re-submission and original submission.

Summary Clinical Safety	Total N	< 1	≥ 1	≥ 3	≥ 6	≥ 12	≥ 24	≥ 36
Re-submission *	132	7	125	119	111	95	49	23
Original submission **	121	8	113	112	96	59	24	4

* As of 01 May 2012. ** As of 01 May 2011.

Comment: There were data on an additional 11 patients in the SCS (re-submission) compared with the SCS (original submission). The main difference between the two SCS documents was the greater number of patients in the re-submission exposed for ≥ 6, ≥ 12, ≥ 24, and ≥ 36 months. The SCS (original submission) has been previously evaluated by the TGA. The total patient-months of exposure was 59% higher in the SCS (re-submission) compared with the SCS (original submission).

8.2.1.2. Clinical program studies contributing to SCS (as of 01 May 2012)

8.2.1.2.1. Completed studies

- Study PB-06-001: a multi-centre, randomized, double-blind, parallel group, dose-ranging trial to assess the safety and efficacy of taliglucerase alfa in ERT-naïve adult subjects with GD. Thirty-two (32) adult patients (16 per group) received IV infusions of either 30 or 60 units/kg taliglucerase alfa every 2 weeks. The duration of study treatment was 9 months.

- Study PB-06-005: a multi-centre, randomized, double-blind, parallel group, dose-ranging trial to assess the safety and efficacy of taliglucerase alfa in ERT-naïve paediatric patients with GD. Eleven (11) paediatric patients received IV infusions of either 30 or 60 units/kg every 2 weeks. The duration of study treatment was 12 months.

8.2.1.2.2. Ongoing studies

- Study PB-06-002: a multi-centre, open-label, switch-over trial to assess the safety and efficacy of taliglucerase alfa in adults and children with GD who had been stabilized on imiglucerase. Subjects received IV infusions of taliglucerase alfa every 2 weeks at the same dose as their previous imiglucerase dose. The duration of study treatment is 9 months. Enrollment in the study started in December 2008, and as of 01 May 2012, 26 adults and 5 children have been treated. Three (3) children are ongoing as of 01 May 2012.
- Study PB-06-003: an open-label extension trial open to adults completing studies PB-06-001 or PB-06-002 and continuing the treatment regimens initiated in the core trials. Treatment duration is up to 30 months. Forty-four (44) patients have been treated in this trial, 26 from PB-06-001 and 18 from PB-06-002. As of the data cutoff date, 8 patients from PB-06-002 were ongoing.
- Study PB-06-007: a multi-centre extension trial to further extend the assessment of the safety and efficacy of taliglucerase alfa in adults who had completed treatment in study PB-06-001 and extension study PB-06-003. The maximum duration of the extension trial is 21 months or until the product is commercially available to the subject at the discretion of the sponsor. Patients continue with the same dose of taliglucerase alfa as received in study PB-06-003.
- Study PB-06-006: an open-label paediatric extension study open to children completing study PB-06-005 or study PB-06-002. The treatment regimens are the same as initiated in the core trials, and the duration of the extension trial is up to 24 months. As of 01 May 2012, 12 patients had received treatment in this study.
- Study PB-06-004: an expanded access study initiated to accommodate the treatment of subjects affected by the shortage of imiglucerase. As of 01 May 2012, 58 subjects had been treated in this study. The majority of these subjects were in the United States or Israel.

8.2.1.3. Demographics

The mean (SD) age of the 116 adult patients was 43.6 (14.6) years, ranging from 18 to 85 years, and including 62 males (53.4%) and 54 (46.6%) females. There were 55 (47.4%) non-Jewish patients and 61 (52.6%) Jewish patients (57 [49.1%] Ashkenazi, and 4 [3.4%] non-Ashkenazi).

The mean (SD) age of the 16 children and adolescent patients was 9.7 (4.4) years, ranging from 2 to 16 years, and including 11 males (68.8%) and 5 (31.3%%) females. There were 12 (85.7%%) non-Jewish patients and 2 (14.3%) Jewish patients (both Ashkenazi); no religious group was provided for 2 patients.

8.2.2. Exposure

8.2.2.1. Duration

8.2.2.1.1. Adults

The 116 adult patients exposed to taliglucerase alfa as of 1 May 2012 have accrued 2,556.3 months of person-time exposure (see Table 11, below).

Table 11: SCS – Adults exposure in completed and ongoing studies; as of 1 May 2012.

Duration of Exposure (months)	N	Person Time (months)
Overall	116	2556.3
< 1*	5	1.6
>= 1	111	2554.7
>= 3	106	2544.7
>= 6	98	2507.9
>= 12	83	2370.4
>= 24	49	1703.2
>= 36	23	958.8

Note: Duration of exposure is computed from date of first dose until last dose before cut-off date. * Limited duration of exposure < 1 month is due to subject withdrawals.

8.2.2.1.2. Children

The 16 children exposed to taliglucerase alfa as of 1 May 2012 have accrued 204.6 months of person-time exposure (see Table 12, below).

Table 12: SCS – Children exposure in completed and ongoing studies, as of 1 May 2012

Duration of Exposure (months)	N	Person Time (months)
Overall	16	204.6
< 1*	2	1.9
>= 1	14	202.7
>= 3	13	201.3
>= 6	13	201.3
>= 12	12	189.3

Note: Duration of exposure is computed from date of first dose until last dose before cut-off date. * Limited duration of exposure < 1 month is due to subject withdrawals.

8.2.2.2. Dose

Total subject exposure to taliglucerase alfa by dose in all completed and ongoing studies by dose in all patients (n=132) is summarized below in Table 13.

Table 13: SCS – Exposure in total population (n=132) by dose, completed and ongoing studies, as of 1 May 2012

Dose (units/kg)	N	Person Time (months)
< 25	34	585.2
25-35	42	866.1
>35 - <55	17	398.2
>=55	39	911.5

Note: Duration of exposure is computed from date of first dose until last dose before cutoff date.

The mean dose in each of the adult and paediatric studies is summarized below in Table 14. The mean dose across all studies was similar, and the mean doses in the 30 units/kg and 60 units/kg groups in the paediatric study (PB-06-005) was similar to the mean doses in the corresponding dosage groups in the adult study (PB-06-001).

Table 14: SCS – Mean dose in completed and ongoing studies, as of 1 May 2012

Average of All Dose Infusions (U/kg)	PB-06-001		PB-06-002	PB-06-004	PB-06-005		Overall
	30 U/kg	60 U/kg			30 U/kg	60 U/kg	
N	16	16	31	58	6	5	132
Mean	32.7	60.4	31.2	34.4	33.1	61.1	37.5
SD	3.7	2.1	16.6	16.4	4.1	2.6	16.9
Median	31.6	60.4	25.8	30.4	31.3	60.3	31.8
Range	30 to 44	57 to 65	11 to 60	13 to 63	30 to 41	58 to 65	11 to 65

Note: Duration of exposure is computed from date of first dose until last dose before cutoff date.

8.2.3. Adverse events

8.2.3.1. Overview

The safety population in the SCS consisted of subjects treated at least once with taliglucerase alfa in a Phase III study. AE severity was defined by WHO Toxicity Criteria as mild (awareness of signs and symptoms, easily tolerated), moderate (discomfort sufficient to interfere, but not prevent daily activity), severe (unable to carry out usual activity), or very severe (incapacitating, requires hospitalization). All AEs in the SCS were treatment-emergent and were collected from the start of treatment until 30 days after the final dose. For extension studies, treatment-emergence was based on the parent study. The study investigator was responsible for determining whether an AE was treatment related (degree: definitely, probably, or possibly, defined as shown below).

***Definitely*:** There is evidence of exposure to the test product, for example, reliable history or acceptable compliance assessment; the temporal sequence of the AE onset relative to the drug is reasonable; the AE is most likely to be explained by the drug treatment than by another cause; the challenge is positive; re-challenge (if feasible) is positive; the AE shows a pattern consistent with previous knowledge of the drug treatment.

***Probably*:** There is evidence of exposure to the test product; the temporal sequence of the AE onset relative to the drug administration is reasonable; the AE is more likely explained by the drug treatment than by another cause; the challenge (if performed) is positive.

***Possibly*:** There is evidence of exposure to the test product; the temporal sequence of the AE relative to the drug administration is reasonable; the AE could have been due to another equally likely cause; the challenge (if performed) is positive.

***Probably not*:** There is evidence of exposure to the drug; there is another more likely cause of the AE; the challenge (if performed) is negative or ambiguous; re-challenge (if performed) is negative or ambiguous.

***Definitely not*:** The patient/patient did not receive the drug treatment; or temporal sequence of the AE onset relative to administration of the drug is not reasonable; or there is another obvious cause of the AE.

All AEs in treated subjects were reported using MedDRA version 15.0, System Organ Class (SOC) and Preferred Term (PT). The overview of AEs is summarized below in Table 15.

Table 15: SCS – Overview of adverse events; patients with at least one event of interest and number of events (N).

Parameter	All adults (n=116)		All paediatrics (n=16)	
	Patients (%)	Events (N)	Patients (%)	Events (N)
Adverse events (AEs)	108 (93.1)	1252	12 (75.0)	73
Mild or moderate AEs	108 (93.1)	1226	11 (68.8)	71
Severe or very severe AEs	17 (14.7)	26	2 (12.5)	2
AEs probably not or definitely not related to study drug	101 (87.1)	969	12 (75.0)	64
AEs possibly, probably or definitely related to study drug	54 (46.6)	283	2 (12.5)	9

Parameter	All adults (n=116)		All paediatrics (n=16)	
	Patients (%)	Events (N)	Patients (%)	Events (N)
Serious adverse events (SAEs)	14 (12.1)	18	2 (12.5)	2

Note (Adults): AEs occurring during treatment in the extension study (PB-06-003 and PB-06-007) are reported under the subjects' original protocol and treatment group. Note (paediatrics): AEs occurring during treatment in the extension study (PB-06-006) are reported under the subjects' original protocol and treatment group. When there are multiple events with the same preferred term in a system organ class for a subject, the most severe event is used. Multiple events in the same system organ class for a subject are only counted once in the statistics of that system organ class. The percentage represents the incidence of an event by the system organ class or the preferred term as a percentage of the total number of subjects in the treatment group. Multiple events with the same preferred term in a system organ class are counted separately for each instance regardless of AE severity.

8.2.3.2. Incidence of common adverse events

The most commonly reported AEs (>10% in any population) in the total safety population in the ongoing and completed studies are summarized below in Table 16.

Table 16: SCS – Adverse events in > 10% of patients in any population; ongoing and completed studies.

SOC/Preferred Term	Number of Subjects with AE (%)		
	Adults N=116	Children N=16	Overall N=132
Gastrointestinal Disorders			
Abdominal Pain*	13 (11.2)	3 (18.8)	16 (12.1)
Diarrhoea	12 (10.3)	2 (12.5)	14 (10.6)
Nausea	12 (10.3)	1 (6.3)	13 (9.8)
Vomiting	9 (7.8)	5 (31.3)	14 (10.6)
General Disorders and Site Administration Site Conditions			
Fatigue	15 (12.9)	0	15 (11.4)
Pyrexia	13 (11.2)	1 (6.3)	14 (10.6)
Infections and Infestations			
Nasopharyngitis	27 (23.3)	3 (18.8)	30 (22.7)
Tonsillitis	0 (0.0)	2 (12.5)	2 (1.5)
Upper Respiratory Tract	23 (19.8)	1 (6.3)	24 (18.2)
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	27 (23.3)	2 (12.5)	29 (22.0)
Back Pain	13 (11.2)	0	13 (9.8)
Pain in Extremity	19 (16.4)	3 (18.8)	22 (16.7)
Nervous System Disorders			
Headache	26 (22.4)	3 (18.8)	29 (22.0)
Respiratory, Thoracic and Mediastinal Disorders			
Cough	18 (15.5)	1 (6.3)	19 (14.4)
Epistaxis	6 (5.2)	2 (12.5)	8 (6.1)
Oropharyngeal Pain	12 (10.3)	0	12 (9.1)
Surgical and Medical Procedures			
Tooth Extraction	5 (4.3)	2 (12.5)	7 (5.3)

*The term 'Abdominal Pain' also includes Abdominal Pain Lower & Abdominal Pain Upper AEs. When there are multiple events with the same preferred term in a system organ class for a subject, the most severe event is used. Multiple events in the same system organ class for a subject are only counted once in the statistics of that system organ class. The percentage represents the incidence of an event by the system organ class or the preferred term as a percentage of the total number of subjects in the treatment group.

AEs reported in > 10% of patients in any group in ERT-naïve patients (n=43) and ERT-experienced patients (n=89) are summarized in the dossier.

> **Comment**: The most commonly reported AEs in adult patients were nasopharyngitis (23.3%), arthralgia (23.3%), headache (22.4%), upper respiratory tract infection (19.8%), pain in extremity (16.4%), cough (15.5%), fatigue (12.9%), abdominal pain (11.2%), pyrexia (11.2%), back pain (11.2%), diarrhoea (10.3%), nausea (10.3%), and

oropharyngeal pain (10.3%). In adults, the proportion of patients with AEs in the ERT-naïve group was higher than in the ERT-experienced group (96.9% [31/32] vs 91.7% [77/84]). In adults, there were 425 AEs in 32 ERT-naïve patients (i.e., 13.3 events per patient), and 827 AEs in 84 ERT-experienced patients (i.e., 9.8 events per patient).

The most commonly reported AEs in paediatric patients were vomiting (31.3%), abdominal pain (18.8%), nasopharyngitis (18.8%), headache (18.8%), pain in extremity (18.8%), tonsillitis (12.5%), diarrhoea (12.5%), arthralgia (12.5%), epistaxis (12.5%), and tooth extraction (12.5%). In children, the proportion of patients with AEs in the ERT-naïve group was higher than in the ERT-experienced group (90.9% [10/11] vs 40.0% [2/5]). In children, there were 68 AEs in 11 ERT-naïve patients (i.e., 6.2 events per patient), and 5 AEs in 5 ERT-experienced patients (i.e., 1 event per patient). The difference between the ERT-naïve and ERT-experienced groups in children as regards AEs should be interpreted cautiously due to the small number of patients in each group.

8.2.3.3. Severity of adverse events

In the total population (n=132), 19 (14.4%) patients (17 adults, 2 children) experienced at least one severe or very severe AE. The number of patients with severe or very severe AEs in the total population patients classed as ERT-naïve or ERT-experienced; and the number (%) of adult patients with AEs by severity are summarized in the dossier. There were 17 (14.7%) adult patients with at least one severe or very severe AE (total of 24 events), and these patients and events are listed below in Table 17.

Table 17: SCS – Listing of adult subjects with a severe or very severe adverse event

Study ID	Preferred Term	Severity/Serious (Y;N)
PB-06-001	Haemangioma	Severe/Y
	Pulmonary Embolism	Very Severe/Y
PB-06-001	Autoimmune Thrombocytopenia	Very Severe/Y
PB-06-001	Diabetes Mellitus	Severe/N
PD-06-001	Osteoarthritis	Very Severe/Y
PB-06-002	Osteoarthritis	Severe/Y
PB-06-002	Haematuria	Severe/N
	Nephrolithiasis	Severe/Y
PB-06-002	Renal Stone Removal	Severe/Y
PB-06-002	Pelvic Prolapse	Severe/Y
PB-06-004	Cytomegalovirus Infection	Severe/Y
PB-06-004	Haemoglobin decreased	Severe/N
	Hip Arthroplasty	Severe/Y
	Procedural Pain	Severe/N
PB-06-004	Arthralgia	Severe/N
PB-06-004	Pain in Extremity	Severe/N
	Oedema Peripheral	Severe/N
PB-06-004	Osteonecrosis	Severe/N
PB-06-004	Pain in Extremity	Severe/N
PB-06-004	Migraine	Severe/N
	Vertigo	Severe/N
PB-06-004	Nephrolithiasis	Severe/N
PB-06-004	Pelvic pain	Severe/N
	Pain in Extremity	Severe/N

[Note: Patient ID information has been redacted from the Table above.]

There were 2 (12.5%) paediatric patients with severe AEs, and no paediatric patients with very severe AEs. The severe AEs in paediatric patients were gastrointestinal inflammation in 1 (6.3%) patient, and pulmonary hypertension in 1 (6.3%) patient.

Comment: There were 17 (14.7%) adult patients with severe events (21 events) or very severe AEs (3 events). The three very severe AEs experienced by adult patients were autoimmune thrombocytopenia (in 1 patient), osteoarthritis (in 1 patient), and pulmonary embolism (in 1 patient). Severe AEs reported in ≥ 2 adult patients were pain in extremity (3 patients), and nephrolithiasis (2 patients). Of the 17 adult patients with severe or very severe AEs, 6 reported more than one severe or very severe AE: haemoglobin decreased, hip arthroplasty, and procedural pain in 1 patient;

haemangioma and pulmonary embolism in 1 patient; haematuria and nephrolithiasis in 1 patient; pain in extremity and peripheral oedema in 1 patient; migraine and vertigo in 1 patient; and pelvic pain and pain in extremity in 1 patient.

In adults, the proportion of patients with severe or very severe AEs was lower in the ERT-naïve group compared with the ERT-experienced group (12.5% [4/32] and 15.5% [13/84]; respectively). The number of severe or very severe AEs per patient in adults was similar both groups (i.e., 0.16 events/patient in the ERT-naïve group [5 events/32 patients] and 0.25 events/patient in the ERT-experienced group [21 events/84 patients]).

In children, there were 2 (12.5%) patients with one severe event each (1 event of gastrointestinal inflammation; 1 event of pulmonary hypertension). Both of these events were categorized as severe and both occurred in the ERT-naïve group (i.e., 0.19 event per patient). There were no severe or very severe AEs in ERT-experienced children (i.e., 0 events in 5 patients).

8.2.3.4. Adverse events with respect to dose

AEs were examined by the proportion of patients in dose groups < 25, 25 to 35, > 35 to < 55, and > 55 units/kg, and by the proportion of patients in the dose groups 30 units/kg and 60 units/kg. The overview of AE categories by dose is summarized in the study report.

AEs summarized by category and study for the 30 units/kg and 60 units/kg dose groups are summarized below in Table 18.

Table 18: SCS – AEs (>10% in any dose group), completed and ongoing studies by dose group (30 and 60 units/kg).

		PB-06-001				PB-06-005		
		30 units/kg	60 units/kg	PB-06-002	PB-06-004	30 units/kg	60 units/kg	OVERALL
PARAMETER		N = 16	N = 16	N = 31	N = 58	N = 6	N = 5	N = 132
WITH AT LEAST ONE ADVERSE EVENT	N	16	16	31	58	6	5	132
	YES	16 (100.0%)	15 (93.8%)	27 (87.1%)	52 (89.7%)	5 (83.3%)	5 (100.0%)	120 (90.9%
	NO	0 (0.0%)	1 (6.3%)	4 (12.9%)	6 (10.3%)	1 (16.7%)	0 (0.0%)	12 (9.1%
WITH AT LEAST ONE MILD OR MODERATE ADVERSE EVENT	N	16	16	31	58	6	5	132
	YES	16 (100.0%)	15 (93.8%)	27 (87.1%)	52 (89.7%)	4 (66.7%)	5 (100.0%)	119 (90.2%
	NO	0 (0.0%)	1 (6.3%)	4 (12.9%)	6 (10.3%)	2 (33.3%)	0 (0.0%)	13 (9.8%
WITH AT LEAST ONE SEVERE OR VERY SEVERE ADVERSE EVENT	N	16	16	31	58	6	5	132
	YES	1 (6.3%)	3 (18.8%)	4 (12.9%)	9 (15.5%)	1 (16.7%)	1 (20.0%)	19 (14.4%
	NO	15 (93.8%)	13 (81.3%)	27 (87.1%)	49 (84.5%)	5 (83.3%)	4 (80.0%)	113 (85.6%
WITH AT LEAST ONE SERIOUS ADVERSE EVENT	N	16	16	31	58	6	5	132
	YES	2 (12.5%)	3 (18.8%)	6 (19.4%)	3 (5.2%)	0 (0.0%)	2 (40.0%)	16 (12.1%
	NO	14 (87.5%)	13 (81.3%)	25 (80.6%)	55 (94.8%)	6 (100.0%)	3 (60.0%)	116 (87.9%
WITH AT LEAST ONE PROBABLY OR DEFINITELY NOT RELATED ADVERSE EVENT	N	16	16	31	58	6	5	132
	YES	15 (93.8%)	15 (93.8%)	26 (83.9%)	47 (81.0%)	5 (83.3%)	5 (100.0%)	113 (85.6%
	NO	1 (6.3%)	1 (6.3%)	5 (16.1%)	11 (19.0%)	1 (16.7%)	0 (0.0%)	19 (14.4%
WITH AT LEAST ONE DEFINITELY, PROBABLY, OR POSSIBLY RELATED ADVERSE EVENT	N	16	16	31	58	6	5	132
	YES	7 (43.8%)	9 (56.3%)	11 (35.5%)	27 (46.6%)	0 (0.0%)	2 (40.0%)	56 (42.4%)
	NO	9 (56.3%)	7 (43.8%)	20 (64.5%)	31 (53.4%)	6 (100.0%)	3 (60.0%)	76 (57.6%)

Comment: The overall AE profile was similar in the 30 units/kg and the 60 units/kg groups in each of the studies contributing to the total safety population, and most AEs in both dose groups were categorized as mild or moderate. There was a higher proportion of patients in the 60 units/kg groups reporting at least one treatment-related AE than in the 30 units/kg groups. In the four dose groups over the range > 25 to < 55 units/kg, the majority of AEs were categorized as mild/moderate, and most were considered to be

unrelated to treatment. Overall, the differences in the AE profiles of the dose groups are unlikely to be clinically meaningful.

8.2.3.5. Treatment-related adverse events

Treatment-related adverse events (judged by the investigator) were reported in 46.6% (n=54) of adult patients and 12.5% (n=2) of paediatric patients. In adult patients (n=116), the most commonly reported treatment-related AEs in ≥ 1% of patients were headache (6.9%), infusion related reaction (6.0%), pruritus (6.0%), hypersensitivity (4.3%), nausea (3.4%), abdominal pain / upper abdominal pain (2.6%), weight increased (2.6%), rhinorrhoea (2.6%), sneezing (2.6%), erythema (2.6%) flushing (2.6%), eye pruritus (1.7%), eye swelling (1.7%), lacrimation increased (1.7%), fatigue (1.7%), infusion site pain (1.7%), peripheral oedema (1.7%), ALT increased (1.7%), arthralgia (1.7%), back pain (1.7%), dizziness (1.7%), paraesthesia (1.7%), throat irritation (1.7%), and rash (1.7%).

In the 2 paediatric patients with treatment-related AEs, the events were gastrointestinal inflammation, vomiting, chest discomfort, pain in the extremity, and throat irritation in 1 patient, and chest discomfort, throat irritation, and pain in extremity in 1 patient.

In adults, 64 events in 32 patients were considered to be treatment related in the ERT-naïve group (i.e., 2 events/patient) compared with 219 events in 84 patients in the ERT-experienced group (i.e., 2.6 events/patient). The proportion of patients with treatment-related AEs was marginally higher in the ERT-naïve group compared with the ERT-experienced group (50.0% [16/32] vs 45.2% [38/84]). In children, there were 2 patients in the ERT-naïve group with a treatment-related AE (18.2% [2/11]) compared with no patients in the ERT-experienced group (0% [0/5])

8.2.3.6. Infusion-related adverse events

AEs were examined by onset within three time-windows: (i) onset during or within 2 hours after the infusion; (ii) onset 2 to 24 hours after the infusion; and (iii) onset greater than 24 hours after the infusion. The number of AEs reported by category in adults and children reported in the specified time-windows are summarized below in Table 19.

Table 19: SCS – AEs reported during or after an infusion (specified time-windows).

Categories	During or within 2 hours		2 to 24 hours after		≥ 24 hours after	
	Adults (n=116)	Children (n=11)	Adults (n=116)	Children (n=11)	Adults (n=116)	Children (n=11)
Adverse events (AEs)	210	14	245	13	794	46
Mild or moderate AEs	210	13	240	12	773	46
Severe or very severe AEs	0	1	5	1	21	0
Serious adverse events (SAEs)	1	1	3	0	14	1

Categories	During or within 2 hours		2 to 24 hours after		≥ 24 hours after	
	Adults (n=116)	Children (n=11)	Adults (n=116)	Children (n=11)	Adults (n=116)	Children (n=11)
AEs probably not or definitely not related to study drug	39	6	174	13	753	45
AEs possibly, probably or definitely related to study drug	171	8	71	0	41	1

Multiple events with the same preferred term in a system organ class are counted separately for each instance regardless of AE severity. Note: Only include the subjects who reported an AE during or after infusion. Subjects may have experienced AEs in more than one temporal window.

In the total population (n=132), the number of patients with AEs (> 5% in any population) reported in each of the specified time-windows is summarized in the study report. AEs occurring in patients during or within 2 hours after completion of the infusion were headache (6 patients, 4.5%), nausea (5 patients, 3.8%), vomiting (5 patients, 3.8%), abdominal pain (4 patients, 3.0%), arthralgia (2 patients, 1.5%), pyrexia (2 patients, 1.5%), and pain, back pain, and cough in 1 (0.8%) patient each.

The investigator-designated treatment-related AEs (> 1% in any population) in adult and paediatric patients reported as being associated with taliglucerase alfa occurring during the first two time-windows are summarized below in Table 20.

Table 20: SCS – Investigator-designated treatment related AEs (> 1%) associated with taliglucerase alfa infusion.

		During or 2 hours after		Between 2 and 24 hours after	
Disorders (SOC)		Adults (n=116)	Children (n=16)	Adults (n=116)	Children (n=16)
Total number of patients with an event		32 (27.6%)	2 (12.5%)	17 (14.7%)	0
Eye	Eye Pruritus	2 (1.7%)	0	0	0
	Lacrimation increased	2 (1.7%(	0	0	0
Gastrointestinal	Nausea	4 (3.4%)	0	1 (0.9%)	0
	Gastrointestinal inflammation	-	1 (6.3%)	-	0
	Vomiting	-	1 (6.3%)	-	0
Immune	Hypersensitivity	5 (4.3%)	0	0	0
Injury, poisoning,	Infusion related	4 (3.4%)	0	4 (3.4%)	0

		During or 2 hours after		Between 2 and 24 hours after	
Disorders (SOC)		**Adults (n=116)**	**Children (n=16)**	**Adults (n=116)**	**Children (n=16)**
procedural,	reaction				
Nervous system	Dizziness	2 (1.7%)	0	0	0
	Headache	4 (3.4%)	0	5 (4.3%)	0
Respiratory, thoracic, mediastinal	Rhinorrhoea	3 (2.6%)	0	1 (0.9%)	0
	Sneezing	3 (2.6%)	0	1 (0.9%)	0
	Throat irritation	2 (1.7%)	1 (6.3%)	0	0
Skin, subcutaneous tissue	Erythema	2 (1.7%)	0	1 (0.9%)	0
	Pruritus	4 (3.4%)	0	4 (3.4%)	0
Vascular	Flushing	3 (2.6%)		0	0
General, administration site	Chest discomfort	-	1 (6.3%)		0

When there are multiple events with the same preferred term in a system organ class for a subject, the most severe event is used. Multiple events in the same system organ class for a subject are only counted once in the statistics of that system organ class. The percentage represents the incidence of an event by the system organ class or the preferred term as a percentage of the total number of subjects in the treatment group Note: only include the subjects who reported an AE during or after infusion. Subjects may have experienced AEs in more than one temporal window.

Comment: In all patients (n=132), there were 53 (40.2%) patients with an AE reported during or within 2 hours after completion of the infusion, 84 (63.6%) patients with an AE reported between 2 and < 24 hours after completion of the infusion, and 105 (79.6%) patient with an infusion reported at least 24 hours after completion of the infusion. In all patients (n=132), there were 224 AEs reported during or within 2 hours after completion of the infusion (i.e., 1.7 events/patient), 358 AEs reported between 2 to < 24 hours (i.e., 2.7 events/patient), and 840 AEs reported as occurring least 24 hours after completion of the infusion (6.4 events/patient). The closer the AEs were to the infusion, the more likely the events were to considered to be treatment related. Of the 224 AEs occurring during or within 2 hours of completion of the infusion, 179 (79.9%) were considered to be treatment related, of the 258 AEs occurring between 2 and < 24 hours after completion of the infusion, 71 (27.5%) were considered to be treatment related, and of the 840 AEs occurring at least 24 hours after the infusion, 42 (5.0%) were considered to be treatment related.

In the adult patients (n=116), 47 (40.5%) patients experienced 210 AEs during or within 2 hours after completion of the infusion, 75 (64.7%) patients experienced 245 AEs between 2 and < 24 hours after completion of the infusion, and 95 (81.9%) patients experienced 794 AEs at least 24 hours after completion of the infusion. Of the 210 AEs occurring during the infusion or within 2 hours of completion of the infusion in adult patients, 171 (81.4%) were considered to be treatment-related.

In the paediatric patients (n=16), 6 (37.5%) experienced 14 AEs during or within 2 hours after completion of the infusion, 9 (56.3%) experienced 13 AEs between 2 and 24

hours after completion of the infusion, and 10 (62.5%) experienced 46 AEs at least 24 hours after the infusion. Of the 14 AEs occurring during the infusion or within 2 hours of completion of the infusion in paediatric patients, 8 (57.1%) were considered to be treatment-related.

Investigator-designated treatment-related AEs occurring during or within 2 hours after completion of the infusion occurred in 27.6% (32/116) of adults and 12.5% (2/16) of children, and the corresponding figures occurring between 2 and 24 hours after completion of the infusion were 14.7% (17/116) and 0% (0/16).

8.2.3.7. Other adverse events of general regulatory interest

8.2.3.7.1. Blood disorders and lymphatic system disorders

In the total population (n=132), AEs in the "blood disorders and lymphatic system disorders" SOC reported in 2 or more patients were lymphadenopathy (5, 3.8%), and spleen disorder (3, 2.3%). All other events of anaemia, macrocytic anaemia, autoimmune thrombocytopenia, splenic cyst, and splenic lesion were each reported in 1 (0.8%) patient.

8.2.3.7.2. Cardiac disorders

In the total population (n=132), AEs in the "cardiac disorders" SOC reported in 2 or more patients were palpitations (3, 2.3%) and supraventricular extrasystoles (2, 1.5%). All other events of atrial fibrillation, diastolic dysfunction, sinus tachycardia, and ventricular extrasystoles were each reported in 1 (0.8%) patient.

8.2.3.7.3. Hepatobiliary disorders

In the total population (n=132), the only AE in the "hepatobiliary disorders" SOC reported in 2 or more patients was cholelithiasis (3, 2.3%). Other events of gallbladder disorder and hepatic cyst were each reported in 1 (0.8%) patient.

8.2.3.7.4. Renal and urinary disorders

In the total population (n=132), AEs in the "renal and urinary disorders" SOC reported in 2 or more patients were haematuria (4, 3.0%) and nephrolithiasis (2, 1.5%). All other events of dysuria, glycosuria, leukocyturia, pollakiuria, and renal colic were each reported in 1 (0.8%) patient.

8.2.3.7.5. Skin and subcutaneous tissue disorders

In the total population (n=132), AEs in the "skin and subcutaneous tissue disorders" SOC reported in 2 or more patients were: pruritus (11, 8.3%); erythema (5, 3.8%); rash (5, 3.8%); skin irritation (4, 3.0%); contact dermatitis (2, 1.5%); dry skin (2, 1.5%); ecchymosis (2, 1.5%); hyperkeratosis (2, 1,5%); ingrown toenail (2, 1.5%); pruritus generalized (2, 1.5%); rash macular (2, 1.5%); rash pruritic (2, 1.5%); and skin lesion (2, 1.5%). There were numerous commonly observed skin and subcutaneous tissue disorders reported in one patient only.

8.2.4. Deaths and other serious adverse events

8.2.4.1. Deaths

No deaths have occurred in the ongoing and completed clinical studies in the taliglucerase alfa clinical program through to 31 January 2013. In the compassionate use program, one subject from Brazil died due to tuberculosis/pneumonia assessed as definitely not related to treatment with taliglucerase alfa.

8.2.4.2. Serious adverse events (SAEs)

In the ongoing and completed studies, SAEs have been reported in a total of 15 (11.4%) patients through to 31 January 2013 (13 [11.2%] adults; 2 [12.5%] children).

In adult patients, 13 (11.2%) experienced a total of 20 SAEs. None of the SAEs were considered to be treatment related. The onset of the SAEs ranged from 83 to 1,564 days after the initiation of taliglucerase alfa, and all patients with SAEs continued treatment with taliglucerase alfa after the onset of the event. The MedDRA SOC disorders including more than one SAE were: "musculoskeletal and connective tissue disorder" (4 events – arthralgia, bone pain, osteoarthritis, osteonecrosis); "injury, poisoning, procedural complications" (3 events - head injury, traumatic pneumothorax, rib fracture); "respiratory, thoracic, mediastinal" (3 events - cough, epistaxis, pulmonary embolism), and "investigations" (2 events - haematocrit decreased, haemoglobin decreased). All other MedDRA SOC disorders included only one preferred term SAE: autoimmune thrombocytopenia; atrial fibrillation; pyrexia; cytomegalovirus infection; haemangioma; nephrolithiasis; pelvic prolapse; and renal stone removed.

In children, SAEs have been reported in 2 (12.5%) patients (1x gastrointestinal disorder [gastrointestinal inflammation]; 1x infections, infestations [dengue fever]). The gastrointestinal inflammation SAE was considered to be treatment-related, and occurred during the first infusion. The SAE was treated symptomatically and resolved the following day. In this patient, vomiting also occurred during the following two infusions, but the patient then completed the study without further infusion-related AEs, with prophylactic Clarityne being given 12 and 2 hours prior to infusion. The SAE of dengue fever was considered to be unrelated to treatment.

8.2.5. Discontinuations due to adverse events

Three (3) adult patients withdrew from treatment due to AEs: 2 patients withdrew from study PB-06-001 due to immune system disorders (2x hypersensitivity); and 1 patient withdrew from study PB-06-004 due to eye disorders (1x eye swelling).

8.2.6. Adverse events of special interest

8.2.6.1. Hypersensitivity reactions

8.2.6.1.1. Type 1 hypersensitivity adverse events (acute allergic reactions)

An AE was classified as a Type I hypersensitivity event if it was included in either the MedDRA Standard Query (SMQ) or in the specified list of PTs. In adults, 17.2% (20/116) of patients experienced one or more Type 1 hypersensitivity AEs (total of 68 events), while 1 (6.25%) paediatric patient experienced 1 event (angioedema) considered to be unrelated to treatment. Type I hypersensitivity AEs reported in adult patients are summarized below in Table 21.

Table 21: SCS - Type 1 hypersensitivity AEs, number (%) of adult patients.

Parameter	PB-06-001		PB-06-002	PB-06-004	Overall
No. of events	30 U/kg	60 U/kg			
No. of subjects	N=16	N=16	N=26	N=58	N=116
AEs	5	14	14	35	68
Subjects with AEs	2 (12.5%)	4 (25.0%)	4 (15.4%)	10 (17.2%)	20 (17.2%)
Mild/Moderate AEs	5	14	14	35	68
Subjects with Mild/Moderate AE	2 (12.5%)	4 (25.0%)	4 (15.4%)	10 (17.2%)	20 (17.2%)
AEs Definitely, Probably, or Possibly Related to Treatment	2	9	9	32	52
Subjects with AEs Definitely, Probably, or Possibly Related to Treatment	2 (12.5%)	4 (25.0%)	2 (7.7%)	8 (13.8%)	16 (13.8%)

When there are multiple events with the same preferred term in a system organ class for a subject, the most severe event is used. Multiple events in the same system organ class for a subject are only counted once in the statistics of that system organ class. The percentage represents the incidence of an event by the system organ class or the preferred term as a percentage of the total number of subjects in the treatment group Note: AEs occurring during treatment in the extension study (PB-06-003, PB-06-006 and PB-06-007) are reported under the original protocol and treatment group.

The clinical relevance of the Type I hypersensitivity AEs reported in the Phase III studies was examined by the sponsor for the 18 patients experiencing investigator-determined treatment-related events (includes 2 patients with verbatim terms related to Type 1 hypersensitivity reactions). Clinically significant Type 1 hypersensitivity AEs were defined as cases reporting a constellation of suspected hypersensitivity signs/symptoms that resulted in discontinuation of treatment, required an intervention such as pre-treatment to continue infusions, or occurred repeatedly with infusions. Fourteen (14) patients were assessed as experiencing clinically significant events (hypersensitivity, 5 patients; pruritus, 5 patients; eye swelling, 2 patients; and face oedema, lip swelling, scleral oedema, 1 patient each). The sponsor undertook an additional examination of hypersensitivity events using the following criteria to assess clinical relevance: 0 = no intervention was implemented and infusions continued uninterrupted; 1 = temporary intervention, interruption of the infusion or a sign/symptom was treated with concomitant medication; 2 = infusions continued with pre-treatment medication; 3 = infusions discontinued. The results of this assessment are summarized below in Table 22.

Table 22: SCS – Sponsor's risk assessment of investigator-determined treatment related Type 1 hypersensitivity AEs.

Adverse Event Preferred Term	Risk Code
Pruritus	0
Pruritus	0
Pruritus	0
Face oedema	0
Pruritus	0
Pruritus Generalized	0
Pruritus	1
Pruritus	1
Lip swelling	1
Pruritus	1
Hypersensitivity	2
Hypersensitivity	2
Pruritus / Eye oedema	2
Hypersensitivity	3
Hypersensitivity	3
Hypersensitivity	3
Eye Swelling	3
Eye Swelling/Scleral Oedema	3

[Note: Patient ID information has been redacted from the Table above.]

Comment: A total of 69 Type 1 hypersensitivity AEs (all causality) were reported in 20 (17.2%) adults and 1 child (6.25%). Events in the total population (n=132) occurring in ≥ 2 patients were pruritus (11 patients, 8.3%), hypersensitivity (5 patients, 3.8%), and eye swelling (2 patients, 1.5%). The only Type 1 hypersensitivity event reported in children was angioedema (1 event in 1 child), and this event was considered to be unrelated to treatment. No severe or very severe Type 1 AEs were reported in either adults or children, with all 69 events being reported as mild or moderate in severity. The majority of Type 1 hypersensitivity AEs in adults were considered to be treatment-related. There were 16 (17.2%) adult patients with at least one treatment-related Type I hypersensitivity reaction (predominantly pruritus, 7 patients followed by hypersensitivity, 5 patients). In study PB-06-001 (adults) the proportion of subjects with Type 1 hypersensitivity AEs was greater in the 60 units/kg group than in the 30 units/kg group, but patient numbers with these events were small in both groups (4 and 2, respectively).

There were 18 adult patients considered to have investigator-designated treatment-related Type 1 hypersensitivity AEs. The majority of patients (10/18) required no intervention or only temporary intervention to manage the events. Eight (8) patients

required persistent premedication or treatment discontinuation: 2 patients with hypersensitivity and 1 patient with pruritus/eye oedema continued infusions under a pretreatment regimen; 4 patients discontinued treatment because of hypersensitivity or hypersensitivity-related events and in 3 of these patients discontinuation occurred with the first infusion; and 1 patient experienced multiple mild AEs of eye swelling in spite of pretreatment and chose to discontinue treatment with taliglucerase alfa and return to imiglucerase therapy. Perusal of the case narratives for the 5 patients experiencing events described as "hypersensitivity" indicates that these included typical acute allergic reactions such as flushing, tightness in the chest, wheezing, urticaria, itching, chills, periorbital oedema, lacrimation and rhinorrhoea.

8.2.6.1.2. Type II-IV hypersensitivity (delayed hypersensitivity reactions)

Type II-IV hypersensitivity AEs were categorized by MedDRA SOC and PTs. In the total population (n=132), 9 (6.8%) patients experienced at least one Type II-IV hypersensitivity AE, and 1 (0.8%) patient experienced a treatment-related event (drug eruption). All Type II-IV AEs occurred in adults.

In adults (n=116), there were 14 Type II-IV hypersensitivity AEs occurring in 9 (7.8%) patients. Of these 14 events, 13 were reported as mild or moderate in severity and 1 was reported as severe (autoimmune thrombocytopaenia, non-treatment related SAE). Treatment-related Type II-IV hypersensitivity AEs were reported in 1 (0.9%) patient (6 events, drug eruption on the left cheek).

Comment: All 14 Type II-IV hypersensitivity reactions occurred in adult patients (9 patients, 7.8%). The only events occurring in more than 1 patient were arthritis (3 patients, 2.3%) and contact dermatitis (2 patients, 1.5%). All other events occurred in 1 (0.8%) patient each (autoimmune thrombocytopenia, drug eruption, dyshidrosis, macula-papular rash). The only severe event was autoimmune thrombocytopenia, which was also classified as a non-treatment related SAE. The only AE reported as treatment-related was drug eruption, which was reported in 1 patient on 6 separate occasions.

8.2.6.2. Immunogenicity

8.2.6.2.1. IgG anti-taliglucerase alfa antibodies

Anti-taliglucerase alfa IgG antibody was measured in adult and paediatric subjects in studies PB-06-001, PB-06-002, and PB-06-003 and paediatric subjects in study PB-06-005. IgG ADA status was defined as follows:

- ADA Negative: Subject with negative antibody status for all samples collected during the study including baseline (pre-treatment).
- ADA Positive: Subject with at least 1 positive antibody sample anytime during the study including baseline (pre-treatment).
- Treatment-Induced ADA Negative:
  - Subject with negative antibody status for all samples collected during the study including baseline (pre-treatment).
  - Subject positive at baseline but does not have any post-infusion samples that are considered treatment-boosted (see definition below).
- Treatment–Induced ADA Positive ("developed ADA"; "treatment emergent ADA"):
  - Subject negative at baseline but has at least 1 positive sample collected at any point after first infusion.

- Subject positive at baseline and has at least 1 treatment-boosted sample collected after first infusion. A sample is considered treatment-boosted if the titre is ≥6-fold the initial baseline titre.
- Subject without a pre-treatment sample who has at least 1 positive sample collected at any point after first infusion (no subjects met this criterion in this dataset).
- Subject positive both pre-treatment and post-treatment but has no titre results from either or both periods (additional assessments may be used to further categorize these subjects e.g., evaluation of differences in the assay signal) (no subjects met this criterion in this dataset).

The results for IgG anti-taliglucerase antibody (anti-drug antibody [ADA]) are summarized below:

- IgG ADA assessment has been carried out in 71 patients (43 ERT-naïve; 28 ERT-experienced), including 58 adults and 13 children. Of these 71 patients, 24 (33.8%) developed treatment-induced Ig ADA.
- Forty-three (43) ERT-naïve patients were assessed (32 adults; 11 children). Of the ERT-naïve patients (n=43), 19 (44.2%) were found to have treatment-induced IgG ADA (17 adults; 2 children). In the adult population, 2 additional patients were IgG ADA positive at baseline (i.e., before exposure); 1 discontinued and 1 maintained low stable titres throughout treatment.
- Twenty-eight (28) ERT-experienced patients were assessed (26 adults, 2 children). Of the ERT-experienced patients (n=28), 5 (17.9%) were found to have treatment-induced IgG ADA (3 adults and 2 children). Of the 5 patients with treatment-induced IgG ADA, 1 was found to have IgG ADA at baseline (i.e., before exposure) that did not change during treatment and was scored by the sponsor as Antibody Negative in further analyses, and 1 was found to have IgG ADA at baseline (i.e., before exposure) that decreased during treatment and was absent from week 12 onwards.
- In the total population (n=71), of the 24 patients who developed treatment-induced IgG ADA, 10 (41.7%) experienced Type I hypersensitivity AEs (all causality). In the 47 patients who were negative for treatment-induced IgG ADA, 10 (21.3%) experienced Type 1 hypersensitivity AEs (all causality). In the treatment-induced IgG ADA positive patients (n=24), 7 (29.2%) developed treatment-related Type 1 hypersensitivity AEs, and in the treatment-induced IgA negative patients (n=47), 6 (12.8%) developed treatment-related Type 1 hypersensitivity AEs.
- In ERT-naïve patients (n=43), the incidence of Type 1 hypersensitivity AEs was higher in the treatment-induced Ig ADA positive patients than in the negative patients (31.6% [6/19] vs 12.5% [3/24], respectively). Similarly, in ERT-experienced patients (n=28) the incidence of Type 1 hypersensitivity AEs was higher in the treatment-induced Ig ADA positive patients than in the negative patients (20.0% [1/5] vs 13.0% [3/23], respectively).
- There appears to be an association between development of IgG ADA and the occurrence of Type I hypersensitivity AEs (overall, ERT-naïve, and ERT-experienced). However, the sponsor comments “given the small number of subjects and the different duration of treatment for individuals, potentially affecting event frequency, these observations should be interpreted with caution”.
- Treatment outcomes in the 20 (28.2%) patients who experienced a Type 1 hypersensitivity AE in the 71 patients assessed for treatment-induced Ig ADA (10 patients negative, 10 patients positive) were: 10 patients continued treatment with no intervention; 3 discontinued treatment due to Type I hypersensitivity AEs, 1 of whom declined premedication; 5 continued treatment with use of medications such as antihistamines for

rash or pruritus; and 2 continued treatment with a pretreatment regimen aimed at controlling the AEs. The breakdown for the outcomes between antibody positive and antibody negative patients could not be identified in the submitted data.

- There were 4/58 (6.9%) adult patients who were IgG ADA pre-dose. Of these 4 patients, 2 fulfilled the criteria for treatment-induced IgG ADA. There were 2/13 (15.4%) paediatric patients who were IgG ADA pre-dose. Of these 2 patients, neither fulfilled the criteria for treatment-induced IgG ADA. It is possible that the 6 patients with pre-dose IgG ADA had pre-existing cross-reactive antibodies to plant glycans shared with taliglucerase alfa.
- IgG ADA results for the individual studies were as follows. In study PB-06-001, 17/32 (53.1%) ERT-naïve subjects developed IgG ADA post-treatment; 2 additional subjects were IgG ADA positive at baseline and 1 of these discontinued the study and 1 maintained stable titres after treatment. In study PB-06-002, 4/28 (12.5%) ERT-experienced patients who switched from imiglucerase to taliglucerase alfa developed IgG ADA after switching, and 2 additional patients who switched from imiglucerase were IgG ADA positive at baseline and became negative or maintained stable titres following treatment with taliglucerase alfa. In the extension study PB-06-003, 13/26 (50%) patients from study PB-06-001 were IgG ADA positive, all of whom had been positive in the original study, and 3/18 (16.7%) subjects from study PB-06-002 were positive, 2 of whom had been positive and 1 of whom had been negative in the original study. In study PB-06-005, 2/11 (18.2%) ERT-naïve paediatric patients developed IgG ADA, and 1 additional patient who was IgG ADA positive at baseline had no post-treatment titre increase.

8.2.6.2.2. Neutralizing antibodies

Two independent assays measuring neutralizing antibody activity were performed, an in vitro assay based on enzyme activity and a cell-based assay that combined both cellular uptake and intracellular enzymatic activity using the same positive control. Assay validation studies of both the in vitro and cell-based assays showed similar sensitivity for the detection of anti-taliglucerase alfa neutralizing antibodies.

Of the 24 adult patients with IgG ADA that were tested for neutralizing antibodies, 3 (12.5%) tested positive for neutralizing antibodies in the in vitro assay but negative in the cell based assay. The efficacy response was reported as not appearing to decrease in the two treatment naïve subjects with neutralizing antibodies. However, the switch-over subject who had neutralizing antibody activity maintained organ volumes compared to baseline, but showed decreases in haemoglobin and platelet count at the last follow up visit. The switch-over subject continued treatment with taliglucerase alfa. Of 13 paediatric patients who were assessed for the presence of IgG ADA, all tested negative for neutralizing antibodies.

8.2.6.2.3. IgE antibodies

Subjects who experienced allergic reactions were tested by ELISA for anti-taliglucerase alfa IgE ADA in addition to anti-taliglucerase alfa IgG ADA testing. There were 2 patients who tested positive for IgE ADA (including pre-dose).

In study PB-06-001, there was 1 adult patient who tested positive for IgE ADA. This patient was positive for IgE ADA pre-dose and discontinued treatment after the first infusion due to an infusion related hypersensitivity reaction. This subject had a similar reaction when exposed to imiglucerase.

In study PB-06-005, there was 1 paediatric patient in the 60 units/kg group with pre- and post-dose IgG ADA and IgE ADA. This patient experienced 8 AEs at various visits (chest discomfort, itchy throat 3x, common cold, otitis media, gastro-enteritis and painful gums) during the study. Itchy throat and chest discomfort during the first infusion and itchy throat during the following two infusion visits were considered hypersensitivity reactions and reported as related to the study treatment. The patient did not discontinue treatment.

8.2.6.3. Bone events

In adult patients (n=116), 55 (47.4%) experienced 182 bone events, of which 11 events in 7 (6.0%) patients were considered severe or very severe. SAE bone events were reported in 2 (1.7%) patients. There were 26 events in 8 (6.9%) adult patients judged by the investigator to be treatment-related, and the majority of treatment related bone events were musculoskeletal discomfort (15 events) which all occurred in 1 patient. Of the treatment-related bone events, 4 events occurred during the infusion or within 2 hours after the completion of the infusion (arthralgia, back pain, muscle spasm, and musculoskeletal discomfort [14 events in 1 patient]). The treatment-related bone AEs reported in the 8 adult patients are summarized below in Table 23.

Table 23: SCS – Adult patients with treatment-related bone pain events in ongoing and completed studies.

Study ID	Preferred Term	Severity	Infusion Time Point
PB-06-001	Arthralgia	Mild	Occurring at least 24 hours after the completion of the infusion
PB-06-003	Arthralgia	Moderate	Occurring during the infusion or within 2 hours after the completion of the infusion
PB-06-004	Back Pain	Moderate	Occurring at least 24 hours after the completion of the infusion
	Musculoskeletal Pain	Moderate	Occurring at least 24 hours after the completion of the infusion
PB-06-004	Back Pain	Mild	Occurring during the infusion or within 2 hours after the completion of the infusion
PB-06-003	Bone Pain	Moderate	Occurring at least 24 hours after the completion of the infusion
PB-06-001	Muscle Spasm (2 events)	Mild	Occurring at least 24 hours after the completion of the infusion
	Muscle Spasm	Mild	Occurring during the infusion or within 2 hours after the completion of the infusion
PB-06-004	Musculoskeletal Discomfort (14 Events)	Mild	Occurring during the infusion or within 2 hours after the completion of the infusion
	Musculoskeletal Discomfort (1 Events)	Mild	Occurring at least 24 hours after the completion of the infusion
PB-06-003	Pain in Extremity	Mild	Occurring between 2 hours and 24 hours after the completion of the infusion

[Note: Patient ID information has been redacted from the Table above.]

Overall, 5 (31.3%) paediatric patients experienced 10 bone events, none of which were considered severe or very severe or classified as SAEs. There was 1 (6.3%) patient with a bone event judged by the investigator to be treatment-related (pain in extremity). None of the bone events occurred during the infusion or within 2 hours of the completion of the infusion. One patient experienced two events of osteonecrosis (right femoral head avascular necrosis and right acetabular necrosis) during the extension study PB-06-003 and both were rated severe. The osteonecrosis was reported as a SAE, but the event was preexisting and not assessed as treatment-emergent. All bone events occurring in the paediatric patients are summarized below in Table 24.

Table 24: SCS – Paediatric patients with bone pain events in ongoing and completed studies.

Study ID	Preferred Term	Severity	Infusion Time Point
PB-06-002	Arthralgia	Mild	Occurring between 2 hours and 24 hours after the completion of the infusion
PB-06-005	Pain in Extremity	Mild	Occurring at least 24 hours after the completion of the infusion
	Pain in Extremity	Mild	Occurring between 2 hours and 24 hours after the completion of the infusion
PB-06-005	Bone Pain (2 events)	Mild	Occurring at least 24 hours after the completion of the infusion
	Pain in Extremity	Mild	Occurring at least 24 hours after the completion of the infusion
PB-06-006	Pain in Extremity*	Mild	Occurring at least 24 hours after the completion of the infusion
PB-06-006	Arthralgia	Mild	Occurring at least 24 hours after the completion of the infusion
	Jaw Disorder	Mild	Occurring at least 24 hours after the completion of the infusion
	Joint Crepitation	Mild	Occurring at least 24 hours after the completion of the infusion

[Note: Patient ID information has been redacted from the Table above.]
*AE considered treatment-related

8.2.6.4. Compassionate use program

In addition to the subjects participating in clinical trials, taliglucerase alfa has also been administered in various Compassionate Use Programs in Europe, Brazil, Australia, Mexico and Israel. The majority of reported AEs in the compassionate use program have been associated with immune-mediated Type 1 hypersensitivity events, and these events were responsible for the majority of treatment discontinuations. However, approximately 50% of patients who received premedication or symptomatic treatment with antihistamines or corticosteroids were able to continue taliglucerase alfa therapy. There were several reports of "anaphylactic reactions" from medically qualified reporters, but these events did not appear to be life-threatening allergic reactions. Nevertheless, the majority of the reported "anaphylactic reactions" required symptomatic treatment, including oxygen support in some cases, and resulted in treatment discontinuation. There has been 1 death due to tuberculosis/pneumonia in the Compassionate Use Program assessed as definitely not related to treatment with taliglucerase alfa for GD. The case was reported from Brazil, and the patient was of unknown age, race and gender.

As of 1 February 2013, there were approximately 260 subjects enrolled in the Compassionate Use Programs. All causality AEs have been reported in 72 patients, including SAEs in 44 patients (114 events) and 28 non-serious AEs (41 events). Of the 72 patients with all causality AEs, 26 experienced serious immune-mediated Type 1 hypersensitivity-related events and 14 experienced non-serious immune Type 1 hypersensitivity-related events. A total of 39 patients discontinued treatment (21 with serious events, 18 with non-serious events). Of the 39 patients discontinuing treatment because of AEs, 26 discontinued due to immune-mediated Type 1 hypersensitivity-related events. No other AEs predominated in the remaining 13 subjects who discontinued due to AEs. Events described as an "anaphylactoid reaction" were reported in 7 patients, 5 of whom discontinued treatment with outcome for the other 2 being unknown.

In cases where age was provided, there were 3 paediatric subjects. One (1) eight year old patient experienced non-serious back pain during infusions and discontinued treatment. Two (2) patients experienced serious hypersensitivity events (tachycardia and dyspnoea resulting in discontinuation in a 17-year old; tonsillitis, odynophagia and various hypersensitivity events in a 10 year old for which the treatment outcome was not given.

Treatment-related SAEs have been reported in 36 patients, 26 with serious immune-mediated Type 1 hypersensitivity-related events and 3 with non-serious hypersensitivity events. There were no other AE trends amongst the remaining 8 patients who experienced serious treatment-

related events. In cases where information was provided, 14 patients with treatment-related SAEs discontinued treatment with taliglucerase alfa, 11 of these following an immune-mediated Type 1 hypersensitivity event. Of the 7 patients reporting an event related to anaphylaxis, each was reported as being related to treatment. There were 8 patients with immune-mediated Type 1 hypersensitivity related events who were apparently able to continue taliglucerase alfa therapy following either premedication with antihistamines and/or corticosteroids or with treatment for emergent symptoms. A further 8 patients with immune-mediated Type 1 hypersensitivity related events discontinued taliglucerase alfa therapy following treatment with antihistamines, corticosteroids or oxygen support and, in 1 case, anticoagulant for superficial phlebitis.

8.2.7. Clinical laboratory tests

Clinical laboratory tests (haematology, biochemistry) were summarized for studies PB-06-001 and PB-06-005 by mean values, shift tables (low/high/normal), mean platelet counts (local laboratory), ESR (local laboratory), and urinalysis (local laboratory). The majority of the clinical laboratory parameters remained at pre-treatment normal levels or improved to normal levels by the end of study following treatment. Review of the available data showed that the elevations in ALT or AST observed in the current dataset were mild and explainable, either due to concomitant medication or illness. All subjects that reported liver function test abnormalities showed either clinical improvement or clinical stability while on taliglucerase alfa treatment. The sponsor commented that intermittent elevations in liver enzymes can occur in subjects with GD without co-existing morbidities.

Clinical laboratory tests reported as AEs were infrequently reported and the only parameters reported as AEs in 2 or more patients were: ALT increased (4/132, 3.0%); AST increased (2/132, 1.5%); hypertriglyceridaemia (3/132, 2.3%); blood cholesterol increased (2/132, 1.5%). Abnormal urinalysis results were reported as AEs in 0.8% (1/132) of patients.

8.2.8. Vital signs, electrocardiogram (ECG) and other tests

8.2.8.1. Vital signs

No clinically significant findings were observed in vital signs in those studies in which the relevant parameters were routinely measured. Vital signs measured during the infusion were generally within normal limits. Asymptomatic decreases in blood pressure were occasionally observed in patients whose blood pressure was routinely measured. Hypertension was reported as an AE in 6.1% (8/132) of patients, while no reports of hypotension as an AE could be identified. Sinus tachycardia was reported as an AE in 0.8% (1/132) of patients, while no reports of bradycardia as an AE could be identified. Increased heart rate was reported as an AE in 1.5% (2/132) of patients and decreased heart rate was reported as an AE in 0.5% (1/132) of patients. Pyrexia as an AE was reported in 10.6% (14/132) of patients. In study PB-06-005 (paediatric study), one patient had a fever of 39oC five days after the Visit 16 infusion considered not to be related to treatment.

8.2.8.2. Electrocardiogram

ECG results were provided for studies PB-06-001, and PB-06-002. ECG results were not available at the cut-off date of 01 May 2012 for studies PB-06-004, PB-06-005, and PB-06-006. During the reporting period there were 2 clinically significant changes from baseline ECG in study PB-06-002, and 1 in study PB-06-001, and these are summarized immediately below.

In study PB-06-002: 1 patient had a clinically significant change from baseline observed at Month 6 of sinus tachycardia (supraventricular on ECG) that was considered to be mild and unrelated to treatment. The patient completed the study and subsequently enrolled in the extension study; 1 patient had significant changes from baseline of occasional supraventricular premature beats following 12 months treatment. The event resolved and was considered to be

unrelated to treatment. The patient completed the study and subsequently enrolled in the extension study

In study PB-06-001: 1 patient had a clinically significant change from baseline observed at Month 36 of left ventricular hypertrophy. The event was considered mild and was considered unrelated to treatment. The patient completed the study and subsequently enrolled in the extension study.

8.2.8.3. Echocardiogram

In studies PB-06-001 and PB-06-005, the percentage of patients with abnormal echocardiograms at screening, Month 9, 12, 24 and 36 were 30.2% (9/63), 20.8% (11/53), 15.4% (2/13), 23.7% (9/24), and 25.0% (6/24), respectively. Three (3) ERT-naïve patients had new ECHO findings during the course of the study: 1 x pulmonary hypertension; 1 x tricuspid incompetence; 1 x mild mitral and tricuspid regurgitation. AEs of pulmonary hypertension were reported for 2 of these patients. There were 2 children with abnormal ECHOs: 1 x mild tricuspid regurgitation at Week 52; 1 x pulmonary hypertension with tricuspid incompetence worsening from baseline in a patient with GD type 3c with characteristic cardiac valve involvement with baseline abnormal AV valves.

8.2.8.4. Pulmonary function tests (PFT)

Pulmonary function tests (PFT) were obtained at screening, Months 9, 24 and 36 for 74 patients (including 11 children) in the safety population from studies PB-06-001 and PB-06-002. Pulmonary function was reported as being stable from screening to Month 24.

8.2.9. Safety in special groups

8.2.9.1. Age

Overall, 108 patients aged 18 to < 65 years were enrolled in the clinical program (i.e., 93.1% of the total adult population). Consequently, the safety data in adult patients are primarily driven by patients aged 18 to < 65 years. Of the 116 adult patients there were only 8 (6.9%) patients aged ≥65 years. It is considered that the number of patients aged ≥ 65 years is too small to make meaningful comparisons between the safety data in this age group and the safety data in patients aged 18 to < 65 years. There were 16 children aged from 2 to < 18 years (i.e., 12.1% of the total safety population). The available safety data suggest that there are no significant differences between the safety profile of taliglucerase alfa in children and adults.

8.2.9.2. Gender

In the adult population (n=116), there were 62 (53.4%) males and 54 (46.6%) females. The proportion of males with at least one AE was 90.3% (56/62) compared with 96.3% (52/54) of females. SAEs were reported in 11.3% (7/62) of males and 13.0% (7/54) of females. Treatment-related AEs were reported 45.2% (28/62) of males and 48.1% (26/54) of females.

The incidence in male vs female adult patients of AEs reported in ≥ 10% of the combine male and female adult population was: arthralgia 24.2% vs 22.2%; nasopharyngitis 22.6% vs 24.1%; pain in extremity 19.4% vs 13.0%; headache 16.1% vs 29.6%; viral upper respiratory tract infection 16.1% vs 24.1%; cough 11.3% vs 20.4%; back pain 11.3% vs 11.1%; fatigue 9.7% vs 16.7%; abdominal pain (including upper and lower abdominal pain) 8.1% vs 14.8%; diarrhoea 6.5% vs 14.8%; nausea 6.5% vs 14.8%; oropharyngeal pain 4.8% vs 16.7%; and pyrexia 3.2% vs 20.4%. Most of the commonly reported AEs occurring in ≥10% of the combined adult population occurred more frequently in females than in males.

In the paediatric population (n=16), there were 11 (69%) males and 5 females (31%). The proportion of males with at least one AE was 72.2% (8/11) compared with 80.0% (4/5) of females. SAEs were reported in 18.2% (2/11) of males and 0% (0/5) of females. Treatment-related AEs were reported in 9.1% (1/11) of males and 20.0% (1/5) of females. The number of

male and female paediatric patients is considered too small to allow meaningful comparisons regarding differences in safety to be drawn.

8.2.9.3. Race

The total population was almost exclusively Caucasian (96.2%, 127/132). Consequently, no conclusion can be drawn concerning differences in safety among racial groups.

8.2.9.4. Other groups

There were no safety studies in patients with hepatic or renal impairment, nor were there drug-drug interaction safety studies. There are limited data in pregnant women from the ongoing and completed studies (4 women with live births). In addition, there have been 5 pregnancies in women exposed to taliglucerase alfa in the Compassionate Use Program, and 1 spontaneous report from post-marketing usage. The limited data in pregnant women does not allow an adequate assessment of the effect of taliglucerase alfa on pregnancy to be undertaken. No studies on the appearance of taliglucerase alfa in breast milk have been conducted.

8.2.10. Addendum, Immunogenicity Overview (2.7.1.3)

The Module 2 document summarising the biopharmaceutic studies included an "Addendum, Immunogenicity Overview" (Section 2.7.1.3).

- The specific concerns addressed in the overview were:

The absence of quantitative data mapping the glycosylation profile and total site occupancy in the glycosylation studies.

- Consideration of the immunogenic potential of xylose and fucose glycans as almost all glycans of taliglucerase alfa contained core β1-2 xylose and many of the glycans had core α1-3 fucose.
- The change of the glycosylation of the drug substance (from 60% to 90% xylosylated high mannose glycans) during development of the manufacturing process

In addition to these concerns, the overview also addressed:

- The assessment of factors generally considered to contribute to the immunogenicity risk profile of protein-based therapeutics.
- The development and implementation of additional assays to more fully understand the immunogenicity risk profile of taliglucerase alfa.
- The risk that may be associated with plant-specific glycan structures.

> **Comment**: The "overview" included a review of IgG ADA cases in the patients exposed to taliglucerase alfa. These cases have been discussed in detail in the body of this CER. The overview also included a discussion of factors with the potential to contribute to the taliglucerase alfa immunogenicity profile (i.e., product related factors; patient related factors; treatment related factors; and analytical factors). The patient related factors discussed were: nature of β-glucocerebrosidase mutation and potentially inadequate immune tolerance to exogenously administered protein; immune dysregulation in GD which might vary with the disease status; pre-existing cross-reactive antibodies; and type of β-glucocerebrosidase mutation. The treatment related factors discussed were: dose; chronic dosing regimen; route of administration; and previous exposure to other ERTs. The sponsor's overview provided a reasonable discussion of the clinical factors. The product related and analytical factors discussed in the "overview" are primarily matters for the Module 3 (quality) evaluator. The sponsor concluded the overview by stating that it "has committed to continued evaluation of taliglucerase immunogenicity".

8.2.11. Post-marketing experience

Since 1 May 2012, taliglucerase alfa has been marketed in the USA for adults with GD. In the post-marketing dataset from 01 May 2012 to 01 February 2013, there have been 2 serious AEs in 2 patients (major depression in 1 patient, and hypertension in 1 patient [non-serious AE of nasopharyngitis also reported in this patient]), and 29 non-serious AEs in 8 patients. Non-serious AEs reported more than once were: weight increased (x3) diarrhoea (x2); weight decreased (x2); and headache (x2). In the 10 patients with spontaneous AEs reports, the events were considered related to treatment in 9 patients. None of the spontaneously reported events were fatal. The post-marketing data is too limited to allow any meaningful conclusions to be drawn.

8.3. Evaluator's overall conclusions on clinical safety

It is considered that the safety data from study PB-06-005 in children are consistent with the previously evaluated safety data in adults. In addition, it is considered that the safety data in the original and updated SCS documents are consistent. Overall, it is considered that the safety of taliglucerase alfa for the treatment of non-neuronopathic GD has been adequately demonstrated in the original and updated submissions. However, the safety assessment is limited due to the small number of patients exposed to the medicine in the ongoing and completed clinical trials, and the absence of a randomized study comparing the medicine with an active control such as imiglucerase or velaglucerase alfa. The safety data are limited to patients with non-neuronopathic GD as there were no data in patients with neuronopathic GD.

The safety assessment is based on data from 132 patients exposed to taliglucerase alfa in the ongoing and completed GD clinical trial program (116 adults; 16 children). Based on the "rule of three", 132 patients exposed to taliglucerase alfa provide a population of sufficient size to support detection of adverse drug reactions (ADRs) occurring with an upper 95% CI of ≥ 2.2% (Jovanovic and Levy, 1997; Jacobsen et al., 2001). However, the safety population (n=132) is of insufficient size to ensure detection of ADRs occurring with a frequency of ≤ 2%. Furthermore, exposures of ≥ 6 and ≥ 12 months have been reported in only 111 patients (98 adults, 13 children) and 95 patients (83 adults, 12 children), respectively. However, the number of patients available for studies assessing the clinical efficacy and safety of taliglucerase alfa for the treatment of GD is limited due to the rarity of the disease. Overall, the limited safety database is considered to be adequate for an orphan drug.

The primary safety concern arising from the original submission was the absence of data relating to the potential immunogenicity of the plant-specific glycans found on taliglucerase alfa. The re-submission provided no data directly assaying the immunogenicity of these plant-specific glycans in patients with GD treated with taliglucerase alfa. However, new in vitro data in the re-submission provides indirect evidence suggesting that the immunogenicity of taliglucerase alfa is likely to arise primarily from the protein backbone of the molecule rather than from the plant-specific glycans. Furthermore, it is considered that the clinical studies have adequately characterized the immune response to taliglucerase alfa, irrespective of whether the response arises from antibodies induced by the protein backbone and/or the plant-specific glycans.

In the clinical studies, assessment of IgG anti-drug antibodies (ADA) was carried out in a total of 71 patients (43 ERT-naïve, 28-ERT experienced). Of the 43 ERT-naïve patients, 19 (44.2%) were found to have treatment-induced IgG ADA (17/32 [53.1%] adults, 2/11 [18.1%] children). Of the 28 ERT-experienced patients, 5 (17.9%) were found to have IgG ADA (3 adults, 2 children). Based on these figures, 24/71 (33.8%) patients were positive for treatment-induced IgG ADA, and the incidence of treatment-induced IgG ADA was notably higher in ERT-naïve patients (44.2%) than in ERT-experienced patients (17.9%).

There appears to be an association between treatment-induced IgG ADA and Type I hypersensitivity AEs in the total, ERT-naïve, and ERT-experienced populations. In the total population (n=71), 10 (44.7%) of the 24 patients with treatment-induced IgG ADA experienced Type 1 hypersensitivity reactions compared with 10 (21.3%) of the 47 patients without treatment-induced IgG ADA. In the 20 patients experiencing Type 1 hypersensitivity reactions, irrespective of treatment-induced IgG ADA status, 10 continued treatment with no intervention, 3 discontinued treatment following Type I hypersensitivity AEs (1 declined premedication), 5 continued treatment with symptomatic use of medications such as antihistamines for rash or pruritus, and 2 continued treatment with a pretreatment regimen aimed at preventing or minimising allergic reactions associated with the infusion. The results suggest that Type 1 hypersensitivity AEs were manageable in the majority of the 20 patients, irrespective of treatment-induced IgG ADA status.

There were 4/58 (6.9%) adult patients who were IgG ADA pre-dose. Of these 4 patients, 2 fulfilled the criteria for treatment-induced IgG ADA. There were 2/13 (15.4%) paediatric patients who were IgG ADA pre-dose. Of these 2 patients, neither fulfilled the criteria for treatment-induced IgG ADA. It is possible that the 6 patients with pre-dose IgG ADA had pre-existing cross-reactive antibodies to plant glycans shared with taliglucerase alfa.

None of 24 adult patients testing positive for IgG ADA tested positive for neutralizing antibodies measured in both independent assays (3 [12.5%] tested positive in the in vitro enzymatic assay but not in the cell based assay). No children tested positive for neutralizing antibodies. Two (2) patients tested positive for IgE ADA (1 adult, 1 child), and both patients were positive at the baseline visit. The adult patient discontinued after the first infusion due to an infusion-related reaction, while the paediatric patient completed the study. It is not possible to determine the incidence of patients with IgE ADA pre-dose or post-dose as not all patients were tested for this antibody. Only patients who experienced allergic reactions were tested for IgE ADA.

In the adult population (n=116), there were 20 (17.2%) patients with all-causality Type 1 hypersensitivity AEs, and all events were reported as being mild/moderate in intensity. The events reported in the 20 adult patients were pruritus in 11 patients (9.5%), hypersensitivity in 5 (4.3%) patients, eye swelling in 2 (1.7%) patients, and eye oedema, scleral oedema, lip swelling, and face oedema in 1 (0.9%) patient each. There were 18 adult patients considered to have investigator-designated treatment-related Type 1 hypersensitivity AEs. Of these 18 patients, 10 required no intervention or only temporary intervention to manage the events, while 8 required premedication or treatment discontinuation. One (1) Type 1 hypersensitivity AE (angioedema) was reported in 1 paediatric patient, and this event was considered by the investigator to be unrelated to treatment.

Type II-IV hypersensitivity AEs (delayed hypersensitivity reactions) were reported only in adults (9/116 [7.8%]). Of the 14 events, 13 were reported as mild or moderate in severity and 1 was reported as severe (autoimmune thrombocytopaenia, non-treatment related SAE). Events reported in more than 1 patient were arthritis (3 patients, 2.3%), and contact dermatitis (2 patients, 1.5%). All other events occurred in 1 (0.8%) patient each (autoimmune thrombocytopenia, drug eruption, dyshidrosis, macula-papular rash). The only event reported as treatment-related was drug eruption (left cheek), which was reported in 1 patient on 6 separate occasions.

Bone events are of special interest in patients with GD. In adults (n=116), 55 (47.4%) patients experienced bone events, and SAE bone events were reported in 2 (1.7%) patients. In 8 (6.9%) patients, bone events were judged by the investigator to be treatment-related. The majority of treatment-related bone events were categorized as musculoskeletal discomfort (15 events, all in 1 patient). Of the treatment-related bone events, 4 events occurred during the infusion or within 2 hours after the completion of the infusion (arthralgia, back pain, muscle spasm, and musculoskeletal discomfort). In children (n=16), 5 (31.3%) patients experienced bone events, and none of the events were considered to be SAEs. There was 1 (6.3%) paediatric patient with

a bone event judged by the investigator to be treatment-related (pain in extremity). None of the bone events in children occurred during the infusion or within 2 hours of the completion of the infusion.

In adult patients, 93.1% (108/116) experienced a total of 1,252 AEs and the most commonly reported AEs (>10% of patients) were nasopharyngitis (23.3%), arthralgia (23.3%), headache (22.4%), viral upper respiratory tract infection (19.8%), pain in extremity (16.4%), cough (15.5%), fatigue (12.9%), abdominal pain (11.2%), pyrexia (11.2%), back pain (11.2%), diarrhoea (10.3%), nausea (10.3%), and oropharyngeal pain (10.3%).

In paediatric patients, 75.0% (12/16) experienced a total of 73 AEs, and the most commonly reported AEs (> 10% of patients) were vomiting (31.3%), abdominal pain (18.8%), nasopharyngitis (18.8%), headache (18.8%), pain in extremity (18.8%), tonsillitis (12.5%), diarrhoea (12.5%), arthralgia (12.5%), epistaxis (12.5%), and tooth extraction (12.5%).

In adults, the proportion of patients with AEs in the ERT-naïve group was higher than in the ERT-experienced group (96.9% [31/32] vs 91.7% [77/84]). There were 425 AEs in the 32 ERT-naïve patients (i.e., 13.3 events/patient), and 827 AEs in the 84 ERT-experienced patients (i.e., 9.8 events/patient). In children, the proportion of patients with AEs in the ERT-naïve group was higher than in the ERT-experienced group (90.9% [10/11] vs 40.0% [2/5]). There were 68 AEs in 11 ERT-naïve paediatric patients (i.e., 6.2 events/patient), and 5 AEs in the 5 ERT-experienced paediatric patients (i.e., 1 event/patient). The difference between the ERT-naïve and ERT-experienced groups in children as regards AEs should be interpreted cautiously due to the small number of patients in each group.

Overall, SAEs were reported in 13 (11.2%) adult patients (20 events), and 2 (12.5%) paediatric patients (2 events). In adults, none of the SAEs were considered to be treatment related while in paediatric patients 1 SAE was considered to be treatment-related (gastrointestinal inflammation). There were no deaths reported in the ongoing and completed studies in the GD clinical program. There was 1 death reported in the compassionate use program considered to be unrelated to treatment (tuberculosis/pneumonia).

The closer the AEs occurred to the taliglucerase alfa infusion the greater the risk of them being considered by the investigator to be treatment-related. Investigator-designated treatment-related AEs occurring during or within 2 hours of completion of the infusion were reported in 27.6% of adult patients (n=32) and 12.5% (n=2) of paediatric patients. The most commonly reported investigator-designated treatment related AEs in adult patients (≥2% of patients) during or within 2 hours of the completion of the infusion were hypersensitivity (4.3%), nausea (3.4%), infusion-related reactions (3.4%), headache (3.4%), pruritus (3.4%), rhinorrhoea (2.6%), sneezing (2.6%) and flushing (2.6%). AEs in paediatric patients designated as treatment-related by the investigator were gastrointestinal inflammation and vomiting in 1 patient, and chest discomfort in 1 patient.

Only 3 adult patients withdrew from treatment due to AEs (2x hypersensitivity; 1 x eye swelling). There were no treatment discontinuations in children due to AEs.

There were no clinically significant changes in laboratory tests, vital signs, ECG, ECHO or PFTs during the course of the study. Commonly reported AEs occurred more frequently in female patients than in male patients, but the observed differences are considered not to require dosing adjustments. The AE profile is similar in children and adults.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of treatment with taliglucerase alfa (30 units/kg; 60 units/kg) in ERT-naïve and ERT-experienced adult and paediatric patients with non-neuropathic GD include reduction in spleen volume, reduction in liver volume, improvement in haemoglobin level, and improvement in platelet count. In addition, taliglucerase alfa has been shown to reduce GD biomarker activity in both adult and paediatric patients (chitotriosidase activity reduced; CCL18 concentration reduced). The duration of treatment with taliglucerase alfa in the pivotal Phase III studies was 12 months in children and adolescents aged 2 to < 18 years in study PB-06-005, and 9 months in adults aged ≥ 18 years in study PB-06-001. In addition, study PB-06-002 showed that in adults and children/adolescents whose disease had been stabilized with imiglucerase, the treatment benefit could be maintained for at least a further 9 months after switching to taliglucerase alfa. Support for treatment benefit achieved with imiglucerase being maintained following switching to taliglucerase alfa was also provided from study PB-06-004 (expanded access treatment protocol). Furthermore, study PB-06-003 showed that patients from studies PB-06-001 and PB-06-002 who had benefited from 9 months treatment with taliglucerase alfa could continue to benefit from further treatment with taliglucerase alfa for at least 15 months.

9.2. First round assessment of risks

Overall, the risks of treatment with taliglucerase alfa for the proposed indication are considered to be acceptable. There are limited data on the safety of the taliglucerase alfa in children and adolescents due to the small number of patients with GD aged ≤ 18 years treated with the medicine in the clinical trial program. However, the available data in children and adolescents suggests that the risks of treatment in this age group are similar to those in adults.

The risks of taliglucerase alfa for the treatment for GD appear to require no specific intervention, or are manageable by symptomatic treatment for both infusion-related and non-infusion related risks, or by prophylactic premedication for infusion-related risks. The risk of treatment discontinuation due to AEs related to taliglucerase alfa is low. Treatment discontinuation due to AEs in the ongoing and completed clinical trial program for GD was reported in only 3 (2.6%) adult patients (2 x hypersensitivity; 1 x eye swelling). No treatment discontinuations resulting from AEs were reported in children.

In adults, 93.1% (108/116) of patients experienced at least one AE (all causality). The most commonly reported AEs (>10% of patients) in adults were nasopharyngitis (23.3%), arthralgia (23.3%), headache (22.4%), viral upper respiratory tract infection (19.8%), pain in extremity (16.4%), cough (15.5%), fatigue (12.9%), abdominal pain (11.2%), pyrexia (11.2%), back pain (11.2%), diarrhoea (10.3%), nausea (10.3%), and oropharyngeal pain (10.3%).

In children, 75.0% (12/16) of patients experienced at least one AE (all causality). The most commonly reported AEs (> 10% of patients) in children were vomiting (31.3%), abdominal pain (18.8%), nasopharyngitis (18.8%), headache (18.8%), pain in extremity (18.8%), tonsillitis (12.5%), diarrhoea (12.5%), arthralgia (12.5%), epistaxis (12.5%), and tooth extraction (12.5%).

In both adults and children, the risk of experiencing AEs is greater in ERT-naïve patients compared with ERT-experienced patients.

The risks of experiencing AEs appear to be minimal for the following groups of disorders (SOC) “blood and lymphatic system”, “cardiac”, “hepatobiliary”, “renal and urinary” and “skin and subcutaneous tissue”.

SAEs were reported in 11.2% (n=13) of adult patients and 12.5% (n=2) of paediatric patients. In adults, none of the SAEs were considered to be treatment related and no single preferred term was reported in more than 1 patient. In children, 1 SAE was considered to be treatment-related (gastrointestinal inflammation). There were no deaths reported in the ongoing and completed studies in the GD clinical program, but there was 1 death reported in the compassionate use program considered to be unrelated to treatment (tuberculosis/pneumonia).

Investigator-designated treatment-related AEs occurring during or within 2 hours of completion of the taliglucerase alfa infusion were reported in 27.6% of adult patients (32/116) and 12.5% (2/16) of paediatric patients. The most commonly reported investigator-designated treatment related AEs reported during or within 2 hours of completion of the infusion in adult patients (≥ 2% of patients) were hypersensitivity (4.3%), nausea (3.4%), infusion-related reactions (3.4%), headache (3.4%), pruritus (3.4%), rhinorrhoea (2.6%), sneezing (2.6%) and flushing (2.6%). In the 2 paediatric patients with investigator-designated treatment-related AEs occurring during the infusion or within 2 hours of completion of the infusion the events were gastrointestinal inflammation and vomiting in 1 patient, and chest discomfort in 1 patient.

There was a risk of Type I hypersensitivity AEs (acute allergic reactions) in patients treated with taliglucerase alfa. These events occurred predominantly in adult patients, but this might reflect the greater number of adults exposed to taliglucerase alfa compared with paediatric patients. The majority of Type I hypersensitivity AEs required no treatment or were manageable with premedication and/or symptomatic treatment. In adults (n=116), 20 patients (17.2%) experienced Type 1 hypersensitivity AEs, and all events were reported as being mild/moderate in intensity. The events reported in the 20 adult patients were pruritus in 11 (9.5%), hypersensitivity in 5 (4.3%), eye swelling in 2 (1.7%), and 1 (0.9%) patient each for eye oedema, scleral oedema, lip swelling, and face oedema. One (1) Type 1 hypersensitivity AE was reported in 1 paediatric patient (angioedema), and this event was considered by the investigator to be unrelated to treatment.

Investigator-designated treatment-related Type 1 hypersensitivity AEs were reported in 18 adult patients. Of these 18 patients, 10 required no intervention or only temporary intervention to manage the events, while 8 required significant intervention characterized by premedication or treatment discontinuation. Of the 8 patients requiring significant intervention; 2 with hypersensitivity and 1 with pruritus/eye oedema continued infusions with premedication; 4 discontinued treatment because of hypersensitivity or hypersensitivity-related events, and in 3 of these discontinuation occurred with the first infusion; and 1 experienced multiple mild AEs of eye swelling in spite of premedication and decided to discontinue taliglucerase alfa and return to imiglucerase. Perusal of the case narratives for the 5 patients experiencing events described as “hypersensitivity” indicates that these included typical acute allergic reactions such as flushing, tightness in the chest wheezing, urticaria, itching, chills, periorbital oedema, lacrimation and rhinorrhoea.

In the clinical studies, assessment of IgG anti-taliglucerase alfa antibody status was carried out in a total of 71 patients (43 ERT-naïve, 28-ERT experienced). Of the 43 ERT-naïve patients, 19 (44.2%) were found to have treatment-induced IgG anti-taliglucerase antibodies (17/32 [53.1%] adults, 2/11 [18.1%] children). Of the 28 ERT-experienced patients, 5 (17.9%) were found to have treatment induced IgG anti-taliglucerase antibodies (3/26 [11.5%] adults, 2/2 [100%] children). There appears to be an increased risk of Type 1 hypersensitivity reactions in patients testing positive for treatment-induced IgG anti-taliglucerase antibodies compared with patients testing negative (10/24 [44.7%] vs 10/47 [21.3%], respectively). In the 20 patients tested for treatment-induced IgG anti-taliglucerase antibodies and experiencing Type I hypersensitivity AEs, 10 continued treatment with no intervention, 3 discontinued treatment following Type I hypersensitivity AEs, 1 of whom declined premedication; 5 continued treatment with use of medications such as antihistamines for rash or pruritus; and 2 who experienced Type I hypersensitivity AEs continued treatment with premedication. The results

suggest that in the majority of the 20 tested patients, Type 1 hypersensitivity AEs were manageable irrespective of the treatment-induced IgG anti-taliglucerase antibodies status.

Type II-IV hypersensitivity AEs (delayed hypersensitivity reactions) were reported only in adults (9/116 [7.8%]). Of the 14 reported events, 13 were categorized as mild or moderate in severity and 1 as severe (autoimmune thrombocytopaenia, non-treatment related SAE). Events reported in more than 1 patient were arthritis (3 patients, 2.3%) and contact dermatitis (2 patients, 1.5%). All other events occurred in 1 (0.8%) patient each (autoimmune thrombocytopenia, drug eruption, dyshidrosis, macula-papular rash). The only event reported as treatment-related was drug eruption (left cheek), which was reported in 1 patient on 6 separate occasions.

Bone events were reported in 55 (47.4%) adult patients, and SAE bone events were reported in 2 (1.7%) adult patients. In 8 (6.9%) adult patients, bone events were judged by the investigator to be related to treatment, and the majority of these events were described as musculoskeletal discomfort (15 events; all in 1 patient). Of the treatment-related bone events in adults, 4 occurred during the infusion or within 2 hours after the completion of the infusion (arthralgia, back pain, muscle spasm, and musculoskeletal discomfort [14 events in 1 patient]). In children, 5 (31.3%) patients experienced bone events, and none of the events were considered to be SAEs. There was 1 (6.3%) paediatric patient with a bone event judged by the investigator to be treatment-related (pain in extremity). None of the bone events reported in children occurred during the infusion or within 2 hours of the completion of the infusion.

The risks of taliglucerase alfa inducing abnormalities in clinical laboratory tests, vital signs, ECGs, ECHOs, or pulmonary function tests appear to be minimal.

Overall, there is limited information on the risks of taliglucerase alfa in patients with GD aged from > 2 years to < 18 years (n=16), and there is no information on the risks of treatment in patients aged ≤ 2 years. There is limited information on the risks of treatment in patients with GD aged ≥ 65 years (n=8). There is no meaningful information on the risks of taliglucerase alfa treatment in non-Caucasian patients (n=5). The risk of experiencing commonly reported AEs appears to be greater in female than in male patients, but there is no evidence that the taliglucerase alfa treatment regimen should differ for females and males.

There are no data on the risks of taliglucerase alfa in patients with neuronopathic GD, patients with pre-existing hepatic disease, patients with pre-existing renal disease or patients with pre-existing cardiovascular disease. There are no data on the potential risks of drug-drug interaction involving taliglucerase alfa and other co-administered medicines.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of taliglucerase alfa, given the proposed usage, is favourable. The data provided in the original and re-submission satisfactorily demonstrate the benefits of taliglucerase alfa in both adult and paediatric patients. The benefits of treatment with taliglucerase alfa in ERT-naïve and ERT-experienced patients with non-neuropathic GD include clinically meaningful reductions in spleen and liver volumes, improvement in haemoglobin level, and improvement in platelet count. In addition, taliglucerase alfa reduced GD biomarker activity in both adult and paediatric patients (chitotriosidase activity reduced; CCL18 concentration reduced). Taliglucerase alfa is intended for chronic administration every 2 weeks. Consequently, the risk-benefit balance of the product over prolonged and potentially life-long administration will only emerge from post-marketing pharmacovigilance data.

The original submission and the re-submission satisfactorily demonstrate that the risks of treatment with taliglucerase alfa in both adults and children with non-neuropathic GD are acceptable. Although AEs occurred very commonly in both adults and children treated with taliglucerase alfa (93.1%, 108/116 and 75.0%, 12/16, respectively), these events generally

required either no intervention or were manageable with symptomatic treatment. Treatment discontinuation due to AEs in the ongoing and completed clinical trial program for GD was reported in only 3 (2.6%) adult patients (2 x hypersensitivity; 1 x eye swelling). No treatment discontinuations resulting from AEs were reported in children.

SAEs were reported in 11.2% (n=13) of adult patients and 12.5% (n=2) of paediatric patients. In adults, none of the SAEs were considered to be treatment related and no single preferred term was reported in more than 1 patient. In children, 1 SAE was considered to be treatment-related (gastrointestinal inflammation). There were no deaths reported in the ongoing and completed studies in the GD clinical program, but there was 1 death reported in the compassionate use program considered to be unrelated to treatment (tuberculosis/pneumonia).

The most clinically important risks of treatment with taliglucerase are considered to relate to Type I hypersensitivity reactions (acute allergic reactions). In adults, 18 (15.5%) patients were reported as experiencing investigator-designated treatment-related Type I hypersensitivity reactions. These reactions were manageable by either no intervention or temporary intervention in slightly more than half of the cases (10/18) or by significant intervention characterized by premedication or treatment discontinuation in slightly less than half of the cases (8/18).

There appears to be an increased risk of Type 1 hypersensitivity reactions in patients testing positive for treatment-induced IgG anti-taliglucerase antibodies compared with patients testing negative (10/24, 44.7% vs 10/47, 21.3%, respectively). However, Type 1 hypersensitivity AEs were manageable irrespective of treatment-induced IgG anti-taliglucerase alfa antibody status. Type II-IV hypersensitivity AEs (delayed hypersensitivity reactions) were reported only in adults (7.8%, 9/116), and the only event considered to be treatment-related was drug eruption (left cheek), which was reported in 1 patient on 6 separate occasions.

The risk of AEs in ERT-naïve adults appears to be greater than in ERT-experienced patients, but the number of paediatric patients in the two subgroups is too small to make a meaningful comparison. There appears to be an increased risk of an IgG ADA response in patients who are ERT-naïve compared with patients who are ERT-experienced.

There is a potential risk of hypersensitivity reactions following taliglucerase alfa administration to patients with pre-existing cross-reactive antibodies to plant glycans. There were 4/58 (6.9%) adult patients and 2/13 (15.4%) paediatric patients who were IgG ADA pre-dose. One of the adult patients discontinued treatment following the first infusion due to a hypersensitivity reaction characterized by typical acute allergic events. It is possible that these 6 patients had pre-existing cross-reactive antibodies to plant glycans.

The major uncertainty relating to the benefit-risk balance relates to the potential effect of treatment-induced IgG ADA on the therapeutic response to taliglucerase alfa. The sponsor states that this matter is “currently unclear”. In the original submission, there were limited data from study PB-06-001 relating to the effect of IgG ADA status on efficacy and pharmacokinetics in adults. In this study, change from baseline to last follow-up visit were assessed for four efficacy endpoints in IgG ADA positive and negative patients in two dosage groups (30 and 60 units/kg). The four efficacy endpoints were %change in spleen volume, %change in liver volume, change in haemoglobin concentration, and change in platelet count.

In the 30 units/kg group, there were no statistically significant differences between IgG ADA positive patients (n=6) and IgG ADA negative patients (n=8) for the 4 efficacy endpoints. In the 60 units/kg group, improvements in each of the four efficacy endpoints were numerically greater in IgG ADA negative patients (n=4) than in IgG ADA positive patients (n=11), with the difference for %change in liver volume being statistically significant (~32% vs ~13%, respectively, p=0.005). However, the efficacy comparison between IgG ADA positive and negative patients in the 60 units/kg group should be interpreted cautiously due to the small sample size. In addition, the results in the 60 units/kg group were inconsistent with the results

in the 30 units/kg group. Overall, it is considered that the data from study PB-06-001 are too limited to conclude that efficacy is impaired in patients positive for IgG ADA.

Pooled PK data from patients in the 30 and 60 units/kg groups in PB-06-001 in the original submission showed that exposure to taliglucerase alfa at Day 38 (i.e., dose normalized C_{max}, AUC_{0-t}, and AUC_{0-inf}) was notably greater in IgG ADA positive patients (n=17) than in IgG ADA negative patients (n=9). In addition, there was no consistent correlation between taliglucerase alfa exposure and the four efficacy outcomes in patients with and without IgG ADA. The re-submission included the time courses of IgG ADA and titre evaluated against each of the four key efficacy endpoints in individual patients from studies PB-06-001, PB-06-002 and PB-06-003. There were no clear associations between IgG ADA status and the efficacy endpoints in the individual time course plots.

There is an important risk-benefit issue relating to whether treatment with taliglucerase alfa should be confined to adult patients with GD (i.e., patients aged ≥ 18 years). The clinical data in children and adolescents (2 to < 18 years) are limited, but suggest that the benefits and risks of taliglucerase alfa are similar in children/adolescents and in adults. Overall, it is considered that treatment with taliglucerase alfa should not be restricted to adult patients aged ≥ 18 years.

10. First round recommendation regarding authorisation

It is recommended that ELELYSO (taliglucerase alfa) be approved for *long-term enzyme replacement therapy for patients with a confirmed diagnosis of Gaucher disease characterized by one or more of the following, splenomegaly, hepatomegaly, anaemia, thrombocytopenia, or bone disease*.

11. Clinical questions

11.1. Biopharmaceutical study

1. In Validation Report#70-66-027R, it was stated that “while testing serum samples of 52 individual healthy subjects, 15.38% (all data included: 24 samples of 156 samples tested, or 8.39% if outliers are excluded, 12 samples of 143) had a % inhibition value above the inhibitory cut-point and could be considered as ‘Positive’ for antibodies to plant glycans on TGA [taliglucerase alfa]”. Why was the ELISA validated in this report not used to test serum samples of patients with GD for antibodies to plant glycans on taliglucerase alfa?

11.2. Efficacy

1. What is the relationship between the taliglucerase alfa formulation used in the paediatric study (PB-06-005) and the formulation proposed for Australian marketing?
2. IgG ADA assessment has been carried out in 71 patients (43 ERT-naïve; 28 ERT-experienced) from studies PB-06-001, PB-06-002, PB-06-003 and PB-06-005. Do these 71 patients include all patients from the relevant clinical studies who could have been tested? If not, what proportion of the total number of patients who could have been tested do these 71 patients represent? If they do not represent the total number of patients who could have been tested what were the reasons for selecting only a proportion of these patients for antibody analysis?
3. IgG ADA assessment has been carried out in 71 patients (43 ERT-naïve; 28 ERT-experienced), and of these patients 24 (33.8%) developed treatment-induced Ig ADA while 47 (66.2%) were negative for treatment induced Ig ADA. Please provide data comparing

efficacy in the 24 patients positive for treatment-induced Ig ADA with efficacy in the 47 patients negative for treatment-induced Ig ADA. The efficacy endpoints should include change from baseline in haemoglobin parameters, spleen volume, liver volume, platelet count and biomarker activity (chitotriosidase and CCL18). Please discuss any differences in efficacy observed between the two groups.

4. In the 71 patients assessed for Ig ADA there were 20 (28.2%) patients who experienced a Type I hypersensitivity reaction (10 antibody positive and 10 antibody negative patients). Please provide data comparing efficacy in the 10 antibody positive patients and the 10 antibody negative patients. The efficacy endpoints should include change from baseline in haemoglobin parameters, spleen volume, liver volume, platelet count and biomarker activity (chitotriosidase and CCL18). Please discuss any differences in efficacy observed between the two groups.
5. The SCS (section 2.7.4.2.1.5.2.2) indicates that of 24 adult subjects with IgG ADA, 3 tested positive for neutralizing activity in the in vitro assay but not in the in vivo assay. The efficacy response was reported as not appearing to decrease in the two ERT-naïve patients with neutralizing antibodies. However, the switch-over patient (i.e., ERT-experienced) who had neutralizing antibody activity maintained organ volumes compared to baseline, but showed decreases in haemoglobin and platelet count at the last follow up visit. Please provide data comparing efficacy in the 3/24 IgG ADA positive patients with neutralizing antibodies with the 21/24 IgG ADA positive patients without neutralizing antibodies. The efficacy endpoints should include change from baseline in haemoglobin parameters, spleen volume, liver volume, platelet count and biomarker activity (chitotriosidase and CCL18). Please discuss any differences in efficacy observed between the two groups.
6. In the "Addendum, Immunogenicity Overview", two appendices were provided showing the time course in individual patients for each of the four key efficacy endpoints of change from baseline in spleen volume, liver volume, haemoglobin and platelet count based on IgG ADA status for studies PB-06-001, PB-06-002, and PB-06-003. Please provide tabulated summary data comparing the four efficacy outcomes in patients with and without IgG ADA at end of study for PB-06-002 and PB-06-003, and for PB-06-001 (if it differs from that provided in the original submission). Please comment on the observed differences in efficacy outcomes between IgG ADA positive and negative patients. It is noted that sponsor's current position is that "the relevance of ADA to therapeutic response is currently unclear" (SCS section 2.7.1.3.1).

11.3. Safety

1. In the Summary of Clinical Safety (SCS), the number of adult patients with at least one severe or very severe AE is reported as 17 in table 12 (consistent with table 21). However, in the first paragraph in section 2.7.4.2.1.1.2 it is stated that 23 adults experienced AEs that were severe of very severe. It is assumed that the 23 patients include separate counts for patients who experienced more than one event. Is this assumption correct?
2. In the SCS, in adults the number of AEs categorized as severe or very severe is given as 26 in table 13, but as 24 in tables 20 and 21. Please account for this apparent discrepancy.
3. In the SCS, treatment outcomes were provided for 20 patients tested for treatment-induced anti-taliglucerase alfa antibodies in whom an immune mediated Type 1 hypersensitivity event occurred: 10 subjects continued treatment with no intervention; 3 subjects discontinued treatment following events of Type I hypersensitivity, one of whom declined premedication; 5 subjects continued treatment with use of medications such as antihistamines for rash or pruritus; and 2 subjects who experienced Type I hypersensitivity continued treatment with a pre-treatment regimen. It is assumed that the 20 patients include the 10 patients who tested positive for treatment-induced anti-taliglucerase

antibodies, and the 10 patients who tested negative for treatment-induced anti-taliglucerase antibodies. If this assumption is correct, please indicate whether the patients identified for each of the outcomes were antibody negative and/or antibody positive.

4. In the SCS (Section 2.7.4.3.1.3), it is stated that there are 13 adult patients with 20 SAEs, while in tables 12 and 13 it is stated that there are 14 patients with 18 SAEs. Please account for the discrepancies.

5. In the SCS, it is stated that analysis of anti-taliglucerase alfa IgG antibody has been carried out with samples from 71 clinical study subjects, of which 24 (34%) had treatment induced antibody (section 2.7.4.2.1.5.2.1). It appears from tables 48 and 49 in the SCS that the 71 patients included 58 adults and 13 children, and that 22/58 adults and 2/13 children were treatment-induced IgG ADA positive. However, other data in the SCS (section 2.7.4.2.1.5.2.1) suggests that of 43 ERT-naïve patients, 19 (44.2%) were found to have treatment-induced IgG ADA (17/32 [53.1%] adults, 2/11 [18.1%] children), and of 28 ERT-experienced patients, 5 (17.9%) were found to have IgG ADA (3/26 [11.5%] adults, 2/2 [100%] children). Therefore, these data suggest that of the 24 patients who were treatment-induced IgG ADA positive, there were 20/58 adults and 4/13 children. It is then stated in section 2.7.4.2.1.5 of the SCS that the incidence of treatment-induced ADA responses were 19 of 32 treatment-naïve adults, 2 of 11 treatment-naïve paediatric subjects, and 5 of 28 subjects previously treated with other ERTs (i.e., 26/71 subjects with treatment–induced IgG ADA).

   To further complicate the issue, it is stated in the "Addendum, immunogenicity overview" that "based on current assay cut-points, the incidence of post-treatment induced ADA responses observed was 17 of 32 treatment-naïve adult subjects who were monitored for up to 39 months (Studies PB-06-001/PB-06-003), 5 of 28 subjects (26 adult, 2 paediatric) previously treated with other ERTs who were monitored for up to 24 months (Studies PB 06- 002/PB-06-003), and 2 of 11 treatment-naïve paediatric subjects who were monitored for up to 12 months (Study PB-06-005)".

   Please explain the apparent discrepancies in the number of patients positive for treatment-induced IgG ADA in the submitted data. Please provide definitive data on the number of ERT-naïve (total, adult, paediatric) and ERT-experienced (total, adult, paediatric) patients who were treatment-induced IgG ADA positive in the clinical trial program.

6. Please comment on the notably higher proportion of ERT-naïve patients who were treatment-induced IgG ADA positive compared with ERT-experienced patients.

7. In the SCS, it is stated that of 24 adult patients with IgG ADA who were tested for neutralizing antibody, 3 were determined to be positive for neutralizing antibody assay and negative in the cellular uptake neutralizing assay. However, Table 48 of the SCS indicates that there were 25 patients assessed as Ig ADA positive (including 22 who were categorized as treatment-induced IgG ADA positive). Therefore, it appears that 1 of the 25 adult patients positive for Ig ADA was not tested for neutralizing antibodies. Please clarify this matter.

8. In the SCS, table 49 indicates that 4 of the 13 paediatric patients tested were IgG ADA positive, and that 2 of these 4 patients were categorized as treatment-induced IgG ADA positive. Please confirm that the 4 IgG ADA positive patients all tested negative for neutralizing antibodies.

9. The SCS indicates that subjects who experienced allergic reactions were tested by ELISA for IgE ADA in addition to the IgG ADA testing. Two patients were reported as testing positive for IgE ADA and both were positive pre- and post-dose. How many patients were tested for IgE ADA and what was the outcome of testing? Please comment on the significance of pre-dose IgE ADA in these two patients. Was consideration given to assessing IgE ADA in all patients irrespective of allergic reactions?

10. In the SCS, table 48 indicates that 4/58 (6.9%) adult patients and 2/13 (15.4%) paediatric patients were IgG ADA pre-dose. Please comment on the significance of pre-dose IgG ADA in these patients.

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

12.1. Overview of the clinical aspects of the response to TGA questions

The sponsor provided comprehensive responses to the clinical questions raised following the first round evaluation of the submission. In the following sections, the questions raised in Section 11 of the CER are referred to by number and the substance of the sponsor's responses provided either in full or abridged is described. In cases where the sponsor's responses have been edited by the evaluator, it is warranted that no changes to the substance of the responses have been made. Comments have been provided on the sponsor's response to the clinical questions arising from the first round clinical evaluation, and additional comments have been provided on the clinical aspects of the sponsor's response to the M3 [quality] evaluator's first round questions 7 and 8. The second round clinical evaluation also includes a review of the Final Study Report for PB-06-002 submitted by the sponsor in response to a request from the RMP evaluator for updated safety information.

The Final Study Report for PB-06-002 was located in M5 of the sponsor's response. Other information included in M5 of the sponsor's response were: (i) a protocol (B3031002) for A Multicenter, Multicountry, Postmarketing Active Surveillance Taliglucerase Alfa Registry in Patients with Gaucher Disease; (ii) an in vitro bioanalytical study detailing the development of an enzyme-linked immunosorbent assay for the detection of anti-taliglucerase alfa plant-specific glycan antibodies in human serum (PCL-12-010); and (iii) an in vitro bioanalytical study describing ELISA based assay to compare the binding of anti- taliglucerase alfa antibodies to taliglucerase alfa with their binding to imiglucerase (PCL-11-020). The evaluation of the protocol for the postmarketing registry is considered to be a matter for the RMP evaluator, and review of the two bioanalytical studies is considered to be a matter for the M3 evaluator. The M5 information also included literature references relevant to the sponsor's response to the clinical questions arising from the first round clinical evaluation.

12.2. Module 5 - Clinical evaluator's first round questions

12.2.1. Biopharmaceutical study Question 1

12.2.1.1. Sponsor's Response

The sponsor indicated that it has now used a validated enzyme-linked immunosorbent assay for the detection of antibodies to plant-specific glycans in taliglucerase alfa in human serum to analyse subjects from four clinical studies and that it has provided the data in Module 3, response to a Question from the quality evaluator. The sponsor provided the results for the analysis of individual confirmed ADA positive samples from GD patients in studies PB-06-001, PB-06-002, PB-06-003 and PB-06-005. The analysis included 192 available samples from 29 subjects who had one or more confirmed ADA positive samples at any time-point, baseline and/or post-treatment). In brief, the results indicated:

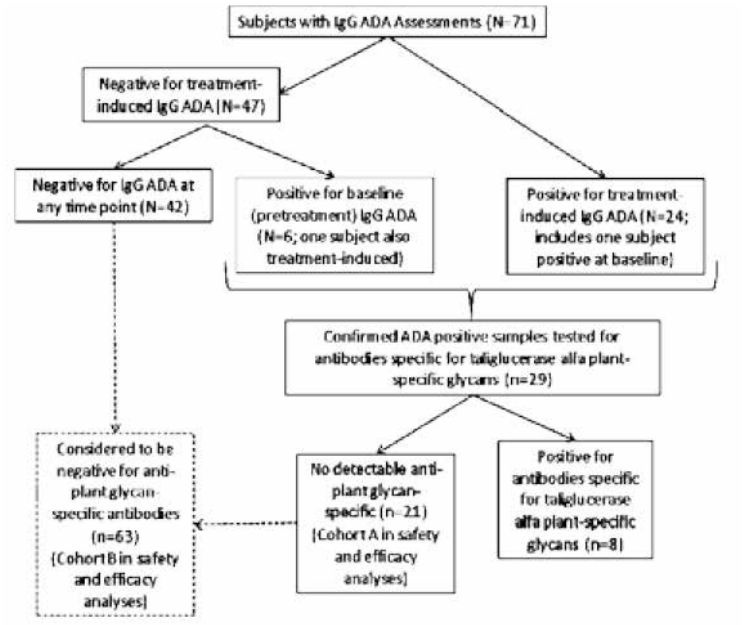
- Of the 29 subjects tested in the validated ELISA for the detection of antibodies for plant-specific glycans on taliglucerase alfa, 8 subjects were positive for anti-plant glycan-specific antibody (had at least one sample that scored positive in the assay pre or post treatment) and 21 subjects had no detectable anti-plant glycan-specific antibodies. Of the 71 subjects tested for anti-taliglucerase alfa ADA for the submission, 8 are considered to be anti-plant

glycan-specific antibody positive and 63 are considered negative for anti-plant glycan-specific antibodies (i.e., 21 had no detectable antibodies to plant-specific glycans on taliglucerase alfa but were IgG ADA positive and 42 were negative for IgG ADA including antibodies to plant-specific glycans on taliglucerase alfa).

- Of the 71 subjects tested for anti-taliglucerase alfa ADA, 6 had pre-existing antibodies for taliglucerase alfa at baseline (i.e., prior to exposure to taliglucerase alfa). Of these 6 subjects, 4 were positive for anti-plant glycan-specific antibody at baseline while 2 were negative for anti-plant glycan-specific antibody at baseline. For the 4 subjects that were positive for anti-plant glycan-specific antibodies at baseline, post-treatment IgG titers were either stable or reduced following continuous exposure to taliglucerase alfa. Although based on a small number of subjects with pre-existing antibodies these results suggest that a) some pre-existing antibodies are specific for plant glycan-specific structures on taliglucerase alfa and b) presence of these antibodies does not appear to increase risk of immune response to taliglucerase alfa based on the lack of observed post-treatment boosting of the anti-taliglucerase alfa ADA levels.
- In the previous analysis, samples from 24 subjects were determined to be positive for treatment-induced anti-taliglucerase alfa of which 1 had-pre-existing anti-taliglucerase alfa. In the analysis reported in the response to TGA questions 4 of these 24 subjects were positive for treatment-induced anti-plant glycan-specific antibodies in at least one sample. These results indicate that taliglucerase alfa treatment may induce antibody responses to the plant-specific glycans on taliglucerase alfa in some subjects, but such responses appear to be limited in magnitude.
- The presence of detectable anti-plant glycan-specific antibodies was not associated with a discernible trend in treatment-related adverse events and no clear demonstrated correlation between the appearance of anti-plant glycan antibodies and an increased clinically relevant risk associated with immunogenicity. Although the presence of detectable anti-plant glycan-specific antibodies appeared to be associated with a greater frequency of certain all causality events, the low number of subjects in this group (n=8) and the low number of events makes comparison challenging because a single occurrence of an adverse event (AE) has a large effect on the calculation of frequency.
- A post-hoc assessment of the change from baseline in the six efficacy endpoints (spleen volume, liver volume, haemoglobin, platelet count, chitotriosidase and CCL18) based on anti-plant glycan ADA status for studies PB-06-001, PB-06-002, the extension study PB-06-003 and PB-06-005 suggests that there is no systematic relationship between presence of anti-plant glycan-specific antibodies and the efficacy outcomes.

It may be concluded that anti plant-specific glycan antibodies occur in a subgroup of Gaucher disease patients pre and post treatment with taliglucerase alfa however the immune response to these structures appears to be limited in magnitude. There is no clear demonstrated correlation between the appearance of anti-plant glycan-specific antibodies and an increased clinically relevant immunogenic risk. Additional experience with taliglucerase alfa and evaluation of its immunogenicity risk profile is being generated in the completed analysis of the PB-06-003 study, two ongoing extension studies, PB-06-006 (extension study for paediatric subjects from PB-06-002 and PB-06-005) for a total of up to 3 years of exposure and study PB-06-007 (treatment-naïve adults who complete PB-06-003) for a total of up to 5 years of exposure. A 10-year post-marketing registry has been initiated to provide additional data. The results for the 71 subjects tested for IgG ADA are summarised in the Figure presented immediately below.

Figure 1: Overview of analysis of anti-taliglucerase alfa ADA and antibodies to plant specific glycans on taliglucerase alfa in clinical trial subjects.



12.2.1.2. Evaluator's comment

The sponsor's response is satisfactory. In addition to the review of the sponsor's response to this question (Biopharmaceutical Study), the sponsor's response to the Module 3 (quality) question relating to taliglucerase alfa plant specific glycans has also been reviewed and the clinically relevant results from the response summarised below.

12.2.1.3. Incidence of subjects with anti-taliglucerase alfa plant glycan-specific antibodies

Of the 205 confirmed positive ADA samples from 29 subjects, a total of 192 archived samples were available for further characterization using the validated ELISA for the detection of antibodies for plant-specific glycans in taliglucerase alfa. Out of the 192 samples, 27 samples from 8 patients were found to be positive in the assay (had detectable antibodies specific for plant-specific glycans on taliglucerase alfa). Therefore, of the 1007 samples serum samples collected from 71 subjects and tested for anti-taliglucerase alfa ADA, 27 (2.7%) samples can be considered positive for detectable antibodies to the plant-specific glycans in taliglucerase alfa. Of the 29 subjects with 192 ADA positive samples at any time-point, 19 were treatment-naïve adults (studies PB-06-001/PB-06-003), 3 were treatment-naïve paediatric subjects (study PB-06-005), 6 were treatment-experienced adults (studies PB-06-002/ PB-06-003), and one was a treatment-experienced paediatric subject (study PB-06-002). IgG ADA and ELISA for detection of antibodies for plant specific glycans in taliglucerase alfa according to study are provided in the study report.

12.2.1.4. Safety in subjects with anti-taliglucerase alfa plant glycan-specific antibodies

The impact of detectable anti-taliglucerase alfa plant-specific glycan antibodies on clinical safety was assessed by comparing treatment-related and all causality AEs in subjects who were determined to be anti-taliglucerase alfa plant-specific glycan antibody positive (n=8), subjects who had no detectable anti-taliglucerase alfa plant-specific glycan antibodies but were IgG ADA positive (n=21, Cohort A), and subjects who had no detectable anti-taliglucerase alfa plant-specific glycan antibodies but were IgG ADA positive plus subjects who were IgG ADA negative (i.e., 21 + 42 = 63, Cohort B). Therefore, of the 71 subjects assessed for IgG ADAs, 8 (11.3%)

were considered to be positive for anti-taliglucerase alfa plant-specific glycan antibodies and 63 (88.7%) were considered to be negative for these specific antibodies.

Of the 8 subjects who were anti-taliglucerase alfa plant-glycan specific antibody positive, 5 were adults and 3 were children. Four (4) of the 8 subjects were positive for these antibodies at baseline, and in these subjects post-treatment IgG titres were either stable or reduced following continuous exposure to taliglucerase alfa. Four (4) of the 8 subjects were negative for anti-taliglucerase alfa plant-specific glycan antibodies at baseline, but became positive following treatment with taliglucerase alfa. Of the 8 subjects with anti-taliglucerase alfa plant-glycan specific antibodies, 7 continued treatment with taliglucerase alfa and 1 discontinued treatment with taliglucerase alfa due to a possible allergic reaction (skin irritation, itching and rash). Further information on the 8 subjects who were anti-taliglucerase alfa plant-specific glycan antibody positive is provided in the study report.

All causality AEs occurred more frequently in subjects who were considered to be anti-taliglucerase alfa plant-specific glycan antibody positive (64 events in 8 patients, estimated frequency of 8 events/patient) compared with subjects who were considered to be negative for these antibodies (463 events in 63 patients, estimated frequency of 7.3 events/patient). In subjects who had no detectable anti-taliglucerase alfa plant-specific glycan antibodies, but were IgG ADA positive, there were 179 events in 21 patients (estimated frequency of 8.5 events/patient). The number and frequency of these events have been calculated by the evaluator from the data provided in the sponsor's response.

All causality AEs occurring more than once in the 8 anti-taliglucerase alfa plant-specific glycan antibody positive subjects and at a greater frequency than in the 21 Cohort A subjects included, diarrhoea (n=2, 25% vs n=2, 9.5%), vomiting (n=3, 37.5% vs n=4, 19%), pain in extremity (n=2, 25% vs n=4, 19%) and headache (n=3, 37.5% vs n=5, 23.8%).

All causality AEs occurring more than once in the 8 anti-taliglucerase alfa plant-specific glycan antibody positive subjects and at a greater frequency than in the 63 Cohort A subjects included, diarrhoea (n=2, 25% vs n=8, 12.7%), vomiting (n=3, 37.5% vs n=8, 12.7%), influenza (n=2, 25% vs n=7, 11.1%), arthralgia (n=3, 37.5% vs n=13, 20.6%), pain in extremity (n=2, 25% vs n=11, 17.5%) and headache (n=3, 37.5% vs n=12, 19%).

Treatment-related AEs occurred more frequently in subjects who were considered to be anti-taliglucerase alfa plant-specific glycan antibody positive (9 events in 8 patients, estimated frequency of 1.4 events/patient) compared with subjects who were considered to be negative for these antibodies (44 events in 63 patients, estimated frequency of 0.7 events/patient). In subjects who had no detectable anti-taliglucerase alfa plant-specific glycan antibodies, but were IgG ADA positive, there were 22 events in 21 patients (estimated frequency of 1 event/patient). The number and frequency of these events have been calculated by the evaluator from the data provided in the sponsor's response, as have treatment-related AEs reported in the three patient groups

In the 8 subjects with anti-taliglucerase alfa plant-specific glycan antibodies, 5 experienced 9 events (i.e., 1 patient with 3 events, pruritus, skin irritation, and rash; 1 patient with 2 events, throat irritation and chest discomfort; 1 patient with 2 events, gastro-enteritis and vomiting; 1 patient with flushing; 1 patient with 1 event of glycosuria). No treatment-related AEs were reported in 3 of the 8 patients.

No treatment-related AEs were experienced by more than one of the 8 subjects with anti-taliglucerase alfa plant-specific glycan antibodies. Treatment-related AEs experienced by more than one of the 21 Cohort A subjects were hypersensitivity (n=3) and arthralgia (n=2). Treatment-related AEs experienced by more than one of the 63 Cohort B subjects were hypersensitivity (n=4), infusion related reaction (n=4), headache (n=4), pruritus (n=3) and arthralgia (n=2).

The sponsor commented that detectable anti-taliglucerase alfa plant-specific glycan antibodies appeared to be associated with a greater frequency of certain all causality events, but the low number of subjects with these antibodies and the low number of events "makes comparison [with other groups] challenging because a single occurrence of an AE has a large effect on the calculation of frequency". The sponsor also commented that with regard to treatment related AEs, "it should be noted that the presence of detectable anti-plant glycan-specific antibodies was not associated with a discernible trend in treatment-related AEs and no clear demonstrated correlation between the appearance of anti-plant glycan antibodies and an increased clinically relevant risk associated with immunogenicity was observed". Nevertheless, the estimated frequency of treatment-related AEs in patients with detectable anti-taliglucerase alfa plant-specific glycan antibodies was greater than in patients without these antibodies (1.4 events/patient vs 0.7 events/patient). However, these figures should be interpreted cautiously due to the marked imbalance in patient numbers between the two groups (i.e., 8 antibody positive and 63 antibody negative). Overall, the 9 treatment-related AEs reported in 5 of the 8 patients with anti-taliglucerase alfa plant-specific glycan antibodies do not give rise to safety signals associated with these antibodies.

12.2.1.5. Efficacy in subjects with anti-taliglucerase alfa plant glycan-specific antibodies

A post-hoc assessment was undertaken of the change from baseline in the six efficacy endpoints (spleen volume, liver volume, haemoglobin, platelet count, chitotriosidase and CCL18) based on anti-taliglucerase alfa plant-specific glycan antibody status for studies PB-06-001/PB-06-003, PB-06-002/PB-06-003 and PB-06-005. Two sets of analyses were performed to evaluate the potential impact of anti-taliglucerase alfa plant-specific glycan antibodies on efficacy.

Analysis 1 included: (a) 9 month data for the ERT-naive study (PB-06-001) combined with the 36 month data for the extension study (PB-06-003) through a cut off of 1 May 2012 for last efficacy measure; (b) 9 month data for the ERT-experienced study (PB-06-002) combined with the 24 month data for the extension study (PB-06-003) through a cut off of 1 May 2012 for last efficacy measure; and (c) 12 month data for the ERT-naive paediatric study (PB-06-005) through a cut off of 1 May 2012. Overall, the data from the individual studies suggest that anti-taliglucerase alfa plant-specific glycan antibodies are unlikely to significantly impair the efficacy taliglucerase alfa. However, the number of subjects with anti-taliglucerase alfa plant-specific glycan antibodies was very small in each of the three studies, which limits the interpretation of the data.

Analysis 2 included: (a) pooled data at end of study from studies PB-06-001, PB-06-002 and PB-06-005; and (b) pooled data at least measure (01 May 2102) from PB-06-001/PB-06-003, PB-06-002/PB-06-003, and PB-06-005. The two populations included adult ERT-naive (studies PB-06-001/PB-06-003) and paediatric ERT-naive, study (PB-06-005) where treatment-effect changes comprised the efficacy endpoints, and ERT-experienced (studies PB-06-002/PB-06-003) where stability of efficacy parameters was the endpoint. Overall, the data from the pooled studies suggest that that anti-taliglucerase alfa plant-specific glycan antibodies are unlikely to significantly impair the efficacy taliglucerase alfa. However, the number of subjects with these antibodies in the pooled data was small (n=8). Consequently, the interpretation of the results of the pooled analysis should be interpreted cautiously.

Overall, the sponsor concludes that there "are limitations in these analyses (e.g., small sample sizes in some of the cohorts) therefore caution should be exercised when evaluating differences. However, when assessing the data for consistency between subject subgroups (treatment naive adults, treatment naive paediatric patients and treatment experienced patients), between the multiple efficacy parameters reviewed and with two time periods, this post-hoc analysis suggests that there is no systematic relationship between anti-taliglucerase alfa plant glycan-specific antibody status and the efficacy outcomes of spleen volume, liver volume, haemoglobin,

platelet count and biomarkers. The anti-taliglucerase alfa plant glycan-specific antibody status did not affect efficacy stability in studies PB-06-002/PB-06-003".

It is considered that the sponsor's overall conclusion concerning the effect of anti-taliglucerase alfa plant-specific glycan antibodies on efficacy is reasonable.

12.2.2. Efficacy Question 1

12.2.2.1. Sponsor's response

The DP for the taliglucerase alfa formulation used in the paediatric study (PB-06-005) and the DP for the formulation proposed for Australian marketing (and in use globally) have been shown to be comparable, based on the main criteria of excipients, range of plant specific glycoforms and DP manufacturing process.

12.2.2.2. Evaluator's Comment

The sponsor's response indicates that the DPs used in PB-060995 and proposed for marketing in Australia are "comparable". The sponsor provided a "detailed description and justification of the significant process changes" relating to the manufacture of taliglucerase alfa drug substance (DS) throughout the development phases. Furthermore, the sponsor states that the changes were "evaluated before their implementation and comparability data are presented in Module 3, Section 3.2.S.2.6". The sponsor states that "the DS used for taliglucerase alfa DP in the paediatric ERT-naive Study PB-06-005 and the DS proposed for DP in Australian marketing (and also the commercial process in Global use) were produced by the same DS manufacturing process for all infusions in Study PB-06-005 except at the beginning of the study where twelve infusions in four paediatric patients had DS input from different manufacturing process iterations. Over 96% of infusions in PB-06-005 used the same DP as proposed for Australian marketing". The sponsor's response appears to be satisfactory, but it is suggested that the Module 3 evaluator comment on the response.

12.2.1. Efficacy Question 2

12.2.1.1. Sponsor's response

A total of 74 subjects were enrolled in the relevant clinical trials; adult treatment naive trial PB-06-001 (n=32), treatment experienced trial PB-06-002 (n=26 adults and 5 children), and the paediatric treatment naive trial PB-06-005 (n=11). The adult extension study PB-06-003 included subjects already accounted for in trials PB-06-001 and PB-06-002.

The cohort of 71 subjects with IgG ADA assessments represents all but three paediatric subjects in study PB-06-002. The IgG ADA assessments were unavailable before the data cut-off for submission (01 May 2012). The IgG ADA data for these three subjects through 31 March 2013 show that none had treatment-induced IgG ADA. One of the three subjects was found to have IgG antibody to taliglucerase alfa at Baseline (before exposure; titer=67) and was positive at week 4 (titer =57). IgG ADA was not detected at later visits, therefore the subject was not considered to be treatment-induced antibody-positive. IgG ADA was not detected in the other two subjects.

12.2.1.2. Evaluator's Comment

The sponsor's response is satisfactory. The safety population in the SCS included 132 patients, 74 patients from studies PB-06-001, PB-06-002, and PB-06-005 and 58 patients from study PB-06-004. The data provided by the sponsor indicates that all 74 patients from studies PB-06-001, PB-06-002 and PB-06-005 have now been tested for IgG ADA, while none of the patients from study PB-06-004 have been tested. However, it is understandable that no patients from study PB-06-004 have been tested as this was an expanded access study initiated to accommodate the treatment of subjects affected by the shortage of imiglucerase. Therefore, patients in this study can be seen as part of a compassionate use program rather than a formal clinical study program.

12.2.2. Efficacy Question 3

12.2.2.1. Sponsor's Response

A post-hoc assessment in six efficacy parameters was performed analysing the cohort of patients with treatment-induced IgG ADA (N=24) and the cohort of patients without treatment-induced IgG ADA (N=47). The assessments include the duration of the primary study (PB-06-001 and PB-06-002, nine months; PB-06-005, twelve months) and through a cut off of 1 May 2012. Thus the nine month assessments reflect pooled data from PB-06-001 and PB-06-002, the twelve month data derive only from PB-06-005 and the last measure data include all three studies (36 months for PB-06-001/003; 24 months for PB-06-002/003; 12 months for PB-06-005).

In addition to the 'time points for end point analysis', 2 different populations with different sets of expected results are pooled in this assessment of 71 patients. The 2 populations are:

- Adult ERT-Naïve (Studies PB-06-001/PB-06-003) and Paediatric ERT-Naive, PB-06-005 where treatment-effect changes comprised the efficacy endpoints; and
- ERT-Experienced (Studies PB-06-002/PB-06-003) where stability of efficacy parameters was the endpoint.

The results for the efficacy assessments displaying the mean absolute and percent changes in the efficacy parameters by treatment-induced IgG ADA status at "end of study" and "last measure" are provided in the study report.

There is a trend in these pooled analyses for the treatment-induced ADA group to have greater improvements in the haemoglobin, platelet count and biomarkers when evaluating the last measure. Decreases in spleen volume were greater at all time points (final study time point of nine months for the combined PB-06-001 and PB-06-002 studies, the 12-month end of study evaluation in PB-06-005 and at the last measure in all three studies combined) in the treatment-induced ADA group. Liver volume trends were inconsistent between time points and studies, and in all cases the differences between the cohort with treatment-induced IgG ADA and the cohort without treatment-induced IgG ADA were small. Although an association with treatment-induced IgG ADA positive subjects and improved efficacy is observed, the mechanism is not clear.

12.2.2.2. Evaluator's comment

The sponsor's response is satisfactory. The absolute change from baseline in the pooled analysis (PB-06-001, PB-06-005) at the last measure (1 May 2012) was consistently greater in the ADA positive group (n=24) compared with the ADA negative group (n=46) across all six efficacy endpoints. However, in general the observed differences between the two groups were not statistically significant ($p \geq 0.05$) for the comparisons. Comparisons statistically significantly favouring the ADA positive group compared with the ADA negative group were % change from baseline in spleen volume (all subjects) at Month 9 ($p=0.006$), and last follow-up to 1 May 2012 ($p=0.030$) and absolute change in spleen size (all subjects) from baseline at Month 12 ($p=0.014$). It is reassuring that there is no diminution in efficacy in ADA positive subjects compared with ADA negative subjects. It is unclear why efficacy is better in ADA positive subjects compared with ADA negative subjects.

12.2.3. Efficacy Question 4

12.2.3.1. Sponsor's response

A post-hoc assessment of the change from baseline in six efficacy endpoints (spleen volume, liver volume, haemoglobin, platelet count, chitotriosidase and CCL18) based on treatment-induced IgG ADA status in subjects with Type I Hypersensitivity reaction was performed. Two subjects (one in study PB-06-005, treatment-induced ADA negative) and (one in Trial PB-06-005, treatment-induced ADA positive) were captured as experiencing a Type 1 Hypersensitivity

reaction. The Subject in study PB-06-005 experienced Rash not associated with administration of taliglucerase alfa. This event was erroneously captured as a Type I Hypersensitivity event according to the definition in the study report. The other Subject experienced Face oedema as a result of sunburn. While this event is captured as a Type I Hypersensitivity event, it is not considered to be a result of treatment with taliglucerase alfa.

The sponsor provided two tables summarising the data: the summary of "Change and % Change in Efficacy Parameters by Treatment-induced IgG ADA Status for Subjects with Type I Hypersensitivity Reaction After Review of Cases (n=18)" includes the revised sample of subjects with confirmed Type I hypersensitivity reaction; the summary of "Change and % Change in Efficacy Parameters by Treatment-induced IgG ADA Status for Subjects with Type I Hypersensitivity Reaction Originally Identified cases (n=20)" includes the entire cohort initially identified subjects with Type I hypersensitivity reaction.

Treatment-induced IgG positive status showed a small but consistent trend for greater improvement as compared with the treatment-induced ADA negative group at month 9 and through last measure for haemoglobin (inclusive of baseline anaemia), spleen volume, liver volume, platelet count (inclusive of baseline thrombocytopenia), chitotriosidase, and CCL18. Liver volume outcomes differentiating treatment-induced ADA positive and negative status were equivocal in subjects with baseline hepatomegaly. Although the limitations of these analyses preclude any definitive interpretation, treatment-induced ADA positive status appears linked to neutral or positive efficacy outcomes in subjects with Type I hypersensitivity reactions.

12.2.3.2. Evaluator's comment

The sponsor's response is satisfactory.

12.2.4. Efficacy Question 5

12.2.4.1. Sponsor's response

A post-hoc assessment in the change from baseline in six efficacy endpoints (haemoglobin, spleen volume, liver volume, platelet count, chitotriosidase and CCL18) comparing efficacy in the 3/24 IgG ADA positive patients with neutralising antibodies with the 21/24 IgG ADA positive patients without neutralising antibodies was performed.

Three adult subjects, two from ERT treatment-naïve study PB-06-001/PB-06-003 and one subject from ERT treatment-experienced study PB-06-002/PB-06-003 had neutralising antibodies in the in vitro assay whereas all three were found to be negative in the cell based assay.

Data were displayed as the mean absolute and percent changes in the efficacy parameters by treatment-induced Neutralising ADA status at nine months and last measure for PB-06-001/PB-06-003 (month 36) and for PB-06-002/PB-06-003 (month 24).

There are limitations in these analyses (e.g., small sample sizes in some of the cohorts) and caution should be exercised. However, when evaluating the data for consistency between patient subgroups (treatment naive adults, treatment experienced adults), between the multiple efficacy parameters reviewed and with two time periods, this post-hoc analysis suggests that there is no systematic relationship between neutralizing ADA status and the efficacy outcomes of haemoglobin, spleen volume, liver volume and platelet count

12.2.4.2. Evaluator's comments

The sponsor concludes that the analysis suggests no systematic relationship between neutralising antibodies ADA status and the efficacy outcomes of haemoglobin, spleen volume, liver volume and platelet count. However, review of the summary data suggests that changes in haemoglobin, spleen volume, platelet count, and chitotriosidase activity favoured subjects negative for neutralising ADAs. The data suggest that the development of neutralising ADAs

might reduce the efficacy of taliglucerase alfa, but is unclear whether the reduction is likely to be clinically significant. Furthermore, the data should be interpreted cautiously due to the small number of subjects who were positive for IgG ADA neutralising antibodies (n=3).

12.2.5. Efficacy Question 6

12.2.5.1. Sponsor's response

A post-hoc assessment of the change from baseline in the four key efficacy endpoints (spleen volume, liver volume, haemoglobin and platelet count) based on IgG Anti-Drug Antibodies (ADA) status for studies PB-06-001, PB-06-002, and the extension study PB-06-003 was performed. The analyses include the nine month duration of the Enzyme Replacement Therapy (ERT)-naïve study (PB-06-001) and ERT-experienced study (PB-06-002) and the extension study (PB-06-003) through a cut off of 1 May 2012 for last efficacy measure. The last efficacy measure for PB-06-001/PB-06-003 corresponds to 36 months of study treatment and for PB-06-002/PB-06-003 corresponds to 24 months of study treatment.

The data are displayed as the mean absolute and percent changes in the efficacy parameters by treatment-induced IgG ADA status at nine months and last measure for PB-06-001/PB-06-003 (month 36) and for PB-06-002/PB-06-003 (month 24).

There are limitations in these analyses (e.g., small sample sizes in some of the cohorts) therefore caution should be exercised when evaluating differences. However, when assessing the data for consistency between subject subgroups (treatment naive adults, treatment experienced adults), between the multiple efficacy parameters reviewed and with two time periods, this post-hoc analysis suggests that there is no systematic relationship between treatment-induced IgG ADA status and the efficacy outcomes of spleen volume, liver volume, haemoglobin and platelet count parameters. The IgG ADA status did not affect efficacy stability in studies PB-06-002/PB-06-003.

12.2.5.2. Evaluator's comment

The sponsor's response is satisfactory. The review of the summary data suggests that there was no marked difference in the four key efficacy endpoints (spleen volume, liver volume, haemoglobin and platelet count) over time between ADA positive and negative subjects in studies PB-06-001/PB-06-003 and in studies PB-06-002/PB-06-003

12.2.6. Safety Question 1

12.2.6.1. Sponsor's response

The sponsor indicated that the information in [dossier] table 17 was correct, but that information in the first paragraph in section 2.7.4.2.1.1.2 was incorrect. Therefore, the assumption in the question is correct that double counting led to an incorrect determination of the number of patients with severe and very severe adverse events, but also the number of events was incorrectly totalled. The first paragraph in Section 2.7.4.2.1.1.2 should read as follows: The severity of AEs is presented in SCS table 7.1, for all ongoing and completed studies, by study and treatment dose. Nineteen subjects (17 adults; 2 children) experienced 24 AEs that were considered severe or very severe.

12.2.6.2. Evaluator's comment:

The sponsor's response is satisfactory.

12.2.7. Safety Question 2

12.2.7.1. Sponsor's Response

In the SCS, table 13 presents the number of adverse events reported in adult subjects in which multiple events with the same preferred term in a system organ class were counted separately for each instance, regardless of AE severity, as noted in the table footnote. Whereas, tables 20

and 21 present the number (%) of adult subjects with adverse events by severity, and a listing of adult subjects with a severe or very severe adverse event respectively. In tables 20 and 21, when there are multiple events with the same preferred term in a system organ class for a subject, the most severe event is used and multiple events in the same system organ class for a subject are only counted once in the statistics of that system organ class, as noted in the footnote. [Dossier] table 13 correctly lists 26 severe or very severe AEs in total, and tables 20 and 21 correctly list 24 AEs when the duplicate AEs for subjects 71-4007 (two separate episodes of left calf pain) and 75-4021 (two separate events of migraine) are counted only once as noted in the table footnote.

12.2.7.2. Evaluator's comment

The sponsor's response is satisfactory.

12.2.8. Safety Question 3

12.2.8.1. Sponsor's response

- Of the 20 subjects who were analysed for the presence of ADA and who experienced a Type I Hypersensitivity event:
- 50% (10/20) of subjects continued treatment with taliglucerase alfa with no intervention; 25% (5/20) were treatment induced ADA positive and 25% (5/20) were treatment induced ADA negative.
- 15% (3/20) of subjects discontinued treatment with taliglucerase alfa; 5% (1/20) were treatment induced ADA positive and 10% (2/20) were treatment induced ADA negative.
- 25% (5/20) of subjects continued treatment with taliglucerase alfa with use of medication to treat symptoms of the adverse event; 15% (3/20) were treatment induced ADA positive and 10% (2/20) were treatment induced ADA negative.
- 10% (2/20) of subjects continued treatment with taliglucerase alfa with a pre-treatment regimen; 5% (1/20) were treatment induced ADA positive and 5% (1/20) were treatment induced ADA negative.

Therefore, there was no effect of antibody status on the clinical action taken in response to an adverse event of Type I Hypersensitivity. Of note, the clinical decisions were made before the patient's samples were tested for ADA.

The data were re-analysed with exclusion of the two subjects with questionable hypersensitivity status (one subject had a rash not associated with taliglucerase alfa, this event was erroneously captured as a Type I hypersensitivity reaction; one subject experienced face oedema as a result of sunburn considered to be unrelated to treatment with taliglucerase alfa) as shown below.

- 50% (9/18) of subjects continued treatment with taliglucerase alfa with no intervention; 28% (5/18) were treatment induced ADA positive and 22% (4/18) were treatment induced ADA negative.
- 17% (3/18) of subjects discontinued treatment with taliglucerase alfa; 6% (1/18) were treatment induced ADA positive and 11% (2/18) were treatment induced ADA negative.
- 22% (4/18) of subjects continued treatment with taliglucerase alfa with use of medication to treat symptoms of the adverse event; 11% (2/18) were treatment induced ADA positive and 11% (2/18) were treatment induced ADA negative.
- 11% (2/18) of subjects continued treatment with taliglucerase alfa with a pre-treatment regimen; 6% (1/18) were treatment induced ADA positive and 6% (1/18) were treatment induced ADA negative.

This analysis also indicated that there was no effect of antibody status on the clinical action taken in response to an adverse event of Type I Hypersensitivity.

12.2.8.2. Evaluator's comment

The sponsor's response is satisfactory.

12.2.9. Safety Question 4

12.2.9.1. Sponsor's response

The discrepancies between SAEs reported in SCS Section 2.7.4.2.1.3 and in-text tables 12 and 13 results from differences in the source data for these components of the SCS. The data in SCS Section 2.7.4.2.1.3 are derived from the safety database and the data in tables 12 and 13 are derived from the clinical database. Whereas the clinical and safety databases for studies conducted within Pfizer are reconciled prior to data extraction, this did not take place across companies. One patient included in the clinical database was excluded from the safety database because events reported as a result of elective surgery for pre-existing conditions were not listed as SAEs in the safety database. Therefore, this case was considered by the sponsor to be invalid. There were also differences in the number and/or coding of SAEs between the two databases for5 other patients. A table comparing the two databases is provided in Table 25, below.

Table 25: SAEs reported from clinical studies in the clinical database and safety database.

SAEs Reported in the Clinical Database*	SAEs reported in the Safety Database**
Head trauma Epistaxis	Head injury Epistaxis
Immune thrombocytopenia	Autoimmune thrombocytopenia
Left knee pain	Osteoarthritis
	Arthralgia
Traumatic fractured 4 ribs and pneumothorax	Rib Fracture
	Pneumothorax traumatic
Cytomegalovirus	Cytomegalovirus infection
	Pyrexia
	Cough
Renal Stone	Nephrolithiasis
Prolapsed rectum bladder and cervix	Pelvic prolapse
Pericutaneous stone removal Left hip replacement	Renal stone removal Haematocrit decreased
	Haemoglobulin decreased
Right acetabular necrosis	Osteonecrosis
Right femoral head necrosis	
Pain due to hemangioma in left knee	Bone pain
	Haemangioma
Pulmonary embolism	Pulmonary embolism
Multiple Tooth Extraction	
Elective surgery of left partial tonsillectomy	
Elective surgery of left vocal cord polypectomy	
Atrial fibrillation	Atrial fibrillation
18	**20**

*Verbatim term as reported in Patient Profiles for studies PB-06-002, PB-06-003 and PB-06-004

**Preferred term as reported in SCS Table 11.2.1 and 11.2.2

[Note: Patient ID information has been redacted from the Table above.] The last row above shows Total events

12.2.9.2. Evaluator's comment

The sponsor's response is satisfactory. The safety database is considered to be an accurate reflection of the SAE experience in the clinical trial program.

12.2.10. Safety Question 5

12.2.10.1. Sponsor's response

The statements noted by the evaluator, from the "Addendum, Immunogenicity Overview" are correct and consistent with the table provided in the response. The sponsor noted that in transferring information from the Addendum, Immunogenicity Overview into the SCS two typographical errors were incorporated into the text. The sponsor identified the errors and provided corrected text. The relevant corrected text has been provided below.

In SCS Section 2.7.4.2.1.5.2.1 Antidrug Antibodies and Clinical Safety the correct sentence follows: Anti-taliglucerase alfa IgG antibody status from 28 ERT experienced subjects from switchover Study PB-06-002 (26 adult and 2 paediatric subjects) and the 20 subjects (18 adults and 2 children) who continued into extension study PB-06-003 was assessed. Five adult subjects (18%) were found to have treatment-induced IgG ADA.

In Section 2.7.4.2.1.5.2.2 Immunogenicity Conclusions, the correct sentence follows: Taliglucerase alfa has induced formation of IgG ADA in the clinical studies with GD patients. The incidence of treatment-induced ADA responses observed was in 17 of 32 treatment-naïve adults and in 2 of 11 treatment-naïve paediatric subjects; and 5 of 28 subjects previously treated with other ERTs.

12.2.10.2. Evaluator's comment

The sponsor's response is satisfactory.

12.2.11. Safety Question 6

12.2.11.1. Sponsor's response

In taliglucerase alfa clinical studies, for subjects who were tested for treatment-induced ADA, 44.2% (19/43) ERT-naïve subjects and 17.9% (5/28) ERT-experienced subjects were treatment-induced ADA positive. The sponsor provided a table identifying the subject IDs patients who were treatment-induced ADA positive. Data in this table indicates that of the 19 ERT-naïve subjects with treatment-induced IgG ADA positive, 17 were adult subjects and 2 were paediatric subjects. Of the 5 ERT-experienced subjects with treatment-induced ADA, all 5 were adults.

Although the number of subjects is small, there appears to be a higher proportion of ERT-naïve subjects (approximately 44%) who were treatment-induced IgG ADA positive compared with ERT-experienced subjects (approximately 18%).

Subjects enrolling into ERT-experienced study PB-06-002 (and thereby subjects transferring from this study into study PB-06-003) were initially excluded from participation in the study if they had antibodies to glucocerebrosidase enzyme. Subjects enrolling into ERT-naïve studies PB-06-001 and PB-06-005 did not have this exclusion criterion, but as ERT-naïve individuals they would not be expected to have significant pre-existing ADA to taliglucerase alfa or to other glucocerebrosidase enzyme. Therefore, a proportion of the ERT-naïve and ERT-experienced clinical study populations were broadly equivalent with respect to anti-glucocerebrosidase ADA status, at least within the sensitivity margins of the assays used in the ERT-experienced population.

However, the exclusion of subjects who had antibodies to glucocerebrosidase or previous allergic reactions to other ERT would be key factors for reducing enrolment of subjects who would have been at higher risk to develop immune responses to taliglucerase alfa. It was noted in Starzyk et al (2007) that subjects who develop IgG antibody to imiglucerase produce

antibodies within 6 months of initiating treatment and rarely develop antibodies after 12 months of therapy and also that 46% of subjects with IgG antibody to imiglucerase have an increased risk of hypersensitivity type reactions. Since treatment experienced subjects in study PB-06-002 had to have been on imiglucerase treatment for at least 2 years, most subjects at higher risk of developing antibodies to glucocerebrosidase would have developed the antibody responses during that 2 year time period. About 46% of the ADA positive subjects, as well as other non-ADA positive subjects, would have had hypersensitivity reactions. These subjects would have been excluded from participation in study PB-06-002.

Therefore, imiglucerase treated subjects eligible for entry into Study PB-06-002 were likely to have been those who were either ADA negative or those who were ADA positive and became negative during their imiglucerase treatment. These subjects, and others who had been previously exposed to ERT and not developed allergic reactions, are likely to have been immune tolerant and less likely to develop antibodies under further treatment with imiglucerase or other glucocerebrosidases.

It has been reported that for VPRIV, 1 of 54 ERT-naïve subjects treated with velaglucerase became ADA positive whereas none of 40 ERT-experienced subjects became ADA positive (VPRIV EPAR) and this 1/94 rate is reported in the VPRIV SmPC. In addition, within the sensitivity margins of the assays used IgG antibodies to imiglucerase are formed in approximately 15% of presumably ERT-naïve Cerezyme treated subjects (CEREZYME SmPC), but no comparable information is available for ERT-experienced subjects. Therefore, the information available from other glucocerebrosidase ERT therapeutic agents does not aid with understanding why there may be a difference in the incidence of ADA in ERT-naïve versus ERT-experienced subjects.

12.2.11.2. Evaluator's comment

The sponsor's response is acceptable. The response suggests that ERT-experienced subjects tested for treatment-induced IgG ADA might have been immune tolerant. Consequently, it is possible that ERT-experienced subjects were less likely to develop ADAs following treatment with taliglucerase alfa than ERT-naïve subjects. However, data referred to by the sponsor indicates that the percentage of both ERT-naïve and ERT-experienced subjects who became ADA-positive following treatment with VIPRIV was lower than for taliglucerase alfa, while the percentage of ERT-naïve subjects who became ADA-positive following treatment with Cerezyme was similar to that for taliglucerase alfa. Overall, the data suggest that there may be differences in the immunogenicity of glucocerebrosidase products.

12.2.12. Safety Question 7

12.2.12.1. Sponsor's response

The evaluator’s statement is correct; whereas 25 patients were assessed as IgG ADA positive, 24 of these patients were tested for neutralizing antibodies (nAb). Patient 20-224 had a single occurrence of positive anti-taliglucerase IgG antibodies with titer of 82, on visit 5. This sample was not available at the time of nAb analysis and since it was a single IgG positive occurrence, this particular sample could not be replaced by a sample from a different visit and therefore this patient was not tested for nAb.

12.2.12.2. Evaluator's comment

The sponsor's response is satisfactory.

12.2.13. Safety Question 8

12.2.13.1. Sponsor's response

The Sponsor confirms that 3 paediatric patients who were IgG ADA positive were tested and were negative for neutralizing antibody by both in-vitro (enzymatic) assay and cell based assay. Another patient, who was also IgG ADA positive, was tested and was negative at visit 3 (Week 4)

for neutralizing antibody. The sample was tested by the in-vitro nAb assay only, not the cell based assay, due to insufficient sample volume.

12.2.13.2. Evaluator's comment

The sponsor's response is satisfactory.

12.2.14. Safety Question 9

12.2.14.1. Sponsor's response

In the taliglucerase alfa clinical protocols, subjects that experienced severe or recurrent hypersensitivity reactions were to be analyzed for IgE antibody formation. In the ongoing taliglucerase alfa exposure registry agreed with by the US FDA the sponsor recommends testing all subjects for IgE anti-taliglucerase alfa antibody at baseline, 6 months, 12 months and 24 months and additionally at the discretion of the investigator when considered to be clinically appropriate for patients with apparent hypersensitivity reactions.

In taliglucerase alfa clinical studies, a total of 6 patients were tested for IgE antibodies to taliglucerase. Two of the 6 subjects had one or more positive results in the IgE anti-taliglucerase antibody assay and 4 were negative. Of the 5 patients that were tested at baseline, 2 were positive at baseline and 3 were negative at baseline. The sponsor provided case narratives for the 5 patients who were tested for IgE ADA at baseline.

In summary, in the taliglucerase alfa clinical studies, a total of 6 subjects were analysed for IgE anti-taliglucerase alfa antibody formation, 5 of these had experienced hypersensitivity reactions and the 6th had experienced a serious event of gastrointestinal inflammation. Overall, due to the small number of subjects who were tested at baseline it is difficult to make a clear association between the IgE positive laboratory results and clinical response. Of the two subjects that were IgE positive at baseline, both experienced hypersensitivity events soon after the first infusion commenced. Two subjects who were IgE negative at baseline also experienced adverse events during the first infusion, one of which was considered to be a hypersensitivity reaction. One further subject who was IgE negative at baseline first experienced a hypersensitivity reaction at Week 20. Therefore, in this small sample size it is not clear whether there is an association between baseline IgE status and immediate onset of adverse events, particularly those associated with hypersensitivity.

The Sponsor is establishing a taliglucerase alfa exposure registry protocol that recommends IgE testing for all patients at baseline (prior to first dose) and at 6, 12 and 24 months after taliglucerase administration and after apparent hypersensitivity reactions. The Sponsor is providing the current version of the protocol for the taliglucerase alfa exposure registry in response to RMP Question 2 [not shown here].

12.2.14.2. Evaluator's comment

The sponsor's response is satisfactory.

12.2.15. Safety Question 10

12.2.15.1. Sponsor's response

The observation of some baseline ADA assay positive results prior to drug exposure is not unusual, especially when sensitive assays are used. The source of such reactivity in naïve subjects varies and is often unknown. In some cases, natural antibodies or antibodies against environmental antigens may cross-react with the drug product. In other cases, prior exposure to the drug and/or a similar product may be the source of pre-existing antibodies. The Sponsor is undertaking measures to characterise the specificity of anti-taliglucerase alfa antibodies, including pre-existing antibodies, for their cross-reactivity with other ERT and plant glycans. Future measures will include assessment of cross-reactivity with plant glycans. The sponsor provided a tabulated summary of subjects who were ADA positive pre-dose. The sponsor also

provided safety information for the 6 subjects who were ADA positive pre-dose. Only one subject was considered to have treatment-induced IgG ADA following exposure to taliglucerase alfa. In summary, subjects who were ADA-positive prior to treatment with taliglucerase did not necessarily progress to develop treatment-induced ADA. Three subjects with pre-treatment ADA experienced treatment-related hypersensitivity events shortly after commencing treatment whereas three others, also with pre-treatment ADA, did not. Therefore, in this small sample there is no clear relationship between pre-treatment IgG status and subsequent hypersensitivity events.

12.2.15.2. Evaluator's comment

The sponsor's response is satisfactory. It is noted that the sponsor is undertaking measures to characterise the specificity of anti-taliglucerase alfa antibodies, including pre-existing antibodies, for cross-reactivity with other ERT and plant glycans.

12.2.16. Module 3 evaluator's questions - response requiring clinical comment

12.2.16.1. M3 evaluator's question number 7

Changes in manufacturing process had effects on the glycosylation of the protein. Most of these effects were not in themselves significant, but the accumulative changes in the same direction rendered the drug substance made by the final commercial process very different in glycosylation to that used in the early stages of the Phase 3 clinical trials. The content of the major fucosylated and xylylated mannose 3 glycan (FcM3X) increased from just over half to over 90% with corresponding decreases in all other glycans – in particular some non-xylylated glycans. Although the proportional increase in FcM3X glycan is probably a good thing as this is the primary glycan which directs the product to be taken up into the lysosome, the inclusion of proportionally more xylose could increase the possibility that there may be an immunogenic response to the product. Thus this would imply that the product used in early Phase 3 clinical trials might have been slightly less efficacious than the commercial product, but is also less likely to have incurred an immunogenic response. Please comment on the difference between the commercial product and the early Phase 3 clinical trial product.

12.2.16.2. Clinical evaluator's comments on the clinical aspects of the sponsor's response

The sponsor comments that “despite the differences in glycan distribution, analysis of clinical data from subjects treated with the early Phase 3 clinical trial product and subject[s] treated with either commercial-like or commercial product has not shown any differences in the immunogenicity, safety, and efficacy of taliglucerase alfa”.

In support of this claim, the sponsor provided relevant clinical data evaluating the effect of the formulation change on immunogenicity, safety and efficacy. The sponsor evaluated the time courses of IgG ADA development and titres in individual subjects, each of the four key efficacy endpoints (change from baseline in spleen volume, liver volume, haemoglobin and platelet count) and AEs from the PB-06-001, PB-06-002, and PB-06-003 studies against the time-points in the studies at which each subject began to receive taliglucerase alfa from the commercial-like process that contained drug substance with commercial product-like glycan patterns (e.g., elevated FcM3X and corresponding decrease in M3). The sponsor comments that additional experience with the commercial product is being generated in 2 ongoing extension studies; study PB-06-006 (extension study for paediatric subjects from studies PB-06-002 and PB-06-005) for a total of up to 3 years of exposure and study PB-06- 007(treatment-naive adults who complete study PB-06-003) for a total of up to 5 years of exposure). A 10-year post-marketing registry has been initiated to provide additional data. The relevant clinical data provided by the sponsor are reviewed below.

- Immunogenicity

In the dataset provided in the SCS, 49 subjects in PB-06-001, PB-06-002 and PB-06-003 had received both taliglucerase alfa from the early processes and from the commercial-like or commercial process. The IgG ADA results for these subjects are summarised in the study report. The 49 subjects had a total of 1544 months of exposure to taliglucerase alfa (per subject average 32 months) of which 844 months (per subject average 17 months) were exposed to taliglucerase alfa with commercial-like plant-specific glycan patterns. A total of 275 samples (per subject average 6) analysed for IgG ADA were collected from these subjects after they were changed to taliglucerase alfa containing commercial-like glycans. The results observed in these 49 subjects are summarised below:

- Of the 49 subjects, 40 had ADA results that were similar in both periods, including 29 that were negative throughout both periods, and 11 that had positive results of peak ADA titres that were within 1 assay dilution factor (i.e. within 3x) in both periods.
- Of the 49 subjects, 2 had increased levels of ADA after the change. Both subjects were IgG ADA negative before the change and became IgG ADA positive after the change. One Subject was treated with the pre-commercial formulation for 12 weeks and then changed to the commercial-like formulation and treated for approximately 26 months. The subject's first positive titre was at week 18 and titre at week 38 (last time-point) was 23045. The other Subject was treated with the pre-commercial formulation for 42 weeks and then changed to the commercial-like formulation and was treated for approximately 7 months. The subject had positive results at month 3 and month 6 following the change to the commercial-like formulation with a peak titre of 573 at month 3, and had negative results for the last three time-points tested (months 9, 12 and 15).
- Of the 49 subjects, 6 were IgG ADA positive before the change but were IgG ADA negative after the change, while 1 patient was Ig ADA positive before the change and was IgG ADA negative after the change, but with decreased titres.
- A subset of 6 subjects changed directly from drug product containing drug substance produced by the early processes to drug product containing only the commercial-like (study PR-2006) or to commercial drug substance (WA016489). All 6 of these subjects were negative for ADAs throughout the course of the study, both before and after the change.

The sponsor comments that “overall, the analysis of subject's ADA status and titers before and after exposure to proportionally more plant glycan species provides no indication of increased immunogenicity. The majority of subjects (47/49) had either no changes or decreases ADA after exposure to the commercial-like drug substance. When individual subjects who experienced ADA titer increases during the period of exposure to commercial-like drug substance are evaluated, there is no indication that these increases are due to the change in drug substance. These subjects had relatively shorter durations of exposure to the early Phase 3 drug substance prior to first exposure to the commercial-like drug substance and plant-specific glycan pattern”. The sponsor's comments on the results of the analysis are considered to be reasonable.

The sponsor also refers to data from study PB-06-005 in “which 96% of all infusions were commercial drug product containing the higher and more uniform levels of plant-specific glycan species, [and] 9 of 11 subjects were negative for treatment-induced ADA throughout the 12 months of monitoring. In the PB-06-001 study in subjects [receiving] only early phase 3 material, 17 of 32 treatment naive subjects monitored for 9 months had treatment-induced ADA”.

The sponsor concludes that collective evaluation of the immunogenicity data relating to the pre-commercial and commercial-like formulations shows “there is no indication that proportionally more plant-specific glycan-containing taliglucerase alfa species increased the immunogenic response to taliglucerase alfa”. The sponsor's conclusion is considered to be acceptable.

· Safety

The sponsor summarised treatment-emergent AE (all causality and treatment-related) for the 51 subjects in studies PB-06-001, PB-06-002 and PB-06-003 who received both taliglucerase alfa drug product from the early processes (before change) and from the commercial-like or commercial process (after change). The sponsor noted that the "number of adverse events before and after the product change for each individual subject appears to be approximately equivalent when the duration of treatment is taken in to account. The number of events is more closely aligned with duration of treatment rather than the batch of product used. This appears to be the case for treatment-related as well as all causality events and for events associated with Type I, II, III or IV hypersensitivity. Moreover, for Type 1 hypersensitivity events, which might be expected to be less dependent on duration of exposure, there were approximately equivalent numbers of reported events with drug product from the early processes and from the commercial-like or commercial process". The tabulated summary of all causality and treatment-related AEs (including specific identification of Type 1, II, III, or IV hypersensitivity events) provided in the sponsor's M3 (Q7) response has been examined and no safety signals have been identified suggesting clinically significant differences between the TEAE profiles before and after the change.

Of the 2 subjects with increased levels of ADA after the change:

- One Subject was ADA negative prior to the change but became ADA positive after the change with ADA's being first detected at week 18 with a peak titre at week 38. This subject experienced no treatment-related AEs prior to the change and treatment-related discomfort, flushing and skin tightness after the change. The post-change treatment-related AEs are considered to be hypersensitivity reaction to taliglucerase alfa.
- The other Subject was ADA negative prior to the change and subsequently had positive results with a peak titer at month 3, and was negative at the last three time points tested (months 9, 12 and 15). This subject experienced no treatment-related AEs either before or after the change, but there was a greater number of all causality AEs after the change compared with before the change (i.e., 16 vs 2 AEs, respectively).

Six (6) subjects changed directly from drug product containing drug substance produced by the early processes to drug product containing only the commercial-like (PR-2006) or commercial drug substance (WA016489). All 6 of these subjects were negative for ADAs throughout the course of the study, both before and after the change. Of these, two subjects experienced treatment-related AEs of headache and another subject experienced a treatment-related AE of lethargy prior to change. No treatment-related AEs were experienced following the change. A Subject also experienced a non-treatment-related AE of arthritis (potentially a chronic hypersensitivity event) after the change.

In study PB-06-001, subjects were exposed only to drug substance produced by the early processes and 3 subjects experienced hypersensitivity and 3 subjects experienced pruritus. In study PB-06-005, subjects were exposed to drug product containing only the commercial-like or commercial drug substance and no subjects experienced treatment-related Type I hypersensitivity events.

Overall, the sponsor concludes "the safety profile of taliglucerase alfa is more closely aligned with duration of treatment rather than the batch of product used. There appears to be a negligible effect of drug production process on product safety". It is considered that the sponsor's conclusion is reasonable. Overall, the provided data suggest that the risks of treatment with the commercial-like formulation are not significantly different from those associated with the pre-commercial formulation.

· Efficacy

The sponsor stated that the "lack of impact of the change in relative abundance of plant glycan species on potency suggests that the change would also not have an impact on clinical efficacy. To assess this hypothesis, the efficacy measurements in the nine month study PB-06-001, in which ERT adult naive subjects received only early phase 3 material containing the lower plant-specific glycan content, were compared with the efficacy measurements in the twelve month study PB-06-005, in which ERT naive paediatric subjects received predominantly taliglucerase alfa from the commercial process containing the commercial plant-specific glycan content". The sponsor noted that this comparison is not ideal "in that different age groups, variations in inclusion criteria resulting in differences in baseline characteristics and study durations are involved. This is mitigated in that adult patients and paediatric patients tend to have similar efficacy responses and the three month additional therapy in study PB- 06-005 would not be expected to create large changes in the evaluated endpoints after 12 months of therapy". The efficacy results for the two studies are summarised in the table below. The results show that mean % change for the 4 efficacy parameters are similar for the two studies, although subject numbers are small. The limited evidence from the cross-study comparison suggests that there are no significant differences in the efficacies of the pre-commercial and commercial-like taliglucerase alfa formulations.

Table 26: Efficacy parameters of mean response (mean % change) for studies PB-06-001 (before commercial-like formulation of taliglucerase alfa) and PB-06-005 (with commercial-like formulation of taliglucerase alfa).

Efficacy Parameter	Absolute (%) Change from Baseline							
	Study PB-06-001 (9 months)				Study PB-06-005 (9 months/12 months)			
	30 U/kg	n	60 U/kg	n	30 U/kg	n	60 U/kg	n
Haemoglobin (g/dL)	1.6(14.6)	14	2.2(22.2)	15	1.0(9.3)/ 1.4(13.8)	6/6	1.3(13.1)/ 1.6(15.8)	5/5
Spleen Volume (mL)	-582.1(-27.3)	15	-756.15(-38.00)	16	-407(-28.6)	6	-499(-41.1)	5
Liver Volume (mL)	-337.4(-10.5)	14	-288.5(-11.1)	15	-98.7(-6.3)	6	-143(-14.0)	5
Platelet Count (/mm3)	11427(13.7)	15	41494(72.1)	16	45500(30.9)	6	72600(73.7)	5
Chitotriosidase (nmol/mL*h)	-13264(-47.3)	14	-12165(-58.4)	15	-12231(-57.2)/ -13210(-58.5)	6/6	-17660(-58.9)/ -20528(-66.1)	4/4*

Source: Supporting Table 1.1.2, Table 1.2.2, Table 1.3, Table 1.4, Table 1.5, Dose data from CSR PB-06-001 03 Statistical Table 16.2; CSR PB-06-005 – Table 6, Table 8, and Table 9, and SCS Table 2.3 (Dose Listing)
*One subject was chitotriosidase deficient; n = number

12.2.17. M3 evaluator's question number 8

The data supplied report that almost all glycans (>90%) in commercial batches contain xylose and some contain fucose. Xylose is not found in mammalian glycans and fucose with the characteristically plant-specific α(1,3) linkage have both been reported as being immunogenic in rats and mice. Human blood donors have been shown to have antibodies against these epitopes. As commented on in the evaluation of the methodologies used in 5.3.1.4 at the end of the [module 3] evaluation, the company developed an assay to determine levels of antibodies against plant-derived glycans in patient sera but do not appear to have used it. It also compared the level of antibodies in patient sera that bind to imiglucerase and taliglucerase alfa. There are more explanations than that assumed (excess binding to taliglucerase was due to plant-derived antibodies) though it does imply that levels of plant-glycan-directed antibodies is not very high. The issue of immunogenicity or the action of pre- existing antibodies on the product has therefore not been adequately dealt with. As stated in the pre-submission meeting on 2 Feb 2011 and in the previous submission, this is a significant issue and must be dealt with exhaustively. Without adequate data it is likely that the Module 3 evaluator must recommend rejection. Please address the issue of the immunogenicity of xylose and α(1,3) fucose.

12.2.17.1. Clinical evaluator's comments on the clinical aspects of the sponsor's response

The clinical aspects of the sponsor's response to the Module 3 (Q8) response have been reviewed above in Section 12.2.1 (Biopharmaceutical study).

12.3. Final study report protocol #pb-06-002

12.3.1. Background

The sponsor's response included the final study report for protocol #PB-06-002 dated 31 May 2013. The report was provided for the purposes of fulfilling the RMP reviewer's request for new safety information. Interim efficacy and safety data from this study have been previously evaluated in the clinical evaluation reports relating to the original submission and in the first round clinical evaluation report of the current submission. In particular, it should be noted that the 3rd Interim Report for this study with a database freeze of 1 May 2011 has been reviewed in the second round Clinical Evaluation Report relating to the original submission to register taliglucerase alfa (CER 1). The efficacy and safety data in the previously evaluated 3rd Interim Report is consistent with that in the Final Study Report. In fact, it appears that the only significant differences between the two reports relate to inclusion of 9 month efficacy data on all 5 paediatric patients included in the study, and the inclusion of a small amount of 9 month safety data on an additional 3 paediatric patients.

In addition to interim clinical data from study PB-06-002 provided in the original submission (including sponsor's Response), it appears that safety data from the 3rd Interim Report has been included in the integrated summary of clinical efficacy provided in the current submission and reviewed in the first round clinical evaluation report (above). The data reviewed below for the Final Study Report for study PB-02-006 should be reviewed in conjunction with the evaluation of the interim data from study PB-02-006 located in the first and second round clinical evaluation reports of the original submission (CER 1), and the first round clinical evaluation report of the current submission (above).

12.3.2. Overview

Study PB-06-002 was a multinational, multicentre, open-label, switchover trial designed to assess the safety and efficacy of taliglucerase alfa in patients, 2 years or older, with GD who had been receiving imiglucerase (Cerezyme) ERT for at least 2 years at a stable maintenance regimen (dose unchanged) for at least the last six months. The study drug dose of taliglucerase alfa was equivalent to the patient's current stable imiglucerase dose. During the treatment period with taliglucerase alfa, the dosage could be increased to a maximum dose of 60 units/kg if the patient experienced GD deterioration according to the defined criteria for platelet count and haemoglobin.

Up to 30 patients were to be enrolled at 5 to 8 investigational centres. The sample size of 30 patients was considered adequate to evaluate the safety endpoints for this orphan disease. The sample size was not based on power calculations. The first patient was enrolled on 15 December 2008 and the last patient completed on 14 January 2013. There have been three interim reports and the release dates of these reports were 30 April 2010 (Version 1), 25 August 2010 (Version 2), and 1 May 2011 (Version 3).

12.3.3. Patient characteristics

Forty-six (46) patients, from 11 study sites across 9 countries, were screened and 33 were eligible for enrollment. Two (2) patients voluntarily withdrew from the study prior to treatment, and 31 patients (26 adults and 5 children) received treatment. Of these 31 treated patients, 8 received a median dose of ≤15 units/kg, 12 received >15 to ≤30 units/kg and 11 received >30 units/kg of taliglucerase alfa. Of the 31 treated patients, 26 were adults with mean age of 47.1 years (range: 18, 66 years) and 5 were children with mean age of 13.0 years (range:

6, 16 years). All patients were Caucasian except for one child who was an Asian/pacific islander. Thirty (30) patients, 25 adults and 5 paediatric patients completed the study. One (1) adult patient discontinued the study after he experienced a moderately severe allergic reaction during the first infusion and declined to continue infusions with premedication.

12.3.4. Patient disposition

The disposition of the 33 enrolled patients is summarised below in Table 27

Table 27: PB-06-002 - Patient disposition.

		Taliglucerase alfa		
		Adults	Pediatric Patients	Combined
NUMBER ENROLLED		28	5	33
NUMBER TREATED		26	5	31
COMPLETED THE STUDY	N	26	5	31
	YES	25 (96.2%)	5 (100.0%)	30 (96.8%)
	NO	1* (3.8%)	0 (0.0%)	1 (3.2%)
REASON FOR DISCONTINUATION	N	1	0	1
	ADVERSE EVENT	0 (0.0%)		0 (0.0%)
	PROTOCOL VIOLATION	0 (0.0%)		0 (0.0%)
	SUBJECT WITHDRAWAL	1 (100.0%)		1 (100.0%)
	INVESTIGATOR RECOMMENDATION	0 (0.0%)		0 (0.0%)
	LOST TO FOLLOW-UP	0 (0.0%)		0 (0.0%)
	OTHER	0 (0.0%)		0 (0.0%)

*One patient experienced an allergic reaction during the first (partial) infusion and declined to continue infusions with premedication

12.3.5. Efficacy

12.3.5.1. Overview

The main efficacy criteria were based on whether the clinical status of the patient was maintained over the treatment period with taliglucerase alfa after switching from imiglucerase. The primary efficacy outcome was clinical stability during treatment with taliglucerase alfa, and the results were summarised using descriptive statistics. Efficacy was determined by evaluation of the following parameters of clinical deterioration over the course of the study:

- Platelet counts - a decrease of >20% from the mean of six Stability Evaluation Period values of ≤ 120,000 and > 40% from the mean of six Stability Evaluation Period values of > 120,000 was considered a clinically relevant deterioration
- Haemoglobin - a decrease of > 20% from the mean of six Stability Evaluation Period values was considered a clinically relevant deterioration
- Spleen volume - a 20% increase in spleen volume by MRI from Baseline to Month 9 was considered a clinically relevant deterioration
- Liver volume - a 10% increase in liver volume by MRI from Baseline to Month 9 was considered a clinically relevant deterioration.

12.3.5.2. Spleen volume

Among the 25 adult patients completing 9 months of treatment, 3 patients had no spleen volume readings due to splenectomy and 2 patients were evaluated by ultrasound rather than MRI and were not included in the analysis. Of the 20 adult patients with spleen volume measured with MRI, the mean spleen volume decreased from 822.4 mL at Baseline to 749.3 mL at Month 9, and the mean reduction was 7.6%. For spleen volume presented using multiples of normal (MN), the mean (SD) spleen volume in the 20 adult patients was 5.5 (4.8) MN at Baseline and 5.1 (5.1) MN at Month 9, and the mean (SD) reduction was 7.9% (13.0)

In the 5 paediatric patients, the mean spleen volume decreased from 313.0 mL at Baseline to 276.3 mL at Month 9, and the mean reduction was 6.6%. For spleen volume presented using MN, the mean (SD) spleen volume decreased from 4.1 (2.7) MN at Baseline to 3.3 (1.8) MN at Month 9, and the mean (SD) reduction was 12.4% (14.4).

In the 5 paediatric patients, after 9 months of treatment, patients in the >15 to ≤30 units/kg (n=11) and >30 units/kg (n=9) dose groups had mean reductions in spleen volume of 9.5% (from mean 4.7 to mean 4.4 MN) and 10.2% (from mean 4.7 to mean 3.9 MN), respectively, while patients in the ≤15 units/kg dose group (n=5) had a mean reduction in spleen volume of 2.2% (from mean 7.3 to mean 7.1 MN).

> **Comment**: Mean spleen volume decreased from Baseline to Month 9 in both adult (n=20) and paediatric patients (n=5) indicating that no clinical deterioration occurred in either age group following switchover from imiglucerase when assessed by this parameter. Of the 20 adult patients with an MRI measurable spleen volume, only 1 patient had a % change from Baseline at Month 9 in spleen volume of > 20% (i.e., pre-defined clinical deterioration). In this patient, spleen volume based on MN increased 19.2% from 5.34 MN at Baseline to 6.37 MN at Month 9. The increase in spleen volume in this patient was considered to be not clinically significant, and the patient had no deterioration in other efficacy parameters. All 5 paediatric patients remained stable, with spleen volume change from Baseline to end of study ranging from - 21.0% to 14.0% (from mean 4.1 MN at Baseline to 3.3 MN at Month 9).

12.3.5.3. Liver volume

Among the 25 adult patients who completed 9 months of treatment, 2 patients were evaluated by ultrasound rather than MRI and were not included in the analysis. Of the 23 patients with available MRI liver volume, the mean absolute liver volume decreased from 1857 mL at Baseline to 1786 mL at Month 9, and the mean reduction was 3.5%. For liver volume presented using MN, the mean (SD) liver volume was 1.0 (0.2) MN at Baseline and 0.9 (0.2) MN at Month 9.

Of the 5 paediatric patients, the mean liver volume was 1346 mL at Baseline and 1393 mL at Month 9, and the mean increase from Baseline was 2.4%. For liver volume presented by MN (SD), calculated by % of body weight, the mean liver volume decreased from 1.3 MN at Baseline to 1.2 MN at Month 9.

In the 5 paediatric patients, after 9 months of treatment the mean absolute liver volume was reduced by 3.3% in the ≤15 units/kg dose group, 1.5% in the >15 to ≤30 units/kg dose group and 3.1% in the >30 units/kg dose group. The MN evaluation showed there was no change from Baseline to Month 9 in liver volume in the >15 to ≤30 units/kg (0.9 MN at both time-points) and in the >30 units/kg (1.1 MN at both time-points) dose groups and a mean decrease of 0.1 MN (from 1.1 to 1.0 MN) in the ≤15 units/kg dose group after 9 months of treatment with taliglucerase alfa.

> **Comment**: Mean liver volume (mL) decreased from Baseline to Month 9 in adults (n=20) and increased in paediatric patients (n=5). However, the mean % increase in liver volume from Baseline to Month 9 in the paediatric patients was only 2.4% indicating that the mean % change in liver volume was not clinically significant. Of the 23 adult patients with an MRI measurable liver volume, only 1 patient had a % change from Baseline at Month 9 in liver volume of > 20% (i.e., pre-defined clinical deterioration). However, in this patient liver volume based on MN increased 15.6% from 0.90 MN at Baseline to 1.04 MN at Month 9. The increase in liver volume in this patient was considered to be not clinically significant, and the patient had no deterioration in other efficacy parameters. All 5 paediatric patients remained stable with liver volume change from Baseline to end of study ranging from -6.0 to 11.0% (from mean 1.3 MN at Baseline to 1.2 MN at Month 9).

12.3.5.4. Haemoglobin

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 remained stable for both adult and paediatric patients following switchover from imiglucerase to taliglucerase alfa.

In adult patients (n=25), mean (SD) baseline haemoglobin was 13.5 (1.6) g/dL and mean haemoglobin levels (% changes from baseline) at Month 3, Month 6 and Month 9 were 13.3 g/dL (-1.7%), 13.2 g/dL (-2.2%), and 13.3 g/dL (-1.8%), respectively.

In paediatric patients (n=5), mean (SD) baseline haemoglobin was 13.5 (0.5) g/dL and mean haemoglobin levels (mean % changes from baseline) at Month 3, Month 6 and Month 9 were 13.6 g/dL (0.8%), 13.4 g/dL (-0.6%), and 13.9 g/dL (3.3%), respectively.

In the total patient population (n=30), mean (SD) baseline haemoglobin was 13.5 (1.4) g/dL and mean haemoglobin levels (mean % changes from baseline) at Month 3, Month 6 and Month 9 were 13.3 g/dL (-1.3%), 13.3 g/dL (-1.9%), and 13.4 g/dL (-0.9%), respectively.

> **Comment**: The results indicate that there were no clinically significant deterioration in haemoglobin levels from Baseline to Month 9 following switchover from imiglucerase to taliglucerase alfa in adults (n=25) and children (n=5). All 30 patients who completed 9 months of treatment with taliglucerase alfa had % changes in haemoglobin levels from Baseline within the range -10.2% to 15.2% at the end of study (> 20% defined as indicating clinical deterioration).

12.3.5.5. 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. The mean platelet count in adult patients was consistent from Baseline through to Month 9, while the mean platelet count in paediatric patients increased from Baseline to Month 9.

In adult patients (n=25), the mean (SD) platelet count at Baseline was 160,447 (79,086) and the mean % changes from baseline at Month 3 (n=25), Month 6 (n=24), and Month 9 (n=25) were -5.2%, -3.5%, and -1.5%, respectively.

In paediatric patients (n=5), the mean (SD) platelet count at Baseline was 164,587 (38.731) and the mean % changes from baseline at Month 3, Month 6, and Month 9 were 5.6%, 3.4%, and 11.7%, respectively.

In the total patient population (n=30), the mean (SD) platelet count at Baseline was 161,137 (73,387) and the mean % changes from baseline at Month 3 (n=30), Month 6 (n=29), and Month 9 (n=30) were -3.4%, -2.3%, and -0.7%, respectively.

> **Comment**: The results indicate that there were no clinically significant deterioration in platelet counts from Baseline to Month 9 following switchover from imiglucerase to taliglucerase in adults (n=25) and children (n=5). The platelet count in all patients remained stable during 9 months treatment with taliglucerase alfa following switching from imiglucerase.

12.3.5.6. Biomarkers

The biomarkers chitotriosidase and CCL18 were measured every three months during the study. Baseline biomarkers were not measured for 2 adult patients, and full biomarker results were available for 23 adult and 5 paediatric patients over the course of 9 months. Of the 28 patients with available Baseline biomarker data, 22 (19 adult and 3 paediatric patients) showed a decrease in chitotriosidase activity and 16 (13 adult and 3 paediatric patients) showed a decrease in CCL18 level from Baseline after 9 months of treatment with taliglucerase alfa. Of these, 5 adult patients were found to have > 50% reduction in chitotriosidase activity and 3 of

these adult patients also had reduction in CCL18 level (approximately 40%) after switching to taliglucerase alfa.

In adult patients, a mean decrease from Baseline in chitotriosidase activity was observed at Month 3 (-13.5%), Month 6 (-21.8%) and Month 9 (-21.3%). In paediatric patients, a mean increase from Baseline in chitotriosidase activity was observed at Month 3 (9.1%), Month 6 (22.7%) and Month 9 (29.7%).

In adult patients, a mean decrease from Baseline in CCL18 level was observed at Month 3 (-1.7%), Month 6 (-7.5%) and Month 9 (-6.6%). In paediatric patients, a mean increase from Baseline in CCL18 level was observed at Month 3 (11.0%), while mean decreases from Baseline were observed at Month 6 (-4.9%) and Month 9 (-4.4%).

12.3.5.7. Evaluator's overall comments on efficacy

In this study, of the 31 enrolled patients 30 patients (26 adult, 5 children) completed 9 months of treatment with taliglucerase alfa following switching from imiglucerase. One (1) of the adult enrolled patients discontinued the study after he experienced a moderately severe allergic reaction with the first infusion and declined to continue infusions with pre-treatment. The efficacy analysis showed no clinically significant deterioration in efficacy in patients who switched from imiglucerase to taliglucerase alfa. The mean % changes from Baseline in spleen size, liver size, haemoglobin level, and platelet count were all less than the pre-specified changes defining clinical deterioration. The results support the efficacy of taliglucerase alfa for the treatment of GD.

12.3.6. Safety

12.3.6.1. Extent of exposure

Twenty-six (26) adults and 5 children received taliglucerase alfa and of these 25 adults and 5 children completed the study after receiving 9 months of taliglucerase alfa. One (1) adult patient discontinued the study after receiving a partial dose at the first infusion (Visit 1).

The mean of the medians of all doses of taliglucerase alfa was 28.8 units/kg for 26 adult patients (range: 9, 60 units/kg) and 42.0 units/kg for 5 paediatric patients (range: 26, 60 units/kg). Overall, the mean of the medians of doses for all 31 treated patients was 31.0 units/kg (range: 9, 60). The median dose of infusions (units/kg) for 25 adult patients (excluding the patient who discontinued the study after receiving a partial first infusion at Visit 1) was 27.9 units/kg, and for 30 combined adult and paediatric patients was 30.2 units/kg.

12.3.6.2. Adverse events

12.3.6.2.1. Overview

The AE profile for the 31 patients (26 adults, 5 children) in the safety population are summarised below in Table 28.

Table 28: PB-06-002, adverse event profile; safety population

Parameter	Adults (n=26)		Children (n=5)		Combined (n=31)	
At least 1 AE	25 (96.2%)	136 events	4 (80.0%)	9 events	29 (93.3%)	145 events
At least 1 mild or moderate AE	25 (96.2%)	133 events	4 (80.0%)	9 events	29 (93.5%)	142 events
At least 1 severe or very severe AE	2 (7.7%)	3 events	0 (0.0%)	0 events	2 (6.5%)	3 events
At least 1 serious AE	3 (11.5%)	3 events	0 (0.0%)	0 events	3 (9.7%)	3 events

Parameter	Adults (n=26)		Children (n=5)		Combined (n=31)	
At least 1 treatment-related AE *	10 (38.5%)	24 events	0 (0.0%)	0 events	10 (32.3%)	24 events

* AEs possibly, probably or definitely related to treatment.

12.3.6.2.2. Commonly occurring adverse events

In the total safety population (n=31), 29 (93.3%) patients experienced 145 events (142 mild/moderate; 3 severe/very severe). AEs occurring in 2 or more patients in the total safety population in descending order of frequency were: infusion related reaction (4, 12.9%); nasopharyngitis (4, 12.9%); arthralgia (4, 12.9%); headache (4, 12.9%); pain in extremity (3, 9.7%); URTI (3, 9.7%); urinary tract infection (3, 9.7%); cough (3, 9.7%); diarrhoea (2, 6.5%); pain (2, 6.5%); epistaxis (2, 6.5%); and pruritus (2, 6.5%). All other AEs in the total safety population each occurred in 1 patient only. Multiple occurrences of the same preferred term AE reported in the same SOC for a subject were counted only once.

In the paediatric population (n=5), 4 (80.0%) patients experienced 9 events (all classed as mild/moderate in severity). None of the events occurred in more than 1 patient. The observed AEs in paediatric patients were: refraction disorder; vomiting; URTI; iron deficiency; arthralgia; headache; cough; and epistaxis. Multiple events in the same system organ class for a subject were only counted once in the statistics of that system organ class.

12.3.6.2.3. Treatment related adverse events

In the total safety population (n=31), 10 (32.3%) patients experienced 24 events considered to be possibly, probably, or definitely related to treatment with taliglucerase. AEs occurring in 2 or more patients in descending order of frequency were infusion related reactions (3, 9.7%) and headache. No AEs reported in children were considered to be possibly, probably, or definitely related to treatment with taliglucerase. Treatment-related AEs are summarised below in Table 29.

Table 29: PB-06-002 - Number of subjects with possibly, probably, or definitely related AEs by MedDRA SOC and preferred term.

	Taliglucerase alfa		
SYSTEM ORGAN CLASS / PREFERRED TERM	Adults N = 26	Pediatric Patients N = 5	Combined N = 31
GASTROINTESTINAL DISORDERS			
DIARRHOEA	1 (3.8%)	0 (0.0%)	1 (3.2%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
LETHARGY	1 (3.8%)	0 (0.0%)	1 (3.2%)
IMMUNE SYSTEM DISORDERS			
HYPERSENSITIVITY	1 (3.8%)	0 (0.0%)	1 (3.2%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
INFUSION RELATED REACTION	3 (11.5%)	0 (0.0%)	3 (9.7%)
INVESTIGATIONS			
ALANINE AMINOTRANSFERASE INCREASED	1 (3.8%)	0 (0.0%)	1 (3.2%)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	1 (3.8%)	0 (0.0%)	1 (3.2%)
WEIGHT INCREASED	1 (3.8%)	0 (0.0%)	1 (3.2%)
NERVOUS SYSTEM DISORDERS			
HEADACHE	2 (7.7%)	0 (0.0%)	2 (6.5%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
PRURITUS	1 (3.8%)	0 (0.0%)	1 (3.2%)
VASCULAR DISORDERS			
FLUSHING	1 (3.8%)	0 (0.0%)	1 (3.2%)

Note: Multiple events in the same system organ class for a subject are only counted once in the statistics of that system.

12.3.6.2.4. Treatment related adverse events by dose

Treatment-related AEs possibly, probably, or definitely related to taliglucerase alfa for the three dosage groups are summarised below in Table 30. No obvious dose relationship for treatment-related AEs in the total safety population was observed, but patient numbers in each of the three dosage groups were small.

Table 30: PB-06-002 - Number of subjects with possibly, probably, or definitely related AEs by MedDRA SOC and preferred term by dose group.

	Taliglucerase alfa		
SYSTEM ORGAN CLASS / PREFERRED TERM	<=15 units/kg N = 8	>15 & <=30 units/kg N = 12	>30 units/kg N = 11
GASTROINTESTINAL DISORDERS			
DIARRHOEA	1 (12.5%)	0 (0.0%)	0 (0.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
LETHARGY	0 (0.0%)	1 (8.3%)	0 (0.0%)
IMMUNE SYSTEM DISORDERS			
HYPERSENSITIVITY	0 (0.0%)	0 (0.0%)	1 (9.1%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
INFUSION RELATED REACTION	2 (25.0%)	0 (0.0%)	1 (9.1%)
INVESTIGATIONS			
ALANINE AMINOTRANSFERASE INCREASED	1 (12.5%)	0 (0.0%)	0 (0.0%)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	1 (12.5%)	0 (0.0%)	0 (0.0%)
WEIGHT INCREASED	1 (12.5%)	0 (0.0%)	0 (0.0%)
NERVOUS SYSTEM DISORDERS			
HEADACHE	1 (12.5%)	1 (8.3%)	0 (0.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
PRURITUS	1 (12.5%)	0 (0.0%)	0 (0.0%)
VASCULAR DISORDERS			
FLUSHING	0 (0.0%)	0 (0.0%)	1 (9.1%)

Note: Multiple events in the same system organ class for a subject are only counted once in the statistics of that system.

12.3.6.2.5. Adverse events of special interest

· Infusion reactions

Infusion related reactions were based on best practice coding of events in MedDRA (preferred term) where the verbatim term in the eCRF indicated that an event occurred during an infusion. Eight (8) adult patients experienced 15 AEs and 1 paediatric patient experienced 1 AE during the infusion or within 2 hours after completion of the infusion Of the 16 events, 10 experienced by 5 adult patients were considered possibly/probably/definitely related to study treatment. Infusion related AEs occurring during or within 2 hours taliglucerase alfa are summarised below in Table 31.

Table 31: PB-06-002 - Adverse events during or within 2 hours of taliglucerase infusion; safety population.

Visit	Adverse Events (CRF term/ MedDRA Preferred term)	TreatmentRelationship
5	Mild worsening of Baseline condition of headaches / Headache	Possibly
6	Headache during infusion / Infusion related reaction	Probably not
2	Itching between thumb and index finger on left hand / Pruritus	Possibly
4	Itching between thumb and index finger on left hand / Pruritus	Probably
1	Allergic reaction / Hypersensitivity	Definitely
3	Numbness on left hand / Hypoaesthesia	Definitely not
3	Intermittent elevated serum glucose level / Blood glucose increased	Definitely not
1	Red area of skin at infusion site in shape of the dressing / Infusion site erythema	Probably not
1	Tired after the infusion / Infusion related reaction	Possibly
2	Feeling weak after infusion / Infusion related reaction	Possibly
2	Fatigue after infusion / Infusion related reaction	Possibly
1	Flushing on forearms / Flushing	Possibly
1	Flushing on top of feet / Flushing	Possibly
1	Flushing on upper chest / Flushing	Possibly
14	Sinus tachycardia (supraventricular) / Sinus tachycardia	Probably not
13	Vomiting / Vomiting	Probably not

[Note: Patient ID information has been redacted from the Table above. The patient described in the last row is a paediatric; others are adults]

Sixteen (16) adults experienced 39 AEs and 2 children experienced 2 AEs between 2 to <24 hours after completion of the infusion, and 11 of the 39 events experienced by adults were considered related to treatment by the investigator. Twenty-one (21) adults experienced 82 AEs and 3 children experienced 6 AEs at least 24 hours after the completion of infusion, and 3 of the 82 events experienced by adults were considered related to treatment by the investigator.

12.3.6.2.6. Other adverse events of interest

a. *Immune System Disorders:* In the total safety population (n=31), immune system disorders were reported in 2 adult patients (1 patient with hypersensitivity and 1 patient with seasonal allergy).

b. *General Disorders and Administration Site Conditions:* In the total safety population (n=31), general disorders and administration site conditions were reported in 6 patients (2 patients with pain, and 1 patient each with asthenia, infusion site erythema, lethargy, and pyrexia).

c. *Skin and Subcutaneous Tissue Disorders:* In the total safety population (n=31), skin and subcutaneous tissue disorders were reported in 6 patients (2 patients with pruritus, and 1 patient each with ecchymosis, rash, skin irritation, and spider naevus).

d. *Renal and Urinary Disorders:* In the total safety population (n=31), renal and urinary disorders were reported in 2 adult patients (1 patient with haematuria and 1 patients with nephrolithiasis).

e. *Hepatobiliary disorders:* No hepatobiliary disorders were reported.

f. *Bone events:* One adult patient in the ≤15 units/kg dose group experienced one GD related bone event (bone pain) during the study. The investigator considered this event to be definitely not related to treatment.

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

No deaths occurred during the study.

Three patients (3) each experienced SAEs during the study (1 patient with epistaxis; 1 patient with renal stone; 1 patient with prolapsed rectum, bladder and cervix). All three events were reported as resolved or resolving, and all three events were considered to be definitely not or probably not related to treatment by the investigator

No patients discontinued prematurely from the study due to an AE. One (1) patient voluntarily withdrew from the study after experiencing hypersensitivity (allergic reaction) during the first infusion of taliglucerase alfa and declined to continue infusions under pretreatment.

12.3.6.4. Anti-taliglucerase alfa antibody results

- Twenty-four (24) patients were negative for the presence of anti taliglucerase alfa IgG antibodies.
- Five (5) adult patients were positive for the presence of IgG antibody. Three (3) adult patients were positive for anti-taliglucerase alfa IgG antibody with highest titres being 3542, 23045 and 2768, respectively. Two Patients were negative for neutralising antibodies (by both in vitro and cell based assays). The other Patient showed positive neutralising activity on the in vitro assay, but not on the cell based assay. None of the patients who had IgG antibody positive samples experienced any treatment-related adverse events during the study. Two (2) of the 3 patients continued in extension Study PB-06-003.
- Two (2) additional adult patients were found to have a single sample positive for IgG antibody to taliglucerase. One patient with a titre of 82 at Visit 5 did not have samples available for neutralising antibody assessment. The second patient, at Visit 1 (before treatment with taliglucerase alfa) was found to have a positive IgG result with a titre of 978, and both in vitro and cell based assays were negative neutralising activity.
- Two (2) paediatric patients were also positive for the presence of IgG antibody with highest titres of 145 and 67, respectively at Visit 1 (before treatment with taliglucerase alfa). One Patient had anti-taliglucerase alfa IgG antibodies detected also at Visits 3 (titre = 103) and 7 (titre = 38), and another patient at Visit 3 (titre = 57). Both were tested by the in-vitro assay for neutralising antibodies and were found to be negative.

12.3.6.5. Laboratory tests

The majority of the laboratory haematology and biochemistry parameters remained at normal levels from screening through to the end of study. Laboratory values of interest are described below.

12.3.6.5.1. Hepatic tests

- Three (3) patients had normal ALT values at Screening which shifted to above the upper ULN at subsequent visits: #10-203 at Visit 5, 44 IU/L; #22-226 at Visit 1, 41 IU/L; #15-223 at Visits 1, 5, 10, 17 and 20, ranged from 63 to 89 IU/L.
- One (1) patient (#15-223) had an 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.
- Three (3) patients had normal AST values at Screening which shifted to above the ULN at subsequent visits: #14-230 at Visit 1, 53 IU/L; #15-223 at Visits 1, 5, 10, 17, ranging from 45 to 52 IU/L; #92-232 at Visit 7, 41 IU/L.
- Five (5) patients had normal total bilirubin values at Screening that shifted above the ULN at subsequent visits.
- No patients had liver transaminase levels > 3 x ULN. No patients had persistent bilirubin elevations, 2 patients had a medical history of Gilbert's disease (#15-223 and #23-204). No patients fulfilled Hy's criteria for hepatotoxicity.

12.3.6.5.2. Elevated serum glucose

Most patients (24 adults and 3 children) had sporadic and transient elevations in serum glucose during the study that did not require investigation or change in clinical care. One (1) patient showed several high serum glucose values, but the HbA1c results were not indicative of a new diagnosis of diabetes mellitus; 2 patients entered the study with diagnosis of Type 2 diabetes

mellitus; and 1 patient showed an elevation of HbA1c at Visit 20 without a medical history of diabetes mellitus.

12.3.6.5.3. Clinical disease deterioration determined by sustained reduction on haemoglobin of platelets

For safety assessment, clinical disease deterioration was determined by a sustained reduction (3 consecutive measurements 2 weeks apart) in haemoglobin level or platelet count that could result in treatment discontinuation or dose increase. One adult patient experienced disease deterioration with reduced platelet counts at Visits 10, 11 and 12 (Week 22). This patient's study dose was increased at Visit 13 (Week 24) from 800 (9.5 units/kg/IV) to 1600 units (20 units/kg/IV), and the platelet count subsequently increased to baseline level. The day after Visit 13 (Week 24), the patient experienced haematuria due to a large renal stone that was removed after several interventions by Visit 17 (Week 32). The 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 treatment.

12.3.6.6. Vital signs

Vital signs (systolic and diastolic blood pressures, pulse rate, temperature and respiration rate) were assessed pre-dose and then post-dose at each visit. There were no clinically significant mean changes from pre-dose findings following taliglucerase alfa administration in adults or children, or by dosage group.

12.3.6.7. Other safety results

- *ECG*: The ECG was assessed at Baseline, Months 3, 6 and 9. One adult patient in the >30 units/kg dose group had a clinically significant change from Baseline observed at Visit 14, which was entered as an AE, sinus tachycardia (supraventricular on ECG). The event resolved and was considered probably not related to treatment. This patient completed the study and subsequently enrolled into the extension study.
- *ECHO*: Echocardiography was undertaken at Screening and Month 9. Abnormal echocardiography results were observed in 10 (38.5%) adult patients at Screening (6 in the ≤15 units/kg; 3 in the >15 to ≤30 units/kg group; 1 in the >30 units/kg group), and 8 (33.3%) adult patients at Month 9 (3 in the ≤15 units/kg group; 2 in the >15 to ≤30 units/kg group; 3 in the >30 units/kg group). No paediatric patients had abnormal echocardiography results during the study.
- *Pulmonary Function Tests (PFTs)*: There were no clinically significant changes from Screening observed at Month 9 in PFTs (FVC; FEV1; TLC; FRC; RRV; DCLO; DCLO/VA).
- *Growth and Development (paediatric patients)*: In the 5 paediatric patients, mean height increased from Baseline at Month 9 by 1.9% (increasing from mean of 156.1 to mean of 160.3 cm), and mean weight increased from Baseline at Month 9 by 6.6% (increasing from mean of 44.1 kg to mean 47.2 kg). The mean growth velocity for the 5 patients was 4.2 cm/year.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the sponsor's response to the M5 clinical questions, and to the clinical aspects of the sponsor's response to the M3 (Q7, Q8) questions it is considered that the benefits of treatment with taliglucerase remain favourable.

The benefits of treatment with taliglucerase alfa (30 units/kg; 60 units/kg) in ERT-naïve and ERT-experienced adult and paediatric patients with non-neuropathic GD include reduction in spleen volume, reduction in liver volume, improvement in haemoglobin level, and improvement in platelet count. In addition, taliglucerase alfa has been shown to reduce GD biomarker activity in both adult and paediatric patients (chitotriosidase activity reduced; CCL18 concentration reduced). The duration of treatment with taliglucerase alfa in the pivotal Phase III studies was 12 months in children and adolescents aged 2 to < 18 years in study PB-06-005, and 9 months in adults aged ≥ 18 years in study PB-06-001. In addition, study PB-06-002 showed that in adults and children/adolescents whose disease had been stabilized with imiglucerase, the treatment benefit could be maintained for at least a further 9 months after switching to taliglucerase alfa. Support for treatment benefit achieved with imiglucerase being maintained following switching to taliglucerase alfa was also provided by study PB-06-004 (expanded access treatment protocol). Furthermore, study PB-06-003 showed that patients from studies PB-06-001 and PB-06-002 who had benefited from 9 months treatment with taliglucerase alfa could continue to benefit from further treatment with taliglucerase alfa for at least 15 months.

Clinical data provided in the sponsor's response to questions in the first round evaluation showed that in the cohort of 71 patients with IgG ADA assessments from the clinical trial program the presence of treatment-induced IgG ADA did not impair the efficacy of taliglucerase alfa. In fact, the absolute change from baseline in the pooled analysis (PB-06-001, PB-06-005) at the last measure (1 May 2012) was consistently greater in the treatment-induced ADA positive group (n=24; 33.8%) compared with the ADA negative group (n=47; 66.2%) across all six efficacy endpoints. The reason for this observation is unclear. Limited data from three IgG ADA positive patients with neutralising antibodies suggests that the presence of neutralising antibodies might have a negative impact on efficacy. However, it is unclear whether the negative impact on efficacy of neutralising antibodies is clinically meaningful.

Clinical data provided in the sponsor's response to questions in the first round evaluation included an assessment of the effect of anti-taliglucerase alfa plant-specific glycan antibodies on efficacy using previous data from the 71 patients with an IgG ADA assessment. This new analysis identified 29 out 71 patients (40.8%) who were IgG ADA positive at any time-point (baseline and/or post-baseline) and 42 out of 71 patients (59.2%) who were IgG ADA negative. The efficacy assessments included comparison of patients positive for anti-taliglucerase alfa plant-specific glycan antibodies (8/71, 11.3%), patients who had no detectable anti-taliglucerase alfa plant-specific glycan antibodies but were IgG ADA positive (21/71, 29.6%), and patients who were IgG ADA negative or were IgA positive but anti-taliglucerase alfa plant-specific glycan antibody negative (63/71, 88.7%). Overall, no significant efficacy differences between patients who were positive or negative for anti-taliglucerase alfa plant-specific glycan antibodies were observed for the efficacy endpoints of spleen volume, liver volume, haemoglobin level, platelet count, chitotriosidase activity and CCL18 level. However, the interpretation of the data is limited by the small number of patients (n=8) who were anti-taliglucerase alfa plant-specific glycan antibody positive.

13.2. Second round assessment of risks

After consideration of the sponsor's response to the M5 clinical questions, and to the clinical aspects of the sponsor's response to the M3 (Q7, Q8) questions it is considered that the risks of treatment with taliglucerase alfa for GD remain favourable. There are limited data on the safety of taliglucerase alfa in children and adolescents due to the small number of patients with GD aged ≤ 18 years treated with the medicine in the clinical trial program. However, the available data in children and adolescents suggests that the risks of treatment in this age group are similar to those in adults.

The data summarised below are from the integrated SCS provided in the current submission unless otherwise stated. The additional safety data relating to the Final Study Report for

PB-06-002 provided in the response to TGA questions (above) were almost identical to the previously evaluated interim safety data for this study. The final safety data from study PB-06-002 have no substantial effect on the general safety conclusions drawn from the evaluation of the integrated SCS.

The sponsor's response to questions in this evaluation included a significant amount of additional data concerning the immunogenicity of taliglucerase alfa and the effect of IgG anti-taliglucerase alfa antibody status (i.e., IgG ADA status) on safety. In the clinical trial program, assessment of IgG ADA status was carried out in a total of 71 patients (43 ERT-naïve, 28-ERT experienced). Of the 43 ERT-naïve patients, 19 (44.2%) were found to have treatment-induced IgG ADAs (17/32 [53.1%] adults, 2/11 [18.1%] children). Of the 28 ERT-experienced patients, 5 (17.9%) were found to have treatment-induced IgG ADAs (3/26 [11.5%] adults, 2/2 [100%] children). The proportion of ERT-naïve patients who developed treatment-induced IgG antibodies was notably higher than in ERT-experienced patients. The sponsor postulates that patients treated with taliglucerase alfa who had been previously exposed to ERT might have been more immune tolerant and less likely to develop antibodies with further glucocerebrosidase treatment than ERT-naïve patients treated with taliglucerase alfa.

The response to TGA questions provides data from an analysis of anti-taliglucerase alfa plant-specific glycan antibodies in the 71 patients who were tested for treatment-induced IgA ADAs. This analysis identified 29 patients who were confirmed IgG ADA at any time-point (baseline and/or post-baseline) of whom 8 were positive for anti-taliglucerase alfa plant-specific glycan antibodies and 21 were negative for these antibodies (Cohort A). Combining the 21 IgG ADA positive patients who were negative for anti-taliglucerase alfa plant-specific glycan antibodies with the 42 IgG ADA negative patients resulted in 63 patients being considered to be negative for anti-taliglucerase alfa plant-specific glycan antibodies (Cohort B). Therefore, of the 71 patients with IgG ADA data, 8 (11.3%) were positive for anti-taliglucerase alfa plant-specific glycan antibodies and 63 (88.7%) were negative for these antibodies.

The sponsor's response included a comparison of safety in the 8 patients with anti-taliglucerase alfa plant-specific glycan antibodies with the 21 patients in Cohort A, and with the 63 patients in Cohort B. Treatment-related AEs occurred more frequently in subjects who were considered to be anti-taliglucerase alfa plant-specific glycan antibody positive (9 events in 8 patients, estimated frequency of 1.4 events/patient) compared with subjects who were considered to be negative for these antibodies (44 events in 63 patients, estimated frequency of 0.7 events/patient). However, these figures should be interpreted cautiously due to the marked imbalance between the two patient groups. Of the 8 patients with anti-taliglucerase alfa plant-specific glycan antibodies, 5 experienced 9 treatment-related AEs while 3 reported no treatment-related AEs. Each of the 9 treatment-related AEs was reported only once. Seven (7) of the 8 patients continued treatment with taliglucerase alfa despite the detection of anti-taliglucerase alfa plant-specific glycan antibodies, while 1 patient discontinued treatment due to a possible allergic reaction (itching, rash, skin irritation). Four (4) of the 8 patients had anti-taliglucerase alfa plant-specific glycan antibodies prior to taliglucerase alfa treatment while the other 4 patients had treatment-induced anti-taliglucerase alfa plant-specific glycan antibodies. Overall, no obvious safety signals of particular concern associated with anti-taliglucerase alfa plant-specific glycan antibodies were identified in the submitted data.

Adverse events (AEs) related to taliglucerase alfa for the treatment of GD appear to require no specific intervention, or are manageable by symptomatic treatment for infusion-related and non-infusion related AEs, or by prophylactic premedication for infusion-related AEs. The risk of treatment discontinuation due to AEs related to taliglucerase alfa is low. Treatment discontinuation due to AEs in the taliglucerase alfa clinical trial program for GD was reported in only 3 (2.6%) adult patients (2 x hypersensitivity; 1 x eye swelling). No treatment discontinuations due to AEs were reported in children.

In adults, 93.1% (108/116) of patients experienced at least one AE (all causality). The most commonly reported AEs (>10% of patients) in adults were nasopharyngitis (23.3%), arthralgia (23.3%), headache (22.4%), viral upper respiratory tract infection (19.8%), pain in extremity (16.4%), cough (15.5%), fatigue (12.9%), abdominal pain (11.2%), pyrexia (11.2%), back pain (11.2%), diarrhoea (10.3%), nausea (10.3%), and oropharyngeal pain (10.3%).

In children, 75.0% (12/16) of patients experienced at least one AE (all causality). The most commonly reported AEs (> 10% of patients) in children were vomiting (31.3%), abdominal pain (18.8%), nasopharyngitis (18.8%), headache (18.8%), pain in extremity (18.8%), tonsillitis (12.5%), diarrhoea (12.5%), arthralgia (12.5%), epistaxis (12.5%), and tooth extraction (12.5%).

In both adults and children, the risk of experiencing AEs was greater in ERT-naïve patients compared with ERT-experienced patients.

The risks of experiencing AEs appear to be minimal for the following groups of disorders (SOC) "blood and lymphatic system", "cardiac", "hepatobiliary", "renal and urinary" and "skin and subcutaneous tissue".

SAEs were reported in 11.2% (n=13) of adult patients and 12.5% (n=2) of paediatric patients. In adults, none of the SAEs were considered to be treatment-related and no single preferred term was reported in more than 1 patient. In children, 1 SAE was considered to be treatment-related (gastrointestinal inflammation). No deaths have been reported in the taliglucerase alfa clinical trial program for GD, but there was 1 death reported in the compassionate use program considered to be unrelated to treatment (tuberculosis/pneumonia).

Investigator-designated treatment-related AEs reported during or within 2 hours of completion of taliglucerase alfa infusions occurred commonly, and were observed in 27.6% of adult patients (32/116) and 12.5% (2/16) of paediatric patients. The most commonly reported investigator-designated treatment related AEs reported during or within 2 hours of completion of the infusion in adult patients (≥ 2% of patients) were hypersensitivity (4.3%), nausea (3.4%), infusion-related reactions (3.4%), headache (3.4%), pruritus (3.4%), rhinorrhoea (2.6%), sneezing (2.6%) and flushing (2.6%). In the 2 paediatric patients, the events were gastrointestinal inflammation and vomiting in 1 patient and chest discomfort in 1 patient.

There was a risk of Type I hypersensitivity AEs (acute allergic reactions) in patients treated with taliglucerase alfa. These events occurred predominantly in adult patients, but this might reflect the greater number of adult patients exposed to taliglucerase alfa compared with paediatric patients. In adults, 20 patients (17.2%) experienced one or more Type 1 hypersensitivity AEs (68 events in total), and all events were reported as being mild/moderate in intensity. The events reported in the 20 adult patients were pruritus in 11 (9.5%), hypersensitivity in 5 (4.3%), eye swelling in 2 (1.7%), and 1 (0.9%) patient each for eye oedema, scleral oedema, lip swelling, and face oedema. One (1) Type 1 hypersensitivity AE was reported in 1 paediatric patient (angioedema).

Treatment-related (investigator designated) Type 1 hypersensitivity AEs were reported in 18 adult patients, and no children. Of the events reported in the 18 adult patients, 10 patients required no intervention or only temporary intervention to manage the events, while 8 patients required significant intervention characterized by premedication or treatment discontinuation. The required interventions in the 8 patients were: 2 patients with hypersensitivity and 1 patient with pruritus/eye oedema continued infusions with premedication; 4 patients discontinued treatment because of hypersensitivity or hypersensitivity-related events, and in 3 of these patients discontinuation occurred with the first infusion; and 1 patient experienced multiple mild AEs of eye swelling in spite of premedication and decided to discontinue taliglucerase alfa and return to imiglucerase. Perusal of the case narratives for the 5 patients experiencing events described as "hypersensitivity" indicates that these included typical acute allergic reactions

such as flushing, tightness in the chest wheezing, urticaria, itching, chills, periorbital oedema, lacrimation and rhinorrhoea.

There appears to be an increased risk of Type 1 hypersensitivity reactions in patients testing positive for treatment-induced IgG ADA compared with patients testing negative (9/24 [37.5%] vs 9/47 [19.1%], respectively). Re-analysed data provided in the response to TGA questions indicate that of the 18 patients who were tested for treatment-induced IgG ADA and experienced Type I hypersensitivity AEs: 50% (9/18) continued treatment with taliglucerase alfa with no intervention (28% [5/18] treatment-induced ADA positive, 22% [4/18] treatment-induced negative); 17% (3/18) discontinued treatment with taliglucerase alfa (6% [1/91] treatment-induced ADA positive, 11% [2/18] treatment-induced negative); 22% (4/18) continued treatment with taliglucerase alfa with use of medications to control symptoms of AEs (11% [2/18] treatment-induced ADA positive, 11% [2/18] treatment-induced ADA negative); and 11% (2/18) continued treatment with taliglucerase alfa with a premedication treatment regimen (6% [1/18] treatment-induced ADA positive, 6% [1/18] treatment-induced ADA negative). The data show that IgG ADA status in the 18 re-analysed patients reported to have experienced Type I hypersensitivity reactions had no effect on the clinical intervention taken to manage the reactions. Consequently, although Type I hypersensitivity reactions occur more commonly in IgG ADA positive patients than in IgG ADA negative patients, clinical management of the events is similar regardless of IgG ADA status.

Type II-IV hypersensitivity AEs (delayed hypersensitivity reactions) were reported only in adult patients (9/116 [7.8%]). Of the 14 reported events, 13 were categorized as mild or moderate in severity and 1 as severe (autoimmune thrombocytopaenia, non-treatment related SAE). Events reported in more than 1 patient were arthritis (3 patients, 2.3%) and contact dermatitis (2 patients, 1.5%). All other events occurred in 1 (0.8%) patient each (i.e., autoimmune thrombocytopenia, drug eruption, dyshidrosis, macula-papular rash). The only Type II-IV hypersensitivity AE reported as treatment-related was drug eruption (left cheek), which was reported in 1 patient on 6 separate occasions.

Bone events were reported in 55 (47.4%) adult patients, and SAE bone events were reported in 2 (1.7%) adult patients. In 8 (6.9%) adult patients, bone events were judged by the investigator to be related to treatment, and the majority of these events were described as musculoskeletal discomfort (15 events; all in 1 patient). Of the treatment-related bone events in adults, 4 occurred during the infusion or within 2 hours after the completion of the infusion (arthralgia, back pain, muscle spasm, and musculoskeletal discomfort [14 events in 1 patient]). In children, 5 (31.3%) patients experienced bone events, and none of the events were considered to be SAEs. There was 1 (6.3%) paediatric patient with a bone event judged by the investigator to be treatment-related (pain in extremity). None of the bone events reported in children occurred during the infusion or within 2 hours of the completion of the infusion.

The risks of taliglucerase alfa inducing abnormalities in clinical laboratory tests, vital signs, ECGs, ECHOs, or pulmonary function tests appear to be minimal.

Overall, there is limited information on the risks of taliglucerase alfa in patients with GD aged from > 2 years to < 18 years (n=16), and there is no information on the risks of treatment in patients aged ≤ 2 years. There is limited information on the risks of treatment in patients with GD aged ≥ 65 years (n=8). There is no meaningful information on the risks of taliglucerase alfa treatment in non-Caucasian patients (n=5). The risk of experiencing commonly reported AEs appears to be greater in female than in male patients, but there is no evidence that the taliglucerase alfa treatment regimen should differ for females and males.

There are no data on the risks of taliglucerase alfa in patients with neuronopathic GD, patients with pre-existing hepatic disease, patients with pre-existing renal disease or patients with pre-existing cardiovascular disease. There are no data on the potential risks of drug-drug interaction involving taliglucerase alfa and other co-administered medicines.

13.3. Second round assessment of benefit-risk balance

After consideration of the clinical aspects of the sponsor's response to TGA questions it is considered that the benefit-risk balance of taliglucerase alfa, given the proposed usage, remains favourable. The data provided in the original and current submissions are considered to have satisfactorily demonstrated the efficacy and safety of taliglucerase alfa for the treatment of non-neuropathic GD in both adult and paediatric patients

The benefits of treatment with taliglucerase alfa in ERT-naïve and ERT-experienced patients with non-neuropathic GD include clinically meaningful reductions in spleen and liver volumes, improvement in haemoglobin level, and improvement in platelet count. In addition, taliglucerase alfa has been observed to reduce GD biomarker activity in both adult and paediatric patients (chitotriosidase activity reduced; CCL18 concentration reduced).

The risks of treatment with taliglucerase alfa in both adults and children with non-neuropathic GD are considered to be acceptable. Although AEs occurred very commonly in both adults and children treated with taliglucerase alfa (93.1%, 108/116 and 75.0%, 12/16, respectively), these events generally required either no intervention or were manageable with symptomatic treatment. Treatment discontinuation due to AEs in the clinical trial program for GD was reported in only 3 (2.6%) adult patients (2 x hypersensitivity; 1 x eye swelling). No treatment discontinuations resulting from AEs were reported in children.

SAEs were reported in 11.2% (n=13) of adult patients and 12.5% (n=2) of paediatric patients. In adults, none of the SAEs were considered to be treatment-related and no single preferred term event was reported in more than 1 patient. In children, 1 SAE was considered to be treatment-related (gastrointestinal inflammation). No deaths have been reported in the GD clinical trial program, but there was 1 death reported in the compassionate use program considered to be unrelated to treatment (tuberculosis/pneumonia).

In 71 patients who were tested for IgG anti-taliglucerase alfa antibodies (ADAs), 24 (33.8% developed treatment-induced IgG ADAs while 47 (66.2%) were negative for these antibodies. However, the presence of IgG ADAs appeared not impair the efficacy of taliglucerase alfa. In addition, the benefits of treatment with taliglucerase were similar in patients considered to be positive for anti-taliglucerase alfa plant-specific glycan antibodies and patients considered to be negative for these antibodies. However, there was a marked imbalance in patient numbers between those considered positive and those considered negative anti-taliglucerase alfa plant-specific glycan antibodies (8/71, 11.3% and 63/71, 87.7%, respectively).

The most clinically important risks of treatment with taliglucerase alfa are considered to relate to Type I hypersensitivity reactions (acute allergic reactions). In adults, 18 (15.5%) patients were reported as experiencing investigator-designated treatment-related Type I hypersensitivity reactions. These reactions were manageable by no intervention or temporary intervention in slightly more than half of the cases (10/18), while slightly less than half of the cases (8/18) were managed by premedication or treatment discontinuation.

There appears to be an increased risk of Type 1 hypersensitivity reactions in patients testing positive for treatment-induced IgG anti-taliglucerase antibodies (ADAs) compared with patients testing negative (9/24 [37.5%] vs 9/47 [19.1%], respectively). However, there did not appear to be a difference in the severity of Type 1 hypersensitivity reactions between IgG ADA positive and negative patients, and management of these reactions was similar in both patient groups. Type II-IV hypersensitivity AEs (delayed hypersensitivity reactions) were reported only in adults (7.8%, 9/116), and the only event considered to be treatment-related was drug-eruption (left cheek), which was reported in 1 patient on 6 separate occasions.

The frequency (events/patient) of treatment-related and all causality AEs was greater in patients considered to be anti-taliglucerase alfa plant-specific glycan antibody positive than in patients considered to be negative for these antibodies. However, as noted previously there was a marked imbalance in patient numbers between those considered to be positive and those

considered to be negative for these antibodies. Furthermore, of the 8 patients considered to be positive for anti-taliglucerase alfa plant-specific glycan antibodies, 7 continued treatment with taliglucerase alfa while 1 discontinued treatment due to what appears to be a hypersensitivity reaction to taliglucerase alfa. Overall, the limited data suggest that the presence of anti-taliglucerase alfa plant-specific glycan antibodies does not present a significant treatment risk.

There is an important risk-benefit issue relating to whether treatment with taliglucerase alfa should be confined to adult patients with GD (i.e., patients aged ≥ 18 years). The clinical data in children and adolescents (2 to < 18 years) are limited, but suggest that the benefits and risks of taliglucerase alfa are similar in children/adolescents and in adults. Overall, it is considered that treatment with taliglucerase alfa should not be restricted to adult patients aged ≥ 18 years.

13.4. Second round recommendation regarding authorisation

After consideration of the sponsor's response to the M5 clinical questions, and to the clinical aspects of the sponsor's response to the M3 (Q7, Q8) questions it is recommended that ELELYSO (taliglucerase alfa) be approved for *"ELELYSO is indicated for long-term enzyme replacement therapy for patients with a confirmed diagnosis of Gaucher disease characterized by one or more of the following, splenomegaly, hepatomegaly, anaemia, thrombocytopenia, or bone disease"*.

14. References

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