CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022458Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	022-458
Priority or Standard	Complete Response Resubmission
Submit Date(s)	July 31, 2011
Received Date(s)	August 1, 2011
PDUFA Goal Date	May 1, 2012
Division / Office	DGIEP/ODE III
Reviewer Name(s)	Carla Epps, MD, MPH
Review Completion Date	April 30, 2012
Established Name	Taliglucerase alfa
(Proposed) Trade Name	Elelyso
Therapeutic Class	Enzyme Replacement Therapy
Applicant	Protalix
Formulation(s)	Lyophilized powder for solution for infusion
Proposed Dosing Regimen	60 units/kg once every 2 weeks
Proposed Indication(s)	Long-term enzyme replacement therapy for adult patients with Type 1 Gaucher disease
Proposed Intended Population(s)	Type 1 Gaucher patients

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval action for ELELYSO for the treatment of type 1 Gaucher disease in adult patients. I recommend that the indication be limited to adult patients because no efficacy data and limited safety data were available for pediatric patients. The recommended dosage is 60 U/kg every other week administered as a 60-120 minute infusion. Physicians can make dosage adjustments based on achievement and maintenance of each patient's therapeutic goals. Clinical trials have evaluated doses ranging from 11 U/kg to 73 U/kg every other week.

There is sufficient evidence of safety and efficacy based on three phase 3 trials to support this indication and to provide adequate directions for use. Evidence of safety is based on a database of 121 patients, including 108 adult and 13 pediatric patients with type 1 Gaucher disease, which is an orphan indication.

1.2 Risk Benefit Assessment

Treatment with taliglucerase alfa appears to have resulted in clinically and statistically significant improvements in major clinical features of Type 1 Gaucher disease in adult patients. Evidence of long-term efficacy is based on 24 adult patients who have been treated for at least 24 months; only three patients have been treated for 36 months. However, additional data should be collected on subpopulations of Gaucher patients. No efficacy data were available for pediatric patients and efficacy and data in pregnant women are extremely limited.

Based on the data available for review, taliglucerase alfa appears to have a similar safety profile to other ERT products. However, because the sample size for the long-term safety and efficacy database for ELELYSO is small, I recommend that the applicant collect additional safety and efficacy data in a registry study as a post-marketing requirement (see post-marketing requirement [PMR] #7). In addition, the applicant should continue to collect safety and efficacy data in patient subpopulations (i.e., pediatric patients, and pregnant and lactating women). I recommend that the applicant be required to complete all trials in which pediatric patients are enrolled (PB-06-002 and PB-06-005) and submit final reports for these trials as a post-marketing requirement (see PMR #5 and #6). Similarly, I recommend that the applicant be required to submit safety and efficacy data for pregnant and lactating women; these data could be collected as a sub-study of the registry study (see PMR #8). In addition, additional data on the impact of immunogenicity on the safety profile of taliglucerase alfa, specifically data on the impact of neutralizing anti-drug antibodies and antibodies to plant sugars specific to ELELYSO, should be required as a PMR (see PMR #4).

Finally, I recommend that the applicant submit additional data on the long-term safety and efficacy of ELELYSO compared to other ERT products for Gaucher disease. As noted by the Statistical reviewer, Behrang Vali, M.S., the inclusion of an active control study within the development program of ELELYSO would have increased the statistical rigor of the evidence presented by the applicant to support an efficacy claim. However, he noted that, from a clinical standpoint, further long-term data may be sufficient as supportive evidence. I agree with this assessment and recommend that the applicant submit a detailed analysis of the taliglucerase alfa safety and effectiveness for 36 months obtained in the clinical development program compared with data available for the same length of treatment for other approved ERT for Gaucher disease (see post-marketing commitment (PMC) #1.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Routine surveillance for adverse events is recommended. In addition, the applicant has agreed to conduct a post-marketing registry study (see PMR #7).

1.4 Recommendations for Post-market Requirements and Commitments

The following post-marketing requirements and post-marketing commitments were being negotiated with the applicant at the time of this review:

Post-marketing Requirement Studies

1. To develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to ELELYSO that is expected to be present in the serum at the time of patient sampling. A summary of the validation exercise including supporting data, a summary of the development data supporting assay suitability for parameters not assessed in the validation exercise, and the assay SOP will be provided to FDA.

Final Protocol Submission:	September 2012
Study Completion Date:	March 2013
Final Report Submission:	July 2013

2. To develop a validated, sensitive, and accurate assay for the assessment of cellular uptake inhibition by cell surface mannose receptors due to the presence of neutralizing antibodies to ELELYSO that is expected to be present in the serum at the time of patient sampling. A summary of the validation exercise including supporting data, a summary of the development data supporting assay suitability for parameters not assessed in the validation exercise, and the assay SOP will be provided to FDA.

Final Protocol Submission: December 2012
Study Completion Date: June 2013
Final Report Submission: October 2013

3. To develop a validated, sensitive, and accurate assay for the detection of antibodies to plant-specific sugars in ELELYSO that is expected to be present in the serum at the time of patient sampling. A summary of the validation exercise including supporting data, a summary of the development data supporting assay suitability for parameters not assessed in the validation exercise, and the assay SOP will be provided to FDA.

   Final Protocol Submission: December 2012
   Study Completion Date: June 2013
   Final Report Submission: October 2013

4. To conduct an assessment of neutralizing anti-drug antibody (ADA) response and presence of antibodies against plant-specific sugars to ELELYSO in patient plasma samples. Validated assays (developed under PMR 1, PMR 2 and PMR 3) capable of sensitively detecting neutralizing ADA responses and antibodies to plant-specific sugars that are expected to be present at the time of patient sampling will be used. The neutralizing ADA response, cellular uptake inhibition and the presence of plant-specific sugar antibodies will be evaluated in all archived sampling time points available from all patients in Phase 3 trials (PB-06-001, PB-06-002, PB-06-003, and PB-06-005). Analysis will evaluate immunogenicity rates and individual patient titers to assess the impact of neutralizing antibody levels, cellular uptake inhibition, and plant-sugar antibody levels on parameters of safety as well as on the pharmacokinetics (PK), pharmacodynamics (PD), and efficacy of ELELYSO where data are available.

   Final Protocol Submission: December 2012
   Study Completion Date: November 2013
   Final Report Submission: March 2014

5. To evaluate the long-term safety and efficacy of ELELYSO in a registry of Gaucher disease patients being treated with ELELYSO. Detailed clinical status information will be collected at study entry and on an annual basis for 10 years. An interim study report will be submitted after completion of the first 5 years of the study.

   Final protocol Submission Date: June 2013
   Interim Study Report Submission: July 2018
   Study Completion Date: October 2023
   Final Report Submission Date: July 2024

6. To evaluate the effect of ELELYSO on pregnancy and fetal outcomes and to collect detailed clinical status information on newborns and infants whose mothers are treated with ELELYSO during lactation. This study may be completed as a sub-study within the registry (PMR 5). An interim study report will be submitted after completion of the first 5 years of the study.

   Final protocol Submission Date: June 2013
   Interim Study Report Submission: July 2018
   Study/Clinical trial Completion Date: October 2023
   Final Report Submission Date: July 2024

7. To complete the ongoing trial PB-06-005, entitled "A Multicenter, Double-blind, Randomized Safety and Efficacy Study of Two Dose Levels of Taliglucerase Alfa in Pediatric Subjects with Gaucher Disease". This study will obtain safety and efficacy data in pediatric patients with Gaucher disease. The trial was initiated in on October 2010.

   Study Completion Date: June 2012
   Final Report Submission: September 2012

8. To complete the ongoing trial PB-06-002, entitled "A Multicenter, Open-label, Switchover Trial to Assess the Safety and Efficacy of Taliglucerase alfa in Patients with Gaucher Disease Treated with imiglucerase (Cerezyme®) Enzyme Replacement Therapy." This trial will obtain safety and efficacy data in adult and pediatric patients with type 1 Gaucher disease. The trial was initiated in the U.S. on April, 2009.

   Study Completion Date: March 2013
   Final Report Submission: June 2013

Post-marketing Commitment Studies

1. To provide a detailed analysis of the taliglucerase alfa safety and effectiveness for 36 months obtained in the clinical development program compared with data available for the same length of treatment for other approved ERT for Gaucher disease.

   Final Report Submission Date: May 2013

2. To revise the cellular uptake potency assay release and stability acceptance criteria after 15 lots of drug product have been manufactured.

   Final Report Submission Date: July 2015

3. To revise Experion automated electrophoresis release and stability acceptance criteria after 15 lots of drug product have been manufactured.

   Final Report Submission Date: July 2015

4. To evaluate and revise as appropriate the minimal percentage of specific uptake of reference standard as a system suitability criterion in the cellular uptake potency assay after at least 80 independent assay runs of release and stability testing of drug substance and drug product lots have been completed..

   Study Completion Date: December 2013
   Final Report Submission Date: March 2014

5. To perform a thorough biochemical characterization of the (b) (4) detected in the imaging capillary electrophoresis (iCE) assay and to evaluate the impact of this heterogeneity on product quality, including any effects on potency (specific uptake, enzyme kinetics, and cellular uptake). The characterization should use additional analytical assays (e.g., peptide mapping (b) (4)) to confirm the identity of the characterized peaks. Perform an assessment regarding the suitability and the implementation of the iCE method and other analytical assays as appropriate in your stability protocol. The results of these studies should guide the revision of the release and stability specifications after at least 30 lots of drug substance and at least 15 lots of drug product have been manufactured.

   Study Completion Date: April 2015
   Final Report Submission Date: July 2015

2 Introduction and Regulatory Background

ELELYSO (taliglucerase alfa) is a recombinant human form of the enzyme acid a-glucosidase (rhGAA) that is produced by recombinant DNA technology in genetically modified carrot cells. ELELYSO is intended for use as an enzyme replacement therapy to treat patients with deficiency of β-glucocerebrosidase activity. However, the product is not intended to treat CNS manifestations of Gaucher disease as the product is not expected to cross the blood-brain barrier. Therefore, ELELYSO is intended for use only in Type 1 or non-neuronopathic Gaucher disease.

Gaucher Disease
Gaucher disease is the most common of the lysosomal storage diseases. It is inherited as an autosomal recessive trait and is caused by a deficiency of β-glucocerebrosidase activity. This enzyme deficiency results in accumulation of glucosylceramide in tissue macrophages, particularly in the liver, spleen, bone marrow, and lungs. These lipid-filled macrophages are the so-called "Gaucher cells" characteristic of the disease.

Gaucher disease is a clinically heterogeneous disorder, with three main phenotypes based on the presence or absence of primary neurologic disease and severity of neurologic disease. Type 1 Gaucher disease is the most common variant and accounts for about 94% of all Gaucher cases. Type 1 Gaucher disease does not involve the CNS. Typical manifestations of Type 1 Gaucher disease include hepatomegaly, splenomegaly, thrombocytopenia, bleeding tendencies, anemia, skeletal pathology, growth retardation, pulmonary disease, and decreased quality of life. The estimated worldwide incidence of Type 1 Gaucher disease is 1 in 50,000 to 100,000.[1]

Patients with Type 2 and Type 3 Gaucher disease have neurologic disease in addition to hematologic, visceral, and bone disease. Patients with Type 2 Gaucher disease present with acute neurological deterioration; death usually occurs by two years of age. Neurologic findings include spasticity and oculomotor palsy. Type 3 disease typically follows a more subacute neurological course, with progression occurring over three to four decades. Neurologic findings include horizontal nuclear palsy, ataxia, dementia, and spasticity. The different types of Gaucher disease are summarized in Table 1:

1 Cox TM, Aerts JMFG et al, Management of non-neuronopathic Gaucher disease with special reference to pregnancy, splenectomy, bisphosphonate therapy, use of biomarkers and bone disease monitoring, *J. Inherit Metab Dis* 2008; 31:319-336.

Table 1: Clinical features of the three types of Gaucher disease

Electronically copied and reproduced from: Mehta A, Epidemiology and natural history of Gaucher's disease, *European Journal of Internal Medicine* 2006; 17(Supp 1):S2-S5.

Most research in developing therapeutic agents to date has focused on strategies for augmenting enzyme levels to compensate for the underlying enzyme deficiency. These strategies include bone marrow transplantation (BMT), gene therapy, substrate reduction therapy (SRT), chaperone-mediated enzyme enhancement therapy, and enzyme replacement therapy (ERT).[2]

ERT is the first-line treatment of Type 1 Gaucher disease, and has been shown to reverse or improve important disease manifestations. SRT is an alternative therapy for patients who do not tolerate ERT. Zavesca (miglustat), an inhibitor of glucosylceramide production, is the only approved SRT for Gaucher disease. ERT and SRT are not approved for neuropathic Gaucher disease. For patients with severe Gaucher disease, primarily those with chronic neurologic involvement (Gaucher Type 3), bone marrow transplantation can be of benefit. However, with the advent of ERT, bone marrow transplantation has become a secondary therapy for patients with Type 1 disease due to its high risk of morbidity and mortality. Supportive care for all Gaucher patients may include blood transfusions for severe anemia and bleeding, analgesics for bone pain, joint replacement or other orthopedic intervention for chronic pain and restoration of skeletal function, and bisphosphonates and calcium for osteopenia.

Prior to the availability of ERT, splenectomy was a common procedure to treat patients with massive splenomegaly and thrombocytopenia. Due the effectiveness of ERT in reducing organomegaly, splenectomy is rarely indicated in treated patients.[3] Similarly, a majority of patients (90%) achieve normal hemoglobin levels within two years of initiation of ERT.[4] Although, ERT has been demonstrated to reduce bone pain, other manifestations of bone involvement has been more refractory to ERT.

2 Pastores GM, Barnett NL, Current and emerging therapies for the lysosomal storage disorders*, Expert Opin Emerging Drugs 2005*: 10(4):891-902.
3 Cox TM, Aerts JMFG et al, Management of non-neuronopathic Gaucher disease with special reference to pregnancy, splenectomy, bisphosphonate therapy, use of biomarkers and bone disease monitoring, *J Inherit Metab Dis* 2008; 31:319-36.
4 Weinreb NJ, Charrow J et al, Effectiveness of enzyme replacement therapy in 1028 patients with type 1

A. Natural History of Type 1 Gaucher Disease

The clinical expression of Gaucher disease is variable within all three subtypes, especially within Type 1 Gaucher disease. Pediatric Type 1 Gaucher disease is common, with more than 50% of Type 1 Gaucher cases in the International Collaborative Gaucher Group (ICGG) Gaucher Registry reporting an onset of disease manifestations in childhood or adolescence. Infants with Type 1 Gaucher disease are clinically normal; in severe cases, organomegaly becomes evident after the first year or two of life, and may progress for some years. The primary clinical manifestations of the disease, hepatomegaly, anemia, and thrombocytopenia, have been related to splenic dysfunction. In an analysis of 1028 Type 1 Gaucher patients in the ICGG Gaucher Registry, 637/677 (94%) patients "with spleen" (i.e., had an intact spleen) had hepatomegaly, anemia, or thrombocytopenia (or a combination of these three abnormalities), compared with 172 (62%) of the 277 patients who had undergone splenectomy ($P<0.01$).[5] Systematic follow-up of a number of patients over age 15 years shows that Gaucher disease-related changes in untreated patients, if they occur at all, are noted over decades. Hematologic measures of anemia and decreased platelet count as well as spleen and liver size exhibit little or no change. Progressive osteopenia and development of new fractures may be observed; however, bone disease usually occurs later than visceral disease. Pediatric-onset disease may represent a more aggressive form of Type 1 Gaucher disease. Furthermore, in adults, rapid progression of previously quiescent disease is unusual. In an analysis of survival data of Type 1 Gaucher patients enrolled in the ICGG Gaucher Registry, the estimated life expectancy at birth for Type 1 Gaucher patients was about 9 years less than the general US population.[6]

Hematologic Effects

Anemia and thrombocytopenia are almost universal in untreated Gaucher disease and may present together or separately in the course of the disease. The pattern of anemia and thrombocytopenia in Gaucher disease is dependent on the degree of splenic dysfunction. Thrombocytopenia is the most common peripheral blood abnormality in patients with Gaucher disease and may result from hypersplenism, splenic pooling of platelets, or marrow infiltration or infarction. Early in the course of the disease, it is usually due to splenic sequestration of platelets and responds to splenectomy. Later, replacement of the marrow by Gaucher cells may be more important etiologically in patients who have undergone splenectomy. Thrombocytopenia may be associated with easy bruising or overt bleeding, particularly with trauma, surgery, or pregnancy.

Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher Registry. *Am J Med* 2002; 113: 112–9.

5 Weinreb NJ, Charrow J et al, Effectiveness of enzyme replacement therapy in 1028 patients with type 1 Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher Registry. *Am J Med* 2002; 113: 112–9.

6 Weinreb NJ, Deegan P et al, Life expectancy in Gaucher disease type 1, *Am J Hematol* 2008;83:896-900.

Anemia may result from hypersplenism. In advanced disease, decreased erythropoiesis is a result of bone marrow failure from Gaucher cell infiltration or medullary infarction. As a result, hemoglobin concentrations and platelet counts are routinely monitored in patients to determine disease burden. Leukopenia may occur, but is rarely severe enough to require treatment.

Organomegaly
Enlargement of the liver is a hallmark in Gaucher patients. In severe cases, the liver may fill the entire abdomen. Minor abnormalities of liver enzymes, consisting of increases in plasma transaminase and gamma-glutamyl transferase activities, are commonly present, even in mildly affected patients. Similarly, splenic enlargement is present in all but the most mildly affected patients with Type 1 Gaucher disease. In patients who are otherwise asymptomatic, splenic enlargement is commonly the presenting sign. As in other diseases in which splenomegaly occurs, splenic infarctions frequently occur. In an analysis of 400 patients in the ICGG Gaucher Registry, 116 patients with data available prior to ERT had a mean enlargement of the spleen 19-fold normal. Liver and spleen size /volume are also routine measures of disease burden in patients. Changes over time in liver occur very slowly, with a slight downward trend in untreated patients with Type 1 Gaucher disease.

Bone disease
Bone involvement results in skeletal abnormalities and deformities, and bone pain crises, and is a frequent presenting feature of Gaucher disease in children. Bone marrow infiltration and splenic sequestration lead to clinically significant anemia and thrombocytopenia respectively. Bone disease occurs in 70-100% of patients with Type 1 Gaucher disease and is the greatest source of morbidity and long-term disability in treated patients. Bone pain and bone crises were reported by 63% and 33% respectively in all Gaucher patients with available information from the ICGG Gaucher Registry. Bone disease may not correlate with the severity of hematologic or visceral involvement. Skeletal abnormalities secondary to bone disease contribute to the chronic growth failure observed in children with inadequately treated disease.

Lung disease
Only 1-2 % of Type 1 Gaucher patients exhibit lung disease, which manifests as interstitial lung disease, pulmonary hypertension, or hepatopulmonary syndrome. Pulmonary hypertension is an important cause of early mortality in Type 1 Gaucher disease; development of pulmonary hypertension may be prevented by avoidance of splenectomy. The spleen serves as the primary reservoir of Gaucher storage cells. Removal of the spleen promotes migration of storage cells to other tissue macrophage pools, including the lungs, liver, and bones.[7]

7 Mistry PK, Sirrs S et al, Pumonary hypertension in type 1 Gaucherr's disease: genetic and epigenetic determinants of phenotype and response to therapy, *Mol Genet Metab* 2002; 77:91-98.

B. Current Therapy

To date, ERT has been the cornerstone of treatment for Gaucher disease. Data from the ICGG demonstrate that approximately 90% of all patients should achieve normal hemoglobin concentration within two years of initiation of treatment. ERT has been shown to reduce organomegaly and improve hematological parameters. Although there is some evidence of the benefit of ERT on the bone-related complications of Gaucher disease, longstanding osseous complications of Gaucher disease may remain refractory to ERT**.** Similarly, the effect of ERT on lung disease is uncertain. *In vivo* studies indicate that exogenous enzyme delivery is decreased in lung tissue compared to other target tissues.[8] Furthermore, since ERT has not been shown to pass the blood brain barrier, it is not indicated for the treatment of patients with Type 2 and Type 3 Gaucher disease.

2.1 Product Information

Taliglucerase alfa is a new molecular entity. It is a recombinant human glucocerebrosidase (GCB) produced from genetically modified carrot plant root cells. Uptake of exogenous glucocerebrosidase into the target cells of Gaucher disease (reticuloendothelial cells) occurs through binding to mannose receptors on the cell surface. Plant-derived glucocerebrosidase contains exposed terminal mannose residues. Production of Cerezyme requires a deglycosylation process to expose mannose residues. Taliglucerase alfa differs from native human glucocerebrosidase by two amino acids at the N-terminal and 7 amino acids at the C-terminal. The molecular weight of taliglucerase alfa protein is approximately 60,800 Daltons.

The proposed indication for taliglucerase alfa is for long-term ERT for patients with Type 1 Gaucher disease. It is administered intravenously with a proposed dosing of 60 U/kg every other week.

8 Ibid.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 2: Currently Available Treatments for Proposed Indications

Drug	Formulation	Indication	Dosage
Cerezyme (imiglucerase)	IV formulation of recombinant DNA using CHO cells culture.	Long-term ERT for pediatric and adult patients with Type 1 Gaucher with anemia, thrombocytopenia, bone disease, or hepatomegaly or splenomegaly	2.5 U/kg three times per week to 60 U/kg every two weeks
VPRIV (velaglucerase alfa)	IV formulation of recombinant DNA using CHO cells culture.	Long-term ERT for pediatric and adult patients with Type 1 Gaucher with anemia, thrombocytopenia, bone disease, or hepatomegaly or splenomegaly	60 Units/kg every other week
Zavesca (miglustat)	Capsule for oral administration	Treatment of adult Type 1 Gaucher patients for whom ERT is not an option.	100 mg three times daily

Cerezyme (imiglucerase)
ERT has been commercially available for the treatment of Type 1 Gaucher disease since 1991, when Ceredase (alglucerase), placentally-derived GCB, received approval as the first enzyme for the treatment of Gaucher disease. Cerezyme (imiglucerase), a recombinant product, received approval in the U.S. for the treatment of Gaucher disease in 1994. Cerezyme has replaced Ceredase. Warning information for Cerezyme includes hypersensitivity and anaphylactic reactions. There are also precautions related to pulmonary hypertension and pneumonia. The pregnancy category is C. See Section 2.4 for other adverse reactions.

VPRIV (velaglucerase alfa)
Velaglucerase alfa was approved in the U.S. in February 2010 for the treatment of Type 1 Gaucher disease. Velaglucerase differs from Cerezyme by one amino acid, and has an identical amino acid sequence to Ceredase. Warning information for VPRIV includes hypersensitivity and anaphylactic reactions. The pregnancy category is B. See Section 2.4 for other adverse reactions.

Zavesca (miglustat)
Zavesca is an inhibitor of the enzyme glucosylceramide synthase, which is a glucosyl transferase enzyme responsible for the first step in the synthesis of glucosylceramide and other glycosphingolipids. An important warning included in product labeling is that Zavesca may cause fetal harm when administered to a pregnant woman (Pregnancy Category X). There is also a warning for potential development of peripheral neuropathy. Patients receiving Zavesca should have neurological evaluations every six months. Other precautions from product labeling include tremor, diarrhea and weight loss, and effect on male fertility. Other common adverse events are: flatulence, abdominal pain, headache, and influenza-like symptoms.

2.3 Availability of Proposed Active Ingredient in the United States

There are currently two approved ERT products for type 1 Gaucher disease in the U.S.; Cerezyme (imiglucerase) and VPRIV (velaglucerase). At the time of this resubmission, there was a drug shortage of Cerezyme due to manufacturing issues which was projected to last into the first quarter of 2012. This is the second time that Cerezyme has been in drug shortage. The first drug shortage began in June 2009; the manufacturer reported the shortage as resolved in January 2011.

2.4 Important Safety Issues With Consideration to Related Drugs

The labeling for Cerezyme notes the following:

1. Approximately 14% of patients experienced adverse reactions related to Cerezyme administration.

2. Some of the adverse reactions were related to the route of administration such as discomfort, pruritus, burning, swelling, or sterile abscess at the site of venipuncture (each reported in <1% of the patient population).

3. Anaphylaxis has been reported in <1% of the patient population. Further treatment with imiglucerase should be conducted with caution. Most patients have successfully continued therapy after a reduction in rate of infusion and pretreatment with antihistamines and/or corticosteroids.

4. Symptoms suggestive of allergic reactions (e.g., pruritus, flushing, urticaria, angioedema, chest discomfort, dyspnea, coughing, cyanosis, and hypotension) have been noted in approximately 6.6% of patients. (Onset of such symptoms has occurred during or shortly after infusions.)

5. Approximately 15% of patients treated and tested have developed IgG antibody to Cerezyme during the first year of therapy. Patients who developed IgG

antibody did so largely within 6 months of treatment, and rarely developed antibodies to Cerezyme after 12 months of therapy.

6. Approximately 46% of patients with detectable IgG antibodies experienced allergic symptoms. Patients with antibody to Cerezyme have a higher risk of hypersensitivity, but not all patients with symptoms of hypersensitivity have detectable IgG antibody.

The labeling for Ceredase also notes adverse reactions related to route of administration, symptoms suggestive of allergy, and a higher risk of allergic reactions in patients with antibody to Ceredase. As per the Ceredase labeling, approximately 13% of patients treated and tested developed antibody to Ceredase.

The labeling for VPRIV notes the following:

1. The most serious adverse reactions in patients treated with VPRIV were allergic reactions.

2. The most commonly reported adverse reactions were infusion-related reactions. (b) (4)

3. Other adverse reactions affecting more than one patient (>3% of treatment-naïve patients and >2% of patients switched from Cerezyme) were bone pain, tachycardia, rash, urticaria, flushing, hypertension, and hypotension.

4. Adverse reactions more commonly seen in pediatric patients compared to adult patients include (>10% difference): upper respiratory tract infection, rash, activated partial thromboplastin time (aPTT), prolonged, and pyrexia.

5. 1 of 54 (2%) treatment-naïve patients treated with VPRIV developed IgG antibodies to VPRIV. Antibodies were neutralizing in this patient. No infusion-related reactions were reported for this patient.

6. In treatment-naïve patients, onset of infusion-related reactions occurred mostly during the first 6 months of treatment and tended to occur less frequently with time.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

For details of presubmission regulatory activity for the first cycle review of this NDA, see my clinical review dated February 22, 2011.

The applicant, Protalix, submitted the original NDA for taliglucerase alfa (NDA 22458) on May 26, 2010. The NDA submission included a single randomized, double-blind trial

(PB-06-001) and interim data for two ongoing trials (PB-06-002 and PB-06-003) to support the efficacy of taliglucerase alfa. The pivotal trial was a 9-month trial in adult patients with Type 1 Gaucher disease with two taliglucerase alfa dose groups (30 Units/kg and 60 Units/kg). PB-06-002 is a 9-month open-label trial in adult and pediatric patients who were switched from imiglucerase to taliglucerase alfa; PB-06-003 is a 9-month extension trial for patients completing PB-06-001 and PB-06-002. The clinical and biostatistical reviewers raised concerns regarding the strength of evidence of effectiveness and the safety profile of taliglucerase alfa provided by the studies submitted for review. Specific clinical deficiencies included the lack of long-term efficacy and safety and lack of interpretable immunogenicity data. These deficiencies were communicated to the applicant in the Complete Response Letter issued on February 24, 2011.

There were no pharmacology/toxicology deficiencies noted by the Nonclinical Pharmacology/Toxicology reviewer, Tamal Chakraborti, PhD.

Several quality deficiencies were noted by the Product Quality reviewer, Richard Ledwidge, Ph.D., and included the following:

- Testing for presence of particles not in place for routine release and stability testing
- Provision of separate reporting for (b) (4) stability data for drug product lots
- Insufficient data in order to evaluate comparability of drug product lots
- Inadequate risk assessment on drug product sampling
- Imprecisely defined time of manufacturing
- Provision of control strategy for several compounds used in manufacturing process
- Incomplete assay validation process for some assays
- Inadequate testing performed in in-use and stress stability studies.
- Incomplete manufacturing process validation

In addition, the Microbiology Product Quality reviewer, Vinayak Pawar, Ph.D. noted the following deficiencies:

- Lack of validation of product bulk hold time, incomplete validation data for sterilization of the lyophilizer, and deficient (b) (4) of rubber stoppers used for container closure at the (b) (4) drug product manufacturing facility.
- Provision of validation summary reports for sterility and bacterial endotoxin test results for the (b) (4) drug product manufacturing facility.

The following issues regarding immunogenicity were identified by Faruk Sheikh, Ph.D., Division of Therapeutic Proteins:

- Unacceptable cut-point for the confirmatory anti-drug antibody assay (cut-point was too high)
- Lack of assay to assess for antibodies that neutralize drug uptake

The Clinical Pharmacology reviewer, Jang-Ik Lee, Ph.D., noted the following deficiencies:

- Inadequate data on the immunogenic potential of taliglucerase alfa and its impact on pharmacokinetic (PK) and pharmacodynamic (PD) parameters

On February 24, 2011, a complete response letter that described all the deficiencies as outlined above was signed by Julie Beitz, MD, Director of ODE III.

The applicant submitted a Complete Response to these deficiencies on August 1, 2011. The submission included clinical data from clinical trials PB-06-001 (pivotal trial), PB-06-002 (switchover trial in patients currently treated with imiglucerase), PB-06-003 (long-term extension trial), and PB-06-004 (treatment protocol). The original PDUFA goal date was February 1, 2012 for this Class 2 resubmission. However, based on discussions with DGIEP on November 11, 2011 (within 3 months of the goal date, the applicant submitted additional reanalyses of immunogenicity assay results using an alternate cut-point. .DGIEP determined that submission of these data by the applicant within 3 months of the goal date constituted a major amendment. Therefore, the PDUFA goal date was extended to May 1, 2012.

2.6 Other Relevant Background Information

(b) (4) the Agency held a teleconference with the applicant to advise that the (b) (4) facility responsible for (b) (4) had been issued a Warning Letter and that the application could not be approved without full resolution of the items listed in the Warning Letter and full re-inspection of this facility. On March 22, 20121, the applicant responded that the site was withdrawn from the application and that testing had been reassigned to other facilities that had already cleared inspection (b) (4) Protalix). The applicant submitted validation reports for the facilities that were found to be acceptable by the Product Quality Microbiology reviewer (see addendum to the Product Quality Microbiology review dated April 18, 2012).

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the data submitted by the applicant was adequate for comprehensive review of the data, and the integrity of the investigators and the conduct of the trial were found to be acceptable by the Division of Scientific Investigation during the first cycle review.

3.2 Compliance with Good Clinical Practices

According to the applicant, these trials were conducted pursuant to the following International Conference on Harmonisation (ICH) guidelines: Good Clinical Practice (ICH E6), Statistical Principles for Clinical Trials (ICH E9), and Choice of Control Group and Related Issues in Clinical Trials (ICH E10).

3.3 Financial Disclosures

Financial disclosures were not required as part of the applicant's Complete Response (see original NDA review by C. Epps, M.D., for review of financial disclosure information).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Taliglucerase alfa drug substance is a single polypeptide chain containing the exact amino acid sequence to human glucocerebrosidase with (b) (4) the plant cell expression vector. an N-terminal and a C-terminal. The molecular weight is ~ 60,800 Da (b) (4) .

Taliglucerase alfa is expressed in carrot cells. The Applicant notes that use of a plant system affords advantages in producing glucocerebrosidase. One advantage is the elimination of issues with mammalian adventitious viral agents. Another advantage is that the glycosylation process in carrot cells results in naturally exposed terminal mannose residues. Production of currently available glucocerebrosidase products, which are produced in mammalian cell systems, includes a deglycosylation process to expose terminal mannose residues.

Taliglucerase alfa is supplied as a sterile, non-pyrogenic, lyophilized product. The quantitative composition of the lyophilized drug include taliglucerase alfa 212 units, D-mannitol 206.7 mg, polysorbate 80 0.56 mg, sodium citrate 30.4 mg. After reconstitution with Sterile Water for Injection, USP, the taliglucerase alfa concentration is 40 U/mL. Reconstituted solutions have an approximate pH of 6.0. (b) (4)

Product quality review
The applicant's responses to Product Quality issues were reviewed by Richard Ledwidge, Ph.D. (see review by Dr. Ledwidge dated March 29, 2012 for full details). The deficiencies listed in the Complete Response letter pertained to the following:

1. Specifications- multiple identity, impurity, and potency assays were revised.
2. Comparability- the effects of changing the components of the growth media in the commercial manufacturing process were evaluated.
3. Process Validation- validation data for particular aspects of manufacturing were provided.
4. Control of Impurities- the levels of several process-related impurities were evaluated.

Dr. Ledwidge determined that all outstanding issues had been resolved, with the exception of the following:

- Revision of the cellular uptake potency assay release and stability acceptance criteria after 15 lots of drug product have been manufactured.
- Revision of Experion automated electrophoresis release and stability acceptance criteria after 15 lots of drug product have been manufactured.
- Evaluation and revision as appropriate of the minimal percentage of specific uptake of reference standard as a system suitability criterion in the cellular uptake potency assay after at least 80 independent assay runs of release and stability testing of drug substance and drug product lots have been completed.
- Characterization of the (b) (4) detected in the iCE assay and to evaluate the impact of this heterogeneity on product quality, including any effects on potency (specific uptake, enzyme kinetics, and cellular uptake). Assessment of the suitability and the implementation of the iCE method and other analytical assays as appropriate into the stability protocol .

Dr. Ledwidge recommended approval of the application and submission of this information as Post-marketing Commitments.

Facility review/inspection
As noted earlier, the Agency held a teleconference on (b) (4), with the applicant to advise that (b) (4) one of the sterility and endotoxin testing facilities named in the application had been issued a Warning Letter and that the application could not be approved without full resolution of the items listed in the Warning Letter and full re-inspection of this facility; the other testing facilities have cleared inspection. (b) (4) was removed from the application on March 22, 2012. The Office of Compliance has recommended an approval action.

Microbiology product quality
The applicant's responses to Microbiology Product Quality issues were reviewed by Vinayak Pawar, Ph.D. (see review by Dr. Pawar dated December 21, 2011 for full details). Dr. Pawar noted that the microbiology product quality deficiencies for the two drug product manufacturing facilities cited in the Complete Response letter had been addressed. Also, as noted earlier, Dr. Pawar found no deficiencies in the sterility and endotoxin testing validation reports submitted by the applicant during this review cycle (see review addendum dated April 18, 2012). Dr. Pawar recommended approval of the application based on resolution of the Microbiology Product Quality deficiencies.

Immunogenicity
The applicant's responses to Immunogenicity issues were reviewed by Faruk Sheikh, Ph.D., in the Division of Therapeutic Products (DTP). See Dr. Sheikh's review by dated December 23, 2011 for full details. Dr. Sheikh noted that the deficiency regarding the

cut-point for the confirmatory assay had been addressed adequately. Dr. Sheikh noted that there were two outstanding deficiencies:

- Development of an detect anti-plant sugar antibodies that cross-react with taliglucerase alfa
- Development of a reliable and sensitive neutralizing antibody assay

The applicant proposed to develop an anti-plant sugar antibody assay and an assay control and to submit the results of assay development and clinical sample analyses by April 2012 and July 2012, respectively. The applicant proposed to submit a report on an appropriate positive control neutralizing antibody for its neutralizing antibody assays by May 2012. DTP stipulated that pending data for the anti-plant sugar and neutralizing antibody assays be included in Post-Marketing Requirements. In addition, DTP noted that the applicant should evaluate the neutralizing ADA response, cellular uptake inhibition and plant-sugar antibodies in all archived sampling time points available from all patients in clinical studies as a PMR.

4.2 Clinical Microbiology

Clinical microbiology considerations do not apply to this application because taliglucerase alfa is not an antimicrobial agent.

4.3 Preclinical Pharmacology/Toxicology

There are no Preclinical Pharmacology/Toxicology issues with this submission to the Complete Response.

4.4 Clinical Pharmacology

The clinical pharmacology review during this review cycle focused on the PK and PD characteristics of taliglucerase alfa in Gaucher patients by immunogenicity status; the PK/PD profile of taliglucerase alfa in healthy volunteers was reviewed in the prior review cycle. The applicant's responses to Clinical Pharmacology deficiencies were reviewed by Lanyan Fang, Ph.D. (see review by Dr. Fang dated April 2, 2012 for full details) and her findings are summarized below. Dr. Fang recommended approval of the application but noted that the impact of immunogenicity on the PK profile, efficacy, and safety of taliglucerase alfa was inconclusive. Dr. Fang recommended the following Post Marketing Commitment:

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

4.4.1 Mechanism of Action

The rationale for enzyme replacement is that exogenous administration of glucocerebrosidase (GCD) should mitigate the deficiency of endogenous enzyme in Gaucher disease. Exogenous GCD must be taken up by target cells via mannose receptors; the enzyme is then taken up by lysosomes where it undergoes conversion to a more active form. The active ingredient of the drug product is taliglucerase alfa, which contains the same amino acid sequence as the naturally occurring human enzyme, glucocerebrosidase (GCD). Taliglucerase alfa naturally contains exposed terminal mannose residues. The applicant proposes that this structural characteristic will facilitate internalization of taliglucerase alfa by target cells.

4.4.2 Pharmacodynamics

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

4.4.3 Pharmacokinetics

Pharmacokinetics (PK)
The PK of taliglucerase alfa was characterized in 31 treatment naïve subjects with Gaucher disease on Day 1 and Week 38 (Month 9) who received taliglucerase alfa 30 units/kg or 60 units/kg via intravenous infusion over 2 hours every other week in Study PB-06-001. The median terminal half life was 18.9 to 31.4 minutes for both dose groups at Day 1 and Week 38. The median systemic clearance (CL) values were approximately 30 L/hr and 20 L/hr for 30 and 60 units/kg, respectively, on Week 38. The median volume of distribution at steady state (Vss) ranged from 9.06 to 12.1 L for both dose groups. No significant accumulation in serum taliglucerase alfa concentrations was observed with repeated doses of 30 or 60 units/kg. Taliglucerase alfa PK did not appear to change over time (Day 1 vs. Week 38). The PK of taliglucerase alfa appeared to be nonlinear with a greater than dose-proportional increase in exposure at the doses studied.

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

Exposure Response Relationship
In Study PB-06-001, both taliglucerase alfa dose groups demonstrated a significant reduction in spleen volume (primary clinical endpoint) at Month 6 visit (30 units/kg, 22.2%; 60 units/kg, 29.9%; $p< 0.0001$) and Month 9 visit (30 units/kg, 26.9%; 60 units/kg, 38.0%; $p < 0.0001$). Although, there appeared to be a trend of greater reduction in spleen volume with increasing dose, the applicant concluded there was no statistically significant difference between the two dose groups at Months 6 and 9 ($p = 0.060$) based on the small sample size.

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

No exposure-response relationship was established for safety as no statistical differences were observed between dose groups. Dr. Fang concluded that overall, the dose-response relationship indicated no statistically significant differences between the two dose groups in terms of observed efficacy and safety.

Immunogenicity Incidence
In PB-06-001 (pivotal trial), 18/32 (56%) patients developed anti-drug antibodies (ADA) following administration of taliglucerase alfa. One additional patient had ADA detected before the first infusion. Dr. Fang noted that the immunogenicity incidence rate increased with dose: 40% (6/15) at 30 units/kg dose and 75% (12/16) at 60 units/kg dose. Two of 18 ADA-positive patients were positive for neutralizing antibodies based on the enzymatic activity inhibition assay; both patients were negative in the cell-based assay.

In PB-06-002 (switchover trial), six of 28 patients were ADA positive; one patients 206) had ADA detected pre-switch and the remaining 5 patients became ADA-positive after the switch. One of 6 patients was positive for neutralizing antibodies based on the enzymatic activity inhibition assay, but negative based on the cell-based assay. Dr. Fang noted that the neutralizing antibody assays developed by the applicant were not sufficiently sensitive, and thus were inadequate to detect neutralizing ADA. Dr. Fang recommended that the applicant develop more sensitive neutralizing antibody assays.

Immunogenicity Impact on PK, Efficacy and Safety
Dr. Fang noted that the impact of ADA on efficacy was inconclusive. In PB-06-001, 17 patients were ADA-positive and 12 patients were ADA-negative at Month 9. In the high dose group, there appeared to be a trend of greater efficacy with respect to reduction in spleen and liver volume in the 4 patients who were ADA-negative compared to 11 patients who were ADA-positive. However, this trend was not observed in the lower dose group (N=6 ADA-positive and N=8 ADA-negative). Dr. Fang commented that the observed results should be interpreted with caution as the study did not have sufficient power to detect PK differences due to the small sample size.
.
No consistent patterns were observed across the two dose groups in terms of the impact of development of ADA on the safety of taliglucerase alfa (e.g., allergic reactions). Dr. Fang noted that an evaluation of the relationship between ADA and safety was limited by the small sample sizes of the clinical trials and the lack of appropriately validated and sufficiently sensitive neutralizing antibody assays. Dr. Fang recommended that the applicant monitor patients who developed ADA with more

sensitive neutralizing antibody assays and assess the impact of neutralizing antibodies (for both cell uptake and enzyme activity) on the long-term safety and efficacy in phase 3 studies as a PMR.

5 Sources of Clinical Data

The applicant submitted the following data for review in their Complete Response: abbreviated clinical study reports for trials PB-06-002 (switch trial) and PB-06-003 (follow-on trial). In addition, the applicant submitted case report forms for two patients from trial PB-06-004 and one patient from trial PB-06-005.

I also completed a literature review (See Section 9.1).

Trials PB-06-002 and PB-06-003 are ongoing. PB-06-002 is a 9-month Phase 3, open-label trial evaluating the safety and efficacy of taliglucerase alfa in patients previously treated with imiglucerase (Cerezyme). PB-06-003 is a Phase 3, open-label extension trial, evaluating the long term safety and efficacy of taliglucerase alfa in patients who completed PB-06-001 and PB-06-002.

5.1 Tables of Studies/Clinical Trials

In addition to data from Phase 3 trials submitted in original application and the Complete Response, the clinical program includes a Phase 1 trial (PB-01-2005), a Phase 3 trial in adult treatment-naïve patients (PB-06-001), a treatment protocol (PB-06-004), and a Phase 3 trial in pediatric patients (PB-06-005). The phase 1 trial investigated the safety of taliglucerase alfa in six healthy volunteers. Data for PB-06-001, the only completed Phase 3 clinical trial submitted by the applicant, were reviewed during the prior review cycle. The treatment protocol was opened in August 2009 in response to a world-wide shortage of imiglucerase that began in June 2009 and is ongoing. Fifty patients were enrolled in the treatment protocol at the time of submission of this application. PB-06-005 has completed enrollment, with 11 pediatric patients enrolled, and is ongoing. To date, a total of 18 pediatric patients have been enrolled in clinical trials (2 patients in PB-06-002, 5 patients in PB-006-004, and 11 patients in PB-06-005). Pediatric patients were excluded from PB-06-001. See Table 3 for a list of taliglucerase alfa clinical trials.

Table 3: Taliglucerase Clinical Trials

Trial (# Sites) Country	Phase	N (# pediatric pts)	Design	Dosing	Inclusion Criteria --- Exclusion Criteria	Duration	Status
P-01-2005 (**)	1	6	Safety	IV once/wk		3 weeks	completed
PB-06-001 (10**) Canada Chile Israel Italy Mexico Serbia South Africa Spain UK	3	33 (pediatric patients excluded)	R/DB Safety /Efficacy	30 U/kg EOW;60 U/kg EOW	•Gaucher pts ≥ 18 yrs •Spleen > 8X normal size •Thrombocytopenia •No anti-GCD antibodies --- •Gaucher-related neurologic disease •Pregnant/lactating women •Allergic to carrots •Allergic to Cerezyme/Ceredase	9 months	completed
PB-06-002 (9) Australia, Canada Israel (2) Serbia Spain UK US(2)	3	30 (2 pediatric patients)	OL Safety /Efficacy	IV over 2 hrs EOW	•Gaucher pts ≥ 2 years old with stable disease •Prior treatment w/ Cerezyme ≥2 yrs & regimen unchanged in past 6 mos --- •Pregnant/lactating women criterion removed •No anti-GCD antibodies criterion removed	9 months	ongoing (all adult patients have completed study)
PB-06-003 (15) Australia Canada Chile Israel (2) Italy Mexico (2) Serbia South Africa Spain UK (2) US (2)	3	60 (44 enrolled to date; no pediatric patients)	OL Safety /Efficacy	30 U/kg EOW;60 U/kg EOW	•Completion of PB-06-001 or 002 --- 	15 months	ongoing

Table 3: Taliglucerase Clinical Trials (cont'd.)

Trial (# Sites) Country	Phase	N	Design	Dosing	Inclusion Criteria --- Exclusion Criteria	Duration	Status
PB-06-004	3	Up to 200 (50 enrolled to date; 5 pediatric patients)	Expanded Access	Same dose as previous ERT	N/A	unspecified	ongoing
PB-06-005	3	11 (enrollment completed)	Pediatric Trial	30 U/kg EOW;60 U/kg EOW		12 months	pending

5.2 Review Strategy

This section discusses trial design and efficacy results for the trials reviewed in this submission. Safety is discussed in Section 7 of this review.

Efficacy parameters evaluated in clinical trials included liver and spleen volume. Normal organ volumes are a function of body weight. Thus, normal organ volumes differ by age and gender. The normal liver and spleen volumes are approximately 2.5% and 0.2% of body weight (kg), respectively. Published literature on Gaucher disease, organ volumes commonly are described in termed of multiples of normal (MN) and percent of body weight in kilograms (%BW) rather than by the specific volume measurement in milliliters.[9,10] Note that the labeling for VPRIV describes organ volume outcomes by percent of body weight. In this review, organ volumes are provided in milliliters, % BW and MN (organ volumes were only presented in milliliters in the first review cycle).

During the first review cycle, I reviewed the efficacy and safety data for the completed phase 3 trial PB-06-001 and preliminary data for ongoing trials PB-06-002 and PB-06-003 (see Clinical Review dated February 22, 2011). The major study objective of PB-06-001 was to evaluate the effect of taliglucerase alfa on four clinical parameters: spleen volume, liver volume, hemoglobin, and platelet count at two dose levels (30 U/kg and 60 U/kg). Twenty-nine of 33 patients who were enrolled in the trial completed the trial.

In PB-06-001, taliglucerase alfa demonstrated a benefit of a 29% reduction of mean spleen volume (mean spleen volume ± SD decreased from 3.1 ± 1.5 %BW [at baseline to 2.2 ± 1.2 %BW at Month 9) and an 15% reduction of mean liver volume (mean liver volume decreased from 4.0 ± 1.0 %BW [1.6 MN] at baseline to 3.4 ± 0.7 %BW [1.3 MN] at Month 9) in the overall treatment population after 9 months of treatment. There was a statistically significant difference observed between the two treatment groups in spleen volume (p=0.014) but not liver volume. After 9 months, there was a statistically significant increase in mean platelet count of 41K for the 60 U/kg treatment group (p=0.003) but not the 30 U/kg treatment group. A statistically significant increase in mean hemoglobin was observed for both treatment groups (p=0.001 and p<0.001 for the 30 U/kg and 60 U/kg treatment groups, respectively) after 9 months of treatment. However, because both treatment groups had normal mean baseline hemoglobin

9 Rosenberg M, Wytske K et al, Immunosurveillance of Alglucerase Enzyme Therapy for Gaucher Patients: Induction of Humoral Tolerance in Seroconverted Patients After Repeat Administration, *Blood* 1999; 6:2081-2088.
10 Multiples of normal (MN) are calculated by dividing spleen volume (mL) by body weight (kg) X2 mL and liver volume by body weight (kg) x 25 mL, respectively.

values, it was difficult to assess the treatment effect of taliglucerase for this clinical parameter. There were no pediatric patients enrolled in PB-06-001; therefore, efficacy in this population could not be established.

Efficacy data for PB-06-002 was limited as only four patients had completed the study. One of four patients (25%) experienced clinical deterioration of ≥ 20% increase in spleen volume after 9 months of treatment with taliglucerase alfa; liver volume remained stable for all four patients. Two of 24 patients experienced clinical deterioration of ≥ 20% decrease in platelet count after six months of treatment ; hemoglobin remained stable for all patients after six months of treatment. Due to the small number of patients, the short treatment duration, and the open-label trial design, no clear conclusions regarding the efficacy of taliglucerase could be made from the preliminary trial data.

No efficacy data were submitted for PB-06-003 during the first review cycle.

Based on the preliminary safety data provided for the first review cycle, the safety profile of taliglucerase alfa in the three studies appeared to be similar to that of other Gaucher ERT products. However, due to the lack of adequately validated immunogenicity assays, the impact of immunogenicity on the efficacy and safety of the product in type 1 Gaucher patients could not be evaluated. This review includes reanalyses of the impact of immunogenicity on safety and efficacy data for the three trials.

5.3 Discussion of Individual Clinical Trials

5.3.1 PB-06-002- Phase 3 "Switchover" Trial

PB-06-002 is a multicenter, open-label trial designed to evaluate the efficacy and safety of taliglucerase every other week (EOW) for 9 months in 30 type 1 Gaucher patients who had previously been treated with Cerezyme (imiglucerase). Patients were required to have been on ERT with Cerezyme for at least 2 years, judged to be clinically stable (defined below), and on a stable maintenance regimen (defined as no dose change within the past 6 months). Exclusion criteria for the trial included a history of allergy to Cerezyme, Ceredase, carrots, beta-lactam antibiotics, or the presence of significant comorbidities (e.g., viral hepatitis, iron deficiency anemia, etc.).

Stable Gaucher disease at baseline was defined as no change in the following parameters within the past year:

- hemoglobin (no value >mean ± 15%)
- platelet count (≥120K:no value >mean ± 40%; <120K: no value >mean ± 40%)
- no spleen or liver volume increase (as measured by MRI)
- no major surgery

- no transfusions or major bleeding episode
- no acute avascular necrosis event

Patients received a starting dose of taliglucerase alfa equivalent to their stable Cerezyme dose. For patients whose Cerezyme treatments have been discontinued due to drug shortage, the starting taliglucerase dose was based on their usual dose prior to drug shortage. During the treatment period, the dosage could be increased to a maximum dose of 60 U/kg if the patient experienced Gaucher disease-related deterioration as defined by a pre-specified decline in organ volume, hemoglobin, or platelet count.

Efficacy was evaluated by monitoring the following parameters for evidence of clinical deterioration (changes less than this magnitude would be defined as clinical stability):

- platelet count (> 120K-40% decrease; ≤ 120K-20% decrease)
- hemoglobin (20% decrease)
- spleen volume (20% increase)
- liver volume (10% increase)

Biomarkers (chitotriosidase and CCL18) were evaluated in a subgroup of patients. Growth and development parameters (change in growth and development, height and weight, Tanner stage, bone age) were evaluated as exploratory endpoints for pediatric patients (patients < 18 years old).

The safety monitoring for Trial PB-06-002 included the same safety measurements as performed in the pivotal trial PB-06-001 (reviewed during the first cycle): adverse events (AEs), concomitant medication use, vital signs, echocardiograms, ECGs, physical examinations, pulmonary function tests, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and antibody testing. In addition, clinical deterioration in hemoglobin or platelet count, defined as three consecutive measures of declining values, was monitored as a safety variable.

An abbreviated clinical study report with interim safety and efficacy data was included in the applicant's Complete Response because the trial was ongoing at the time of the submission. Currently, 30 patients have been enrolled, including 28 adult and 2 pediatric patients. Twenty-five of 28 adults patients have completed the study (3 patients withdrew prematurely); treatment of the two pediatric patients is ongoing (see Table 5). The abbreviated study report includes efficacy and safety data up to a date of May 1, 2011. The safety data for this study will be reviewed in Section 7.

The protocol was amended five times during the trial. Major amendments to protocol criteria included:

- Allowed infusion administration at a local infusion center or at home (Version 2 dated May 7, 2009)

- Addition of an interim safety analysis by a Data Monitoring Committee (DMC) on an ad hoc basis (Version 2 dated May 7, 2009)
- Amended enrollment criteria to allow enrollment of patients affected by the short-term shortage of Cerezyme (Version 3 dated June 26, 2009)
- Expanded enrollment from 15 to 30 patients (Version 4 dated September 10, 2009)
- Addition of interim integrated clinical and statistical report of the first 15 patients completing the study (either completing treatment or withdrawing prematurely) (Version 4 dated September 10, 2009)
- Amended enrollment criteria to allow enrollment of pediatric patients aged 2 years and older (Version 5 dated January 19, 2010)
- Addition of study assessments to assess growth and development in pediatric patients (Version 5 dated January 19, 2010)
- Removed pregnancy or nursing as exclusion/discontinuation criteria and removed requirement for pregnancy testing (Version 5 dated January 19, 2010)
- Amended other exclusion criteria (presence of anti-glucocerebrosidase antibodies deleted; allergy to beta-lactam antibiotics added) (Version 5 dated January 19, 2010)
- Allowed extended treatment under PB-06-002 protocol if extension study (PB-06-003) was not approved (Version 5 dated January 19, 2010)

Reviewer comment: From a safety perspective, none of the protocol changes likely would have affected the study results in an adverse way, with the potential exception of removal of the exclusion criterion for pregnant and lactating women. The safety of any of the ERT products for Gaucher diseases in pregnant and lactating women remains unknown. The applicant cited data from published literature on pregnancy outcomes in women treated with ERT during pregnancy. In one retrospective study of 43 pregnancy women (17 treated with ERT and 26 untreated), no differences in pregnancy outcome, spontaneous abortions, or postpartum bleeding.[11] In another retrospective review of 398 pregnancies, 42 women had been treated with ERT. A statistically significant reduction in spontaneous abortions was observed in treated women (9.5% compared to 17.1% in untreated women). The incidence of infection was higher in women treated with ERT while the incidence of antepartum and postpartum bleeding were higher in untreated women.[12] As discussed later, no adverse pregnancy outcomes were reported in this study (see Section 7.6.2)

Otherwise, the protocol amendments did not impact safety monitoring adversely; some of the amendments in fact expanded safety monitoring. The protocol in place for

11 Elstein Y, Eisenberg V et al, Pregnancies in Gaucher disease: A 5-year study, *Am J Obstet Gynecol* 2004; 190: 435-441.
12 Zimran A, Morris E et al, the female Gaucher patient: the impact of enzyme replacement therapy around key reproductive events (menstruation, pregnancy and menopause), *Blood Cells Mol Dis* 2009: 43: 264-288.

monitoring for and managing allergic reactions was sufficient to allow infusion administration outside of study center sites and enrollment of patients with positive anti-glucocerebrosidase antibodies. The amendment to enroll pediatric patients was accompanied by an amendment to assess growth and development in these patients. It is unclear why allergy to beta-lactam antibiotics was added as an exclusion criterion; this reviewer was unable to locate any information about adverse events related to beta-lactam antibiotics in the safety data.

Note that the trial population (i.e., patients with stable clinical disease on a stable treatment regimen) was well defined and that clinical criteria for eligibility were not amended during the trial. Therefore, the protocol amendments that expanded trial enrollment likely enhanced the ability to interpret efficacy results since they increased the sample size of the trial.

A. Treatment

PB-06-002 was comprised of a screening period, a 3-month "stability evaluation" period and a 9-month treatment period.

Screening evaluations included a medical history and physical examination, medications, laboratory assessments, and echocardiogram. For adult patients, chest X-ray (CXR) and pulmonary function tests (PFTs) were also included in the screening evaluation.

During the stability evaluation period, patients continued on imiglucerase treatment. Hemoglobin and platelet counts were assessed every 2 weeks for a total of 6 measurements. Clinical stability of patients who were enrolled into the study due to a drug shortage of Cerezyme was determined by a review of the previous 6 months of clinical data for each patient.

During the treatment period, baseline assessments were performed on Day 1. Baseline assessments included physical examination, concomitant medications, laboratory assessments, genotyping, electrocardiogram (ECG), MRI measurements of liver and spleen volume, and skeletal x-ray series. In addition, anti-human taliglucerase antibody titers and biomarker levels (chitotriosidase or PARC/CCL18) were obtained. Baseline growth and development assessments for pediatric patients included hand and wrist x-rays for bone age and Tanner Stage

During the treatment period, patients received up to a total of 20 IV infusions of taliglucerase alfa at a dose equivalent to their stable dose of imiglucerase. As noted earlier, the protocol allowed for an increase in taliglucerase dose up to a maximum of 60 U/kg to maintain clinical stability (as defined above).

Table 4 summarizes the schedule of assessments for PB-06-002:

Table 4: PB-06-002 Schedule of Trial Assessments

Activity	Screening Week -12	Stability Evaluation Weeks -10 to -2	Treatment Day 1, Weeks 2 to 38							Premature Withdrawal
	Visit 0		Visit 1 Baseline	Visits 2-6	Visit 7 Month 3	Visits 8-13	Visit 14 Month 6	Visits 15-19	Visit 20 Month 9	
Medical History	X									
Physical Exam	X		X		X		X		X	X
Height & Weight	X		X		X		X		X	X
Vital signs			X		X		X		X	X
Adverse Events			X	X	X	X	X	X	X	X
Current/Concomitant Medications	X		X	X	X	X	X	X	X	X
Hemoglobin & platelet count	X	X	X	X	X	X	X	X	X	X
Laboratory	X		X	X	X	X	X	X	X	X
TSH, transferrin, B12 and folic acid	X								X	X
Protein electrophoresis	X								X	X
Hemoglobin A1c	X								X	X
Serology	X									
Glucocerebrosidase activity & Mutation analysis	X									
X-ray Skeletal Evaluation			X							
Bone age & Tanner Stage (pediatric pts)			X		X				X	X
ECG			X		X		X		X	X
CXR, Echo, PFTs	X								X	X
Organ volumes			X						X	X
Biomarkers			X		X		X		X	X
Anti-human taliglucerase alfa antibodies			X	X	X	X	X	X	X	X

Concomitant Medications
Patients were allowed to take medications for allergic reactions, anemia, bone disease, and analgesia. All concomitant medications taken during the trial were recorded.

Prohibited Medications
Patients were prohibited from taking miglustat (Zavesca), alglucerase (Ceredase), or imiglucerase (Cerezyme); velaglucerase (VPRIV) was not an approved product at the time the trial was conducted. Patients also were prohibited from taking another experimental drug for any condition.

Safety Considerations/Monitoring
Safety was assessed by adverse events (AEs), concomitant medication use, vital signs, echocardiograms, ECGs, physical examinations, pulmonary function tests, clinical laboratory tests (hematology, serum chemistry, transferrin, folic acid, Vitamin B12 monitoring, and urinalysis), and antibody testing. Pregnancy testing

In addition, an independent Data Monitoring Committee (DMC) was chartered to conduct protocol defined interim safety analyses as well as *ad hoc* safety analyses as requested by the investigator, or required events as defined in the protocol. For PB-06-002, the DMC also was specifically charged to monitor for evidence of clinical deterioration.

B. Statistical Analysis Plan
The applicant provided descriptive statistics for the study efficacy and safety variables. Two interim analyses were planned. The first interim analysis, presented in the abbreviated clinical study report submitted in the previous review cycle, was performed on data collected as of April 30. 2010. The second interim analysis, presented in the current submitted abbreviated clinical study report, was performed on data collected as of May 1, 2011.

Determination of Sample Size
Sample size for this trial was not based on specific power calculations. The applicant considered the sample size of 30 patients to be adequate for evaluation of safety.

C. Patient Disposition

Patient Disposition
Of the 43 patients screened in this trial, 30 patients were eligible for enrollment, including 28 adult and 2 pediatric patients. Of the 30 enrolled patients, 28 patients received treatment and 25/30 patients (89%) completed the trial. Two patients (20-212 and 30-213) withdrew from the trial before treatment. One patient (13-228) withdrew from the study after the first infusion; the patient experienced an allergic reaction and declined to continue infusions with premedication. Two pediatric patients (14-229 and 14-230) continue on treatment.

Table 5: PB-06-002 Patient Disposition

Disposition	Adult patients N(%)	Pediatric patients N(%)
Enrolled	28 (100%)	2 (100%)
Discontinued from study	1(4%)	0
Withdrew consent	2 (7%)	0
Completed study	25 (89%)	0
Enrolled into PB-06-003	18 (64%)	N/A

Patient Compliance
All patients who completed the study received all 20 scheduled infusions of study drug. The only adult patients who did not receive all 20 scheduled infusions were patients that discontinued the study as described above. Treatment of the two pediatric patients is ongoing.

Protocol Deviations and Compliance
There were a total of eight patients with protocol deviations. Deviations consisted of missed study visits or study assessments, and study visits or assessments that occurred outside of the study schedule window.

Patient Demographics
Table 6 summarizes baseline patient characteristics for PB-06-002. Mean patient age at time of enrollment was 45 years. Men enrolled into the trial were slightly older than the women (mean baseline ages of 48 and 41 years, respectively). Patients ranged in age from 13 years to 66 years at the time of enrollment. Mean baseline values for the overall population were within normal range for all clinical parameters except for spleen volume (mean baseline spleen volume was 822 ml and mean spleen volume normalized for body weight was 1.1% of body weight [BW], representing 5.5 multiples of normal [MN] volume). Mean baseline normalized spleen volume was larger in women compared to men (1.6 % BW [6.5 MN] and 0.9% BW [5.0 MN], respectively).[13] Baseline hemoglobin and platelet values were defined as the mean of all available values for these parameters measured during the Stability Evaluation Period (up to six values). Baseline hemoglobin was lower in women than in men but within normal range for gender for both genders (baseline mean hemoglobin 14.6 g/dL and 12.4 g/dL for men and women, respectively). Baseline platelet count (152K and 171K for men and women, respectively) and liver volume (2.4 % BW [0.9 MN] and 2.5% BW [1 MN] for men and women respectively) were similar for both genders.

[13] Normal spleen and liver volumes are 0.2% of body weight (2mL X body weight [kg]) and 2.5% of body weight 25 mL X body weight [kg]), respectively. Multiples of normal (MN) are calculated by dividing spleen volume (mL) by body weight (kg) X2 mL and liver volume by body weight (kg) x 25 mL, respectively.

Table 6: PB-06-002 Baseline Characteristics

Characteristic	Total (N=28)
Age Years)	
n	**28**
Mean (SD)	44.7 (15.1)
Median	46.5
Min, Max	13,66
Gender- n(%)	
Female	15 (54%)
Male	13 (46%)
Race/Ethnicity- n(%)	
Caucasian	28 (100%)
Weight (kg)	
n	28
Mean (SD)	**76.5 (17.23)**
Median	74.5
Min, Max	45,112
Average of all Dose Infusions (units/kg)	
n	28
Mean (SD)	**29.2 (15.90)**
Median	25.5
Min, Max	11,60
Spleen Volume (mL)	
n	20
Mean (SD)	**822.4 (603.70)**
Median	814.2
Min, Max	14, 2151
(normal: 0.2% BW)	**1.1% BW (5.5 MN)**
Liver Volume (mL)	
n	23
Mean (SD)	**1857.4 (440.00)**
Median	1816.5
Min, Max	1167, 2659
(normal: 2.5% BW)	**2.4% BW (1.0 MN)**
Hemoglobin (g/dL)	
n	28
Mean (SD)	**13.6 (1.50)**
Median	13.7
Min, Max	11,16
(normal: > 11.5-12.0 g/dL)	
Platelet Count (_/mm^3)	
n	28
Mean (SD)	**169K (81K)**
Median	176K
Min, Max	38k, 322K
(normal: > 120K)	

MN= multiples of normal; %BW= percent of body weight in kg

Review of Efficacy

Efficacy Summary

Taliglucerase alfa appears to have demonstrated maintenance of treatment benefit in patients switched from imiglucerase in a majority of type 1 Gaucher patients studied. Organ volumes and hematological parameters for the overall study population remained stable after 9 months of treatment with taliglucerase alfa after switching from maintenance treatment with imiglucerase. However, four of 28 patients experienced clinically significant deterioration in one of the four clinical parameters (see below) evaluated in the trial (spleen volume, liver volume, hemoglobin, and platelet count) during the course of the trial; one of these patients stabilized his platelet count after his taliglucerase dose was increased from 9.5 U/kg to 19 U/kg).

The impact of immunogenicity on efficacy was not clear from the data provided for review. A smaller decrease in spleen volume was observed in antibody-positive patients compared to antibody-negative patients, while other efficacy results for other clinical parameters were similar. As noted earlier, the sensitivities of the neutralizing antibody assays used in the trial were not adequate. These data preclude the evaluation of the effect of neutralizing antibodies on long-term efficacy and safety and will be important to evaluate in the future. The observed difference in spleen volume results raises the concern that immunogenicity may potentially adversely impact the efficacy of this drug. Therefore, additional data should be collected on the long-term safety and efficacy of taliglucerase alfa as a post-marketing requirement.

Although taliglucerase alfa appeared to demonstrate a treatment effect in this trial, the trial data are not sufficient to draw clear conclusions regarding the long-term efficacy of taliglucerase due to the small number of patients and the short time period of treatment with taliglucerase, and the lack of a treatment arm in which an approved ERT product was the active comparator group. In addition, two retrospective surveys of patients withdrawn from ERT treatment for various reasons (e.g., medical complications, financial constraints, drug shortage) indicated that clinical parameters of Gaucher disease remained stable or did not deteriorate precipitously up to 6 months after treatment withdrawal.[14,15] In the earlier survey, some patients were clinically stable after more than two years without ERT treatment. Therefore, the treatment duration for this trial may not have been long enough to identify a treatment difference in patients transitioned from imiglucerase.

14 Elstein D, Abrahamov A et al, Withdrawal of enzyme replacement therapy in Gaucher's disease, *Br. J Haematol* 2000; 110(2):488-492.
15 Zimran A, Altarescu G, Elstein D, Nonprecipitous changes upon withdrawal from imiglucerase for gaucher disease because of a shortage in supply, *Blood Cells Mol Dis* 2011: 46 (1):111-114.

Finally, as noted earlier, the applicant has not completed PB-06-002; two pediatric patients are receiving ongoing treatment. The applicant should complete the trial and submit a final report as a post-marketing requirement.

1. Clinically Relevant Deterioration

Four of 28 patients (14%) experiencing clinical deterioration, including one patient who experienced spleen enlargement > 20%, one patient who experienced liver enlargement > 10%, and 2 patients who experienced decreases of > 20% in platelet count. No patient experienced clinical deterioration in more than one clinical parameter. One patient (20-224) developed transiently positive antibody titers (positive at Week 8 [specific titer was not done]); the other three patients had negative ADA titers. One patient's (18-219) taliglucerase dose was increased due to a clinically relevant deterioration in his platelet count, with subsequent improvement. Specific results for these patients are discussed below.

2. Spleen and Liver Volume

Liver and spleen volume measurement were performed by quantitative abdominal MRI of the liver and spleen using a standardized protocol. Images were collected and sent to two central radiographic reviewers who remained blinded to the trial medication and the order in which the images were taken. A third reader was available for adjudication of reading results; no adjudication review was required during the trial. Organ volume measurements that were not obtained using the protocol (i.e., ultrasound measurements) were excluded from efficacy analyses. Two patients who refused MRI measurements due to claustrophobia had ultrasound measurements of organ volumes.

Data on spleen volume were available for 20/25 patients and data on liver volume were available for 23/25 patients completing 9 months of treatment (see Table 7). Three splenectomized patients were not included in the analysis of spleen volume. In addition, organ volumes were assessed by ultrasound in 2 patients and therefore these results were not included in organ volume analyses.

The mean baseline spleen volume was 822 ml (1.1 % BW [5.5 MN]). The overall mean baseline liver volume was within normal limits; however, 5/23 patients had liver volumes > 2.5% BW [1 MN] (range was 2.6% BW [1.1 MN] to 4.1% BW [1.7 MN]). Overall Mean spleen and liver volume were both within normal limits at Month 9. The mean percent change in spleen and liver volume at Month 9 was -8% $\pm$13% and -4% $\pm$ 8%, respectively. The mean change in spleen and liver volume as %BW was -0.1% and -0.1%, respectively. One patient (10-203) experienced clinical deterioration in spleen volume (spleen volume increased 22% from 814 mL [1.1% BW] to 989 mL [1.3% BW%]) and another patient (10-205) experienced clinical deterioration in liver volume (liver volume increased 22% from 2131 mL (2.3% BW) to 2604 mL (2.5% BW)); both patients had negative ADA levels. Neither patient experienced clinical deterioration in hematological parameters or disease biomarkers. No change was made in the

treatment regimen of either patient. The applicant stated that it was not clear that the observed changes in these patients represented clinically relevant deterioration in their Gaucher disease, noting that all other clinical parameters, including disease biomarkers remained stable in these patients.

Reviewer Comment: This reviewer agrees with that the observed changes are not clinically significant. Both patients had mild visceral disease at baseline and experienced increases in organ volume that resulted in minimal changes in organ volume as a percent of their body weight. Note also that patient 10-205 had a normal liver volume as percentage of BW at Month 9. However, this reviewer disagrees with the applicant's rationale for asserting that the observed changes were not clinically relevant. The trial protocol stated that a decision to increase dosing for patients experiencing clinical deterioration was left to the discretion of the investigator. Therefore, patients that experienced clinically relevant deterioration would not necessarily be treated with a higher dose of taliglucerase alfa. However, the applicant's assessment that the two patients may not have experienced clinically relative deterioration clearly contradicts the pre-specified criteria for identifying clinically relevant deterioration.

Table 7: PB-06-002 Organ Volume & Clinically Relevant Deterioration at Month 9

Visit	Spleen n=20	Liver n=23
	(normal: 0.2% BW)	(normal: 2.5% BW)
Baseline Volume (ml)		
Mean ± SD	822 ± 604	1857 ± 440
Median	814	1817
Min, Max	14, 2151	1167, 2659
Baseline Volume (% BW)		
Mean ± SD	1.1% ± 1.0	2.4 ± 0.6
Median	0.9	2.3
Min, Max	<0.1, 4.1	1.8, 4.3
	5.5 MN	**1.0 MN**
Month 9 Volume (ml)		
Mean ± SD	749 ± 560	1786 ± 424
Median	697	1801
Min, Max	15, 2141	1276, 2604
Month 9 % Change in Volume	-8 ± 13	-4 ± 8
	-7	-4
	-33, 22	-16, 22
Month 9 Volume (% BW)		
Mean ± SD	1.0 ± 1.0	2.3 ± 0.5
Median	0.7	2.3
Min, Max	<0.1, 4.6	1.8, 3.3
	5.1 MN	**0.9 MN**
Month 9 Change in Volume (% BW)		
Mean ± SD	-0.1 ± 0.2	-0.1 ± 0.1
Median	-0.1	-0.1
Min, Max	-0.4, 0.5	-0.3, 0.3
Clinically Relevant Deterioration at Month 9		
Yes	1/20 5%)	1/23 (4%)
No	19/20 (95%)	22/23 (96%)

3. Hematology Parameters

Data on hemoglobin and platelet count were available for 25/25 patients completing 9 months of treatment (see Table 8). Overall mean hemoglobin levels remained stable after 9 months of treatment. The mean change in hemoglobin at 9 months was -0.3 g/dL ± 0.7. The percent change in mean hemoglobin ranged from -10% to +7% at Month 9. Three patients had baseline abnormal hemoglobin values; none of these patients achieved normal values but maintained stable hemoglobin levels.

The overall mean change in platelet count at 9 months was -3K/mm^3 ± 30K/ mm^3. Eight of 25 patients (32%) had an abnormal platelet count (< 120K/mm^3) at baseline. Three of 28 patients (11) experienced a clinically relevant deterioration in platelet count as defined by the protocol. Patient 10-201 experienced a 36% decrease from 61 K/mm^3 to 39K/mm^3 at Month 9; patient 20-224) experienced a 22% decrease from 104K/mm^3 to 81 K/mm^3 at Month 9. Both patients had a baseline platelet count of < 120K/mm^3. A third patient (18-219) experienced a decline in platelet count from 190K/mm^3 at baseline to 92K/mm^3 at Week 22. The patient's dose of taliglucerase alfa was doubled (dose increased from 9.5 U/kg to 10 U/kg) at Week 24. At Month 9, the patient's platelet count had increased to 190K/mm^3. Patient 10-201 and patient 18-219 had negative ADA titers; patient 20-224 had transiently positive antibody ADA titers (positive at Week 8 [specific titer was not done]).

Table 8: PB-06-002 Hematologic Parameters & Clinically Relevant Deterioration at Month 9

Visit	Hemoglobin n=25			Platelet Count n=25		
	g/dL	Change	% Change	/mm^3	Change	% Change
Baseline Mean ± SD Median Min, Max	 13.5 ± 1.6 13.6 11, 16			 160K ± 88K 177K 38K, 310K		
Month 9 Mean ± SD Median Min, Max	 13.3 ± 1.6 13.6 10, 16	 -0.3 ± 0.7 -0.3 -1.3, 1	 -1.8 ± 4.9 -2.6 -10.2, 7.4	 158K ± 87K 163K 38K, 310 K	 -3K ± 30K -2K -89K, 56K	 -1.5 ± 22 -2.2 -36, 69
Clinically Relevant Deterioration at Month 9 n Yes No	 25 0 25 (100%)			 25 2 (12%) 23 (88%)		

4. Biomarkers

Chitotriosidase and CCL18 levels were measured as additional endpoints; the applicant did not specify whether they were secondary or tertiary endpoints. Chitotriosidase and CCL18 levels were available for 25/28 patients and 15/28 patients at baseline and at Month 9, respectively. A 21% mean decrease in chitotriosidase levels was observed in the overall group. Five of 25 patients experienced no change or increases in chitotriosidase levels, including one patient who had a baseline normal chitotriosidase level that remained within normal range at Month 9 (normal range: 0-150 nmol/hr/mL). A 9% mean decrease in CCL18 levels was observed in the overall group. Six of 15 patients experienced no change or increases in CCL18 levels.

Reviewer Comments: Chitotriosidase and CCL18 are biomarkers present in Gaucher cell. Clinically, these biomarkers are used both for diagnostic purposes and in assessment of treatment response. Although extremely high plasma chitotriosidase levels are pathognomonic for Gaucher disease, moderately elevated levels can occur in patients with other conditions, including other lysosomal storage diseases. In addition, some Gaucher patients have normal or minimally elevated plasma chitotriosidase levels, due to a commonly occurring genetic mutation that causes inactivation of chitotriosidase activity. Approximately one-third of the general population, including Gaucher patients, possess a mutation of the chitotriosidase gene.[16,17] CCL18, a chemokine present in Gaucher cells, has been used as an alternative diagnostic biomarker for Gaucher disease in patients who are deficient in chitotriosidase activity. Both biomarkers appear to correlate strongly to visceral and hematologic Gaucher disease; however, they do not appear to correlate with bone events.[18]

5. Immunogenicity

Anti-drug antibody (IgG)
An important consideration with all enzyme replacement therapies for lysosomal storage diseases is the potential development of immune responses to the enzyme therapy. These immune responses can be associated with the development of allergic and immune-mediated reactions as well as potential attenuation of long-term effectiveness of treatment.

A deficiency noted in the Complete Response Letter included the lack of an acceptable cut-point for the confirmatory anti-drug antibody assay (cut-point was too high). Therefore, the applicant provided a new cut-point for assessment of ADA responses as part of the Complete Response. Based on a reanalysis of antibody testing results by the Applicant using a lower cut-point agreed upon with the Agency, 5/28 (18%) patients developed anti-GCD antibodies during the study (See Table 51 in Section 7.4.6).

The applicant also evaluated ADA responses from baseline to Month 9, classifying patients as Negative, Persistent Positive (i.e., the titer increased and remained high), Tolerized Positive (i.e., titers increased to a peak level and then decreased), and Transient Positive (i.e., the presence of one positive sample or low titer). The applicant classified patients who developed positive titers prior to treatment that did not increase over the baseline value during treatment were classified as negative. I do not agree with the applicant's definition of Negative status since it is not possible to distinguish

[16] Malaguarnera L, *Chitotriosidase: the yin and yang*, Cell Mol Life Sc 2006; 63: 3018-3029.
[17] Boot RG, van Breemen MJ et al, Gaucher disease: a model disorder for biomarker discovery, *Expert Rev Proteonomics* 2009: 6(4): 411-419.
[18] Deegan PB, Pavlova E et al, Osseous manifestations of adult Gaucher disease in the era of enzyme replacement therapy, *Medicine* 2011; 90(1):52-60.

between patients who had persistent antibodies from baseline and patients who newly developed low antibody titers during treatment.

Table 9 and Table 10 summarize efficacy results by ADA status. Patients in both groups experienced an improvement in organ volumes and maintained stability of hematologic parameters. A greater mean decrease in spleen volume was observed in ADA-positive patients compared ADA-negative patients (decrease in %BW of -20% and -8%, respectively). Decreases in liver volume were similar in the two groups, with observed mean decrease in %BW of 3% in ADA-negative patients and 7% in ADA-positive patients. Both groups had baseline hematologic values within the normal range that remained stable over 9 months of treatment.

Table 9: PB-06-002 Organ Volume Efficacy Results by Antibody Status

Clinical Parameter		
Spleen (normal = 0.2% BW)	**Antibody Negative n=15**	**Antibody Positive n=5**
Mean Spleen Volume (mL) ± SD		
Baseline	826 ± 659	810 ± 461
Month 9	782 ± 622	652 ± 345
Mean Spleen Volume (%BW) ± SD		
Baseline	1.2 ± 1.1 (6.0 MN)	0.8 ± 0.4 (4.1 MN)
Month 9	1.2 ± 1.1 (5.7 MN)	0.7 ± 0.3 (3.3 MN)
Change in Volume from Baseline to Month 9 (ml)		
Mean ± SD	-45 ± 140	-159 ± 149
Median	-22	-91
Min, Max	-316, 176	-334, -30
Change in Volume from Baseline to Month 9 (%BW)		
Mean ± SD	0	-0.2 ± 0.1
Median	0	-0.1
Min, Max	-0.4, 0.5	-0.3, 0
% Change in Volume (ml) from Baseline to Month 9		
Mean Percent ± SD	-4 ± 13	-17 ± 11
Median	-5	-15
Min, Max	-28, 22	-33, -5
% Change in %BW from Baseline to Month 9		
Mean ± SD	-8 ± 10	-20 ± 14
Median	-5	-21
Min, Max	-25, 11	-33, 0

Table 9: PB-06-002 Organ Volume Efficacy Results by Antibody Status (cont'd)

Clinical Parameter		
Liver (normal = 2.5% BW)	**Antibody Negative** **n=15**	**Antibody Positive** **n=5**
Mean Liver Volume (mL) ± SD Baseline Month 9	 1782 ± 388 ml 1717 ± 397	 2130 ± 553 2033 + 467
Mean Liver Volume (%BW) ± SD n Baseline Month 9	 18 2.5 ± 0.6 (1.0 MN) 2.4 ± 0.5 (0.9 MN)	 5 2.2 ± 0.2 (0.9 MN) 2.1 ± 0.4 (0.8 MN)
Change in Volume from Baseline to Month 9 (ml) Mean ± SD Median Min, Max	 -64 ± 162 -78 -262, 473	 -97 ± 199 -37 -437, 85
Change in Volume from Baseline to Month 9 (%BW) Mean ± SD Median Min, Max	 -0.1 ± 0.2 -0.1 -0.3, 0.3	 -0.2 ± 0.1 -0.1 -0.3, -0.1
% Change in Volume (ml) from Baseline to Month 9 Mean Percent ± SD Median Min, Max	 -3 ± 8 -4 -12, 22	 -4 ± 8 -1 -16, 5
% Change in %BW from Baseline to Month 9 Mean Percent ± SD Median Min, Max	 -3 ± 6 -4 -12, 13	 -7 ± 4 -5 -13, -4

Table 10: PB-06-002 Hematologic Parameters Efficacy Results by Antibody Status

Clinical Parameter		
Hemoglobin	**Antibody Negative n=21**	**Antibody Positive n=5**
Mean Hemoglobin (g/dL) ± SD n Baseline Month 9	 21 13.6 ± 1.6 13.3 ± 1.5	 5 13.3 ± 1.6 13.0 ± 2.0
Change from Baseline to Month 9 ((g/dL)* n Mean ± SD Median Min, Max	 21 0.2 ± 0.6 0.2 -1.2, 0.7	 n=5 -0.3 ± 0.8 0 -1.3, 1.0
% Change from Baseline to Month 9 n Mean Percent ± SD Median Min, Max	 21 -1.6 ± 2 2 -8, 6	 5 -2 ± 6 -3 -10, 7
Platelet Count	**Antibody Negative n=21**	**Antibody Positive n=5**
Mean Platelet Count (_/ (mm^3) ± SD n Baseline Month 9	 21 168K ± 92K 167K ± 102K	 5 158K ± 57K 157K ± 74K
Change from Baseline to Month 9 (_/ (mm^3) n Mean ± SD Median Min, Max	 21 -1 K ± 32K -2K -89K, 56K	 5 -0.5K ± 31K -2K -23K, 54K
% Change from Baseline to Month 9 n Mean Percent ± SD Median Min, Max	 21 -0.5 ± 23 -1 -36, 69	 5 -3 ± 19 -9 -22, 29

Reviewer comments: Immunogenicity did not appear to adversely impact efficacy in this trial. In fact, there was a greater observed decrease in spleen volume in ADA-positive patients compared to ADA-negative patients. However, it appears that the immunogenicity of taliglucerase alfa may be higher than the immunogenicity of the approved ERT products for Gaucher disease. Note that the immunogenicity rate for taliglucerase alfa in this trial was 18%, compared to rates of 15% and 2% for Cerezyme and VPRIV. However, no definitive comparison of taliglucerase with other ERT products is possible at this time for several reasons. First, the trial did not include

treatment arms in which patients were treated win an approved ERT product. An additional trial should be conducted to evaluate the efficacy of taliglucerase alfa compared to approved ERT products for Gaucher disease as a PMR; the trial should also compare the impact of immunogenicity on efficacy for the products. Information from a comparative trial should be addressed as a post-marketing commitment. In addition, it is unclear if the observed immunogenicity observed in this trial was due to patients developing anti-plant sugar antibodies or anti-drug antibodies. Development of this assay should be addressed as a post-marketing requirement.

Neutralizing antibodies
One patient (20-220) developed neutralizing antibodies based on the enzymatic activity inhibition assay, but negative based on the cell-based assay. All 5 patients completed the trial.

Reviewer Comment: As noted earlier, the sensitivities of the neutralizing antibody assays (enzyme activity and cellular uptake) used in the trial were not adequate. Therefore, the impact of both types of neutralizing antibodies on efficacy remains unknown. Development of this assay will be required as a post-marketing requirement.

5.3. PB-06-003- Phase 3 Extension Trial

PB-06-003 is a multicenter, extension trial to assess the safety and efficacy of taliglucerase alfa in Gaucher disease patients who completed 9 months of treatment in studies PB-06-001 and PB-06-002. Patients are being continued on their previous dose of taliglucerase alfa (maximum dose of 60 U/kg).

Efficacy variables are spleen and liver volume, platelet count, hemoglobin, and biomarkers; no primary efficacy variable was selected for analysis of the study. Safety variables are adverse events, clinical laboratory, anti-prGCD antibodies, ECG, echocardiogram, PFTs, and hypersensitivity reactions.

The original duration of the trial was at least 15 months, however, the protocol was amended to extend the trial until marketing approval is obtained or for a maximum of 30 months. The trial is ongoing and is being conducted in 15 sites across Australia, Canada, Chile, Israel (2 sites), Italy, Mexico (2 sites), Serbia, South Africa, Spain, UK (2 sites), and the US (2 sites). The first patient was enrolled on June 9, 2010.

Major protocol amendments include:

- Amended eligibility criteria to including patients completing PB-06-002 patients (Version 3 dated January 19, 2010)
- Extended study treatment period from 15 months to 30 months or until receiving market approval (Version 3 dated January 19, 2010)

- Removed pregnancy or nursing as exclusion/discontinuation criteria and removed requirement for pregnancy testing (Version 3 dated January 19, 2010)

The applicant submitted an abbreviated trial report with interim efficacy and safety data as the trial is ongoing. The abbreviated study report includes efficacy and safety data for 44 patients up to a database freeze date of May 1, 2011. The safety data for this study will be reviewed in Section 7.

Reviewer Comment: As discussed earlier, the safety of any of the ERT products for Gaucher diseases in pregnant and lactating women remains unknown. No adverse pregnancy outcomes were reported for this trial (see Section 7.6.2). The protocol amendments to include PB-06-002 patients and to extend the trial duration enhanced the ability to collect long-term safety and efficacy data for this product.

A. Treatment

During PB-06-003, patients continue to receive the same dose they were receiving in the previous studies every 2 weeks and have the option of receiving infusions at the study center, infusion center or at home. PB-06-001 patients continue to receive their allocated dose in a blinded fashion up to two years of treatment, at which time dosing may be unblinded at the Investigator's discretion. The protocol states that patients in the 30 U/kg dose group can have their dose increased up to a maximum of 60 U/kg "if clinically indicated" (clinical indications not specified).[19] Dosing is based on the patient's weight at the end of PB-06-001; doses are not adjusted for weight changes during the course of the trial. As discussed later in this section, the blind was removed for three patients due to clinical deterioration, and subsequently their doses were increased from 30 U/kg to 60U/kg.

PB-06-002 patients continue to receive open-label dosing. As in PB-06-002, patients can receive a dose increase up to a maximum of 60 U/kg if they experience clinical deterioration in organ volume or hematologic parameters.

PB-06-003 consists of two parts: Part A and Part B. Part A is a 15-month treatment period. Trial assessments are performed during six visits (Day 1 and Months 3, 6, 9, 12, and 15). Adverse events, concomitant medications, and vital signs are recorded at each infusion. Spleen and liver volumes are measured at Month 3 and Month 15. Evaluations at Months 3, 6, 9, 12, and 15 include physical exam (including body weight), clinical laboratory assessments, biomarkers, ECG, and antibody testing. Chest X-Ray, X-Ray skeletal evaluation, echocardiography, and pulmonary function tests are performed at Month 15. TSH, transferrin, B12 and folic acid tests are performed at Month 15.

[19] Three patients from PB-06-001 in the 30 U/kg treatment group had dose adjustments during the extension trial (see p. 57-58 of this review for further details).

In addition, DEXA and QCSI assessments are performed for a sub-group of PB-06-001 patients at Months 3 and 15.
Part B consists of up to 5 visits (Months 18, 21, 24, 27, and 30). Adverse events, concomitant medications, and vital signs are recorded at each infusion. Evaluations at Months 18, 21, 24, 27, and 30 include physical exam (including body weight), clinical laboratory assessments, biomarkers, ECG, and antibody testing. TSH, transferrin, B12 and folic acid tests are performed at Month 27. Echocardiography and pulmonary function tests are performed at Month 30.

In addition, DEXA and Quantitative Chemical Shift Imaging (QCSI) assessments are performed for a sub-group of PB-06-001 patients at Month 27.

The protocol notes that if marketing approval were received prior to the end of Part A, patients were not to proceed to Part B. If marketing approval were received prior to the end of Part b, patients had to complete the end of study assessments (i.e., Months 27 and 30 assessments) in the earliest upcoming study visit. Table 11 summarizes the schedule of assessments for PB-06-003.

Table 11: PB-06-003 Schedule of Trial Assessments

Visit	Day 1	Month 3	Month 6, 9, 12	Month 15	Month 18, 21, 24	Month 27	Month 30
Adverse Events	X	X	X	X	X	X	X
Current/Concomitant Medications	X	X	X	X	X	X	X
Weight & Physical Exam	X	X	X	X	X	X	X
ECG	X	X	X	X	X	X	X
Chest x-ray	X			X			
X-ray Skeletal Evaluation	X			X			
Echocardiogram	X			X		X	
PFTs	X			X		X	
Organ Volumes (MRI)	X	X		X		X	
DEXA & QCSI	X	X		X	X	X	
Antibody testing	X	X	X	X	X	X	X
Laboratory*	X	X	X	X	X	X	X
TSH, transferring, B12, folic acid				X		X	
Biomarkers	X	X	X	X	X	X	X

* Laboratory= chemistry, hematology, urinalysis

Concomitant Medications
Patients were allowed to take medications for allergic reactions, anemia, bone disease, and analgesia. All concomitant medications taken during the trial were recorded.

Prohibited Medications
Patients were prohibited from taking miglustat (Zavesca), alglucerase (Ceredase), or imiglucerase (Cerezyme). Patients also were prohibited from taking another experimental drug for any condition.

Safety Considerations/Monitoring
The safety monitoring for Trial PB-06-003 included the same safety measurements as performed in PB-06-001 and PB-06-002.

B. Statistical Analysis Plan
The applicant performed an interim analysis of efficacy and safety data collected on or before May 1, 2011, providing descriptive statistics for the study efficacy and safety variables. The following exploratory analyses were performed by the applicant to evaluate for a difference in efficacy between treatment groups:

- Changes in organ volume and percent changes in organ volume (spleen and liver) from Baseline to Month 12 and Month 24
- Changes in hemoglobin and platelet count from Baseline to Month 12 and Month 24

Changes in the Conduct of the Study
Several patients had delayed entry into the study due to delays in obtaining Investigational Review Board (RB) approval at some centers (7 patients from PB-06-001 and 10 patients from PB-06-002). PB-06-001 patients experienced a 1- to 5-month interruption in treatment following their last PB-06-001 study infusion. Nine of 10 PB-06-002 patients continued infusions without interruption under an amendment to the PB-06-002 protocol that allowed patients to continue treatment until approval of the PB-06-003 protocol; the remaining patient experienced a one month interruption in treatment following her last PB-06-002 study infusion.

Reviewer comment: See discussion below regarding the effect of treatment interruptions on overall efficacy in this study.

C. Patient Disposition

Patient Disposition
Forty-four patients were enrolled, including 26/29 patients who completed PB-06-001 and 18/25 patients who completed PB-06-002. No information was available on patient disposition after completion of PB-06-001 for the three PB-06-001 patients who did not elect to enter PB-06-003. Five patients that completed PB-06-002 elected to

receive taliglucerase alfa treatment through a local compassionate use program. One patient was discontinued from continuation into PB-06-003 due to personal issues, and one patient was discontinued after providing informed consent for PB-06-003 due to noncompliance with the protocol.

As of May 1, 2011, 21 patients from PB-06-001 and 16 patients from PB-06-002 are continuing treatment. No pediatric patients were enrolled at the time of the Complete Response submission. Table 12 summarizes patient disposition for PB-06-003:

All 26 patients from PB-06-001 have completed at least 15 months (total 24 months) of treatment in PB-06-003. One patient was discontinued after a possible allergic reaction at Month 27 (total 36 months) of treatment; the second patient was discontinued due to logistical issues regarding her infusion schedule after Month 15 (total 24 months) of treatment. Two patients completed the study after 30 months (total 39 months) of treatment and one patient completed the study after 15 months (total 24 months) of treatment. PB-06-001 patients who completed the study protocol are still receiving taliglucerase alfa under various compassionate programs

Of the 18 patients enrolled from PB-06-002, two voluntarily withdrew from the study. One patient was not satisfied with the results of treatment after 6 months (total 15 months) of treatment; the second patient wanted to pursue another research medication after 27 months (total 36 months) of treatment.

Table 12: PB-06-003 Patient Disposition

	PB-06-001 30 U/kg (n=12)	PB-06-001 60 U/kg (n=14)	PB-06-002 (N=18)	Total (n=44)
Ongoing Treatment	11 (92%)	10 (71%)	16 (89%)	37 (84%)
Discontinued	0	2 (14%)	2 (11%)	4 (9%)
Completed Study	1 (8%)	2 (14%)	0	3 (7%)

Patient Compliance
Thirteen of 44 patients missed one or more infusion doses. Nine patients missed one infusion dose; four patients missed two infusion doses.

Reviewer comment: These reported episodes of non-compliance with dosing do not appear to have had any impact on trial results.

Protocol Deviations and Compliance
There were a total of 11 patients with protocol deviations. Deviations consisted of missed study visits or study assessments, and study visits or assessments that occurred outside of the study schedule window.

Reviewer comment: These reported episodes of deviation or non-compliance with the protocol do not appear to have had any impact on trial results.

Patient Demographics

Table 13 summarizes baseline demographics for patients enrolled in PB-06-003 as of May 2, 2011. Baseline values obtained at the start of PB-06-001 or PB-06-002 served as the baseline values for PB-06-003. The age range was 18-74 years old. Patients enrolling from PB-06-002 (mean age 45 years) were older than patients enrolling from PB-06-001 (mean age 39 years and 36 years for patients in the I30 U/kg and 60 U/kg dose groups, respectively). The age difference between PB-06-01 patients and PB-06-002 patients likely was due to a shorter duration from the time of diagnosis to initiation of treatment for PB-06-001 (i.e., treatment-naïve) patients.

Table 13: PB-06-003 Patient Baseline Demographics (Interim Population)

Characteristic	PB-06-001		PB-06-002	Total
	30 U/kg (N=12)	60 U/kg (N=14)	(N=18)	(N=44)
Age (yrs) Mean ± SD Min-Max	 38.9 ± 12.1 24-74	 35.6 ± 12.0 19-58	 45.4 ± 13.5 18-66	 40.5 + 13.1 18-74
Sex Male Female	 5 (42%) 7 (58%)	 6 (43%) 8 (57%)	 9 (50%) 9 (50%)	 20 (46%) 24 (54%)
Race/Ethnicity Caucasian Other	 12 (100%) 0	 13 (93%) 1 (7%)	 18 (100%) 0	 43 (98%) 1 (2%)
Weight (kg) Mean ± SD Min-Max	 73.4 + 13.0 53-99	 72.4 ± 9.0 60-88	 75.7 ± 14.3 53-109	 74.0 ± 2.3 53-109

PB-06-002 patients had milder disease compared to PB-06-001 patients. With the exception of spleen volume, mean baseline values were normal or just outside the upper limits of normal for PB-06-002 patients; with the exception of hemoglobin, baseline values for PB-06-001 patients were abnormal (see Table 14). The difference in disease severity between the two groups of patients likely is due to the patient population for PB-06-002 being limited to patients with stable disease after chronic ERT treatment (i.e., who would be expected to have achieved normal or near normal values for clinical parameters [see Section 9.4]).

Table 14: PB-06-003 Patient Baseline Disease Severity (Interim Population)

Clinical Parameter	PB-06-001 Treatment Group		PB-06-002 Treatment Group	Total
	30 U/kg (N=12)	60 U/kg (N=14)	(N=18)	(N=44)
Screening Spleen Volume (mL) n Mean ± SD Min-Max % BW (normal: 0.2 %)	 12 2324 ± 1209 1026-4901 **(3.3 % BW)** **19.4 MN**	 14 2120 ± 1427 914-5418 **(3.4% BW)** **17.7 MN**	 15 778 ± 666 14-2151 **(1.1 % BW)** **6.5 MN**	 41 1689 ± 1310 14-5418 **(2.5 % BW)** **14.1 MN**
Screening Liver Volume (mL) n Mean ± SD Min-Max % BW (normal: 2.5%)	 12 3000 ± 779 2282-5096 **(4.3 % BW)** **2.0 MN**	 14 2471 ± 485 1758-3297 **(3.7 % BW)** **1.6 MN**	 15 1776 ± 434 1167-2643 **(2.5% BW)** **1.1 MN**	 41 2357 ± 751 1167-5096 **(3.4% BW)** **1.6 MN**
Screening Hemoglobin (g/dL) n Mean ± SD Min-Max (normal: > 11.5-12.0 g/dL)	 12 **12.5 ± 1.8** 7.9-14.6	 14 **11.4 ± 2.7** 5.5-16.0	 18 **13.6 ± 1.6** 10.7-16.1	 44 **13.7 ± 1.7** 8.6-16.9
Platelet Count (_/mm3) n Mean ± SD Min-Max (normal: > 120K)	 12 **65K ±30K** 27K-112K	 14 **61K ± 23K** 28K-103K	 18 **164K ± 96K** 39K-328K	 44 **104K ± 81K** 27K-328K

MN= multiples of normal; %BW= percent of body weight in kg

Review of Efficacy

Efficacy Summary

Taliglucerase alfa appears to have demonstrated persistent efficacy in treatment-naïve patients treated at least 2 years (24 months) and in patients switched from imiglucerase treated at least 1 year (12 months).

Regarding dose response, taliglucerase alfa appeared to be more efficacious at the higher dose (60 U/kg), based on the observed finding of a greater decrease in spleen volume in patients in the 60 U/kg treatment group compared to patients in the 30 U/kg treatment group and the normalization of platelet count in the 60 U/kg treatment group

but not the 30 U/kg treatment group. However, the trial was not powered to detect a treatment difference between groups.

The impact of immunogenicity on efficacy was not clear from the data provided for review. A smaller decrease in spleen volume was observed in antibody-positive patients compared to antibody-negative patients, while other efficacy results for other clinical parameters were similar. As noted earlier, the sensitivities of the neutralizing antibody assays used in the trial were not adequate. These data preclude the evaluation of the effect of neutralizing antibodies on long-term efficacy and safety and will be important to evaluate in the future. Therefore, additional data should be collected on the long-term safety and efficacy of taliglucerase alfa as a post-marketing requirement.

Due to the small number of patients, the shorter time period of treatment with taliglucerase, and the open-label, uncontrolled design of this long-term extension study, the data from this trial cannot be used to draw clear conclusions regarding the long-term efficacy of taliglucerase in Gaucher patients. As noted by the Statistical Reviewer, approval of VPRIV for use in patients switched from imiglucerase was based on evidence from a head-to-head trial comparing the two products. Additional information should be collected on this patient population, including information from a trial conducted using an active comparator group, as a post-marketing commitment.

In addition, the applicant has not provided any data on the efficacy of this product in pediatric Gaucher patients. Additional data should be collected in this population. Specifically, completion of the PB-06-005 pediatric study should be included as a post-marketing requirement.

The efficacy data tables in this section present data by *total* number of weeks on treatment since enrollment in PB-06-001 or PB-06-002 (i.e., initiation of treatment). Baseline indicates values measured at baseline for PB-06-001 or PB-06-002

1. Clinical Deterioration

Three patients from the 30 U/kg dose group had dose increases during the trial. Two patients received a dose increase due to observed clinical deterioration (patient 10-001) or lack of clinical improvement (patient 42-025). A third patient (11-014) received a dose increase following an adverse event (bone crisis) that was assessed as possibly related to treatment. Patient narratives for the two patients with clinical deterioration or lack of clinical improvement are provided below; the patient narrative for the patient with the bone event is discussed in Section 7.3.4.

Patient 10-001

The patient is a 28 year-old male with a medical history of alopecia, hemorrhoids, bleeding tendency and Vitamin B12 corrected by medication. After 9 months of treatment in PB-06-001, the patient achieved a 29% reduction in spleen volume and 8%

reduction in liver volume (baseline volumes were 3226 mL [4.2% BW] and 2914 mL [3.8% BW], respectively). His hemoglobin increased from 14.3 g/dL to 16.5 g/dl. Increase in platelet count was minimal (28K to 38K). The investigator unblinded the patient's dose after 30 months of treatment, due to an observed decreased in platelet count to 28K. The dose was increased to 60 U/kg and the patient completed the study (total of 39 months of treatment). The platelet count at the end of the study remained 28K. The patient was ADA-positive.

Patient 42-025
The patient is a 36 year-old female with a medical history of cholelithiasis, hypothyroidism, dermatitis, vitiligo, intermittent bilateral hip pain, and dysmenorrhea. The patient completed PB-06-001 and entered PB-06-003 after a one-month interruption in treatment, due to delays in regulatory approval of the PB-06-003 protocol. After 24 months of treatment, the patient is reported to have achieved a 32% and 18% decrease in spleen volume and liver volume, respectively (baseline volumes were 3001 mL [5.6 %BW] and 2282 mL [4.3% BW]). She also experienced a clinically significant increase in hemoglobin (increased from 11.6 g/dL at baseline to 14.4 g/dL) but a minimal increase in platelet count (increased from 27K at baseline to 33K). The patient's dose was increased to 60 U/kg at Month 26 and the patient is continuing treatment at this dose. The latest available platelet count value was 25K at Month 27. The patient is ADA-negative.

Reviewer Comment: The significance of the findings of a minimal, transient increase in platelet count in these two patients is unclear. It is notable that these two patients had the lowest baseline platelet count values of all patients in PB-06-003. One question is whether these findings were due to underdosing. Both patients experienced decreased in organ volumes that were clinically significant and achieved or maintained normal hemoglobin values with doses of 30 U/kg. Thus, the 30U/kg dose appeared to be sufficient for some degree of treatment response in platelet count. Patient 10-001 was treated at the higher dose for 9 months, which likely was a sufficient period of time to observe a treatment response resulting from a dose change. Note that the therapeutic goals for ERT for Gaucher disease include achievement of a doubled platelet count in patients with severe thrombocytopenia after one year of treatment (see Section 9.4). Although normalization of platelet count is not expected, substantial improvement of platelet count values are considered to be achievable after 12-24 months of treatment. Therefore, although the two patients had more severe disease, they were treated for a sufficient period of time to observe a treatment response. There was no clear indication from the patient medical histories that either patient had a co-morbidity that may have contributed to the observed degree of thrombocytopenia. Immunogenicity did not appear to be a factor, since one patient was ADA-positive and one patient was ADA-negative.

2. Spleen and Liver Volume

Tables 16-21 summarize changes in organ volume (spleen and liver) and percent change in organ volume for the interim population, including organ volume measurements performed at the end of PB-06-001 and PB-06-002 (i.e., after 9 months of treatment. In PB-06-003, organ volume measurements were performed after 12, 24 and 36 months of treatment. Of 44 patients enrolled in PB-06-003, data on organ volume were available for 35 patients (26 PB-06-001 patients and 9 PB-06-002 patients) after 12 months of treatment and for 27 patients (26 PB-06-001 patients and 1 PB-06-002 patient) after 24 months of treatment. Two PB-06-001 patients (one from each treatment group) had organ volume data after 36 months of treatment. Two patients who had ultrasound measurements of organ volume (patients refused MRI measurements) were not included in the analyses of organ volumes. In addition, one splenectomized patient was not included in the analysis of spleen volume.

In the 60 U/kg treatment group, mean spleen volume decreased 59% from baseline (2120 mL [3.4% BW]) to Month 24 (947 mL [1.3%BW]. In the 30 U/kg treatment group, mean spleen volume at Month 24 also decreased compared to baseline (43% decrease). Mean spleen volume was 2324 mL (3.3% BW) at baseline and 1420 mL (1.9% BW) at month 24. A slight increase in mean spleen volume was observed at Month 12 (1707 mL) compared to Month 9 (1691 mL). Note, however, spleen volume by %BW did not change between Month 9 and Month 12 (2.3%BW at both time points).

In the PB-06-002 treatment group, mean spleen volume decreased at Month 9 (707 mL [1.0 MN] compared to Baseline (778 mL [1.1 MN]) but increased compared to baseline at Month 12 (807 mL [1.3 MN]). Mean percent change at Month 12 was 9%. Only 1 patient from the PB-06-002 treatment group had a spleen volume evaluation at Month 24.

Mean liver volume decreased at all measurement time points in the 30 U/kg and 60 U/kg treatment groups compared to baseline. Mean liver volume was 3000 [4.3% BW], 2471 [3.8% BW]] at Baseline and 2516 [3.4% BW], 2119 [3.0% BW], and 1719 mL [2.6 % BW] at Month 12, respectively. These represented decreases of 18% each for the two treatment groups. At month 24, mean liver volume decreased 24 % in the 30 U/kg and 22% in the 60 U/kg treatment group (mean liver volumes were 2363 mL [3.2% BW] and 1998 mL [2.8%BW] for the 30 U/kg and 60 U/kg treatment groups, respectively.

Mean liver volume increased slightly at Month 12 (1719 mL [2.5 % BW]) compared to baseline (1776 mL [2.4% BW]) in the PB-06-002 treatment group but remained within the normal range. Only 1 patient from the PB-06-002 treatment group had a liver volume evaluation at Month 24.

Reviewer Comment: The significance of the observed changes in mean spleen volume from Month 9 to Month 12 in the 30 U/kg) and PB-06-002 treatment groups is unclear. I

reviewed the efficacy data for the 8 patients who had experienced interruptions in treatment due to delayed entry into PB-06-003 to evaluate whether there was an impact on overall efficacy results (see Table 15).

All patients with treatment interruptions greater than one month (i.e. all patients who missed more than one treatment infusion) were from PB-06-001. Six of 8 patients had treatment interruptions of 3 to 5 months (3 patients each in the 60 U/kg and 30 U/kg treatment groups. Four of the six patients with treatment interruptions of 3-5 months experienced an increase in spleen volume from Month 9 to Month 12; these 4 patients also experienced decreased deterioration (i.e., increased liver volume or decreased hemoglobin or platelet count) in at least one other clinical parameter. One patient in the 30 U/kg) had a 1-month treatment interruption (i.e., missed one treatment infusion).

As noted earlier, one patient in the PB-06-002 treatment group had a 1-month treatment interruption (i.e., missed one treatment infusion); the remaining PB-06-002 patients had no treatment interruptions. Thus, although treatment interruption may have contributed to the trend in spleen volume observed at the Month 12 time point for patients in the 30U/kg treatment group, it does not appear to have impacted efficacy results in the PB-06-002 treatment group. The data for the 30 U/kg treatment group are not consistent with published data that describe no changes in clinical parameters with decreases or interruptions in doses of up to 12 months.

Table 15: Month 12 Clinical Results for PB-06-003 Patients Experiencing Treatment Interruptions Due to Delayed Study Entry

Patient ID #	Treatment Group	Length of treatment interruption (months)	Clinical Parameters			
			Spleen Volume	Liver Volume	Hemoglobin	Platelet count
			Increase from Month 9 to Month 12?		Decrease from Month 9 to Month 12?	
11-007	60 U/kg	3	Yes	Yes	No	Yes
40-017	30 U/kg	4	No	No	No	Yes
40-018	60 U/kg	4	No	No	No	No
41-020	60 U/kg	4.5	Yes	No	No	Yes
41-021	30 U/kg	5	Yes	Yes	No	No
41-022	30 U/kg	5	Yes	Yes	No	no
42-025	30 U/kg	1	No	No	No	No
10-021	PB-06-002	1	Yes	Yes	Yes	Yes

Table 16: Spleen Volume by Pivotal Study Week (Interim Population)

Spleen Volume (mL)	PB-06-001 30 units/kg (N = 12)	PB-06-001 60 units/kg (N = 14)	PB-06-002 Total (N=18)	Grand Total (N = 44)
Baseline[1]				
n	12	14	15	41
Mean (SD)	2324.0 (1208.97)	2120.1 (1426.5)	778.0 (666.3)	1688.8 (1309.92)
Median	1656.9	1699.5	548.7	1481.5
Min, Max	1026, 4901	914, 5418	14, 2151	14, 5418
Study Week 38/9-Month[2]				
n	12	14	15	41
Mean (SD)	1690.7 (956.43)	1352.0 (1096.81)	706.7 (608.85)	1215.1 (971.40)
Median	1226.1	1044.6	518.6	989.5
Min, Max	754, 3894	483, 4220	15, 2141	15, 4220
Study Week 52/12-Month				
n	12	14	8	34
Mean (SD)	1707.7 (1069.53)	1267.9 (1114.05)	807.3 (736.1)	1314.8 (1051.02)
Median	1135.2	937.1	685.6	947.3
Min, Max	693, 4332	442, 4339	14, 2178	14, 4339
Study Week 104/24-Month				
n	12	14	1	27
Mean (SD)	1420.4 (852.33)	946.7 (699.6)	2037.5 (0)	1197.7 (797.5)
Median	1054.9	721.4	2037.5	926.0
Min, Max	503, 3317	368, 3013	2037.5, 2037.5	368, 3317

Source: Statistical Reviewer's Table.
Note: Study Weeks presented within this table correspond to those from study PB-06-001/PB-06-002.
[1]: PB-06-001 patients: Screening visit from PB-06-001 study. PB-06-002 patients: Study Day 1 visit from PB-06-002 study.
[2]: This is Study Day 1 of the PB-06-003 study.

Table 17: Percentage Change from Screening/Baseline in Spleen Volume by Pivotal Study Week (Interim Population)

Percentage Change (%)	PB-06-001 30 units/kg (N = 12)	PB-06-001 60 units/kg (N = 14)	PB-06-002 Total (N=18)	Grand Total (N = 44)
Baseline[1] to Study Week 38/9-Month[2]				
n	12	14	15	41
Mean (SD)	-27.9 (7.79)	-39.3 (8.75)	-7.5 (13.09)	-24.3 (17.02)
Median	-27.9	-38.2	-8.2	-27.9
Min, Max	-43, -16	-56, -20	-28, 22	-56, 22
Baseline[1] to Study Week 52/12-Month				
n	12	14	8	34
Mean (SD)	-28.9 (8.17)	-43.5 (11.39)	-11.1 (11.56)	-30.7 (16.31)
Median	-28.7	-43.4	-9.6	-31.3
Min, Max	-44, -12	-64, -17	-28, 4	-64, 4
Baseline[1] to Study Week 104/24-Month				
n	12	14	1[3]	27
Mean (SD)	-40.5 (9.61)	-54.9 (12.79)	. (.)	-46.7 (15.51)
Median	-37.5	-56.3	.	-46.8
Min, Max	-58, -28	-75, -30	., .	-75, -5

Source: Statistical Reviewer's Table.
Note: Study Weeks presented within this table correspond to those from study PB-06-001/PB-06-002.
[1]: PB-06-001 patients: Screening visit from PB-06-001 study. PB-06-002 patients: Study Day 1 visit from PB-06-002 study.
[2]: This is Study Day 1 of the PB-06-003 study.
[3]: No statistics were displayed due to there being only one patient with exposure at 24 months.

Table 18: Liver Volume by Pivotal Study Week (Interim Population)

Liver Volume (mL)	PB-06-001 30 units/kg (N = 12)	PB-06-001 60 units/kg (N = 14)	PB-06-002 Total (N=18)	Grand Total (N = 44)
Baseline[1]				
n	12	14	16	42
Mean (SD)	2999.7 (779.45)	2470.5 (484.9)	1775.7 (434.39)	2357.0 (750.83)
Median	2794.3	2440.1	1625.0	2327.7
Min, Max	2282, 5096	1758, 3297	1167, 2643	1167, 5096
Study Week 38/9-Month[2]				
n	12	14	16	42
Mean (SD)	2584.5 (577.8)	2189.5 (390.87)	1737.3 (440.13)	2130.1 (575.11)
Median	2473.2	2094.7	1575.3	2094.7
Min, Max	2000, 4122	1654, 2894	1276, 2604	1276, 4122
Study Week 52/12-Month				
n	12	14	9	35
Mean (SD)	2515.6 (642.08)	2118.7 (318.09)	1718.7 (411.56)	2151.9 (555.62)
Median	2461.7	2157.1	1582.7	2097.0
Min, Max	1944, 4255	1678, 2600	1157, 2544	1157, 4255
Study Week 104/24-Month				
n	12	14	1	27
Mean (SD)	2362.8 (518.68)	1998.2 (291.88)	1532.3 (0)	2143.0 (452.03)
Median	2321.8	2040.6	1532.3	2119.4
Min, Max	1729, 3558	1522, 2430	1532.3, 1532.3	1522, 3558

Source: Statistical Reviewer's Table.
Note: Study Weeks presented within this table correspond to those from study PB-06-001/PB-06-002.
[1]: PB-06-001 patients: Screening visit from PB-06-001 study. PB-06-002 patients: Study Day 1 visit from PB-06-002 study.
[2]: This is Study Day 1 of the PB-06-003 study.

Table 19: Percentage Change from Screening/Baseline in Liver Volume by Pivotal Study Week (Interim Population)

Percentage Change (%)	PB-06-001 30 units/kg (N = 12)	PB-06-001 60 units/kg (N = 14)	PB-06-002 Total (N=18)	Grand Total (N = 44)
Baseline[1] to Study Week 38/9-Month[2]				
n	12	14	16	42
Mean (SD)	-13.2 (4.96)	-10.8 (6.84)	-1.9 (8.56)	-8.1 (8.56)
Median	-14.1	-12.2	-3.8	-10.0
Min, Max	-19, -3	-22, 2	-11, 22	-22, 22
Baseline[1] to Study Week 52/12-Month				
n	12	14	9	35
Mean (SD)	-15.9 (5.20)	-13.2 (8.89)	-3.8 (5.54)	-11.7 (8.36)
Median	-16.4	-11.3	-2.1	-12.8
Min, Max	-26, -5	-33, -2	-13, 2	-33, 2
Baseline[1] to Study Week 104/24-Month				
n	12	14	1[3]	27
Mean (SD)	-20.6 (6.87)	-17.5 (13.29)	. (.)	-18.6 (10.67)
Median	-18.2	-15.8	.	-17.6
Min, Max	-34, -11	-41, 9	., .	-41, -9

Source: Statistical Reviewer's Table.
Note: Study Weeks presented within this table correspond to those from study PB-06-001/PB-06-002.
[1]: PB-06-001 patients: Screening visit from PB-06-001 study. PB-06-002 patients: Study Day 1 visit from PB-06-002 study.
[2]: This is Study Day 1 of the PB-06-003 study.
[3]: No statistics were displayed due to there being only one patient with exposure at 24 months.

Table 20: PB-06-003 Organ Volumes (%BW) by Treatment Group

Clinical Parameter	PB-06-001		PB-06-002 n=18	Total n=44
	30 U/kg n=12	60 U/kg n=14		
Baseline Spleen % BW				
n	12	14	15	41
Mean ± SD	3.3 ± 1.7	3.4 ± 2.8	1.1 ± 1.1	2.5 ± 2.2
Median	2.8	2.2	0.7	1.9
Min, Max	1.5, 6.9	1.6, 10.8	<0.1, 4.1	<0.1, 10.8
	(15.3 MN)	**(18.3 MN)**	**(5.6MN)**	**(12.6 MN)**
Month 9 Spleen % BW				
n	12	14	15	41
Mean ± SD	2.3 ± 1.3	2.0 ± 1.9	1.0 ± 1.1	1.7 ± 1.6
Median	1.8	1.4	0.7	1.4
Min, Max	1.1, 5.3	0.8, 7.0	<0.1, 5.9	<0.1, 7.0
	(10.6 MN)	**(11.3 MN)**	**(5.1 MN)**	**(8.7 MN)**
Month 12 Spleen % BW				
n	12	14	8	34
Mean ± SD	2.3±1.4	1.9 ± 1.9	1.3 ± 1.3	1.9 ± 1.6
Median	1.6	1.2	1.1	1.4
Min, Max	1.0,5.7	0.7, 7.0	< 0.1, 4.1	<0.1, 20.5
	(11.7 MN)	**(9.3 MN)**	**(6.4 MN)**	**(9.4 MN)**
Month Spleen 24 % BW				
n	12	14	1	
Mean ± SD	1.9 ± 1.1	1.3 ± 1.0	3.8	1.7 +1.2
Median	1.4	1.0		1.3
Min, Max	0.8, 4.3	0.5, 4.4		0.5, 4.4
	(9.6 MN)	**(6.6 MN)**	**(19.8 MN)**	**(8.4 MN)**

Table 20: PB-06-003 Organ Volumes (%BW) by Treatment Group (cont'd)

Clinical Parameter	PB-06-001		PB-06-002 n=18	Total n=44
	30 U/kg n=12	60 U/kg n=14		
Baseline Liver % BW				
n	12	14	9	42
Mean ± SD	4.3 ± 1.0	3.8 ± 1.1	2.4 ± 0.6	3.4 ± 1.2
Median	4.0	3.6	2.3	3.5
Min, Max	3.4, 7.2	2.1, 4.9	1.7, 4.1	1.7, 7.2
	(1.7 MN)	**(1.5 MN)**	**(1.0 MN)**	**(1.4 MN)**
Month 9 Liver % BW				
n	12	14	16	42
Mean ± SD	3.6 ± 0.7	3.1 ± 0.7	2.4 ± 0.6	3.0 ± 0.8
Median	3.5	3.0	2.2	3.0
Min, Max	2.8, 5.6	2.1, 4.9	1.8, 3.8	1.6, 5.6
	(1.4 MN)	**(1.2 MN)**	**(1.0 MN)**	**(1.2 MN)**
Month 12 Liver % BW				
n	12	14	9	35
Mean ± SD	3.5 ± 0.8	3.0 ± 0.5	2.5 ± 0.6	3.0 ± 0.7
Median	3.4	2.9	2.3	3.0
Min, Max	2.7, 5.6	2.2, 4.3	1.6, 3.5	1.6, 5.6
	(1.4 MN)	**(1.2 MN)**	**(1.0 MN)**	**(1.2 MN)**
Month Liver 24 % BW				
n	12	14	1	35
Mean ± SD	3.2 ± 0.5	2.8 ± 0.5	2.9	3.0 ± 0.5
Median	3.2	2.7	--	2.9
Min, Max	2.6, 4.6	2.2, 4.0	--	2.2, 4.6
	(1.3 MN)	**(1.1 MN)**	**(1.2 MN)**	**(1.2 MN)**

Table 21: PB-06-003 Percent Change in Organ Volumes (%BW) by Treatment Group

Clinical Parameter	PB-06-001		PB-06-002 n=18	Total n=44
	30 U/kg n=12	60 U/kg n=14		
Spleen				
Baseline Spleen Volume n (%BW) ± SD	 12 3.3± 1.7	 14 3.4± 2.8	 16 1.1 ± 1.1	 42 2.6 ± 2.2
% Change at Month 9 n Mean ± SD Median Min, Max	 12 -31 ± 7 -30 -45, -21	 14 -42 ± 10 -43 -56, -21	 16 -8 + 14 -10 -25, 21	 42 -26 ± 18 -27 -56, 21
% Change at Month 12 n Mean ± SD Median Min, Max	 12 -31 ± 7 -32 -43, -17	 14 -47 ± 11 -49 -66, -22	 9 -9 ± 14 -9 -26, 14	 35 -34 ±17 -35 -66, 5
% Change at Month24 n Mean ± SD Median Min, Max	 12 -43 + 9 -41 -58, -34	 14 -59 + 12 -62 -75, -35	 1	 27 -50 + 15 -51 -75, -6
Liver				
Baseline Liver Volume (% BW) n Mean ± SD	 4.3 ± 1.0	 3.7 ± 1.1	 2.5 ± 0.6	 3.4 ± 1.2
% change at Month 9 n Mean ± SD Median Min, Max	 12 -15 ± 4 -15 -22, -8	 14 -15 ± 10 -16 -32, 0	 16 -1 ± 6 0 -10, 12	 42 -10 ± 10 -10 -32, 12
% change at Month 12 n Mean ± SD Median Min, Max	 12 -18 ± 5 -19 -26, -9	 14 -18 ± 13 -19 -37, 13	 9 -4 ± 6 -4 -15, 5	 35 -14 ± 11 -15 -37, 13
% Change at Month 24 n Mean ± SD Median Min, Max	 12 -24 ± 7 -23 -36, -11	 14 -22 ± 17 -22 -44, 13	 1 -9	 27 -22 ± 13 -22 -44, 13

3. Hematologic Parameters

Tables 22-25 summarize values and changes from baseline (mean, median) for hematologic parameters (hemoglobin and platelet count) for interim data from study PB-06-003, including hematologic parameter measurements performed at the end of PB-06-001 and PB-06-002 (i.e., after 9 months of treatment. In PB-06-003, hematologic parameters were measured at 3-month intervals. Of 44 patients enrolled in PB-06-003, data on hematologic parameters were available for 38 patients (26 patients for PB-06-001 and12 patients for PB-06-002) after 12 months of treatment and for 26 patients (PB-06-001 patients only) after 24 months of treatment. Ten patients (PB-06-001 patients only) had data available after 30 months of treatment.

It should be noted that baseline mean hemoglobin was normal for the 30 U/kg (12.5 g/dL) and PB-06-002 (13.6 g/dL) treatment groups and just below the lower limits of normal for the 60 U/kg group (11.4 g/dL). Twelve patients had abnormal baseline values, including 10 patients from PB-06-001 and 2 patients from PB-06-002. All of the patients from PB-06-001 achieved normal hemoglobin values. The two patients from PB-06-002 achieved increased hemoglobin values but the values remained within the abnormal range.

Mean hemoglobin increased in the 30 U/kg treatment group from Baseline (12.5 g/dL) to Month 12(14.2 g/dL). A slight decrease in mean hemoglobin was observed at Month 24 (13.8 g/dL) compared to Month 12 (14.2 g/dL), but the mean hemoglobin remained above the baseline value. The mean change in hemoglobin at Month 24 was 1.2 g/dL. Mean hemoglobin at Month 36 was 13.4 g/dL (n=5).

Mean hemoglobin increased from Baseline (11.4 g/dL) to Month 24 (13.8 g/dL)) in the 60 U/kg treatment group, with a mean increase of 1.6 g/dL at Month 24 (n=25). Mean hemoglobin at Month 36 was 13.1 g/dL (n=5). The mean hemoglobin for the 60 U/kg group was within the normal range from Month 12 onward.

At Month 36, all 10 patients from PB-06-001 (5 in each treatment group) had normal hemoglobin values and 7/10 patients had experienced an increase $\geq$ 1 g/dl in hemoglobin from baseline.

Mean hemoglobin increased at all time points from Baseline to Month 12 (13.6 g/dL)) in the PB-06-002 60 U/kg treatment group, with a mean increase of 1.6 g/dL at Month 12 (n=12).

Baseline mean platelet count was abnormal for the 30 U/kg (65K) and 60 U/kg (61K) treatment groups (Study PB-06-001) but within normal limits for patients in the PB-06-002 (164K) group. Mean platelet count increased at all time points from Baseline to Month 24 in the 30 U/kg treatment group (93K) and the 60 U/kg treatment group (141K), with a mean platelet count increase at Month 24 of 28 K and 72K, respectively. Mean

platelet count at Month 36 for the 30 U/kg and for the 60 U/kg treatment groups was 104K and 144 K, respectively (n=5 in each group). The mean platelet count for the 60 U/kg group was within the normal range from Month 12 onwards; mean platelet count for the 30 U/kg group remained abnormal.

Mean platelet count increased in the PB-06-002 treatment group from Baseline to Month 9 (166K) and then decreased to 141K at Month 12, a net decrease in mean platelet count. The mean change from baseline in platelet count at Month 12 was 11K.

Reviewer Comment: Hematologic parameters appeared to improve in treatment-naïve patients in both treatment groups through Month 24. It is difficult to interpret efficacy findings at Month 36 due to the limited sample size.

Hematologic parameters appeared to remain stable in patients switched from imiglucerase at Month 12. There were observed decreases in hemoglobin and platelet count from Month 9 to Month 12 in the PB-06-002 treatment group. However, because the observed values were well within the normal range at both time points, these findings may not be clinically significant and may represent normal fluctuations. The reason for these observed differences is unclear. The reason for these observed differences is unclear. As noted earlier, although it is unlikely that gaps in treatment due to delayed entry into PB-06-003 impacted PB-06-002 patients. The sole PB-06-002 patient who experienced a treatment gap missed only one infusion during the transition period.

Taliglucerase alfa appeared to demonstrate a short-term treatment effect (i.e., 9 months) in switch patients. However, it is difficult to draw clear conclusions regarding the long-term efficacy of taliglucerase due to the small number of patients and the short time period of treatment with taliglucerase, and the lack of an active comparator group.

Table 22: Hemoglobin Concentration by Pivotal Study Week (Interim Population)

Hemoglobin Concentration (g/dL)	PB-06-001 30 units/kg (N = 12)	PB-06-001 60 units/kg (N = 14)	PB-06-002 Total (N=18)	Grand Total (N = 44)
Baseline[1]				
n	12	14	18	44
Mean (SD)	12.49 (1.822)	11.39 (2.746)	13.64 (1.600)	12.61 (2.252)
Median	12.95	10.60	13.67	13.10
Min, Max	7.9, 14.6	5.5, 16.0	10.7, 16.1	5.5, 16.1
Study Week 38/9-Month[2]				
n	12	14	18	44
Mean (SD)	14.22 (1.408)	13.63 (2.057)	13.42 (1.674)	13.70 (1.733)
Median	13.80	14.25	13.75	13.90
Min, Max	12.2, 16.9	8.6, 16.5	10.3, 15.7	8.6, 16.9
Study Week 52/12- Month				
n	12	14	12	38
Mean (SD)	14.21 (1.687)	13.63 (2.560)	13.63 (1.705)	13.81 (2.022)
Median	14.00	13.80	13.50	13.70
Min, Max	11.3, 17.4	7.3, 17.1	10.0, 16.6	7.3, 17.4
Study Week 104/24-Month				
n	11	14	0	25
Mean (SD)	13.75 (1.595)	13.78 (1.840)	. (.)	13.77 (1.701)
Median	14.00	13.70	.	13.90
Min, Max	10.9, 17.2	11.3, 17.6	.,.	10.9, 17.6

Source: Statistical Reviewer's Table.
Note: Study Weeks presented within this table correspond to those from study PB-06-001/PB-06-002.
[1]: PB-06-001 patients: Study Day 1 visit from PB-06-001 study. PB-06-002 patients: Mean of up to six stability evaluation visits including the screening day visit from PB-06-002 study.[2]: This is Study Day 1 of the PB-06-003 study.

Table 23: Change from Baseline in Hemoglobin Concentration by Pivotal Study Week (Interim Population)

Hemoglobin Concentration (g/dL)	PB-06-001 30 units/kg (N = 12)	PB-06-001 60 units/kg (N = 14)	PB-06-002 Total (N=18)	Grand Total (N = 44)
Baseline[1] to Study Week 38/9-Month[2]				
N	12	14	18	44
Mean (SD)	1.73 (1.494)	2.24 (1.474)	-0.23 (0.613)	-1.09 (1.63)
Median	1.60	1.75	-0.13	0.71
Min, Max	-0.1, 5.8	0.5, 5.1	-1.3, 0.7	-1.3, 5.8
Baseline[1] to Study Week 52/12-Month				
N	12	14	12	38
Mean (SD)	1.72 (1.135)	2.24 (1.472)	0.01 (0.733)	1.37 (1.493)
Median	1.60	1.85	-0.05	1.15
Min, Max	0.0, 4.1	0.9, 6.2	-1.2, 1.3	-1.2, 6.2
Baseline[1] to Study Week 104/24-Month				
N	11	14	0	25
Mean (SD)	1.30 (1.723)	2.39 (2.312)	. (.)	1.91 (2.106)
Median	1.20	1.60	.	1.30
Min, Max	-1.2, 5.0	-1.5, 7.3	., .	-1.5, 7.3

Source: Statistical Reviewer's Table.
Note: Study Weeks presented within this table correspond to those from study PB-06-001/PB-06-002.
[1]: PB-06-001 patients: Study Day 1 visit from PB-06-001 study. PB-06-002 patients: Mean of up to six stability evaluation visits including the screening day visit from PB-06-002 study.
[2]: This is Study Day 1 of the PB-06-003 study.

Table 24: Platelet Count by Pivotal Study Week (Interim Population)

Platelet Count (/mm^3)	PB-06-001 30 units/kg (N = 12)	PB-06-001 60 units/kg (N = 14)	PB-06-002 Total (N=18)	Grand Total (N = 44)
Baseline[1]				
n	12	14	18	44
Mean (SD)	64900.0 (30132.62)	61471.4 (23257.17)	163722.2 (95953.30)	104236.4 (80896.88)
Median	55000.0	53500.0	138000.0	77000.0
Min, Max	27000, 112000	28000, 103000	39000, 328000	27000, 328000
Study Week 38/9-Month[2]				
n	12	14	18	44
Mean (SD)	75350.0 (45283.52)	112892.9 (53329.23)	165555.6 (97770.57)	124197.7 (81160.76)
Median	66500.0	110500.0	165000.0	108500.0
Min, Max	20000, 166000	25000, 241000	37000, 361000	20000, 361000
Study Week 52/12-Month				
n	12	14	12	38
Mean (SD)	80325.0 (41805.98)	122857.1 (53857.16)	145250.0 (97426.08)	116497.4 (71192.77)
Median	70000.0	137500.0	121500.0	110500.0
Min, Max	23000, 153000	25000, 228000	47000, 352000	23000, 352000
Study Week 104/24-Month				
n	12	14	0	26
Mean (SD)	93333.3 (53327.60)	141071.4 (73896.46)	. (.)	119038.5 (68409.49)
Median	79000.0	141500.0	.	1100500.0
Min, Max	31000, 180000	29000, 271000	.,.	29000, 271000

Source: Statistical Reviewer's Table.
Note: Study Weeks presented within this table correspond to those from study PB-06-001/PB-06-002.
[1]: PB-06-001 patients: Study Day 1 visit from PB-06-001 study. PB-06-002 patients: Mean of up to six stability evaluation visits including the screening day visit from PB-06-002 study.
[2]: This is Study Day 1 of the PB-06-003 study.

Table 25: Change from Baseline in Platelet Count by Pivotal Study Week (Interim Population)

Platelet Count (/mm^3)	PB-06-001 30 units/kg (N = 12)	PB-06-001 60 units/kg (N = 14)	PB-06-002 Total (N=18)	Grand Total (N = 44)
Baseline[1] to Study Week 38/9-Month[2]				
n	12	14	18	44
Mean (SD)	10450.0 (22341.67)	43850.0 (49818.51)	1722.2 (32739.02)	17506.8 (40569.87)
Median	7100.0	40500.0	-1833.3	8833.3
Min, Max	-25000, 59000	-15000, 186000	-88500, 56000	-88500, 186000
Baseline[1] to Study Week 52/12-Month				
n	12	14	12	38
Mean (SD)	15425.0 (22003.06)	53814.3 (51270.23)	10888.9 (24473.38)	28136.0 (40545.54)
Median	14450.0	53500.0	9250.0	19750.0
Min, Max	-33000, 42000	-15000, 173000	-21667, 58000	-33000, 173000
Baseline[1] to Study Week 104/24-Month				
n	12	14	0	26
Mean (SD)	28433.3 (31996.43)	72028.6 (68156.69)	. (.)	51907.7 (57941.79)
Median	15350.0	49000.0	.	43200.0
Min, Max	-14000, 87000	-10000, 202000	., .	-14000, 202000

Source: Statistical Reviewer's Table.
Note: Study Weeks presented within this table correspond to those from study PB-06-001/PB-06-002.
[1]: PB-06-001 patients: Study Day 1 visit from PB-06-001 study. PB-06-002 patients: Mean of up to six stability evaluation visits including the screening day visit from PB-06-002 study.
[2]: This is Study Day 1 of the PB-06-003 study.

4. Biomarkers

The applicant provided data on chitotriosidase levels for patients in the 30U/kg and 60 U/kg treatment groups for up to 24 months of treatment. Mean chitotriosidase levels decreased >50% from baseline during the PB-06-001 trial and continued to decrease during PB-06-003 (see Table 26).

Table 26: PB-06-003 Chitotriosidase Levels for Patients from PB-06-001

Chitotriosidase Levels (nmol/hr/mL)	Treatment Group	
	30 U/kg n=12	60 U/kg n=14
Baseline		
n	12	13
Mean ± SD	21557 ± 1030	19165 ± 13871
Median	22876	17652
Range	7965 to 34448	4208 to 50696
Month 9		
n	12	13
Mean ± SD	14328 ± 8643	11425 ± 15219
Median	13960	4380
Range	2866 to 34528	619 to 53283
Month12		
n	10	13
Mean ± SD	11335 ± 6459	7967 ± 9686
Median	10835	3802
Range	2405 to 24533	334 to 33555
Month24		
n	12	13
Mean ± SD	8726 ± 5739	5530 ± 7118
Median	7059	3012
Range	1299 to 21719	137 to 26594

5. Other endpoints

Bone disease, as measured by DEXA scan and QSCI, were evaluated as exploratory endpoints in PB-06-001; these measures continued to be collected during PB-06-003. No formal statistical analyses were performed.

DEXA

Lumbar spine, femoral neck and total hip DEXA scans were obtained at the screening visit and at the end of PB-03-001, and after 12, 24, and 36 months of treatment (Months 3, 15, and 27 of PB-06-003), with measurements of T-score, Z-score, and bone mineral density (BMD). The mean baseline values were within the normal range (not lower than -1) in both PB-06-001 treatment groups, with the exception of lumbar spine T- and Z- scores. Normal values were observed for all measurement in both treatment group at Month 24. Only two patients (1 patient in each treatment group) had DEXA scan measurements for Month 36. Table 27 summarizes DEXA scan results.

Reviewer Comment: This reviewer notes that although patients had evidence of bone involvement by other bone assessments (i.e. QCSI or skeletal x-rays), baseline DEXA scans values were normal in this trial population. Thus, DEXA scan values might not represent a clinically meaningful endpoint for this population. DEXA scans have been used to predict risk factor for fractures in other populations (post-menopausal women). However, the relationship of osteoporosis (i.e., bone mineralization) to fracture risk in Gaucher patients has not been established. General limitations in using DEXA scans to assess therapeutic response include false normal or high values with certain bone abnormalities, and lack of normative data for the pediatric population.[20]

Table 27: PB-06-003 DEXA Scan Results

DEXA Measurement	30 U/kg Group n=12				60 U/kg Group n=14			
	Screening	Month 9	Month 12	Month 24	Screening	Month 9	Month 12	Month 24
Lumbar Spine								
Mean T Score	Normal n=13	Normal n=13	Normal N=10	Normal N=9	Abnormal (-1.2) n=14	Abnormal (-1.1) n=14	Normal N=13	Normal N=13
Mean Z Score	Normal n=14	Normal n=14	Normal N=11	Normal N=10	Abnormal (-1.2) n=15	Normal n=15	Normal N=12	Normal N=13
Mean BMD	Normal n=11	Normal n=11	Normal N=12	Normal N=12	Normal n=13	Normal n=13	Normal N=13	Normal N=14
Femoral Neck								
Mean T Score	Normal N=13	Normal N=13	Normal N=11	Normal N=10	Normal N=15	Normal N=15	Normal N=12	Normal N=14
Mean Z Score	Normal N=14	Normal N=14	Normal N=11	Normal N=11	Normal N=15	Normal N=15	Normal N=13	Normal N=14
Mean BMD	Normal N=11	Normal N=11	Normal N=12	Normal N=12	Normal N=15	Normal N=15	Normal N=13	Normal N=14
Total Hip								
Mean T Score	Normal N=4	Abnormal (-1.2) N=4	Abnormal (-1.4) N=3	Abnormal (-1.2) N=3	Normal N=6	Abnormal (-1.1) N=6	Abnormal (-1.1) N=4	Normal N=4
Mean Z Score	Normal N=5	Normal N=5	Normal N=4	Normal N=4	Normal N=6	Normal N=6	Normal N=4	Normal N=5
Mean BMD	Normal N=5	Normal N=5	Normal N=4	Normal N=4	Normal N=6	Normal N=6	Normal N=4	Normal N=5

20 Cox TM, Aerts JMFG, et al, Management of non-neuronopathic Gaucher disease with special reference to pregnancy, splenectomy, bisphosphonate therapy, use of biomarkers and bone disease monitoring, *J Inherit Metab Dis* (2008) 31:319–336

QCSI

Quantitative chemical shift imaging (QCSI) was used to measure bone marrow fat fraction content as an exploratory endpoint in a subgroup of patients from PB-06-001. QCSI was performed at the PB-06-001 screening visit for 10 patients (5 patients from each treatment group) and at the end of trial visit for nine patients. Eight patients continued treatment in PB-06-003. After 24 months of treatment, 6/8 (75%) of patient achieved a fat fraction> 0.23, compared to 2/8 (25%) of patients at Baseline. Two patients (15-016 and 30-011) had bone pain events after 12 and 30 months of treatment, respectively. Table 28 summarizes QCSI results for PB-06-003.

At Month 24, the mean increase in fat fraction was higher in the high dose group (0.175) compared to the low dose group (0.1125). The clinical significance of these results is unclear. One patient (41-020 in the 60 U/kg treatment group) experienced a bone-related complication (femoral head and acetabular avascular necrosis) during the trial period. The larger mean increase in fat fraction observed in the high dose group suggests a dose-related effect on this clinical parameter. However, interpretation of these results is limited by the small number of patients evaluated.

Comment: Fat fraction content is a recognized parameter for invasion of bone marrow by Gaucher disease. In a published study by Maas et al, the authors note that although QCSI is the state of the art modality for assessing bone marrow disease, its use is limited because it is not widely available. In addition, QCSI has not been validated for the Gaucher population.

Table 28: PB-06-003 QCSI Summary Table

Patient ID Number	Baseline	9 Month	12 Month	24 Month	36 Month	Change from Baseline
Taliglucerase alfa 30 units/kg						
10-001	0.16		0.20	0.16	0.26	0.10
10-028	0.11	0.17	0.19	0.20		0.09
15-015	0.23	0.24	0.26	0.31		0.08
30-008	0.22	0.39	0.38	0.39	0.40	0.18
Mean	**0.18**	**0.267**	**0.2575**	**0.265**	**0.33**	**0.1125**
Taliglucerase alfa 60 units/kg						
10-005	0.35	0.42	0.38	0.38	0.40	0.05
15-016	0.33	0.43	0.45	0.43		0.10
30-009	0.14	0.27	0.28	0.37	0.40	0.26
30-011	0.13	0.30	0.32	0.41	0.42	0.29
Mean	**0.24**	**0.36**	**0.36**	**0.40**	**0.407**	**0.175**

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Immunogenicity:
A deficiency noted in the Complete Response Letter included the lack of an acceptable cut-point for the confirmatory anti-drug antibody assay (cut-point was too high). Therefore, the applicant provided a new cut-point for assessment of ADA responses as part of the Complete Response. Based on a reanalysis of antibody testing results by the Applicant using a lower cut-point agreed upon with the Agency, 20/44 (45%) patients in PB-06-003 developed ADA titers, including 1 patient (22-226) who developed ADA titers during the study (See Table 51 in Section 7.4.6 for a list of patients). Four patients who were ADA-positive during PB-06-001 or PB-06-002 were ADA-negative in PB-06-003. Three patients (1 in each treatment group) had neutralizing antibodies based on the enzymatic activity inhibition assay; all were negative for neutralizing antibodies based on the cell-based assay. Two patients with positive antibodies were discontinued from the study (both were in the 60 U/kg treatment group); one patient was discontinued due to an adverse event (allergic reaction) and the other patient was discontinued for administrative reasons.

The applicant also evaluated ADA responses over time in Study P-06-003. Patients were classified as previously described. I reclassified one patient (30-012 from PB-06-001) as Tolerized Positive rather than Negative because the patient had positive titers at all visits, with a pretreatment titer (Day 1) of 47 and a peak titer of 184 at Week 34 of PB-06-001 and a titer of 151 at Month 3 (12 months of treatment) of PB-06-003.

Efficacy Results by Immunogenicity Status

Tables 29-32 summarize efficacy results for patients in the 30U/kg and 60 U/kg treatment groups according to antibody titer status. All patients from PB-06-001 had ADA-titers evaluated during the extension study. Due to the small number of patients in the PB-06-002 treatment group with positive antibody titers, these results are reviewed later in the discussion of efficacy results by titer categories (i.e., persistent positive, tolerized positive, transient positive, and negative).

There were some differences in baseline disease severity between ADA-positive and ADA-negative patients. In the 30 U/kg group, the baseline mean hemoglobin value was abnormal for ADA-positive patients but normal for ADA-negative patients. Otherwise, the two subgroups were similar at baseline. In the 60 U/kg group, the baseline mean spleen volume was considerably lower in ADA-positive patients (1947 mL; 14.6 MN) compared to anti-body negative patients (2552 mL; 22.4 MN).

Table 29 and Table 30 summarize organ volume efficacy results by immunogenicity status.
There were no clear differences in efficacy for organ volume between ADA-positive and ADA-negative patients after 24 months of treatment, with the exception of spleen volume for patients in the 60U/kg group. At Month 24, ADA-negative patients achieved a lower mean spleen volume compared to ADA-positive patients (mean spleen volumes

were 661 mL [5.0 MN] and 995 mL [6.7 MN], respectively). This finding is especially notable because the baseline mean spleen volume for ADA-negative patients was over 30% larger than the baseline mean spleen volume for ADA-positive patients. Mean spleen volumes and mean changes in spleen volume were similar for patients in the 30 U/kg treatment group irrespective of antibody status.

Table 29: PB-003 Spleen Efficacy Results by Immunogenicity Status for the 30 U/kg and 60U/kg Treatment Groups

Spleen Volume (ml)	PB-06-001 30 U/kg Group/ Antibody Status		PB-06-001 60 U/kg Group/ Antibody Status	
	Positive n=6	Negative n=6	Positive n=10	Negative n=4
Baseline				
Mean ± SD	2324 ± 1088	2461 ± 1453	1947 ± 1240	2552 ± 1964
MN	15.7	17.9	14.6	22.4
Mean %BW	3.0 ± 1.0	3.6 ± 2.2	2.9 ± 2.1	4.5 ± 4.3
Month 9				
Mean ± SD	1611 ± 827	1827 ± 1183	1295 ± 1069	1494 ± 1321
% Change ± SD	-32 ± 7	-27 ± 7	-37 ± 8	-45 ± 10
MN	10.4	13.1	9	11.7
Mean %BW	2.0 ± 0.7	2.6 ± 1.8	1.9± 1.8	2.4 ± 2.4
Mean Change % BW	-0.9 ± 0.4	-1.0 ± 0.5	-1.0± 0.4	-2.1 ± 1.9
Month12				
Mean ± SD	1729 ± 827	1902 ± 1453	1231 ± 1115	1087 ± 1279
% Change ± SD	-33 ± 7	-27 ± 8	-41 ± 10	-40 ± 14
MN	10.3	13.5	8.8	8.4
Mean %BW	2.0 ± 0.7	2.7 ± 1.9	1.8 ± 1.9	2.1 ± 2.2
Mean Change % BW	-1.0 ± 0.3	-0.9 ± 0.3	-1.1 ± 0.5	-2.4 ± 2.1
Month 24				
Mean ± SD	1391 ± 767	1502 ± 1047	995 ± 765	661 ± 582
% Change ± SD	-42 ± 11	-42 ± 8	-51 ± 11	-66 ± 10
MN	8.9	10.6	6.7	5.0
Mean %BW	1.7 ± 0.6	2.2 ± 1.5	1.4 ± 1.1	1.3 ± 1.1
Mean Change % BW	-1.2 ± 0.5	-1.4 ± 0.8	-1.5 ± 1.1	-3.2 ± 3.2

At Month 24, the observed mean change in liver volume in ADA-negative patients was greater compared to ADA-positive patients in the 60 U/kg (mean volume changes of -32% and -12%, respectively). However, both subgroups of patients achieved normal or near normal mean liver volumes at Month 24 (1862 ml [1.0 MN] and 2053 mL [1.1 MN], respectively. At Month 24, there were negligible differences in mean liver volumes and mean changes in liver volume between ADA-negative and ADA-positive patients (2394 mL [-21%] and 2332 mL [-18%], respectively).

Table 30: PB-003 Liver Efficacy Results by Immunogenicity Status for the 30 U/kg and 60U/kg Treatment Groups

Liver Volume (ml)	PB-06-001 30 U/kg Group/ Antibody Status		PB-06-001 60 U/kg Group/ Antibody Status	
	Positive n=6	Negative n=6	Positive n=10	Negative n=4
Baseline				
n	6	6	10	4
Mean ± SD	2847 ± 393	3152 ± 1061	2367 ± 483	2730 ± 480
%BW	4.0 ± 0.4	4.5 ± 1.4	3.5 ± 0.8	4.5 ± 1.5
MN	1.6	1.8	1.4	1.8
Month 9				
n	6	6	10	4
Mean ± SD	2483 ± 283	2689 ± 792	2143 ± 393	2305 ± 452
% Change ± SD	-13 ± 4	-14 ± 6	-9 ± 7	-16 ± 5
%BW	3.4 ± 0.4	3.8 ± 0.9	3.0 ± 0.5	3.0 ± 0.5
Change in % BW	-0.6 ± 0.2	-0.7 ± 0.4	-0.5 ± 0.4	-0.5 ± 0.4
MN	1.4	1.5	1.2	1.4
Month 12				
n	6	6	10	4
Mean ± SD	2405 ± 286	2948 ± 893	2095 ± 381	2178 ± 382
% Change ± SD	-15 ± 3	-17 ± 7	-11 ± 7	-20 ± 10
%BW	3.3 ± 0.4	3.6 ± 1.0	2.9 ± 0.4	3.2 ± 0.8
Change in % BW	-0.7 ± 0.2	-0.9 ± 0.3	-0.6 ± 0.5	-1.3 ± 0.8
MN	1.3	1.4	1.2	1.3
Month 24				
n	6	6	10	4
Mean ± SD	2332 ± 396	2394 ± 670	2053 ± 266	1862 ± 350
% Change ± SD	-18 ± 5	-21 ± 8	-12 ± 11	-32 ± 7
%BW	3.1 ± 0.3	3.3 ± 0.7	2.9± 0.5	2.7± 0.8
Change in % BW	-0.9 ± 0.3	-1.2 ± 0.7	-0.6 ± 0.5	-1.8 ± 0.7
MN	1.3	1.3	1.1	1.0

Reviewer Comment: The observed difference in spleen volume efficacy results at 24 months for patients in the 60 U/kg treatment group (-51% vs. -66% from baseline) raises the concern that efficacy may be attenuated in patients who develop immunogenicity to taliglucerase alfa. However, there is a persistent decline in spleen volume in all treatment groups regardless of antibody status.

Table 31 and Table 32 summarize hematologic parameters results. There were differences observed in efficacy for hematologic parameters between ADA-positive and ADA-negative patients in the 30 U/kg treatment group but not the 60 U/kg group. Hematologic parameters in ADA-positive patients in the 30 U/kg treatment group improved from baseline, but in an inconsistent manner. Mean hemoglobin in this

subgroup increased from 11.8 g/dL at Baseline to 13.6 g/dL at Month 9, and then decreased to 12.9 g/dL at Month 24 (mean change of -0.7 g/dL from Month 9 to Month 12). Mean hemoglobin appeared to increase again at Month 30 (13.1 g/dL); however, interpretation of this finding is difficult, due to the small sample size at Month 30 (n=3). Similarly, mean platelet count for ADA-positive patients in the 30 U/kg group decreased to below the mean baseline value (81K) at Month 12 (76K), then increased to slightly higher than the mean baseline value at Month 24 (86K). Month 30 data were not evaluable because there were no patients in the 60U/kg ADA-negative group with available data for review.

At Month 24, mean hemoglobin and platelet counts for ADA-negative patients in the 30 U/kg group were 14.8 g/dL and 115K. At Month 24, mean hemoglobin for ADA-positive and ADA-negative patients in the 60 U/kg treatment group were 13.7 g/dL and 14.0 g/dl, respectively; mean platelet counts were 137K and 152K, respectively. Note that both ADA-positive and ADA-negative patients in the 60 U/kg treatment group achieved normal mean platelet values by Month 24; the ADA-negative subgroup achieved mean normal platelet values by Month 9.

Table 31: PB-003 Hemoglobin Efficacy Results by Immunogenicity Status for the 30 U/kg and 60U/kg Treatment Groups

Hemoglobin (g/dL)	PB-06-001 30 U/kg Group/ Antibody Status		PB-06-001 60 U/kg Group/ Antibody Status	
	Positive n=6	Negative n=6	Positive n=10	Negative n=4
Baseline				
n	6	6	10	4
Mean ± SD	11.8 ± 2.2	13.2 ± 1.0	11.4 ± 2.9	11.4 ± 2.6
Month 9				
n	6	6	10	4
Mean ± SD	13.9 ± 1.7	13.9 ± 0.7	13.5 ± 2.2	14.1 ± 2.0
Mean Change ± SD	2.1 ± 2.0	1.2 ± 0.7	2.1 ± 1.3	2.7± 2.0
Month 12				
n	6	6	10	4
Mean ± SD	13.6 ± 1.7	14.8± 1.5	13.2 ± 2.6	14.6 ± 2.6
Mean Change ± SD	1.8 ± 1.3	1.6± 1.1	1.9 ± 1.1	3.2 ± 2.0
Month 24				
n	6	5	10	4
Mean ± SD	12.9 ± 1.3	14.8± 1.4	13.7 ± 1.6	14.0 ± 2.5
Mean Change ± SD	1.1 ± 2.2	1.5 ± 1.2	2.3 ± 1.8	2.6 ± 3.7

Table 32: PB-003 Platelet Count Efficacy Results by Immunogenicity Status for the 30 U/kg and 60U/kg Treatment Groups

Platelet count (_/mm^3)	PB-06-001 30 U/kg Group/ Antibody Status		PB-06-001 60 U/kg Group/ Antibody Status	
	Positive n=6	Negative n=6	Positive n=10	Negative n=4
Baseline				
n	6	6	10	4
Mean ± SD	81K ± 30K	62K ± 33K	73K ± 30K	59 K ± 24K
Month 9				
n	6	6	10	4
Mean ± SD	113K ± 58K	64K ± 3K	102K ± 35K	120K ± 61K
Mean Change ± SD	21K ± 19K	33K ±19 K	39K ± 23K	90K ± 92K
Month 12				
n	6	6	10	4
Mean ± SD	76K ± 38K	85K ± 48K	120K ± 43K	131K ± 84K
Mean Change ± SD	9K ± 20K	22K ± 18K	47K ± 36K	72K ± 83K
Month24				
n	6	6	10	4
Mean ± SD	85K ± 44K	115K ± 64K	137K ± 71K	152K ± 92K
Mean Change ± SD	18K ± 27K	47K ± 35K	64K ± 60K	93K ± 92K
Month 30				
n	3	2	5	0
Mean ± SD	65K ± 33K	162K ± 12K	144K ± 59K	
Mean Change ± SD	-1K ± 6K	59K ± 25K	55K ± 39K	

Reviewer Comments: It is unclear from the hematologic results whether development of ADA titers affects efficacy. All subgroups of patients achieved or maintained normal mean hemoglobin values. Both subgroups of patients in the 60 U/kg treatment group achieved normal mean platelet values; mean platelet values appeared to normalize after a shorter period of treatment in the ADA-negative subgroup. However, due to the small number of patients in each group, it is difficult to draw conclusions regarding the effect of ADA titers on efficacy. Although mean hemoglobin decreased in ADA-positive patients in the 30 U/kg treatment group at Month 24, the observed decrease of 0.7 g/ dL is not likely to be clinically significant. However, the observed decrease in platelet count in this subgroup is not concerning because all patients attained normal hemoglobin levels. Thus, differences may represent normal fluctuations. However, the mean platelet count increased after 9 months of treatment and then decreased back to baseline after 24 months of treatment in ADA-positive patients in the 30 U/kg treatment group. Again, the small sample size of the study precludes any definitive determination of the impact of immunogenicity on efficacy, particularly long-term efficacy. The long-term impact of the immunogenicity of this product on efficacy should continue to be monitored.

I also analyzed efficacy results by antibody titer categories to evaluate for differences in treatment response. Table 33 summarizes organ volume efficacy results for patients from the 30U/kg (n=4) and 60 U/kg (n=5) treatment groups in the Persistent Positive category. Efficacy results for Persistent Positive patients were compared with efficacy results for ADA-negative patients. It should be noted that these subgroup analyses are exploratory as the study was not powered to detect differences based on these subgroups.

There were differences in baseline disease severity between Persistent Positive and ADA-negative patients for organ volume, with Persistent Positive patients having smaller baseline organ volumes than ADA-negative patients in both treatment groups. Baseline mean spleen volumes for Persistent Positive patients in the 30/kg and 60 U/kg treatment groups were 1922 mL and 1443 mL, respectively; baseline mean liver volumes were 2843 mL and 2070 mL. Baseline mean spleen volumes for ADA-negative patients in the 30/kg and 60 U/kg treatment groups were 2461mL and 2552 mL, respectively; baseline mean liver volumes were 3252 mL and 2730 mL. Hematologic parameters were similar for Persistent Positive and ADA-negative patients in both treatment groups.

At Month 24, the mean change in spleen volume for Persistent Positive patients in the 30 U/kg and 60 U/kg groups was -35% and -45%; the mean change in ADA-negative patients was -42% and -66%, respectively. These changes correspond to mean spleen volumes of approximately 6 MN for the Persistent positive subgroup and 5MN for the ADA-negative subgroup. At Month 24, the mean change in liver volume for Persistent Positive patients in the 30 U/kg and 60 U/kg groups was -16% and -8%, respectively; mean change in liver volume in ADA-negative patients was -21% and -32%, respectively. These correspond to normal mean liver volumes for both groups.

Table 33: PB-003 Organ Volume Efficacy Results for Patients with Persistent Positive Antibodies in the 30 U/kg and 60 U/kg Treatment Groups

Persistent Positive Titers	Treatment group		
	30U/kg	60 U/kg	Total
Spleen Volume (mL)	**n=4**	**n=5**	**n=9**
Baseline			
Mean ± SD	1922 ± 870	1443 ± 557	1655 ± 709
Mean % BW ± SD	2.8 ± 1.0	2.1 ± 0.7	2.4 ± 0.9
Month 9			
Mean ± SD	1414 ± 598	918 ± 425	1139 ± 541
Mean % Change ± SD	-26 ± 8	-38 ± 6	-32 ± 9
Mean % BW ± SD	2.0 ± 0.7	1.3 ± 0.5	1.6 ± 0.7
Mean Change % BW ± SD	-0.8 ± 0.4	-0.8 ± 0.2	-0.8 ± 0.3
Month 12			
Mean ± SD	1381 ± 643	846 ± 327	1084 ± 537
Mean % Change ± SD	-29 ± 6	-42 ± 5	-36 ± 9
Mean % BW ± SD	1.9 ± 0.8	1.2 ± 0.4	1.5 ± 0.7
Mean Change % BW ± SD	-0.9 ± 0.4	-0.9 ± 0.4	-0.9 ± 0.4
Month 24			
Mean ± SD	1249 ± 568	826 ± 412	1014 ± 505
Mean % Change ± SD	-35 ± 7	-45 ± 11	-41 ± 11
Mean % BW ± SD	1.7 ± 0.7	1.2 ± 0.5	1.4 ± 0.6
Mean Change % BW ± SD	-1.1 ± 0.5	-1.0 ± 0.4	-1.0 ± 0.4
Liver Volume (mL)			
Baseline			
Mean ± SD	2843 ±244	2070 ± 372	2414 ± 536
% BW ± SD	4.1 ± 0.4	3.1 ± 0.7	3.5 ± 0.8
Month 9			
Mean ± SD	2480 ± 243	1879 ± 244	2146 ± 390
Mean % Change ± SD	-12 ± 5	-9 ± 7	-10 ± 6
Mean % BW ± SD	3.5 ± 0.3	2.7 ± 0.5	3.1 ± 0.6
Mean Change % BW ± SD	-0.6 ± 0.3	-0.3 ± 0.3	-0.4 ± 0.3
Month 12			
Mean ± SD	2438 ± 252	1855 ± 212	2114 ± 375
Mean % Change ± SD	-14 ± 3	-10 ± 7	-12 ± 6
Mean % BW ± SD	3.4 ± 0.3	2.7 ± 0.3	3.0 ± 0.5
Mean Change % BW ± SD	-0.8 ± 0.2	-0.4 ± 0.5	-0.6 ± 0.4
Month 24			
Mean ± SD	2377 ± 290	1888 ± 242	2105 ± 357
Mean % Change ± SD	-16 ± 4	-8 ± 11	-12 ± 9
Mean % BW ± SD	3.3 ± 0.3	2.6 ± 0.2	2.9 ± 0.4
Mean Change % BW ± SD	-0.9 ± 0.3	-0.5 ± 0.7	-0.6 ± 0.6

Table 34 summarizes hematologic parameter results for patients from the 30U/kg (n=4) and 60 U/kg (n=5) treatment groups in the Persistent Positive category.. Mean hemoglobin normalized or was maintained within normal limits in both ADA-negative patients and Persistent Positive patients in both dose groups by Month 9. At Month 24, mean change from baseline in hemoglobin for Persistent Positive patients in the 30 U/kg and 60 U/kg groups was -0 g/dL and 1.6 g/dL, respectively, compared to a mean change in ADA-negative patients of 1.5 g/dL and 2.6 g/dL, respectively.

Mean platelet count normalized in both ADA-negative patients and Persistent Positive patients in the 60 U/kg treatment group by Month 24. Note that ADA-negative patients achieved mean normal platelet values by Month 9. Mean platelet count increased but did not normalize for either patient subgroup in the 30 U/kg treatment group. Mean platelet count in Persistent Positive patients in the 30 U/kg treatment group appeared to plateau after Month 9, while mean platelet count in ADA-negative patients in the 30 U/kg treatment group continued to increase. At Month 24, the mean change from baseline in platelet count for Persistent Positive patients in the 30 U/kg and 60 U/kg groups was 26K and 47K respectively; mean change from baseline in ADA-negative patients was 47K and 93K respectively.

Table 34: PB-003 Hematologic Parameters Efficacy Results for Patients with Persistent Positive Antibodies in the 30 U/kg and 60 U/kg Treatment Groups

Persistent Positive Titers	Treatment group		
	30U/kg n=4	60 U/kg n=5	ADA-negative n=10
Hemoglobin (g/dL)			
Baseline			
Mean ± SD	12.6 ± 1.6	11.7± 1.4	12.5 ± 1.9
Month 9			
Mean ± SD	13.9 ± 2.1	13.7 ± 1.0	14.4. ± 1.5
Mean Change ± SD	1.3 ± 1.0	2.1 ± 1.4	1.9 ± 1.6-5
Month 12			14.7 ± 1.7
Mean ± SD	13.6±1.8	13.7± 1.4	2.1 ± 1.5
Mean Change ± SD	1.0 ± 0.3	2.0 ± 1.4	
Month 24			(n=9)
Mean ± SD	12.5±1.4	13.3 ± 1.4	14.4 ± 1.9
Mean Change ± SD	0 ± 1.0	1.6 ± 1.1	2.0 ± 2.4
Platelet count (_/mm^3)			
Baseline			
Mean ± SD	69K ± 35K	80K ± 38K	61K ± 28K
Month 9			
Mean ± SD	91K ± 54K	115K ± 42K	91K ± 68K
Mean Change ± SD	22K ± 26K	35K ± 28K	31K ± 61K
Month 12			
Mean ± SD	86K ±45K	125K ± 36K	103K ± 65K
Mean Change ± SD	18K ± 18K	45 K ± 30K	42K ± 56K
Month 24			
Mean ± SD	95K ± 54K	127K ± 44K	122K ± 76K
Mean Change ± SD	26K ± 28K	47K ± 23 K	61K ± 65K

Reviewer Comments: The observed differences in organ volume efficacy results for the 60 U/kg treatment group suggest that efficacy was reduced in patients with persistently positive ADA titers to taliglucerase alfa compared to ADA-negative patients in the 60 U/kg treatment group However, as noted earlier, at least part of the observed difference in changes from baseline in organ volume can be attributed to the presence of milder baseline disease in the Persistent Positive 60U/kg subgroup. The observed differences in changes in platelet count values, which were similar at baseline for Persistent positive and ADA-body negative patients in both treatment groups may be evidence of decreased efficacy due to immunogenicity. It should also be noted that efficacy appeared to wane over time in Persistent Positive patients in the 30 U/kg treatment group. In the 60 U/kg treatment group, although both subgroups achieved normal platelet values, platelet values normalized earlier during treatment in the ADA-negative

subgroup. However, as stated above, these subgroup analyses are exploratory as the study was not powered to detect differences based on these subgroups.

Due to the small number of patients, I did not perform an analysis by treatment group for patients classified as having Tolerized Positive or Transient Positive antibodies, or for patients in the PB-06-002 treatment group with Persistent Positive antibody titers. Individual patient results are listed in Tables 35-38. All but one of the patients demonstrated improvement in all clinical parameters from baseline up to Month 24. Patient 14-210 (PB-06-002 treatment group) was classified as Persistent Positive; the patient experienced a decrease in platelet count at Month 24 but remained stable in the other clinical parameters.

Table 35: PB-003 Spleen Volume Efficacy Results for Individual Patients with Positive Antibodies (Excluding Patients with Persistent Positive Antibodies in the 30 U/kg and 60U/kg Treatment Groups)

Spleen Volume					
Patient ID#	Titer Status	Baseline	Month 9	Month 12	Month 24
30 U/kg					
22-031	(b) (4)				
30-010					
60 U/kg					
10-013					
11-007					
14-027					
30-009					
30-011					
PB-06-002					
14-210					

Table 36: PB-003 Liver Volume Efficacy Results for Individual Patients with Positive Antibodies (Excluding Patients with Persistent Positive Antibodies in the 30 U/kg and 60 U/kg Treatment Groups)

Liver Volume					
Patient ID#	Titer Status	Baseline	Month 9	Month 12	Month 24
30 U/kg					
22-031	(b) (4)				
30-010					
10-013					
60/kg					
11-007					
14-027					
30-009					
30-011					
PB-06-002					
14-210					

Table 37: PB-003 Hematology Efficacy Results for Individual Patients with Positive Antibodies (Excluding Patients with Persistent Positive Antibodies in the 30 U/kg and 60 U/kg Treatment Groups)

Hemoglobin					
Patient ID#	**Titer Status**	**Baseline**	**Month 9**	**Month 12**	**Month 24**
30 U/kg					
22-031	(b) (4)				
30-010					
60 U/kg					
10-013					
11-007					
14-027					
30-009					
30-011					
PB-06-002					
14-210					
20-220					
22-226					
23-206					

Table 38: PB-003 Hematology Efficacy Results for Individual Patients with Positive Antibodies (Excluding Patients with Persistent Positive Antibodies in the 30 U/kg and 60 U/kg Treatment Groups)

		Platelet Count			
Patient ID#	**Titer Status**	**Baseline**	**Month 9**	**Month 12**	**Month 24**
30 U/kg					
22-031	(b) (4)				
30-010					
60 U/kg					
10-013					
11-007					
14-027					
30-009					
30-011					
PB-06-002					
14-210					
20-220					
22-226					
23-206					

6 Review of Efficacy

6.1 Indication

The applicant proposes the following indication:

(b) (4)

(b) (4)

I recommend that the indication be revised to be consistent with the labeled indication for other ERT products for Gaucher disease:

"Taliglucerase alfa is indicated for long-term enzyme replacement therapy (ERT) for adult patients with a confirmed diagnosis of Type 1 Gaucher disease."

For a final version of the indication for ELELYSO, please see final product labeling.

Efficacy is discussed in Section 5 of this review.

7 Review of Safety

Safety Summary

Taliglucerase alfa is generally well tolerated in adult patients with Type 1 Gaucher disease, including treatment-naïve patients and patients transitioned from imiglucerase to taliglucerase. There were no deaths in any of the clinical trials. Additionally, only of one of the 15 serious adverse events (SAEs) appear to be directly related to taliglucerase treatment (gastroenteritis in a pediatric patient). The most common AEs (>10%) reported among all patients were infusion reactions, upper respiratory infections/colds, headaches, and arthalgia/back pain. The applicant reported that 31/83 (37%) patients experienced events considered to be related to the use of taliglucerase. Adverse reactions considered related to the use of taliglucerase as reported by the applicant include infusion reactions, headache, hypersensitivity, fatigue, pruritis, and erythema. Based on my independent analysis of reported adverse events, 3/121 (2%) patients in the safety database definitely or possibly experienced anaphylactic reactions; insufficient information was available to definitively determine whether one of the patients had experienced an anaphylactic reaction. In addition, the applicant reported 2 events of anaphylaxis in patients being treated through compassionate use programs. In addition to the adverse reactions listed by the applicant, arthralgia/back pain and urticaria/rash/drug eruption were other common adverse reactions. According to the applicant's reanalysis of antibody results, 25/ 62 (40%) of patients treated in clinical trials PB-06-001, PB-06-002 and PB06-003 thus far have developed ADA titers to taliglucerase. Overall safety results do not appear to be different for these patients. However, the ability to interpret immunogenicity data for this product is limited by inadequacies in the immunogenicity assays (i.e., lack of adequately sensitive neutralizing antibody assays for enzyme activity and cellular uptake, as well as antibody assays for plant sugars found on the product) used for the clinical trials. The impact of immunogenicity on the safety profile of this product will need to be re-evaluated once adequate immunogenicity assays have been developed. These data will be required as a PMR. Based on review of the safety data available for this review cycle, my independent safety analysis did not uncover major discrepancies compared with the applicant's analysis.

Overall, the safety profile of taliglucerase alfa appears to be similar to ERT products already approved for the treatment of Type 1 Gaucher disease. However, information on the long-term safety of taliglucerase alfa in patients transitioned from imiglucerase beyond 12 months of treatment remains limited. The applicant will be required to collect this information through a registry study as a PMR. In addition, because the sponsor did not conduct a trial comparing taliglucerase alfa to an approved Gaucher ERT product (i.e., Cerezyme and/or VRPIV), data for a direct comparison of the safety of this product with other available ERTs are not available. The applicant has agreed to present a comparative analysis of taliglucerase alfa and other ERT products as a PMC.

Furthermore, additional safety data also should be collected in other populations. Safety data in pediatric patients are extremely limited, as the applicant provided data on only two pediatric patients (enrolled in PB-06-002) in the Complete Response submission. However, a pediatric trial is underway currently; submission of the final report for the pediatric trial should be required as a post-marketing requirement. As noted earlier, the applicant will be required to complete trials PB-06-002 and PB-06-005, and submit a final report as PMRs.

In addition, taliglucerase alfa was not evaluated in pregnant or lactating women. Finally, as noted earlier, the immunogenicity of this product will need to be re-evaluated with the appropriate assays to resolve outstanding questions about the immunogenicity of the product (i.e., the impact of neutralizing antibodies and cross-reacting anti-plant sugar antibodies). Data regarding the use of taliglucerase alfa in pregnant and lactating women and additional immunogenicity data will be required as PMRs.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety information for this clinical review includes compete study data from PB-06-001 and interim safety data for PB-06-002 and PB-06-003. The database cut-off date for the interim safety data was May 1, 2011. The applicant also included adverse event data from PB-06-004, PB-06-005 (see Table 41 in Section 7.3.2 for summary of serious adverse events), and compassionate use programs outside the United States (Europe, Brazil, Australia, Mexico, and Israel) in an integrated safety summary.

7.1.2 Categorization of Adverse Events

The applicant coded AEs by System Organ Class (SOC) and AE preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). I revised AE preferred terms and SOC terms so that AE terms were clustered together to allow for a more meaningful description of the AE profile of taliglucerase alfa (e.g., upper respiratory tract infection and nasopharyngitis were grouped together).

Reporting of adverse events included information such as classification of AE using standard medical terminology (MedDRA Version 10.1), system organ class (SOC), timing of AE in relationship to the infusion, classification of relationship to study medication, classification of severity of AE, and date of onset and resolution of AE. These appear to be adequate to assess the safety profile of taliglucerase alfa.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data from the various studies were not pooled as the type and quality of data collected and the duration of data collection varied. Only data from PB-06-001, PB-06-002, and PB-06-003 were submitted in electronic datasets.

7.2 Adequacy of Safety Assessments

Safety parameters for the three trials reviewed included ECG, echocardiogram, PFT, DEXA, QCSI, clinical chemistry, hematology, and urinalysis, and determination of ADA titers, including neutralizing antibodies for enzyme activity.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The safety database includes 121 patients with type 1 Gaucher disease (treatment-naïve or transitioning from imiglucerase) treated with taliglucerase alfa every other week with doses from 11 to 73 U/kg (see Table 39).

As of May 1, 2011, 59/121 (49%) patients had completed 12 months of treatment with taliglucerase alfa and 26/121 (21%) had completed 24 months of treatment.[21] Eighteen of 28 adult patients (64%) who were transitioned from imiglucerase to taliglucerase have completed 12 months of treatment.

Table 39: Total Patient Exposure to Taliglucerase Alfa

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

*Number of patients enrolled and treated as of May 1, 2011

Reproduced from applicant's submission

21 N.B. There is an error in the applicant's table. Twenty-six patients (all PB-06-001 patients) have completed 24 months of treatment. The table lists 24 patients.

The demographic data for PB-06-001, PB-06-002, and PB-06-004 were similar (See Table 40). The applicant noted that the mean age for patients in the switch-over trial and treatment protocol was about 10 years older than the mean age for patients in PB-06-001 (i.e., treatment-naïve patients). The applicant suggested that this difference could be explained by the fact that previously treated patients likely had received ERT for many years prior to trial enrollment; however, the submission did not include individual patient information regarding length of prior ERT treatment. Therefore, this assertion could not be substantiated. There were roughly equal numbers of males and females enrolled in the trials, with the exception of the pediatric trial PB-06-005 (males=8 [73%]; and females =3 [27%]).

Table 40: Baseline Demographics for Safety Population

Baseline Characteristics	Trial & Treatment Group					
	PB-06-001 30U/kg N=16	PB-06-001 60 U/kg N=16	PB-06-002 N=28	PB-06-004 N=50	PB-06-005 N=11	Overall N=121
Age						
Mean ± SD	36.3 ± 11.8	36.0 ± 12.2	44.7 ± 15.1	46.6 ± 15.9	8.2± 3.8	39.9 ± 17.7
Min-Max	19 to 74	19 to 58	13 to 66	21 to 85	2 to 14	2 to 85
Sex						
Male	8 (50%)	8 (50%)	15 (54%)	28 (56%)	8 (73%)	67 (55%)
Female	8 (50%)	6 (50%)	13 (46%)	13 (44%)	3 (27%)	54 (45%)
Race/Ethnicity						
White	16 (100%)	15 (94%)	28 (100%)	48 (96%)	10 (91%)	117 (97%)
Native American	0	0	0	1 (2%)	0	(1 (1%)
Other	0	1 (6%)	0	1 (2%)	1 (9%)	3 (2%)

7.2.2 Explorations for Dose Response

Relationship between dose and response was evaluated in PB-06-003. There was no clear dose response relationship in terms of safety signals seen. See Section 7.5.1 for evaluation of AEs and various dosages of taliglucerase treatment.

7.2.4 Routine Clinical Testing

Routine safety laboratory studies were performed for trials PB-06-002 and PB-06-003. Local laboratory facilities were used for measurements of platelet count, erythrocyte sedimentation rate, and urinalysis due to the instability of these measurements associated with shipping time and conditions. All other safety laboratory studies were performed in a single central laboratory center. Laboratory results are discussed in Section 7.4.2.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adequate evaluation for potential adverse events for the other ERTs for type 1 Gaucher disease was performed through a literature search by the Applicant. The literature review included analyses of a pharmacovigilance database for imiglucerase. The most common events reported in adults and adolescents were headache, pruritis, and rash; the most common events reported in children included dyspnea, fever, nausea, flushing, vomiting, and coughing.

All ERT products have the potential to produce anaphylaxis, severe allergic reactions, immune-mediated reactions, and infusion reactions. The labeling for Cerezyme notes that an anaphylactoid reaction has been reported in less than 1% of the patient population. The labeling for Lumizyme includes a box warning noting the risk for development of immune-mediated reactions. These reactions occurred several weeks to three years after initiation of Lumizyme infusions. Diminished therapeutic response due to the development of neutralizing antibodies has also been reported with the use of ERT products.

7.3 Major Safety Results

The major safety results reviewed in this section are from PB-06-002 and PB-06-003 except where noted otherwise. The reader is referred to my clinical review for the first cycle for details of the safety results for PB-06-001. Safety data from other studies submitted to this application are also reviewed and are presented in Section 7.4.

In PB-06-001, taliglucerase alfa appeared to be well tolerated. There were no reported deaths or serious adverse events. Three patients were withdrawn from the trial due to adverse events, including one patient who experienced anaphylaxis and one patient who experienced an allergic reaction; the third patient was withdrawn due to pregnancy. One patient who experienced an allergic reaction completed the trial. There were no other significant adverse events reported for PB-06-001.

The most commonly reported adverse events in PB-06-001 (occurring in more than 10% of patients) were infusion reaction (44%), upper respiratory infections/colds (22%) pharyngitis/throat infection, headaches (each 19%), and influenza/flu and arthalgia/back pain (13%). The most common infusion reactions were headache, chest pain/discomfort, arthralgia/back pain, flushing and allergic reaction/anaphylaxis. Nineteen of 32 patients developed ADA titers to taliglucerase. Safety results did not appear to be different for ADA-positive patients.

7.3.1 Deaths

No deaths have been reported in clinical trials to date. One patient treated in the Brazilian compassionate use program died from non-treatment related causes (tuberculosis and pulmonary disease).

7.3.2 Nonfatal Serious Adverse Events (SAEs)

Twelve SAEs were reported for the safety population, including 3 SAES in 3 patients during PB-06-002. One SAE (gastroenteritis in a patient in PB-05-005) was considered by the investigator to be related to treatment. Table 41 lists the specific serious adverse events reported in the clinical trials for taliglucerase. As noted earlier, there were no SAEs reported in PB-06-001.

Table 41: Summary of Serious Adverse Events in Taliglucerase Trials

PB-06-001	PB-06-002	PB-06-003	PB-06-004	PB-06-005
0/32	3/28 (11%) • Epistaxis (previous history of epistaxis) • Nephrolithiasis •Prolapsed rectum/bladder/cervix	8/44 (18%) • Idiopathic immune thrombocytopenia • Pain (secondary to knee hemangioma) • Pulmonary embolism • Multiple tooth extraction • Surgical repair of femoral head avascular necrosis • Rib fractures/ pneumothorax (trauma injuries) •Percutaneous stone removal •Knee replacement surgery	0/50	1/11 (9%) •Gastroenteritis

Narratives for the reported SAEs:

I reviewed the SAES of epistaxis, nephrolithiasis, and idiopathic immune thrombocytopenia in the first review cycle and did not consider these events to be treatment-related (see my first cycle review for further details). The patient narratives for the remaining SAEs are as follows:

Patient 20-211
SAE: prolapsed rectum bladder and cervix
The patient is a 64-year old white female with a history of uterine prolapse that began two years prior to study enrollment. Other medical history included spondylosis, osteopenia, breast cancer, and right shoulder replacement. Prior to enrollment, the patient had been treated with imiglucerase since July 1995. The patient enrolled in PB-06-002 and began treatment on October 22, 2009, receiving a dose of 3600 unit dosage every two weeks. The patient underwent surgery to correct the prolapsed rectum, cervix and bladder on (b) (6) with no reported complications.

Comment: This reviewer agrees that the event does not appear to be treatment-related.

Patient 10-013
SAE: Head Trauma due to Seizure
The patient is a 35-year old white male. His medical history included epilepsy, accessory spleen, cholelithiasis and splenic nodules. Medications included valproic acid for epilepsy. The patient completed treatment in PB-06-001 (60 U/kg treatment group) on May 5, 2009 and received his first infusion in PB-06-003 on May 18, 2009. His last infusion prior to the SAE was on September 7, 2010. On (b) (6), the patient was hospitalized due to a head trauma with bleeding caused by an epileptic seizure. The event resolved on September 18, 2010. The patient continued in the study through Month 15.

Comment: This reviewer agrees that the event does not appear to be treatment-related.

Patient 41-020
SAE: Right Femoral Head Avascular Necrosis and Acetabular Necrosis
The patient is a 33-year old white male enrolled male, The patient completed treatment in PB-06-001 (60 U/kg treatment group) on Jul 28, 2009 and received his first infusion in PB-06-003 on December 9, 2009. The patient's medical history included knee and hip osteomyelitis. The patient had a history of hip pain and limited movement since 2005 and had been evaluated for surgery but not scheduled for administrative reasons. Due to a history of worsening pain and limited movement for two years, the patient was referred for an orthopedic evaluation in January 2011 and was diagnosed with right acetabular and femoral head necrosis. The patient underwent right hip replacement on (b) (6) without operative or post-operative complications. His taliglucerase infusions were not interrupted perioperatively. The patient continued in the study.

Comment: This reviewer agrees that the event does not appear to be treatment-related.

Patient 41-022
SAE: Pain due to Haemangioma in Left Knee and Pulmonary Embolism
The patient is a 43-year old Hispanic male. His medical history included bilateral hip pain, left knee mass, airway disease treated with bronchodilators), and grade I diastolic dysfunction and cardiac murmur. In addition, the patient had a history of bleeding (hematomas, epistaxis, bleeding from the gums), with a severe epistaxis episode in 2004 that required treatment with tamponade, intubation and blood transfusions. The patient completed Protocol PB-06-001 (30 U/kg treatment group), receiving his last infusion on July 15, 2009. Due to delays in regulatory approval of the protocol, the patient was not enrolled into PB-06-003 until November 17, 2009. He received his first infusion in the extension study on December 9, 2009. The patient began to report increased bone pain associated with his left knee mass. He was evaluated for the pain and the evaluating physician recommended removal of the knee mass. The patient's last infusion prior to the surgery was on February 19, 2011 (Infusion #30). The ambulatory procedure was performed on (b) (6) as an outpatient. However, a defect in the bone remained post-operatively. Diagnostic evaluations (biopsy and CT scan) revealed a venous hemangioma of the left anterior tibia. An orthopedist recommended correction of the defect and the patient underwent a surgical repair of the left tibia (bone graft and titanium intramedullary nail placement) on (b) (6) without intraoperative problems. On April 10, 2011, the patient started complaining of fatigue, dyspnea and palpitations. His physical exam was significant for hypertension, tachypnea, tachycardia, and decreased oxygen saturation; the patient was afebrile and did not have bronchospasms. He was treated with oxygen by nasal cannula, nebulizer, and antibiotics. On April 11, 2011, the hypertension, tachypnea, and tachycardia persisted, and the patient continued to require supplemental oxygen by nasal cannula. An echocardiogram was performed which revealed a mean arterial pulmonary pressure 40mmHg and LVEF 0.55 with no thrombus seen. The patient was transferred to the coronary intensive care unit. Management included Clexane (enoxaparin sodium), ceftriaxone, amikacin and omeprazole. On April, 12, 2011, the patient's status was unchanged. CT angiography was performed which revealed no defects in the primary vessels, but micronodular edema was detected in peripheral regions suggestive of vasogenic pulmonary edema. On April 13, 2011, the patient continued to require oxygen, which was administered via a partial rebreathing mask. He experienced clinical improvement, with normalization of his blood pressure and decreased tachycardia but persisting tachypnea. The investigator diagnosed the patient as having pulmonary embolism. The event was resolved without sequelae and the patient was discharged from the hospital on (b) (6). The patient continued in the study.

Comment: This reviewer agrees that the event does not appear to be treatment-related.

Patient 42-025
SAE: Multiple Tooth Extraction
The patient is a 36-year old white female. The patient's medical history included cholelithiasis, hypothyroidism, intermittent bilateral hip pain, and dysmenorrhea. The patient completed Protocol PB-06-001 (30 U/kg treatment group) and received her last infusion on July 20, 2009. Due to delays in regulatory approval of the protocol, she received her first infusion in PB-06-003 on August 31, 2009. Her last infusion prior to the SAE was on Aug30, 2010 (Infusion #27). The patient was admitted as an inpatient on (b) (6) for dental surgery (defocation, plasty, and bimaxillary curettage) because she required a platelet transfusion (platelet count 30K/mm^3) prior to the procedure. The procedure was performed on (b) (6) and the patient was discharged on (b) (6). The patient continued in the study.

Comment: This reviewer agrees that the event does not appear to be treatment-related.

Patient 14-216
SAE: Right Gonarthrosis (Baseline Event)
The patient is a 47-year-old Hispanic male. He was diagnosed with Gaucher disease in 1971 and was treated with splenectomy in 1982. He started treatment with imiglucerase in 1998. The patient's medical history included arterial hypertension, hemorraghia, vertebral collapse, pneumonia, septicemia, bone pain, spinal fusion surgery, and bilateral leg bone infarcts. The patient completed his last infusion in PB-06-002 on July 21, 2010 and received his first infusion in PB-06-003 on August 4, 2010. The patient received 3600 Units (56 U/kg) every 2 weeks. His last infusion prior to the SAE was on October 27, 2010 (Infusion #7). The patient was admitted on (b) (6) for surgery on his right knee to place prosthesis. The surgery was planned in advance (January 20, 2010). The patient was discharged on (b) (6). The patient continued in the study.

Comment: This reviewer agrees that the event does not appear to be treatment-related.

Patient 15-222
SAE: Traumatic Fractured Four Ribs and Pneumothorax
The patient is a 23-year old white female. Her medical history included functional heart murmur, tricuspid valve regurgitation, minimal scoliosis, spina bifida occulta of S1, and accessory spleen. The patient completed her last infusion in PB-06-002 on September 7, 2010 and received her first infusion in PB-06-003 on September 21, 2010. The patient was receiving 800 Units (36 U/kg) every two weeks. Her last infusion prior to the SAE was on December 29, 2010 (Infusion #8). On (b) (6), the patient was hospitalized with a severe (Grade 3) traumatic fracture of four ribs (details of the trauma and hospitalization were not available). The patient was discharged on (b) (6). The patient continued in the study.

Comment: This reviewer agrees that the event does not appear to be treatment-related.

Patient 20-220
SAE: Percutaneous Renal Stone Removal
The patient is a 49-year old white male. His medical history included renal stone of left kidney, gall stones, hypothyroid, slightly decreased bone tubulation in extremities (bilateral hand, femur, and tibia), and degenerative disc disease of the cervical spine. The patient received his last infusion in PB-06-002 on September 7, 2010. He enrolled into PB-06-003 and received his first infusion on September 21, 2010. The patient is receiving taliglucerase alfa 3000 Units (28 U/kg) every two weeks. His last infusion prior to the SAE was on February 2, 2011 (Infusion #10). On (b) (6), the patient was admitted to the hospital for percutaneous removal of kidney stones and was discharged on (b) (6). The patient had no post-operative complications. The patient missed Infusion #11 and continued in the study.

Comment: This reviewer agrees that the event does not appear to be treatment-related.

Patient 11-5005
SAE: Gastroenteritis
The patient is an 8-year old South African male diagnosed with Gaucher disease in 2006. His medical history included disease related hepatosplenomegaly, anemia, thrombocytopenia, decreased appetite, tiredness and vitamin B12 deficiency. This patient was enrolled into Study PB-06-005 on November 8, 2010 and received his first taliglucerase alfa infusion on December 8, 2010. During the infusion, the patient experienced a severe (grade 3) gastroenteritis event. The infusion was stopped and the patient was given Zofran with improvement of his symptoms; the infusion then was re-started and completed. The investigator admitted the patient for observation and rehydration overnight. The patient stabilized and symptoms resolved; he was discharged the next morning. On December 23, 2010, One hour after starting his second infusion, the patient started to perspire, said that he was not feeling well, and subsequently vomited. The infusion was interrupted for 10 minutes and the patient was given loratadine with improvement of his symptoms. The infusion was re-started and completed. The patient stabilized and symptoms resolved. The investigator considered the event to be definitely related to taliglucerase alfa treatment. The patient was treated with loratadine prior to subsequent infusions. At the time of database freeze on May 1, 2011, the patient is continuing in the study. The patient completed his Week 20 infusion on April 26, 2011 without recurrence of the event. The sponsor determined that there was a reasonable possibility that taliglucerase caused the event of gastroenteritis.

Comment: This reviewer agrees that the event appears to be treatment-related.

7.3.3 Dropouts and/or Discontinuations

A total of 12 patients were withdrawn from treatment, including 3 patients who were withdrawn from PB-06-001 for safety reasons (one patient with anaphylaxis, one patient with an allergic reaction, and one patient who became pregnant), 1 patient from PB-06-002 with an allergic reaction, 3 patients withdrawn from PB-06-003 (1 patient enrolled from PB-06-001 with a possible allergic reaction, and 2 patients enrolled from PB-06-002 for reasons not related to safety) and 5 patients who voluntarily withdrew from PB-06-004 for reasons not related to safety. No further information was provided on the dropouts from PB-06-004.

In addition, the applicant reported that 12 patients discontinued from compassionate use programs due to an AE, including 5 patients with hypersensitivity reactions, 2 patients with anaphylactic reactions, 2 patients with urticaria, and one patient each with infusion site pruritis, facial swelling, and chest pain/fear of death. No further information was provided on these patients. However, the descriptions of these adverse events are consistent with allergic reactions and/or anaphylaxis.

7.3.4 Significant Adverse Events

Severe Adverse Events
Ten patients experienced 15 severe AEs. The applicant reported that none of these events were treatment-related, except for an event of severe gastroenteritis in a pediatric patient (patient 11-5005) in PB-06-005.

Three patients from PB-06-001 experienced 4 severe AEs during PB-06-003:

- 41-022 (60 U/kg treatment group): pain due to left knee hemangioma, pulmonary embolism
- 11-007 (60 U/kg treatment group): autoimmune thrombocytopenia
- 40-018 (60 U/kg treatment group): new onset Type 1 diabetes mellitus

Two patients from PB-06-002 experienced 3 severe AEs during PB-06-003:

- 18-219: hematuria; nephrolithiasis; pelvic prolapse
- 20-220: hospitalization for renal stone removal

Five patients in PB-06-004 experienced 6 severe AEs:

- 04-4013: history of left hip pain which worsened
- 71-4007: left calf pain (pt had history of ligament injury and bone infarct)
- 71-4011: back pain (pt had history of Gaucher related bone disease)
-
- 75-4021: migraine
- 78-4043: left leg pain and swelling

Reviewer Comment:
I agree with the applicant's assessment of the reported severe adverse events.

Allergic Reactions
The Applicant searched the safety database for all clinical trials for suspected allergic adverse events, including Type 1 events (including events with the preferred terms of anaphylactic reaction, anaphylactic shock, angioedema, hypersensitivity, and pruritis) and Type II, III, and IV allergic events. The applicant reported Type 1 allergic reactions in 15 patients, including 7 patients experiencing pruritis, 3 patients experiencing edema (1 patient each with facial edema, lip swelling, and eye swelling), and 5 patients experiencing hypersensitivity (see Table 42). Nine of the 15 patients required no intervention or minor intervention (i.e., temporary interruption of the infusion or treatment, or treatment of sign/symptom with medication) for management of the event. Six patients required pre-medication (e.g., antihistamines, steroids, etc.) with subsequent infusions or discontinuation of infusions, including 5 patients who experienced hypersensitivity reactions and 1 patient who experienced eye swelling. One patient (10-001) experienced a Type III allergic event of fixed drug eruption and has continued on infusions without any clinical interventions.

Table 42: Patients Experiencing Allergic Reactions in All Clinical Trials

Patient ID#	Adverse Event Preferred Term
10-218	Pruritis
42-026	Pruritis
04-4012	Pruritis
70-4035	Face edema
77-4044	Pruritis
78-4043	Generalized Pruritis
10-013	Pruritis
42-025	Pruritis
03-4008	Lip swelling
30-009	Hypersensitivity
70-4022	Hypersensitivity
10-002	Hypersensitivity
10-003	Hypersensitivity
13-228	Hypersensitivity
20-4026	Eye swelling

Source: applicant's submission

I reviewed the patient narratives for the six patients that required premedication or discontinuation of in fusions due to allergic reactions. See Section 7.3.5 for patient narratives for patients 13-228 and 20-4026. Patient narratives for the remaining

patients were reviewed during the first review cycle (see my first cycle review for further details).
In addition, as noted earlier, the applicant reported 11 patients in compassionate use programs that discontinued treatment due to allergic reactions, including 5 patients with hypersensitivity reactions, 2 patients with anaphylactic reactions, 2 patients with urticaria, and 1 patient each with infusion site pruritis and facial swelling. No further information was provided on these patients.

Bone events
The applicant reviewed the safety database for bone events, defined as including events with the following Preferred Terms: bone disorder, bone infarction, osteonecrosis, bone pain, bone swelling, and musculoskeletal pain. Ten (8.3%) patients experienced 15 bone events. These included 8 patients in PB-06-004, 6 patients in PB-06-003 (all enrolled from PB-06-001), and 1 patient in PB-06-002. One patient (11-014 from PB-06-003) had bone pain (bone crisis) and 1 patient (04-4023 from PB-06-004) had musculoskeletal pain that was considered by the investigator to possibly be treatment related.[22]

One patient (41-020) from PB-06-001 had severe events of osteonecrosis of the right femoral head and right acetabulum during PB-06-003. Patient (30-011 reported spine pain (patient had a history of surgery for spinal disc hernia). None of the bone events were assessed as severe, with the exception of the events reported for patient 41-020.

One patient (11-014) experienced a bone crisis event that resulted in the patient's dose being increased (dose increased from 30 U/kg to 45 U/kg). The patient is a 38 year-old white male with a medical history of bone pain and bilateral knee surgery. The patient was randomized into the 30 U/kg treatment group in PB-06-001. He completed PB-06-001 and entered PB-06-003. Approximately one week after his infusion (about Month 29 of treatment), the patient reported a Grade 2 bone crisis adverse event that the investigator assessed as possibly related to treatment. The patient was evaluated by MRI (MRI results not provided) and treated with meloxicam and ibuprofen. The patient's dose was increased to 45 U/kg beginning with his 39th infusion. The event resolved and has not recurred. The patient is continuing treatment on the same dose. The patient is ADA-negative.

Reviewer Comment: As discussed earlier in Section 2, bone disease contributes significantly to the morbidity of Gaucher disease. The data provided in the applicant's submission is insufficient to assess for safety or efficacy related to bone disease since no information was provided on the baseline incidence of bone disease in study patients. It is unclear why any bone events were assessed as possibly treatment

22 The applicant also reported patient 30-011 as having bone pain that was assessed as treatment-related. However, no bone pain events for this patient were assessed as treatment –related in the adverse event analysis datasets.

related. None of the bone events for PB-06-002 or PB-06-003 occurred in association with an infusion (no information was available on the timing of the event related to an infusion for patient 41-0200. The bone adverse events described above are consistent with underlying Gaucher-related bone disease in these patients.

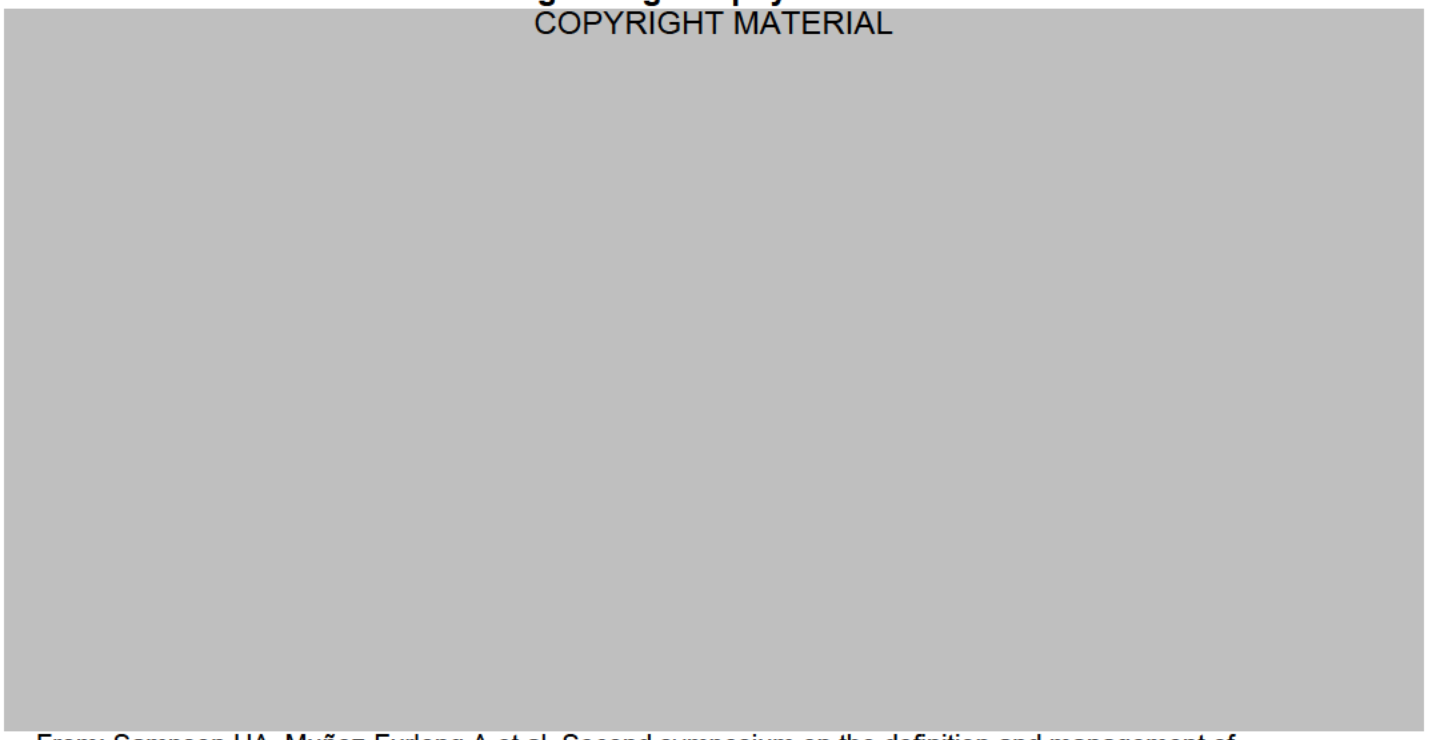
7.3.5 Submission Specific Primary Safety Concerns

Anaphylaxis and Severe Allergic Reactions
The Applicant performed standardized MedDRA queries on the safety data for the following: anaphylactic reactions, anaphylactic shock, angioedema, toxic septic shock, asthma and bronchitis, and hypersensitivity. Hypersensitivity events included events with a preferred term of pruritis or generalized pruritis. The Applicant excluded cases of pruritis that occurred as an isolated event or were not associated with an infusion.

There were no cases found under anaphylactic shock, toxic septic shock, or asthma and bronchitis. All events of anaphylactic reaction, angioedema, pulmonary hypertension, and extravasation were classified as mild or moderate.

In addition, I reviewed AEs reported under the preferred term allergic reaction or hypersensitivity and patient narratives provided by the applicant using the criteria developed by the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) to diagnose anaphylaxis (see Table 43).

Table 43: Clinical Criteria for Diagnosing Anaphylaxis



From: Sampson HA, Muñoz-Furlong A et al, Second symposium on the definition and management of anaphylaxis: Summary report- second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium, *J Allergy Clin Immunol* 2006; 117: 391-7.

Based on these criteria and the AE reports reviewed during the current review cycle and the prior review cycle, 3 patients in clinical trials definitely or possibly experienced anaphylaxis. One patient (10-002) in PB-06-001 and one patient (30-009) in PB-06-003 definitely experienced anaphylaxis; both patients were in the 60 U/kg treatment group. There was insufficient information for one patient (patient 74-4022 in PB-06-004) to determine if he had developed anaphylaxis. These events were reviewed during the first review cycle (see my first cycle review for further details).

In addition, the applicant reported that 2 patients being treated in compassionate use programs had experienced anaphylactic reactions; these events resulted in the patients being discontinued from treatment.

Narratives for the reported allergic reaction AEs:

Patient 13-228 (PB-06-002)
The patient experienced an allergic reaction (urticaria, diffuse rash, and pruritis) during her initial infusion. The patient was administered a corticosteroid and antihistamine with resolution of her symptoms. The patient was negative for IgG and IgE antibodies. The

patient declined continuation of treatment with premedication and withdrew from the study.

Comment: The patient's symptoms do not meet anaphylaxis criteria.

Patient 20-4026 (PB-06-004)
The patient developed symptoms of sneezing, runny nose, and throat congestion shortly after the start of her initial infusion. The infusion was stopped and the patient was treated with an antihistamine; the infusion was restarted and completed. The patient was premedicated with loratadine and omeprazole for her second infusion. She experienced a runny nose. She continued to experience allergy-like symptoms with all subsequent infusions, including sneezing, runny nose, itching, water and puffy eye, cough, and tightness and burning with chest. She was administered an antihistamine for her last four infusions (Infusion#7-10). She withdrew from the study after her 10th infusion and resumed treatment with imiglucerase. No information was provided on her antibody status.

Comment: The patient's symptoms do not meet anaphylaxis criteria.

Infusion reactions
At the request of DGIEP, the applicant submitted datasets on the timing of the AE in relationship to the infusion and divided the AEs into 3 categories: 1) AE onset during the infusion or within 2 hours of completion of infusion 2) AE onset between 2-24 hours post- infusion 4) AE onset greater than 24 hours post- infusion. I independently re-evaluated the relationship of the AE to the study drug. Many AEs that occurred during the infusion or within two hours after completion of the infusion were classified as unlikely related to the study medication by the applicant. I analyzed the clinical context of the AEs and recoded them as possibly related to the study drug if the event occurred during the infusion or within 24 hours after completion of the infusion. The preferred terms that were recoded as possibly related included: abdominal/epigastric discomfort, arthralgia, asthenia chest pain/discomfort, dizziness, drug eruption, dyspnea, erythema, fatigue, feeling hot, flushing, infusion related reaction, headache, hyperglycemia, hyperhidrosis, hypersensitivity, hypertension, lethargy, nausea, pain, palpitations, presyncope, pruritis, pyrexia, rash/skin irritation, swelling, tachycardia, and vomiting. Table 44 summarizes the number of infusion reaction AEs and number of patients experiencing infusion reaction AEs based on recoding of AEs.

Table 44: Summary of Infusion Reaction Events by Trial

PB-06-001 n=32 Events/Patients (%)	PB-06-002 n=28 Events/Patients (%)	PB-06-003 n=44 Events/Patients (%)
39/14 (44%)	38/13 (46%)	44/18 (41%)

Table 45 lists the most commonly reported infusion reaction AEs (infusion reaction AEs reported in two or more patients). The reported number of patients with allergic reactions in the table includes patients with reactions that met the criteria for anaphylaxis. The most commonly reported infusion reactions were infusion-related reaction, headache, arthralgia/back pain, and urticaria/rash/ drug eruption. Overall, infusion reaction AEs were mild in severity and did not impact the patient's ability to receive their scheduled infusions.

Table 45: Most Commonly Reported Infusion Reactions (Occurring During or up to 24 hours Post-infusion) in All Clinical Trials

System Organ Class Preferred Term	**PB-06-001** **N=32**	**PB-06-002** **N=28**	**PB-06-003** **N=44**
General Disorders and Administration Site Conditions (N=13)			
Infusion related reaction	0	4 (14%)	2 (5%)
Asthenia	0	2 (7%)	0
Chest pain/discomfort	2 (6%)	0	0
Fatigue	0	1 (4%)	2 (5%)
Nervous System Disorders (N=13)			
Headache	5 (16%)	2 (7%)	1 (2%)
Hypoesthesia/paraesthesia	1 (3%)	1 (4%)	1 (2%)
Dizziness/Presyncope	1 (3%)	0	1 (2%)
Skin and Subcutaneous Tissue Disorders (N=10)			
Erythema	1 (3%)	1 (4%)	2 (5%)
Urticaria/rash/drug eruption	0	1 (4%)	3 (7%)
Pruritis	1 (3%)	1 (4%)	0
Gastrointestinal Disorders (N=8)			
Abdominal/Epigastric discomfort	1 (3%)	1 (4%)	1 (2%)
Diarrhea	1 (3%)	1 (4%)	1 (2%)
Vomiting	1 (3%)	0	1 (2%)
Musculoskeletal and Connective Tissue Disorders (N=7)			
Arthralgia/back pain	2	2 (7%)	3 (7%)
Vascular Disorders (N=6)			
Flushing	2 (6%)	1 (4%)	0
Hypertension/increased blood pressure	1 (3%)	0	2 (5%)
Immune System Disorders (N=3)			
Allergic reactions*	3 (9%)	0	1 (2%)

*Includes patients with allergic reactions meeting criteria for anaphylaxis.

Immune-mediated Reactions
As noted earlier, immune-mediated reactions have been reported in patients treated with other ERTs (see Section 7.2.6). As noted earlier, one patient (10-001 in the 30 U/kg treatment group) experienced a Type III allergic event of fixed drug eruption. The drug eruption was first noted after the patient's 12th infusion in PB-06-003 (about 15 months of treatment). The time interval between initiation of ERT and development of drug eruptions in this patient is consistent with what has been reported for other ERT products (weeks to 3 years).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Overall, the frequency of AEs was similar across trials with infusion reactions, nasopharyngitis/URI, arthralgia/back pain, and headaches being included in the most commonly reported AEs in all three studies (see Table 46).

Table 46: Most Commonly Reported Adverse Events (>5% of treated patients) for Trials PB-06-001, PB-06-002, and PB-06-003

		PB-06-001	PB-06-002	PB-06-003
System Organ Class	**Preferred Term**	**N=32**	**N=28**	**N=44**
Infections and Infestations				
	URI/Nasopharyngitis	7 (22%)	5 (18%)	18 (41%)
	Pharyngitis/Throat infection	6 (19%)	1 (4%)	3 (7%)
	Eye infection	2 (6%)		
	Influenza/Flu	4 (13%)	1(4%)	2 (5%)
	UTI/Pyelonephritis	3 (9%)	3 (11%)	
	Gastroenteritis	2 (6%)		2 (5%)
	Otitis externa	2 (6%)		
	Sinusitis			4 (9%)
	Fungal infection	2(6%)		(
	Fungal skin infection/Onychomycosis	1 (3%)		2 (5%)
Nervous System Disorders				
	Headache	6 (19%)	3(11%)	8 (18%)
	Dizziness	3 (9%)		

Table 46: Most Commonly Reported Adverse Events (>5% of treated patients) for Trials PB-06-001, PB-06-002, and PB-06-003 (cont'd)

		PB-06-001	PB-06-002	PB-06-003
System Organ Class	**Preferred Term**	**N=32**	**N=28**	**N=44**
Musculoskeletal and Connective Tissue Disorders				
	Arthralgia	4 13%)	3 (11%)	8 (18%)
	Back pain	1(3%)	2 (7%)	4 (9%)
	Bone pain			3 (7%)
	Extremity pain		3 (11%)	5 (11%)
	Limb/musculoskeletal discomfort			2 (5%)
	Myalgia			2 (5%)
	Synovial cyst			2 (5%)
Gastrointestinal disorders				
	Vomiting	2 (6%)		4 (9%)
	Diarrhea		2 (7%)	3 (7%)
	Abdominal pain	2 (6%)		
	Toothache			3 (7%)
General disorders				
	Infusion reaction		13 (46%)	18 (41%)
	Fatigue/tiredness	3 (9%)		3 (7%)
	Feeling hot/Pyrexia	2 (6%)	1 (4%)	5 (11%)
	Asthenia		2 (7%)	
	Pain		2 (7%)	44 (9%)
Skin and Subcutaneous disorders				
	Itching	2 (6%)		
	Contact dermatitis			2 (5%)
	Erythema		1 (4%)	3 (7%)
	Pruritis		2 (7%)	4 (9%)
	Rash		1 (4%)	2 (5%)
	Skin lesion			2 (5%)
Vascular disorders				
	Flushing	2 (6%)	2 (7%)	
	Hypertension/high BP	2 (6%)		
Blood and lymphatic system disorders				
	Enlarged lymph nodes	2 (6%)		
	Spleen disorder		3 (11%)	
Immune system disorders				
	Hypersensitivity	2 (6%)		
Respiratory, Thoracic, and Mediastinal Disorders				
	Epistaxis	2 (6%)		3 (7%)
	Cough		2 (7%)	3 (7%)
	Pharyngolaryngeal pain			3 (7%)

PB-06-002
All of the patients in PB-06-002 treated with taliglucerase alfa experienced at least one AE, for a total of 150 AEs. Two patients experienced severe AEs unrelated to treatment (events of hematuria and nephrolithiasis in one patient and pelvic prolapse in another patient). All other reported AEs were mild or moderate in intensity. Ten patients (36%) experienced 24 AEs that were considered treatment related by the investigator, (21 infusion reactions in 8 patients, weight increase in 1 patient, and 2 events of increased liver transaminases in 1 patient). AEs reported in more than 1 patient included infusion reactions (13 patients, 46%), nasopharyngitis (5 patients, 18%), arthralgia, respiratory tract infection (each 4 patients, 14%), headache, extremity pain, spleen disorder (each 3 patients, 11%), pain, back pain, abdominal pain, urinary tract infection, cough, asthenia, flushing, diarrhea, and fever/pyrexia (each 2 patients, 7%)

The most commonly experienced AEs were infusion reactions (13 patients, 46%) and nasopharyngitis (5 patients, 18%). Infusion reaction symptoms included headache, itching, fatigue/tiredness, flushing, lethargy, and feeling weak. Table 47 lists adverse events reported by two or more patients in PB-06-002.

Table 47: PB-06-002- Most Commonly Reported Adverse Events (>5% of treated patients)

System Organ Class	Preferred Term	Number of patients N=28
Infections and Infestations		
	URI/nasopharyngitis	5 (18%)
	UTI	3 (11%)
Musculoskeletal and Connective Tissue Disorders		
	Arthralgia/back pain/ extremity pain	4 (14%)
Nervous System Disorders		
	Headache	3(11%)
Gastrointestinal Disorders		
	Diarrhea	2 (7%)
	Abdominal pain	
General Disorders and Administration Site Conditions		
	Asthenia	2 (7%)
	Infusion reaction	13 (46%)
	Fever/pyrexia	2 (7%)
	Pain	2 (7%)
Blood and Lymphatic System Disorders		
	Spleen disorder	3 (11%)
Respiratory, Thoracic, and Mediastinal Disorders		
	Cough	2 (7%)
Vascular Disorders		
	Flushing	2 (7%)

PB-06-003

The most common AEs (≥10%) reported in all patients were infusion reactions, nasopharyngitis/URI (18 patients each, 41%), infusion reactions (13 patients, 30%), arthralgia, headache (8 patients each, 18%), extremity pain, pyrexia, and hypertension/increased blood pressure (5 patients each, 11%). Table 48 lists adverse events reported by two or more patients in PB-06-003.

Table 48: PB-06-003- Most Commonly Reported Adverse Events (>5% of treated patients)

System Organ Class	Preferred Term	PB-06-001 N=26		PB-06-002 N=18	All Pts N=44
		30 U/kg N=12	60 U/kg N=14		
Infections and Infestations					
	Gastroenteritis	1 (8%)	1 (7%)	0	2 (5%)
	Influenza	0	2 (14%)	0	2 (5%)
	Nasopharyngitis/URI	5 (42%)	6 (43%)	7 (25%)	18 (41%)
	Pharyngitis	2 (17%)		1 (4%)	3 (7%)
	Sinusitis	0	3 (21%)	1 (4%)	4 (9%)
Musculoskeletal and Connective Tissue Disorders					
	Arthralgia	4 (33%)	3 (21%)	1 (4%)	8 (18%)
	Back pain	2 (17%)	1 (7%)	1 (4%)	4 (9%)
	Bone pain	1 (8%)	2 (14%)	0	33 (7%)
	Extremity pain	1 (8%)	3 (21%)	1 (4%)	5 (11%)
	Limb/musculoskeletal discomfort	0	1 (7%)	1 (4%)	2 (5%)
	Myalgia	1 (8%)	1 (7%)	0	2 (5%)
	Synovial cyst	1 (8%)	0	1 (4%)	2 (5%)
Nervous System Disorders					
	Headache	4 (33%)	4 (29%)		8 (18%)
General Disorders and Administration Site Conditions					
	Fatigue	1 (8%)	2 (14%)	0	3 (7%)
	Infusion Reaction	7 (58%)	8 (57%)	3 (11%)	18 (41%)
	Pain	2 (17%)	1 (7%)	1 (4%)	44 (9%)
	Pyrexia		3 (21%)	2 (7%)	5 (11%)
Skin and Subcutaneous Tissue Disorders					
	Contact dermatitis	1 (8%)	1 (7%)	0	2 (5%)
	Erythema	3 (25%)	0	0	3 (7%)
	Pruritis	1(8%)	2 (14%)	1 (4%)	4 (9%)
	Rash	1 (8%)	1 (7%)	0	2 (5%)
	Skin lesion	1 (8%)	1 (7%)	0	2 (5%)

Table 48: PB-06-003- Most Commonly Reported Adverse Events (>5% of treated patients) – cont'd

System Organ Class	Preferred Term	PB-06-001 N=26		PB-06-002 N=18	All Pts N=44
		30 U/kg N=12	60 U/kg N=14		
Respiratory, Thoracic, and Mediastinal Disorders					
	Cough	0	2 (14%)	1 (4%)	3 (7%)
	Epistaxis	2 (17%)	1 (7%)	0	3 (7%)
	Pharyngolaryngeal pain	1 (8%)	2 (14%)	0	3 (7%)
Gastrointestinal disorders					
	Diarrhea	2 (17%)	0	1 (4%)	3 (7%)
	Toothache	1 (8%)	1 (7%)	1 (4%)	3 (7%)
	Vomiting	1 (8%)	1 (7%)	2 (7%)	4 (9%)
Vascular Disorders					
	Hypertension/increased blood pressure	3 (25%)	2 (14%)	0	5 (11%)
Surgical and Medical Procedures					
	Tooth extraction	1 (8%)	1 (7%)	1 (4%)	3 (7%)
Injury, Poisoning and Procedural Complications					
	Limb Injury	0	2 (14%)	0	2 (5%)
Metabolism and Nutrition Disorders					
	Hypertriglyceridemia	0	2 (14%)	0	2 (5%)
Psychiatric Disorders					
	Depression	1 (8%)	1 (7%)	0	2 (5%)

7.4.2 Laboratory Findings

PB-06-002

Six patients experienced 7 laboratory AEs: including increased alanine aminotransferase (ALT) and gamma-glutamyl transaminase (GGT) in a patient with Gilbert syndrome (15-223), decreased blood folate(14-210), increased blood glucose (18-219), increased cholesterol (20-209), prolonged activated partial thromboplastin time (23-206), and abnormal urinalysis (18-221). All of these laboratory abnormalities were assessed as mild. The events of elevated transaminases were assessed as possibly related to treatment. All events resolved except for the events of increased ALT and GGT in patient 15-223. The patient with increased cholesterol was treated with an unspecified medication with resolution of the increased cholesterol.

Five patients experienced increases in liver transaminase values to above the upper limit of normal (ULN), including two patients with increased ALT values (10-203, 22-226, and 15-223) and two patients with increased AST values (12-230 and 15-223).[23] None of the increases were > 3 times ULN. Of these five patients, the applicant noted that two patients (15-223 and 23-204) had a medical history of Gilbert disease.

Four patients experienced transient increases in total bilirubin values above ULN (14-216, 15-223, 23-204, and 60-208); abnormal values ranged from 1.3 mg/dL to 1.9 mg/d. Of these four patients, one patient (15-223) had a medical history of Gilbert disease. The applicant also stated that there was no laboratory evidence fulfilling Hy's Law for hepatotoxicity.

Fourteen patients experienced elevations in non-fasting serum glucose from normal values at baseline. Most patients had transient elevations. Hemoglobin A1c levels were obtained on all patients at baseline and at 9 months (or at the withdrawal visit). Three patients were noted to have elevated hemoglobin A1c levels, including two patients with a known diagnosis of Type 2 diabetes mellitus and one patient without a known diagnosis of diabetes. One patient who had a normal hemoglobin A1c level had several episodes of elevated glucose values (18-219).

PB-06-003
There was one report of hypertriglyceridemia and one report of diabetes mellitus in 2 individual patients; both patients were in the 60 U/kg treatment group. The event of hypertriglyceridemia was reported as not resolved; the patient was not treated for hypertriglyceridemia. The patient with diabetes mellitus was treated with insulin.

Overall
In both trials, the majority of laboratory hematology and biochemistry parameters remained at normal baseline levels. All reported laboratory AEs were classified as mild in severity. All laboratory AEs resolved, with the exception of events reported in patients with underlying medical conditions (Gilbert syndrome, diabetes mellitus) and two events of hyperlipidemia in two individual patients.

Reviewer Comment: This reviewer notes that the two patients with underlying hepatocellular disease had the most persistent elevations in liver transaminases. This finding prompts the question of what the exposure of this product would be in patients who had significant liver function impairment. Long-term safety monitoring for this product should include monitoring of liver function. Otherwise, there did not appear to be any pattern in the laboratory findings concerning for a possible safety signal.

23 Patient 15-223 had abnormal ALT values at screening.

7.4.3 Vital Signs

Vitals signs were measured at each infusion visit for 210 minutes- prior to infusion, every 15 minutes up to 2 hours during the infusion, and three additional measurements every 30 minutes

One AE of body temperature increased was reported in PB-06-003 that occurred at least 24 hours after an infusion. Otherwise, all vital sign AEs reported were assessed as related to allergic reactions.

7.4.4 Electrocardiograms (ECGs) and echocardiograms

Two patients had ECG AEs (23-206 [Study PB-06-002]: sinus tachycardia and 15-222 [Study PB-06-003]: supraventricular extrasystole) that were reported as unrelated to treatment. However, this reviewer notes that both AEs occurred during or within 2 hours of an infusion; both events resolved. Otherwise, no clinically significant ECG changes from baseline were observed during PB-06-002 or PB-06-003.

No clinically significant echocardiogram changes from baseline were observed during PB-06-002 or PB-06-003. In PB-06-003, two patients with baseline abnormalities (patient 15-016: congenital bicuspid valve, mild tricuspid valve regurgitation, mild pulmonary hypertension; patient 42-026: mild atrial dilatation) continued to have abnormal results after 24 months of treatment. Two other patients with baseline abnormalities (patient 10-013: mild mitral regurgitation and tricuspid regurgitation; patient 23-204: abnormal LV diastolic filling, mild aortic valve insufficiency, and mitral valve regurgitation) continued to have abnormal results after 36 months of treatment. Three of the patients were in the 60 U/kg treatment group; one patient (23-204) was in the PB-06-002 treatment group.

Reviewer Comment: None of the observed echocardiogram abnormalities appear to be concerning for a possible safety signal.

7.4.6 Immunogenicity

An important safety consideration with all enzyme replacement therapies for lysosomal storage diseases is the development of immune responses to the enzyme therapy. These immune responses can be associated with the development of allergic and immune-mediated reactions as well as potential attenuation of long-term effectiveness of treatment. A deficiency noted in the Complete Response Letter included the lack of an acceptable cut-point for the confirmatory anti-drug antibody assay (cut-point was too high). Therefore, the applicant provided new cut-point for assessment of ADA responses as part of the Complete Response. The applicant submitted re-analyses of antibody testing results in this submission using a lower cut-point agreed upon with the

Agency. Tables 49-51 summarize antibody testing results for PB-06-001, PB-06-002, and PB-06-003. Adverse events listed in the table include adverse events that I classified as infusion reactions.

As stated in Section 5, the applicant also evaluated ADA responses for the duration of the trials (i.e., for 9 months in PB-06-001 and in PB-06-002 and up to 30 months in PB-06-003). Patients were classified as Negative, Persistent Positive (i.e., the titer increased and remained high), Tolerized Positive (i.e., titers increased to a peak level and then decreased), and Transient Positive (i.e., the presence of one positive sample or low titer). Patients who developed positive titers prior to treatment that did not increase over the baseline value during treatment were classified as negative. I do not agree with the applicant's definition of Negative status since it is not possible to distinguish between patients who had persistent antibodies from baseline and patients who newly developed low antibody titers during treatment.

Immunogenicity data for each trial are reviewed below. Fifteen of 18 ADA-positive patients in PB-06-001 enrolled into PB-06-003. Three of 5 ADA-positive patients in PB-06-002 enrolled into PB-06-003. As discussed in the review of PB-06-003 immunogenicity data, some patients experienced a change in immunogenicity status during PB-06-003 from their status at the end of PB-06-001 or PB-06-002.

PB-06-001
Based on the Applicant's reanalysis, 18/ 32 treated patients developed ADA titers during the trial. Two patients who were ADA-positive developed allergic reactions. Patient 10-003 (30 U/kg treatment group) had a positive IgE antibody titer pre-infusion on Day 1. He experienced an allergic reaction within a few minutes after the start of his initial infusion and was discontinued from the trial. Patient 10-002 experienced an anaphylactic reaction; he was discontinued from the study. Two patients developed inhibitory antibodies (30-008 from the 30 U/kg treatment group and 15-016 from the 60 U/kg treatment group) developed inhibitory antibodies but did not experience any adverse events during PB-06-001. Both patients completed the study and enrolled into PB-06-003.

Table 49: PB-06-001 Patients with Positive Antibodies

Patient ID#	Initial IgG Titer	Highest IgG Titer	Trial End IgG Titer	IgG Titer Assessment	IgE Antibody	Adverse Events	Allergic reaction?
30 U/kg Treatment Group							
10-001	2333 (Wk 30)	8094 (Wk 38)	8094 (Wk 38)	Persistent Positive	negative	vomiting facial flushing	No
10-003	Negative (Day 1)	--	1361 (Wk 38)	Negative	positive (Day 1)	allergic reaction	**Yes**
10-028	872 (Wk 16)	NA872 (Wk 16)	negative (Wk 6)	Persistent Positive	negative		No
17-032	NA (Wk 26)	NA	NA (Wk 38)	Persistent Positive	negative		No
30-008	NA (Wk 24)	6355 (Wk 24)	negative (Wk 38)	Persistent Positive	positive		No
30-010	47 (Day 1)	184 (Wk 34)	NA (Wk 38)	Tolerized Positive	negative		No
60 U/kg Treatment Group							
10-002	1097 (Wk 20)	1649 (Wk 22)	1649 (Wk 22)	Persistent Positive	negative	anaphylactic reaction	**Yes**
10-004	6999 (Wk 16)	6999 (Wk 16)	6999 (Wk 16)	Tolerized Positive	negative		No
10-005	96 (Wk 2)	96 (Wk 2	96 (Wk 2	Persistent Positive	negative		No
10-013	160 (Wk 16)	1119 (Wk 34)	1119 (Wk 34)	Tolerized Positive	negative		No
11-007	100 (Wk 12)	100 (Wk 12)	100 (Wk 12)	Transient Positive	negative		No
12-024	172 (Wk 4)	1467 Wk 26)	1467 (Wk 26)	Persistent Positive	negative		No
14-027	NA (Wk 24)	NA (Wk 24)	NA (Wk 24)	Transient Positive	negative		No
15-016	452 (Wk 24)	452 (Wk 24)	452 (Wk 24	Persistent Positive	positive		No
22-030	NA (Wk 24)	NA	NA	Persistent Positive	negative		No
30-009	NA (Wk 34)	NA	NA	Tolerized Positive	negative		No
30-011	NA (Wk 6)	207 (Wk 8)	207 (Wk 8)	Transient Positive	negative		No
42-026	NA (Wk 30)	NA	NA	Persistent Positive	negative		No

NA= Quantitative IgG titer was not done

PB-06-002

Based on the Applicant's reanalysis, 5/28 (18%) patients developed anti-GCD antibodies during the study. None of the patients had antibodies to imiglucerase. All 5 patients completed the trial. One patient (13-228) with negative antibody titers withdrew

from the study after the first infusion; the patient experienced an allergic reaction and declined to continue infusions with premedication.

Table 50: PB-06-002 Patients with Positive Antibodies

Patient ID#	Initial IgG Titer	Highest IgG Titer	End of Trial IgG Titer	IgG Titer Assessment	IgE Antibody	Adverse Events	Allergic reaction?
14-210	NA (Screening)	3542 (Week 24)	658 (Month 9)	Persistent Positive	Negative	asthenia pruritis	No
20-220	NA (Week 18)	23045 (Month 9)	23045 (Month 9)	Persistent Positive	Positive		No
20-224	NA (Week 8)	NA (Week 8)	negative (Month 9)	Transient Positive	Negative		No
23-206	NA (Screening)	978 (Day 1)	negative (Month 9)	Transient Positive	Negative	sinus tachycardia flushing prolonged PTT	No
60-217	810 (Week 24)	2768 (Week 30)	2430 (Month 9)	Persistent Positive	Negative	none	No

NA= Quantitative IgG titer was not done

PB-06-003

Based on the applicant's reanalysis of antibody testing results, 20/44 (45%) patients in PB-06-003 were ADA-positive, including 1 patient (22-226) who developed transient ADA titers during the study (see Table 51). Four patients who were ADA-positive during PB-06-001 (3 patients) or PB-06-002 (1 patient) were ADA-negative in PB-06-003. Two patients who were ADA-positive were discontinued from the study (both were in the 60 U/kg treatment group). One patient (10-013) was discontinued from the study due to a suspected allergic reaction. One patient (22-030) was discontinued for administrative reasons (patient unable to change her infusion schedule).

Table 51: PB-06-003 Patients with Positive Antibodies

Patient ID#	Initial IgG Titer	Highest IgG Titer	IgG Titer Assessment	IgE Antibody	Adverse Events*	Allergic reaction?
30 U/kg Treatment Group						
10-001	2333 (Week 30)	25475 Month 18	Persistent Positive	negative	drug eruption erythema local swelling	No
10-028	872 (Week 16)	6913 (Month 21)	Persistent Positive	negative		No
17-032	NA (Week 26)	9081 (Month 18)	Persistent Positive	negative		No
22-031	NA (Week 4)	NA (Week 4)	Transient Positive		paraesthesia erythema fatigue arthralgia dyspnea hyperhidrosis blood pressure increased macular rash	No
30-008	1297 (Week 8)	21870 (Month 21)	Persistent Positive	positive		No
30-010	47 (Day 1)	184 (Week 34)	Tolerized Positive	negative		No
60 U/kg Treatment Group						
10-005	96 (Week 2)	2002 (Month 18)	Persistent Positive	negative	infusion reaction infusion site pain ecchymosis	No
10-013	NA (Week 2)	1119 (Week 34)	Tolerized Positive	negative	pain infusion site rash/rash pruritis	No
11-007	100 (Week 12)	100 (Week 12)	Transient Positive	negative	pyrexia immune thrombocytopenia	No
12-024	172 (Week 4)	27860 (Month 24)	Persistent Positive	negative		No
14-027	NA (Week 24)	1093 (Month 12)	Transient Positive	negative	arthralgia	No
15-016	452 (Week 24)	51398 (Month 18)	Persistent Positive	positive	pulmonary hypertension supraventricular extrasystoles	No

NA= Quantitative IgG titer was not done

Table 51: PB-06-003 Patients with Positive Antibodies (cont'd)

Patient ID#	Initial IgG Titer	Highest IgG Titer	IgG Titer Assessment	IgE Antibody	Adverse Events	Allergic reaction?
60 U/kg Treatment Group						
22-030	NA (Week 24)	40799 (Month 24)	Persistent Positive	negative	fatigue	No
30-009	NA (Week 24)	6276 (Month 12)	Tolerized Positive	negative	allergic reaction hypertension	**Yes**
30-011	339 (Week 6)	339 (Week 6)	Transient Positive	negative		No
42-026	525 (Week 30)	528 (Month 21)	Persistent Positive	negative		No
PB-06-002 Treatment Group						
14-210	NA (Screening)	3542 (Week	Persistent Positive	negative		No
20-220	NA (Week 18)	23045 (Week 38)	Persistent Positive	positive	**flushing** **discomfort** **skin tightness**	No
22-226	NA (Month 12)	NA (Month 12)	Transient Positive	negative		No
23-206	978 (Screening)	978 (Day 1)	Transient Positive	negative		No

NA= Quantitative IgG titer was not done

Neutralizing antibodies

PB-06-001

Two patients developed inhibitory antibodies (30-008 from the 30 U/kg treatment group and 15-016 from the 60 U/kg treatment group) developed inhibitory antibodies but did not experience any adverse events during PB-06-001. Both patients completed the study and enrolled into PB-06-003.

PB-06-002

One patient (20-220) developed neutralizing antibodies based on the enzymatic activity inhibition assay, but negative based on the cell-based assay.

PB-03-003

Three patients (1 in each treatment group) had neutralizing antibodies based on the enzymatic activity inhibition assay; all were negative for neutralizing antibodies based on the cell-based assay

Reviewer Comment: Due to inadequacies in the immunogenicity assays (i.e., inappropriate cut-point for the confirmatory assay and lack of an assay for cellular uptake neutralizing antibodies) used for the clinical trials, I am unable to make a complete assessment of the risks of taliglucerase alfa at this time. The applicant will need to submit the results of a confirmatory assay using an appropriate cut-point. In addition, the applicant will need to submit assay results for both cellular uptake and enzyme activity neutralizing antibodies. At the time of the NDA submission, the applicant had not yet developed an assay for cellular uptake neutralizing antibodies.

7.4.7 Other Safety Parameters

Pulmonary function tests
In PB-06-002, no clinically significant changes were observed in PFT parameters from baseline to the end of the trial. In PB-06-003, no clinically significant changes were observed in PFT parameters from baseline to Month 24 of treatment for patients from PB-06-001. PFT values were available for only 1 patient from PB-06-002.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

PB-06-001 and PB-06-003 provide information on this safety analysis in treatment naïve patients. Although a higher proportion of patients treated with 60 U/kg developed antibodies compared to patients treated with 30 U/kg. However, the incidence of adverse events appears to be similar for the two treatment groups. Therefore, there does not appear to be an obvious dose dependency for adverse events. However, the study population was extremely small, and therefore clear conclusions about the dose dependency for adverse events cannot be drawn from the data provided.

7.5.2 Time Dependency for Adverse Events

I reviewed adverse event reporting for infusion reactions for PB-06-001, PB-06-002 and PB-06-003. The vast majority of patients experiencing infusion reactions in the PB-06-003 had infusion reactions during treatment in their previous study. Overall, most patients experienced their first infusion reaction within the first 3 months of treatment initiation. However, one patient was discontinued after a possible allergic reaction at Month 27 (total 36 months of treatment). There was one patient who developed a potential immune-mediated reaction. This patient developed a fixed drug eruption (assessed as a possible type IV hypersensitivity reaction) at Week 24 (6 months of treatment).

Information was not provided for other AEs by treatment visit; therefore, I was unable to directly assess the data for time trends for other events. However, the type and frequency of AEs reported in PB-06-003 (i.e., after 15 months of treatment) were similar to those reported in PB-06-001 and PB-06-002. Therefore, there does not appear to be a change in occurrence over time.

7.5.3 Drug-Demographic Interactions

There do not appear to be any significant differences in adverse events based on gender. No safety subgroup analyses were performed for race or age since the vast majority of patients were white and there is very limited data on the small number of pediatric patients enrolled in the trials to date.

7.5.4 Drug-Disease Interactions

No data are available for drug-disease interactions.

7.5.5 Drug-Drug Interactions

No drug-drug interactions were examined with regard to safety data.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There was no evidence of human carcinogenicity in the safety evaluation.

7.6.2 Human Reproduction and Pregnancy Data

Cerezyme has a Pregnancy category C. Velaglucerase has a Pregnancy category B. One patient (10-012) was discontinued from PB-06-001 (30 U/kg treatment group) due to pregnancy after receiving 10 doses of trial drug. She was followed through her pregnancy and delivered a term, healthy baby girl. The spouse of a male patient in PB-06-001 became pregnant while the patient was being treated. The spouse delivered a healthy baby girl.

No studies have been conducted on the appearance of taliglucerase alfa in milk.

Reviewer Comment: There are insufficient data to assess the impact of taliglucerase alfa on pregnancy or lactation. This reviewer recommends that collection of data on pregnancy and lactation be addressed through a post-marketing commitment. .

7.6.3 Pediatrics and Assessment of Effects on Growth

As noted earlier, data collection in pediatric patients is ongoing. Thus, the safety data provided in the Complete Response are extremely limited. Two pediatric patients in PB-06-002 experienced adverse events. Each patient experienced two adverse events (iron deficiency and epistaxis; vomiting and arthralgia); all events were assessed as mild in severity. Six of 11 (55%) pediatric patients in PB-06-005 experienced 23 adverse events. All of these events were assessed as mild or moderate in severity, with the exception of one severe adverse event (also reported as a serious adverse event, see Section 7.3.2 above) of gastroenteritis. Other adverse events reported in PB-06-005 included vomiting (2 patients), diarrhea, influenza, nasopharyngitis, headache, cough, and pain in extremity (1 patient each). The applicant did not provide pediatric-specific adverse event data or the compassionate use programs. As noted earlier, there are no pediatric patients enrolled in PB-06-004.

No data were provided on growth and development in this submission.

Reviewer Comment: There were insufficient data in this submission to assess safety or effects on growth and development. This reviewer recommends that completion of pediatric trial PB-06-005 and collection of long-term pediatric efficacy and safety data be post-marketing requirements.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No data are available. Taliglucerase is unlikely to be of drug abuse potential given the mechanism of action and because treatment is administered by trained medical personnel. The highest dose administered has been 73 U/kg every two weeks.

7.7 Additional Submissions / Safety Issues

An information request was sent to the applicant on September 26, 2011 regarding development of improved neutralizing antibody assays and assays to detect anti-plant sugar antibodies. The applicant advised the Agency that reports on these assays would be submitted between April and July 2012. Therefore, these data were not available for review during this review cycle.

8 Postmarket Experience

None.

9 Appendices

9.1 Literature Review/Reference

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9.2 Labeling Recommendations

This is labeling for a new molecular entity and will be in PLR format. Content and formatting were reviewed to meet the latest best-practices. Labeling for other enzyme replacement therapies were reviewed to ensure consistency across ERT products. The final labeling contains all of the labeling revisions negotiated with the applicant.

I recommend that taliglucerase alfa be indicated for long-term enzyme replacement therapy for adults with a confirmed diagnosis of Type 1 Gaucher disease. The recommended dosage is 60 U/kg administered every other week as a 60-120 minute intravenous infusion. Physicians can make dosage adjustments based on achievement and maintenance of each patient's therapeutic goals. Clinical studies have evaluated doses ranging from 11 U/kg to 73 U/kg.

The Warnings and Precautions section (Section 5) should include warnings for anaphylaxis, allergic and infusion reactions. The Clinical Trials Experience section (Section 6.1) should list allergic events not described elsewhere in the label, specifically, the event of a Type III immune-mediated skin reaction in one patient. The Pediatric Use section, (Section 8.4) should state that the safety and effectiveness of ELELYSO in pediatric patients have not been established. In addition, the section should describe significant safety events observed in pediatric patients to date, specifically, the serious adverse event of gastroenteritis reported in an 8 year-old patient.

When describing efficacy results in the Clinical Studies section (Section 14), organ volume measurements should be described in terms of organ volume normalized for patient body weight, specifically percent of body weight (%BW) and multiples of normal (MN). These units of measurement are consistent with organ volume measurements reported in the labeling for VPRIV and provide a clearer description of organ volume changes observed in clinical trials.

9.4 Therapeutic Goals for Treatment of Gaucher Type 1 Disease

Specific therapeutic goals for treatment of GD1 (from 23 October 2003 Global Experts Meeting on Therapeutic Goals for the Treatment of Gaucher Disease)[24]

Bone

- Lessen or eliminate bone pain within 1-2 years
- Prevent bone crises
- Prevent osteonecrosis and subchondral joint collapse
- Improve BMD
  - Pediatric patients
    - Attain normal or ideal peak skeletal mass
    - Increase cortical and trabecular BMD by year 2
  - Adult patients
    - Increase trabecular BMD by 3-5 years

Anemia

- Increase hemoglobin levels within 12-24 months to $\geq$ 11 g/dL for women and children and $\geq$12 g/dL for men
- Eliminate blood transfusion dependency
- Reduce fatigue, dyspnea, angina
- Maintain improved hemoglobin values achieved after the first 12 -24 months of therapy

Thrombocytopenia

- Increase platelet count during Year 1 sufficiently to prevent surgical, obstetrical and spontaneous bleeding
- Patients with splenectomy: normalization of platelet count by 1 year of treatment
- Patients with an intact spleen:
  - Moderate baseline thrombocytopenia: increase 1.5-2.0 fold by Year 1
  - Severe baseline thrombocytopenia: increase 1.5 fold by Year 1 and continue to increase slightly during Years 2-5 (doubling by Year 2) but normalization is not expected
  - Avoid splenectomy
  - Maintain stable platelet counts to eliminate risks of bleeding after a maximal response has been achieved

24 Pastores GM, Weinreb NJ, Aerts H, et al. Therapeutic goals in the treatment of Gaucher disease. *Semin Hematol* 2004;41 (Suppl. 5):4-14.,

Specific therapeutic goals for treatment of GD1 (from 23 October 2003 Global Experts Meeting on Therapeutic Goals for the Treatment of Gaucher Disease)- cont'd.

Hepatomegaly

- Reduce and maintain liver volume to 1-1.5 times normal
- Reduce volume by 20-30% within Year 1 and by 30-40% by Year 3-5

Splenomegaly

- Reduce and maintain spleen volume to 2-8 times normal
- Reduce spleen volume by 30-50% within Year 1 and by 50-60% by year 2-5
- Alleviate symptoms due to splenomegaly: abdominal distension, early satiety, new splenic infarction
- Eliminate hypersplenism

Growth (Pediatric Patients)

- Normalize growth such that patient achieves a normal height according to population standards within 3 years of treatment
- Achieve normal onset of puberty

Pulmonary

- Reverse hepatopulmonary syndrome and dependency on oxygen
- Ameliorate pulmonary hypertension (ERT plus adjuvant therapies)
- Improve functional status and quality of life
- Prevent rapid deterioration of pulmonary disease and sudden death
- Prevent pulmonary disease by timely initiation of ERT and avoidance of splenectomy

Functional Health and Well-being

- Improve or restore physical function for carrying out normal daily activities and fulfilling functional roles
- Improve scores from baseline of a validated quality-of-life instrument within 2-3 years or less depending on disease burden

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/s/

CARLA L EPPS
04/30/2012
NDA 22458 Complete Response Resubmission- Clinical Review

Recommendation: Approval

LYNNE P YAO
05/01/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 24, 2011

FROM: Julie Beitz, MD

SUBJECT: Office Director Memo

TO: NDA 022458 Elelyso (taliglucerase alfa) for injection
Protalix Ltd.

Summary

Gaucher disease is a serious disease that affects approximately 1 in 40,000 people in the general population.[1] An autosomal recessive inherited disorder, Gaucher disease results in a deficiency of the lysosomal enzyme glucocerebrosidase (GCB) and causes an accumulation of glucocerebroside within macrophages (Gaucher cells). This leads to multi-organ dysfunction involving the liver, spleen, and bone marrow. In a minority of patients, central nervous system (CNS) involvement leads to progressive neurological decline. Of the three clinical types of Gaucher disease, Type 1 accounts for more than 90% of all cases, affecting 30,000 individuals worldwide. Typical manifestations of Type 1 Gaucher disease which may range from mild to severe include hepatomegaly, splenomegaly, thrombocytopenia, bleeding tendencies, anemia, hypermetabolism, bone pain and fractures, growth retardation, and pulmonary disease. Type 1 disease does not involve the CNS.

Enzyme replacement therapy (ERT) designed to compensate for the underlying enzymatic defect has been the cornerstone of treatment for Gaucher disease. ERT has been shown to reduce organomegaly and improve hematological parameters. Although there is some evidence that ERT improves the bone-related complications of Gaucher disease, longstanding osseous complications of Gaucher disease may remain refractory to ERT. Since ERT has not been shown to pass the blood brain barrier, it has limited effects on CNS manifestations.

ERT has been commercially available since 1991 with the approval of Genzyme's Ceredase (alglucerase), a placentally-derived GCB. This product was eventually replaced by Genzyme's recombinant product, Cerezyme (imiglucerase), approved in 1994. VPRIV (velaglucerase alfa) is a GCB produced by gene activation technology in a human fibroblast cell line; it differs from Cerezyme by one amino acid, and has an identical amino acid sequence to Ceredase. VPRIV was approved on February 26, 2010.

The subject of this NDA, Elelyso (taliglucerase alfa), is produced from genetically modified carrot plant root cells, a novel expression system. Its amino acid sequence is identical to that of human GCB but includes additional amino acids at the N- and C-terminals.

Treatment with taliglucerase alfa appears to be effective for treatment-naïve adult patients with Type 1 Gaucher disease. Ongoing open-label trials will assess the long-term efficacy and safety of taliglucerase alfa, both in patients who are treatment-naïve or previously treated with Cerezyme. The potential for the development of immunogenicity and its impact on taliglucerase alfa efficacy, safety, pharmacokinetics and pharmacodynamics have not been fully evaluated. This memo documents my concurrence with the Division of Gastroenterology Product's (DGP's) recommendation for a complete response action for Elelyso (taliglucerase alfa) for the treatment of Type 1 Gaucher disease.

[1] Emory Genetics Laboratory. (2009, Dec 20). *Gaucher Disease.* Retrieved from http://genetics.emory.edu/egl/test.php?test_id=102

Before this application may be approved, satisfactory resolution of the identified deficiencies involving 1) clinical, 2) clinical pharmacology, 3) immunogenicity 4) product quality, and 5) microbiology issues will be required. Discussions regarding the product label will be deferred to the next review cycle. Deficiencies identified during inspections of the Protalix Ltd. and the (b) (4) manufacturing facilities have been adequately addressed and do not preclude approval.

Dosing

Taliglucerase alfa is available as a lyophilized powder (in 200 U single-use vials) to be reconstituted and diluted for infusion. The recommended initial dose of taliglucerase alfa is (b) (4) 60 Units/kg administered as a 1-2 hour infusion every other week. Dosage adjustments can be made based on achievement of each patient's therapeutic goals.

Regulatory History

On March 28, 2007, Protalix Ltd. submitted a special protocol assessment request for Trial PB-06-001, a proposed phase 3 clinical trial evaluating two doses of taliglucerase alfa in adult patients with Gaucher disease. In a written response dated May 11, 2007, DGP requested clarification regarding the proposed method of analyzing MRI images to assess liver and spleen volumes. In a subsequent written response dated August 22, 2007, DGP indicated that the applicant's proposal to expand clinical development of taliglucerase alfa to pediatric patients and to patients switched from Cerezyme was acceptable. Further discussion of the evaluation of MRI images and the applicant's proposed statistical analysis plan for PB-06-001 occurred during a Type C meeting held on April 14, 2008. Additional comments regarding MRI evaluations were provided at the pre-NDA meeting held with the applicant on May 21, 2009.

Taliglucerase alfa received orphan designation for the treatment of Type 1 Gaucher disease on September 3, 2009. A treatment protocol (PB-06-004) was submitted and allowed to proceed on August 14, 2009 that provided patients with Gaucher disease access to ERT at a time when supplies of Genzyme's Cerezyme were compromised by manufacturing problems.

NDA 022458, submitted by Protalix Ltd. on April 26, 2010, was filed and granted a standard review. An Advisory Committee was not held due to the product's similarity to other approved enzyme replacement therapies for Type 1 Gaucher disease.

Efficacy

In the current application, the efficacy of taliglucerase alfa was assessed in 33 adult patients with treatment-naïve Type 1 Gaucher disease (PB-06-001). Three additional clinical trials are ongoing and information regarding efficacy and safety from these trials is limited. PB-06-002 is a switch-over trial in which 30 Gaucher disease patients previously treated with Cerezyme for at least 2 years will receive open label taliglucerase alfa for 9 months; 25 patients have enrolled as of June 30, 2010. At the time of the NDA submission, the applicant included preliminary data in only six of these patients. PB-06-003 is a 15-month open label extension trial for up to 60 patients who were previously enrolled on PB-06-001 or PB-06-002; 27 patients have enrolled. PB-06-004 is the applicant's treatment protocol that has enrolled 26 patients; up to 200 patients may enroll for an unspecified duration. In addition, the applicant plans to conduct PB-06-005 in which 10 pediatric patients will be randomized to either 30 or 60 Units/kg for 12 months.

Treatment-naïve Type 1 Gaucher disease. Trial PB-06-001 was a 9-month, randomized, double-blind, controlled trial in 33 patients aged 19 to 74 years. Patients were required to have Gaucher disease-related splenomegaly (>8 times normal by MRI) and thrombocytopenia (platelet count <120,000/mm^3). Patients were randomized to receive taliglucerase alfa at a dose of either 30 Units/kg (n=16) or 60 Units/kg (n=17) every other week. After nine months of therapy, patients in both dose groups showed a 33% decrease in the mean change from baseline in spleen volume (a 27% decrease for patients receiving 30 Units/kg and a

38% decrease for patients receiving 60 Units/kg).[2] Both dose groups also demonstrated increases in the mean change from baseline in platelet counts and hemoglobin levels, and reductions in liver volumes as assessed by MRI. Reductions were also noted in the biomarker, chitotriosidase, in both dose groups.

Safety

The safety of taliglucerase alfa was assessed in 83 patients with Type 1 Gaucher disease who were dosed every other week in clinical trials. Thirty-two patients were naïve to ERT, while 51 patients switched from Cerezyme to treatment with taliglucerase alfa at the same dose. Of the 83 patients, 27 have received taliglucerase alfa treatment for 12 months, and 20 have received treatment for 18 months.

The most commonly reported adverse reactions in patients treated with taliglucerase alfa were upper respiratory infections, headaches, arthralgias, hypersensitivity reactions, and infusion-related reactions. Headaches were reported somewhat more frequently in patients receiving 60 Units/kg than in patients receiving 30 Units/kg.

Immunogenicity

The applicant has developed assays for the detection of anti-taliglucerase alfa antibodies, neutralizing antibodies, and antibody subtypes (IgG and IgE). In PB-06-001, five patients were identified as having developed IgG antibodies at the end of the trial based on the immunogenicity reviewer's assessment of the data provided by the applicant. However, the applicant reported that (b) (4) were identified as having developed IgG antibodies at the end of the trial. Furthermore, the immunogenicity reviewer disagrees with the applicant's cut-point for the confirmatory immunodepletion assay for anti-taliglucerase alfa antibodies. The cut-point chosen by the applicant is unacceptably high and consequently fails to classify several patients as developing anti-taliglucerase alfa antibodies. If all patients who developed IgG antibodies at any time during the trial are counted (as is the customary practice), and a cut-point similar to that used in approvals for other ERTs is used, then 10-13 additional patients would be considered to have seroconverted. The applicant reported that none of the patients that were reported to have seroconverted (i.e., two patients) developed neutralizing antibodies for enzymatic activity. However, an assay to detect the development of antibodies to enzyme uptake[3], has not yet been developed and validated by the applicant. Therefore, the assessment of neutralizing antibodies on taliglucerase alfa efficacy and safety cannot be determined at the present time, and the frequency of seroconversion and its impact on the product's efficacy, safety, pharmacokinetics and pharmacodynamics will need to be further investigated in the next review cycle.

Deficiencies involving assay validation, particularly for the detection of anti-taliglucerase alfa IgG antibodies and antibodies that neutralize taliglucerase alfa uptake by macrophages preclude approval and will be conveyed to Protalix Ltd. in the complete response letter.

Clinical Pharmacology Considerations

Pharmacokinetic (pK) assessments were performed in Trial PB-06-001 at Day 1 and Week 38 in patients with Gaucher disease receiving either 30 Units/kg or 60 Units/kg every other week. Pharmacokinetic parameters do not appear to be dose proportional. The mean half life was approximately 25 minutes for patients on the 30 Units/kg dose group at Day 1 and Week 38; in patients on the 60 Units/kg dose group, the mean half life was 25 and 36 minutes at Day 1 and Week 38, respectively. Pharmacokinetic samples were not collected at the end of the infusion so C_{max} could not be determined.

[2] In written correspondence to Protalix Ltd. dated August 22, 2007, DGP stated that a 20% mean improvement in spleen volume would represent a clinically relevant improvement.
[3] IgG antibodies that neutralize enzyme uptake by macrophages appear to be the primary mechanism for neutralization of activity of enzyme replacement therapies such as taliglucerase alfa.

No drug-drug interaction trials have been performed. The effect of age, gender, or presence of hepatic or renal impairment on the pharmacokinetics of taliglucerase alfa have not been studied. A thorough QT trial was not performed.

Pediatric Considerations

Pediatric Use. The safety and effectiveness of taliglucerase alfa have not been established.

Required Pediatric Assessments. Because taliglucerase alfa for this indication has an orphan drug designation, Protalix Ltd. is exempt from conducting required pediatric studies under the Pediatric Research Equity Act (21 USC 355c).

Product Quality Considerations

While use of a carrot root cell expression system has the advantage that growth media is devoid of serum or any other mammalian-derived products, several deficiencies involving product quality have been identified that preclude approval.[4] These include: 1) information is needed regarding particulate testing and appearance testing on reconstituted drug product; 2) (b) (4) information is needed to assess the stability of drug product lots that are manufactured from drug substance made in (b) (4) 3) a potency assay that quantitatively measures specific receptor binding and/or high affinity internalization into cells is required, 4) head-to-head comparisons are needed of three drug substance lots (b) (4) of taliglucerase alfa, and 5) process validation is needed with drug product vials (b) (4) to confirm consistency of the lyophilization process; results for moisture content will be needed.

Inspectional Issues

Several deficiencies were noted during FDA's inspections of two taliglucerase alfa manufacturing facilities, Protalix, Ltd. and (b) (4), however, these do not preclude approval of the application.

The Protalix Ltd. facility is involved in the manufacture of the drug substance, packaging, quality control, release, stability, storage, testing of finished product (excluding microbial testing and water content), labeling and re-labeling. This facility was inspected from October 10-17, 2010. The FDA Form 483 noted the following observations: 1) inadequate control of the manufacturing process for taliglucerase alfa; (b) (4) 2) inadequate investigations and/or corrective actions regarding contaminations during upstream manufacturing of taliglucerase alfa; 3) inadequate risk assessments regarding bioburden contamination of the drug substance; 4) incomplete process validation for taliglucerase alfa; 5) incomplete assay validation; the level of sensitivity to monitor taliglucerase alfa variants with SEC-HPLC is unknown; 6) components of the taliglucerase alfa manufacturing process are not adequately qualified for their intended use; 7) inadequate procedures for documenting investigations of out-of-specification test results, deviations do not specify time limits for their completion, and investigations and corrective/preventative actions are not always timely; 8) written procedures and batch records are lacking; and 9) deficient calibration programs for laboratory and production equipment. Protalix Ltd. provided written responses to these deficiencies that were found adequate by the Office of Compliance.

The (b) (4) facility is involved in the manufacture of the drug product (formulation, (b) (4), lyophilization), microbial testing (sterility, bacterial endotoxin), water content of finished product, and storage. This facility was inspected from (b) (4), during which inspectors noted that the firm had failed to open investigations regarding the presence of (b) (4)

[4] For further details see Dr. Richard Ledwidge's review dated February 24, 2011.

[redacted] taliglucerase alfa for specific batches used in clinical trials. An FDA Form 483 was issued. The Office of Compliance also issued an Untitled Letter to [redacted] on January 24, 2011, stating that the firm must provide documentation regarding the identification of the [redacted], an impact assessment regarding the presence of [redacted], and reasons why pre-specified acceptance criteria were not met. [redacted] replied that manufacturing instructions have been updated to include a statement that [redacted] is not considered a deviation. The Division of Therapeutic Proteins and DGP agree with this assessment; the complete response letter will request that the applicant revise the drug substance specifications for appearance accordingly.

Microbiology

Microbiology deficiencies were identified at the two drug product manufacturing sites, [redacted], and will be conveyed in the complete response letter to Protalix Ltd. At the [redacted] site, additional information is needed 1) regarding bioburden, to justify the hold time between the [redacted]; and 2) to demonstrate successful sterilization of the lyophilizer. Regarding the [redacted] site, the submission did not include validation summary reports for sterility and bacterial endotoxin test methods.

Tradename Review

The Division of Medication Error Prevention and Analysis (DMEPA), in consultation with the Division of Drug Marketing, Advertising, and Communications (DDMAC), have concluded that the applicant's proposed tradename "Elelyso" is acceptable. In a letter dated February 1, 2011, Protalix Ltd. was notified that the proposed tradename was acceptable but that it will be re-reviewed 90 days prior to the approval of the NDA. If the name is found unacceptable following the re-review, the applicant will be notified.

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/s/

JULIE G BEITZ
02/24/2011

Cross-Discipline Team Leader Review

Date	February 24, 2011
From	Lynne Yao, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 22-458
Applicant	Protalix
Date of Submission	Dated April 26, 2010; Received April 26, 2010
PDUFA Goal Date	February 26, 2011
Proprietary Name / Established (USAN) names	Elelyso Taliglucerase alfa
Dosage forms / Strength	Lyophilized powder for solution for injection 200 Units/vial (b) (4)
Proposed Indication(s)	Long-term enzyme replacement therapy for patients with type 1 Gaucher disease
Recommended:	*Complete Response*

1. Introduction

This new drug application (NDA 22-458) was received on April 26, 2010, as an electronic submission. The application is for Elelyso, a formulation of taliglucerase alfa, a new molecular entity. Taliglucerase alfa is a recombinant form of glucocerebrosidase, which is intended "for the long-term enzyme replacement therapy for patients with type 1 Gaucher disease."

Taliglucerase alfa is manufactured using a novel carrot cell expression system; an expression system has not been previously evaluated by the Agency. A stringent review of the complete characterization of the drug substance and product, manufacturing, and controls developed by the applicant to ensure consistency and comparability of final lots of drug product was performed. The CMC review has uncovered several deficiencies in the application relating to the particulate testing and appearance of the drug product, the comparability of product produced after the media was switched (differences in phase 3 trial material compared to the to-be-marketed product), development of an acceptable potency assay for the drug product, process validation for the drug product, and acceptable characterization and release testing of the drug substance and product. Additionally, the product quality microbiology review also noted deficiencies that must be addressed before the application can be approved. These included deficiencies in product bulk hold time, sterilization of lyophilizers used, and microbiological analytical procedures.

The manufacturing facilities for taliglucerase alfa were also inspected, and serious deficiencies were noted by the Office of Compliance in two facilities (Protalix, Ltd., and (b) (4)) involved in the manufacturing of taliglucerase alfa. However, the responses to these manufacturing deficiencies submitted by the applicant were reviewed by the Office of Compliance and the current classification for both facilities is voluntary action indicated (VAI). Therefore, the Office of Compliance has recommended that the application is approvable.

Additionally, the application relies upon a single, randomized, dose comparison study. Issues regarding the sufficiency of evidence to support the clinical efficacy compared to other approved enzyme replacement therapies for Gaucher disease will be discussed. Furthermore, the impact of adequate immunogenicity assays in evaluating the potential impact of development of anti-product IgG antibodies on efficacy, safety, and relevant pharmacokinetic and pharmacodynamic parameters will also be discussed.

Therefore, the CMC, product quality microbiology, immunogenicity, pharmacology/toxicology, clinical pharmacology, clinical, and statistical reviewers have all recommended that a complete response action be taken for this application.

This memo documents my concurrence with the review teams' recommendations for a complete response (CR) action.

2. Background

A. Clinical Background

Gaucher disease is the most common lysosomal storage disease. The incidence of Gaucher disease varies based on ethnicity. The greatest incidence occurs in Ashkenazi Jews, with an estimated incidence of 1:450 to 1:1000. The estimated incidence in non-Jews ranges from 1:20,000 to 1:57,000. Gaucher disease is a chronic multisystem disease resulting from deficient or absent activity of the lysosomal hydrolase glucocerbrosidase. Glucocerbrosidase is an enzyme responsible for the breakdown of glucocerebroside (glucosylceramide). Deficiency or absence of glucocerbrosidase results in the accumulation of glucosylceramide within lysosomes predominately in monocyte-derived macrophages which are most commonly found in spleen, lymph nodes, liver (Kupffer cells), bone marrow, and to a lesser degree in lung, resulting in the clinical consequences of Gaucher disease. Patients with Gaucher disease typically develop hepatosplenomegaly. Hepatic synthetic function is generally preserved, but splenomegaly generally results in anemia and thrombocytopenia due to splenic sequestration. Bone involvement is caused by accumulation of glucosylceramide in bone marrow macrophages and results in decreased osteoblast activity leading osteopenia, and pathologic fractures. Avascular necrosis, bone infarcts, and abnormal bone remodeling can also lead to bone pain crises in Gaucher patients. Pulmonary complications, including interstitial fibrosis are uncommon, but can occur. Gaucher disease is clinically divided into three distinct subtypes, although, there is some overlap in these subtypes; Type 1 disease, or non-neuronopathic disease; Type 2 or acute neuronopathic disease, and Type 3, or sub-acute neuronopathic disease. Neuronopathic disease is caused by accumulation of glucocerebroside within neurons can also lead to accumulation of glucosylsphingosine, a lysosphingolipid derivative. Glucosylsphingosine is toxic to neurons, although this may not be the only mechanism that produces neuronopathic disease.

There are several treatments available for targeting specific therapeutic paths. Enzyme replacement therapies (ERTs) have been developed to replace the deficient enzyme with exogenous glucocerbrosidase. The first ERT approved was Ceredase (alglucerase) (Genzyme, 1991, NDA 20-057). Ceredase is glucocerbrosidase derived from human placenta. Subsequently, Cerezyme (imiglucerase), a synthetic enzyme produced in Chinese Hamster Ovary (CHO) cells (Genzyme, NDA 20-367) was approved in the U.S. in 1994. Ceredase is still available in the U.S., but its use is negligible. Velaglucerase (Shire, NDA 22-575) was approved in February 2010, and is also a synthetic form of glucocerebrosidase that is produced in CHO cells.

Other specific therapeutic strategies include substrate reduction therapy, gene therapy, and bone marrow transplantation. Substrate reduction therapy, or perhaps, more accurately, substrate synthesis inhibition, is an approach that aims to reduce the accumulation of toxic substrates. Zavesca (miglustat) (Actelion Pharmaceuticals, NDA 21-348) was approved in the U.S. in 2003. However, substrate synthesis inhibition therapy with Zavesca is indicated only for patients for whom enzyme replacement therapy is not a therapeutic option (e.g., due to constraints such as allergy, hypersensitivity, or poor venous access). Bone marrow transplantation has been shown to “cure” Gaucher disease but the high mortality and morbidity of the procedure preclude its use and is rarely performed now. Finally, gene therapy is

currently being evaluated, but there are currently no approved gene therapies approved in the U.S. However, if gene therapy proves successful, this treatment strategy may prove to be curative.

B. Regulatory Background

Presubmission Regulatory Activity

Taliglucerase was developed under IND 69,703. The following list includes highlights of the development of taliglucerase:

- June 30, 2004: Pre-IND meeting held to discuss design of Phase 1 trial (PB-06-001). The meeting minutes state that a single Phase 3 trial to support submission of an NDA could be sufficient if, ". . . the results are sufficiently robust, statistically significant and there is an adequate safety profile."

- June 15, 2005: The initial IND for taliglucerase alfa (IND 69,703) was submitted.

- July 15, 2005: The IND was placed on Partial Hold due to missing nonclinical animal studies (chronic toxicity and reproductive toxicology studies or a single bridging study comparing taliglucerase alfa to Cerezyme).

- Feb 21, 2007: Type B meeting held to discuss partial clinical hold. Agreement was made that 9-month chronic toxicity study in monkeys could serve as the basis to remove partial clinical hold; the study did not have to demonstrate similarity to Cerezyme.

- March 28, 2007: The sponsor (Protalix) submitted a special protocol assessment (SPA) for a proposed phase 3 clinical trial. No agreement was reached on the SPA due to deficiencies in MRI methodology and the statistical analysis plan.

- April 16, 2007: The Partial Hold was removed after review of the 9-month chronic toxicity data. The Division recommended additional nonclinical studies (reproductive toxicology studies) be conducted prior to Phase 3 trials.

- May 21, 2009: Pre-NDA meeting to discuss contents of NDA submission (see Meeting Minutes archived in DARRTS June 29, 2009). Additional comments regarding MRI evaluation of spleen volume, appropriate statistical analyses, and plans for clinical development in the pediatric population were discussed. Additional requirements for the NDA submission relating product quality, nonclinical pharmacology/toxicology, and clinical pharmacology were also discussed.

- July22, 2009: A drug shortage develops because of manufacturing deficiencies at Genzyme's Allston Landing facility that affect the global Cerezyme supply. The applicant submits an expanded access treatment protocol for review.

- August 14, 2009: Expanded access treatment protocol was allowed to proceed.

- August 24, 2009: Fast Track Designation was granted for "the investigation of taliglucerase for treatment of type 1 Gaucher disease."

- Orphan Designation was granted for taliglucerase alfa on September 3, 2009.

- September 14, 2009: Applicant submits NDA as rolling review.

- December 9, 2009: Applicant submits final sections of NDA; however, the application was deemed to be incomplete because of missing CMC data. Therefore, the application is not filed, and the rolling review continued.

- April 26, 2010: Final sections of NDA were submitted by the applicant and review clock was initiated.

Current Submission and Review
The application was submitted on April 26, 2010. This submission was granted a standard review.

Clinical Review by C. Epps, dated February 22, 2011
Statistical Review by B. Vali, dated February 24, 2011
Pharmacology/Toxicology Review by T. Chakraborti, dated December 3, 2010
Clinical Pharmacology Review by I.J Lee with concurrence by G. Burkhart, dated January 13, 2011
Product Quality Review (Division of Therapeutic Proteins) by R. Ledwidge, and Product Quality Executive Summary by G. Johnson, with concurrence by B. Cherney and A. Rosenberg, dated February 24, 2011
Product Quality Immunogenicity Review by F. Sheikh, with concurrence by S. Kirshner, dated February 8, 2011
Product Quality Microbiology Review by V. Pawar, with concurrence by B. Riley, dated February 10, 2011
Division of Scientific Investigation Summary by K. Malek, dated January 21, 2011
Division of Medication Error Prevention and Analysis (DMEPA) Proprietary Name Review by Z. Oleszczuk, dated February 1, 2011

3. CMC/Device

The reader is referred to the Product Quality Review by R. Ledwidge, dated February 24, 2011 and the Product Quality Executive Summary by G. Johnson, dated February 24, 2011 for complete information.

A. General product quality considerations

Taliglucerase is produced from genetically modified carrot plant root cells. Taliglucerase alfa has a molecular weight of approximately 60,800 Daltons (b) (4) . The amino acid sequence identical to the human glucocerebroside sequence but includes (b) (4) amino acids at the N-terminal and C-terminal. These additional amino

acids were introduced by a specific plant expression cassette. (b) (4) Therefore, unlike Cerezyme, additional modification of the enzyme to incorporate additional terminal mannose residues is not required. (b) (4)

The final drug product is a lyophilized powder and will be diluted in sterile diluent. The excipients of the diluent include mannitol, polysorbate 80, and sodium citrate. The final drug product is stored in glass vials and will be filled in 200 unit (b) (4) vials. The applicant states that the drug product is stable for up to 24 months while stored at 2-8°C.

The use of a carrot root cell expression system is novel and this expression system has not previously been evaluated by CMC. The CMC reviewer notes important advantages to this expression system; the growth media is devoid of any mammalian derived products (b) (4) which eliminates the risk of mammalian adventitious viral agents, N-glycosylation modification (exposure of terminal mannose residues) can be performed in the plant vacuole and therefore further processing to expose terminal mannose residues are not required with this system.

However, this novel carrot root cell expression system also carries the potential for manufacturing problems that are completely different from traditional mammalian cell-based expression systems. Therefore, stringent review of the complete characterization of the drug substance and product, manufacturing, and controls developed by the applicant to ensure consistency and comparability of final lots of drug product was performed.

Product Quality Review

The CMC reviewer concluded that the information in the application was insufficient at the present time to conclude that the manufacturing of the product is well-controlled and leads to a pure and potent product. Several deficiencies have been identified by the CMC Reviewer that include problems with adequate specifications and assay validation; comparability; process validation; and control of impurities are outlined below:

1. Unacceptable particulate testing and appearance criteria for the drug product
2. Inadequate information to assess development of (b) (4) This may have an impact on the comparability of the lots tested in the Phase 3 trial and the to-be-marketed product.
3. Unacceptable potency assay for the drug product
4. Inadequate information to assess the effect of switching to (b) (4) on the glycan profile for the drug product.
5. Inadequate process validation for the drug product.
6. Inadequate acceptance criteria for moisture content for the drug product.
7. Inadequate stability testing for the drug product.
8. Inadequate testing for plant specific viruses in the master cell bank.

9. Inadequate description of the process for manufacturing of clinical trial material, and time limits for individual manufacturing steps.
10. Inadequate release testing and characterization of drug substance and drug product.

Based on these deficiencies, the following comments will be provided to the applicant in the complete response letter, and represent deficiencies that must be addressed in their complete response.

Adequate specifications and assay validation

1. Results of USP <788> particulate testing and appearance testing on reconstituted drug product have not been submitted to the NDA. Both tests provide a useful measure of product quality that is not monitored by other tests you have proposed. Add these tests to the release and stability specifications and provide available results for release and stability testing of the three conformance lots and any additional results you may have.

2. A potency assay that quantitatively measures specific receptor binding and/or high affinity internalization into cells is required since internalization is a critical component of taliglucerase alfa's mechanism of action and it is not fully assessed in your current potency assay. The assay should use multiple taliglucerase alfa concentrations to generate a complete dose-response curve in order to calculate the half-maximal effective concentration (EC_{50app}). Develop and implement this assay for use in release and stability testing.

3. Some SE-HPLC chromatographs exhibit a (b) (4) (b) (4), it should be identified and, if necessary, controlled. Characterize the protein (b) (4) and determine whether a control strategy that better monitors this product attribute(s) should be implemented. Provide the results of your analyses and any proposed changes to your specifications.

4. RP-HPLC chromatograms suggest that taliglucerase alfa variants (b) (4) The risk to product quality is expected to vary depending on the nature of the variant. Thus, in order to establish an appropriate control strategy, you should identify and control for the quantity of these variants, if present. It may be useful to alter assay conditions or gradients (b) (4). Provide information on the presence of unresolved variants and, if present, provide a revised specification that more accurately quantitates and controls these variants together with supporting data.

5. Enzyme kinetic parameters and specific activity are measured using synthetic p-nitrophenyl-glucopyranoside (pNP-Glc) substrate. pNP-Glc (b) (4) Provide enzyme kinetic data to determine the enzyme kinetic parameters, Km and kcat (b) (4) on three lots manufactured (b) (4)

[redacted] Include a detailed description of the assay, supporting assay qualification data, as well as a justification for why this test should not be added to the release and stability specifications.

6. Stability testing of diluted drug product in infusion bags did not include USP <788> particulate testing or information on the impact of dilution on subvisible particulates that are between [redacted]. USP <788> testing results are critical to mitigate the risk associated with occlusion of small blood vessels and small subvisible particles may pose an immunogenicity risk. Provide USP <788> particulate testing data for in-use stability studies and an analysis of particulates between [redacted].

7. The mannose content specification is based on a MALDI-TOF analysis of taliglucerase alfa. However, the property that is being measured in the MALDI-TOF analysis is mass to charge ratio, not mannose content. Thus, the acceptance criterion should be set around the mass to charge ratio and the mannose content acceptance criterion should be removed from the MALDI-TOF specification. Provide the new specification together with supporting data.

8. The acceptance criterion for moisture content in drug product is [redacted] for both release and stability testing. Release and stability testing results consistently show moisture content to be below [redacted] and no data were submitted indicating that a [redacted] moisture content would not have an adverse impact on product stability throughout the product's dating period. Amend the moisture content acceptance criterion to reflect your manufacturing capability and consideration of any additional knowledge you may have concerning the impact of moisture on product stability and provide the new specification, if appropriate, together with supporting data.

9. Monosaccharide content and glycan structure analysis submitted in the characterization section of the NDA contained inconsistent results. Monosaccharide content analysis on two batches indicated that the [redacted] whereas the glycan analysis data determined that [redacted] of the glycan structures have a [redacted] Provide an explanation for these results or submit data that identify the more accurate analysis using batches made in [redacted]

10. The acceptance criteria for the enzyme kinetic parameters K_m and V_{max} are [redacted] respectively. An analysis of 40 drug substance batches resulted in mean and standard deviations for K_m and V_{max} equal to [redacted] respectively. Consequently, the acceptance criteria appear too wide and should be amended to reflect process capability and clinical experience. Provide the revised specification for enzyme kinetic parameters or your justification as to why your proposal ensures reproducible product potency.

11. In a [redacted] vial drug product fill, the sampling plan calls for [redacted] to be collected for moisture content testing. [redacted] vials are tested and the mean value is reported on the certificate of

analysis. Because the moisture content in an individual vial will vary within any given lot, the proposed sampling plan should provide a reasonable assessment of the variability of the results within a lot. While data from a robust validation study will provide a basis for establishing the sampling plan for the moisture specification, your current sample size and the mean value set as the reportable result are insufficient to assess the moisture content of the final drug product. Submit the revised specification for moisture content with these considerations in mind and provide a justification for your proposal.

12. Chromatograms for drug substance and drug product RP-HPLC analyses contain data from (b) (4). Perform the RP-HPLC analysis such that data from (b) (4) from (b) (4) (b) (4) is included so that all potential impurities and contaminants can be detected and controlled if necessary. Provide chromatograms where all data are shown (b) (4) on lots evaluated in the (b) (4) comparability studies.

13. The isoelectric focusing (IEF) assay has acceptance criteria of (b) (4) in a pI range of (b) (4) reportedly because of assay variation. This level of assay variability is not consistent with the expected validation characteristics for this type of assay. Develop, implement and provide data on a validated IEF method in which the reference standard always produces the same number of bands in a consistent pI range. In addition, each gel should have a quantity of reference standard loaded near the limits of detection to verify the sensitivity of the analysis.

14. The (b) (4) assay results are rounded off to the nearest integer which can mask significant differences in (b) (4) between lots. Report all (b) (4) assay results to two significant digits without rounding off to the nearest integer, revise the acceptance criterion accordingly and submit the revised specification.

15 (b) (4)

16. The peptide map specification calls for (b) (4) peptide peaks where a countable peak is defined as (b) (4) Justify the use of this acceptance criterion in light of the potential amounts of impurities and contaminants that would be acceptable, or revise the criteria for countable peaks. Also, include a revision of the acceptance criteria such that relative peak areas on several selected peptides are specified. Provide the new specification together with supporting data.

17. A host cell protein standard curve is used to determine the levels of host cell proteins in the drug substance. The data from the standard curve is fit to a four parameter logistic regression model even though the data do not reach a plateau and the fitted curve is not fully determined. However, there is a simple linear relationship between host cell protein and assay response. Provide a justification for the use of a four parameter logistic regression model or use a linear regression model to generate a host cell protein standard curve. Submit the revised specification along with the supporting analytical method validation data.

Comparability

18. The relative amounts of the individual glycans in the glycan profile shifted upon the switch to (b) (4). Since the glycan structures are critical to taliglucerase alfa's mechanism of action, a change in the concentration of the glycan structures has the potential to adversely impact clinical performance. Using a potency assay that quantitatively measures specific receptor binding and/or high affinity internalization into cells (see previous comment), perform a head-to-head comparison of three drug substance lots of taliglucerase alfa manufactured in (b) (4)

19. Results for SE-HPLC data provided in the NDA are reported as (b) (4) As (b) (4) may represent a different risk to product quality, they should be independently monitored and controlled. To support your revised acceptance criteria, provide all SE-HPLC data available to date in the application with (b) (4) reported separately. For comparison purposes, provide tabulated drug product stability SE-HPLC data separating drug product lots that were manufactured with drug substance made exclusively in (b) (4)

20. Your SE-HPLC test method employed a UV detector. However, use of a light scattering detector may allow (b) (4) that migrate in the void volume to be observed following SE-HPLC. This provides a much more sensitive qualitative method for monitoring this product attribute. Perform a head-to-head comparison of three drug product lots manufactured exclusively from drug substance made in (b) (4) using light scatter detection and provide the results in your resubmission.

Process Validation

21. The time limits for individual manufacturing steps and for the complete manufacturing process are not clearly defined in the NDA. For example, strict limits for (b) (4) Provide this information and relate it to the processes used to manufacture clinical study lot PB-06-001, commercial validation lots and the genomic stability sequencing study.

22. Process validation reports indicate that vials containing drug product were put on (b) (4) Validation of the lyophilization process should include assessment of vials (b) (4) and in different positions within a shelf to confirm consistency of the lyophilization process. Provide a revised validation protocol and report including the results for moisture content testing.

23. (b) (4)

Control of Impurities

24. The testing to demonstrate that the master cell bank was free of plant specific viruses tabulated the results without providing data on the suitability of the PCR methods to detect viruses. In order to interpret the results you provided, the suitability of methods for their intended purpose needs to be assessed. Provide the assay qualification data and a description of the system suitability controls for each PCR method used to detect plant specific viruses.

25. The compound (b) (4) is a component (b) (4) and levels in drug substance or drug product were not determined (b) (4) may exhibit toxicity to humans (b) (4) and is therefore viewed as a (b) (4) impurity that should be well controlled. Provide a control strategy to either include a limit on (b) (4) to a level that will not impact product quality as it may relate to safety or efficacy, or validate that the process can clear (b) (4) to an appropriate level.

26. (b) (4), but its final concentration in drug product has not been determined. The label should accurately describe the final concentration of all excipients which should be confirmed at release. Provide the results on the (b) (4) concentration for three drug product lots and provide your

justification for not implementing the determination of [redacted] as a drug product release test.

Conclusions and Recommendations
Based on these deficiencies, the product quality reviewer is recommending a Complete Response Action for this application. I agree with the product quality reviewer's recommendation.

B. Facilities review/inspection

The applicant included 10 facilities that are involved in the manufacturing of taliglucerase alfa. Pre-approval inspections were performed at several facilities including Protalix, Ltd. And [redacted], where there has been no previous inspection history. One site, [redacted] has also not had a previous inspection history, but the applicant subsequently removed this site from the application.

There are significant deficiencies noted in the inspections at two facilities; [redacted] and Protalix, Ltd. The [redacted] facility is involved in the manufacture of drug product [redacted] This facility was inspected from [redacted]. Significant deficiencies were noted during the inspection of this facility and were documented in the Establishment Inspection Report (EIR) and in a Form 483 letter that was sent to [redacted]. Furthermore, it was also noted during the inspection that the company failed to open investigations regarding [redacted] of taliglucerase alfa for specific batches used in clinical trials. The presence of [redacted] clearly does not meet the pre-determined acceptance criteria for drug substance. Therefore, Office of Compliance determined that the [redacted] facility's GMP status is Official Action Indicated (OAI) and recommended a Withhold approval action for the application. Furthermore, the Office of Compliance issued an Untitled Letter (UL) to [redacted], stating the following issues that the company must respond to with supporting documentation:

1. Please provide documentation regarding the identification of the [redacted], as well as an impact assessment regarding the presence of [redacted].

2. The in-process test for Appearance (Ic) in the Interim Process Validation Report for batch 004268 states that the [redacted] Please explain why the results page for in-process testing of this process validation batch indicates the batch "complies" with this specification, while the executed batch record for batch 004268 contains notations [redacted]. It should be noted that the batch records for all three process validation batches (004268, 014461, and 016489) contain notations o[redacted].

3. The Interim Process Validation Report for batch 004268 also includes a specification for Appearance during the [redacted]. The acceptance criteria for appearance is, [redacted]. The result for batch 004268 at the [redacted]. This does not appear to satisfy your pre-determined acceptance criteria. Please explain why the summary and conclusions section of the Interim Process Validation Report states that, "all in-process and release test results conform with the specifications."

4. Please explain why the Certificates of Conformance for [redacted] 200U (taliglucerase alfa) batches 004268,014461, and 016489 indicate that there were no deviations in the manufacturing and the "agreed part of quality control" for the batches, although [redacted] were noted during the compounding of these batches.
5. The in-process test, [redacted] for batch 016489 failed to meet specifications for [redacted]. The application (NA 22458) specifies the acceptance limits for [redacted]. Batch 016489 failed to meet these specifications with a result of [redacted] and what impact this might have on batch 016489.

The applicant provided responses to these deficiencies late in the review cycle. However, the Office of Compliance reviewed the applicant's responses and deemed them to be adequate. Therefore, the official classification of the facility is voluntary action indicated (VAI).

The Protalix facility is involved in the manufacturing [redacted]. This facility was inspected from October 10-17, 2010. The deficiencies noted in the Form 483 letter sent to Protalix, Ltd., include the following observations:

1. Inadequate control of the manufacturing process for taliglucerase alfa. No demonstration that the [redacted]

2. Inadequate investigations and/or corrective actions regarding contaminations during upstream manufacturing of taliglucerase alfa

3. Inadequate risk assessments regarding Bioburden contamination of taliglucerase alfa.

4. Process Validation for taliglucerase alfa is incomplete.

5. Assay validation is incomplete. The level of sensitivity to monitor taliglucerase alfa variants with SEC-HPLC is unknown

6. Components of the taliglucerase alfa manufacturing process are not adequately qualified for their intended use.

7. Inadequate procedures for documenting investigations. The procedures for conducting investigations of out-of-specification test results and deviations do not specify time limits for their completion, and investigations and corrective/preventative actions (CAPAs) are not always timely.

8. Written procedures and batch record are lacking

9. Deficient calibration program for laboratory equipment

10. Deficient calibration program for production equipment

The applicant provided written responses to address all of these deficiencies. The Office of Compliance reviewed the applicant's responses to the 483 letter and determined that the responses were adequate. Therefore, the classification of the facility is voluntary action indicated (VAI).

Conclusions and Recommendations
Based on the VAI status of these two manufacturing facilities and the NAI status of the other facilities involved in the manufacturing of taliglucerase alfa, the Office of Compliance has recommended that the applicant can be approvable. I agree with this compliance recommendation.

C. Other notable issues:

Immunogenicity
The reader is referred to the Product Quality Immunogenicity Review by F. Sheikh dated February 8, 2011 for complete information.

The assays used to assess immunogenicity of taliglucerase alfa were reviewed. The applicant included validation information for several anti-taliglucerase antibody assays, including IgG, IgE, and neutralizing antibody assay for enzyme activity. The immunogenicity reviewer noted several deficiencies in the anti-taliglucerase antibody assay validation information submitted by the applicant. Additional information to address these deficiencies was sent to the applicant in the 74-day letter. The applicant provided additional information to address some of the deficiencies identified by the immunogenicity reviewer. However, several issues remain outstanding. Specifically, the applicant has not completed the development and validation of an assay to evaluate for neutralizing antibodies for enzyme uptake by macrophages. IgG antibodies for enzyme uptake appear to be the main mechanism for neutralization of activity of ERTs based on data from other approved ERTs. Therefore, development and validation of this assay should be required to fully assess the immunogenicity of taliglucerase alfa.

Additionally, the immunogenicity reviewer disagrees with the criteria used by the applicant to identify patients who develop anti-taliglucerase IgG antibodies. The cut-point chosen by the applicant for the immunodepletion assay used to confirm the presence of anti-taliglucerase IgG

antibodies was determined to be unacceptable. Furthermore, the applicant included patients as having developed IgG antibodies only if the immunodepletion assay was positive at the end of the study. This is not consistent with the definition used in other ERT applications. The Agency has consistently defined patients who develop IgG antibodies as any patient who developed a positive antibody titer *at any time point in the study*, not only the last time point. The immunogenicity reviewer notes that using a more stringent cut-point for the immunodepletion assay may result in an additional 10-13 patients who are determined to have developed anti-taliglucerase alfa antibodies by the end of the phase 3 trial. Therefore, the determination of an appropriate cut-point for the confirmatory immunodepletion assay will be required to clearly establish the efficacy and safety of the product. Finally, the immunogenicity reviewer cited specific issues with the lack of a low level positive control (rabbit anti-taliglucerase alfa IgG) for anti-taliglucerase alfa antibody assay as well as issues with the choice of positive control for the drug tolerance assay (see below). Therefore, the immunogenicity reviewer is unable to fully assess the immunogenicity of the product and the impact of immunogenicity on safety, PK, and efficacy.

The following comments will be provided to the applicant in the complete response letter, and represent deficiencies that must be addressed in their complete response.

1. The concentration of rabbit anti-taliglucerase alfa IgG antibodies (b) (4) that you used for the positive control-1 (PC-1) for the anti-product IgG assay quality assessment (binding assay) was high. The agency recognizes that the limit of detection may be different due to affinity differences of the antibodies in the assay. However, in order to ensure reliable performance of the assay, a lower concentration for the positive control that will produce a signal close to the established cut-point of the assay should also be used. Confirm that your assay contains a low concentration positive control that can reproducibly produce a response closer to the established cut-point of your assay.

2. You set the cut-point at (b) (4) for the immunodepletion assay to confirm the antibody status of patients. The agency recommends that the confirmatory cut-point be set based on assay precision. Re-establish the immunodepletion assay cut-point based on assay precision using serum from healthy human subjects and from treatment-naïve patients, if available.

3. In your drug tolerance study, you used control antibodies at a concentration of (b) (4) l to assess drug tolerance. Your assay is insufficient to address drug tolerance at low concentrations of anti-product antibodies. Repeat your drug tolerance study in the presence of low concentrations of control antibodies.

4. Develop appropriate quality controls in the neutralizing antibody assay and establish acceptance criteria based on these controls.

5. The specificity assessment should be designed to show that the drug product specifically binds to the antibodies induced by the product in human serum in the presence of exogenously added interfering molecules of similar size and charge (e.g., inclusion of IgG in IgE assay development).

6. We recognize that an alternative control for the anti-product IgE antibody assay may be required if a human positive control is not available, and that the detection limit may vary depending on antibody affinity. However, an estimation of assay sensitivity expressed in mass units is necessary to ensure assay suitability and performance for the intended purpose. Determine assay sensitivity and report the results.

Conclusions and Recommendations
Based on these deficiencies, the product quality immunogenicity reviewer is recommending a Complete Response action for this application. I agree with the product quality reviewer's recommendation.

Product Quality Microbiology
The reader is referred to the Product Quality Microbiology Consult Review by V. Pawar, dated February 10, 2011 for complete information.

This review evaluated the manufacturing processes relating to product quality microbiology including (b) (4) . These steps in the manufacturing process occur at two sites; (b) (4)

The reviewer noted several deficiencies in product quality microbiology at these two sites that must be addressed before an approval action can be taken. These deficiencies include the following:

1. (b) (4)

3. Inadequate microbiological analytical procedures (i.e., missing validation summary reports for sterility and bacterial endotoxin test methods).

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The following comments will be provided to the applicant in the complete response letter, and represent deficiencies that must be addressed in their complete response.

1. With regard to the validation of process (b) (4) , provide a bioburden data summary to justify this (b) (4) .

2. For the (b) (4) Lyophilizer, provide summary data from three consecutive successful (b) (4) with acceptable (b) (4) results.

    a. (b) (4) .

(b) (4)

3. Provide validation summary reports for sterility and bacterial endotoxin test methods.

Conclusions and Recommendations
Based on these deficiencies, the product quality microbiology reviewer is recommending that the application cannot be approved until these issues have been satisfactorily addressed. I agree with the product quality reviewer's recommendation.

1. Nonclinical Pharmacology/Toxicology

The reader is referred to the Pharmacology/Toxicology Review by T. Chakraborti, dated December 3, 2010 for complete information.

The application included the following Good Laboratory Practices (GLP) safety pharmacology/toxicology studies that were reviewed:

1. Acute single dose toxicity studies in mice and cynomolgus monkeys
2. One 4-week, repeat dose study in cynomolgus monkeys
3. One 39-week, repeat dose study in cynomolgus monkeys
4. One Segment I fertility and early embryonic development study in Sprague Dawley (SD) rats
5. One Segment II teratology study in rats and New Zealand white rabbits

Additionally, two non-GLP studies were also performed and reviewed by the nonclinical reviewer. These studies included one 14-day repeat dose study in marmoset monkeys, one 29-day repeat dose study in marmoset monkeys.

The nonclinical program evaluated doses of taliglucerase about 14 times the maximum proposed clinical dose of 60 U/kg (60 U/kg is equivalent to 2 mg/kg). In acute toxicity studies in mice and monkeys, taliglucerase alfa was non-lethal at the maximum doses tested (18 mg/kg, or nine time the maximum proposed clinical dose). For the chronic repeat dose and reproductive toxicology studies the dose and drug product used were comparable to the drug product used in the phase 3 clinical trial. A no observed adverse effect level (NOAEL) was noted to be 11mg/kg/day (approximately six times the maximum clinical dose) in a non-GLP, 29-day, repeat dose study in marmoset monkeys. Anti-taliglucerase antibodies were detected in some animals, but neutralizing antibodies were not detected based on the assay used. A NOAEL was noted to be 27.8 mg/kg (about 14 times the maximum clinical dose) in a GLP, 28-day, repeat dose study in cynomolgus monkeys. A target organ of toxicity in this study could not be identified. Similar to the marmoset monkey study, anti-taliglucerase antibodies were detected in some animals, however, none of the animals developed neutralizing antibodies based on the assay used.

Segment I fertility and embryonic development study was performed in SD rats. No treatment related adverse effects were noted in either sex. A Segment II teratology study was performed in both rats and rabbits and no findings were noted. Thus, the nonclinical reviewer concluded that taliglucerase is not teratogenic.

Genetic toxicology and carcinogenicity studies were not conducted or required because this product is a biologic product.

The nonclinical reviewer also provided recommendations for specific sections of product labeling (i.e., section 8.1 Pregnancy, section 8.3 Nursing Mothers, and section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility). These sections were not negotiated with the applicant during this review cycle.

Conclusions and Recommendations
The nonclinical reviewer concluded that the nonclinical program for taliglucerase was adequate that that there were no significant safety concerns uncovered in the nonclinical program. Thus, based on the results of the nonclinical studies, there appears to be no significant safety concerns at the intended clinical doses for the proposed indication. Additionally, there are no outstanding nonclinical studies that need to be addressed. I agree with the nonclinical reviewer's conclusions.

6. Clinical Pharmacology/Biopharmaceutics

The reader is referred to the Pharmacology/Toxicology Review by I.J. Lee, dated January 13, 2011 for complete information.

The applicant included a phase 1 pharmacokinetic (PK) study report P-01-2005 in healthy subjects and a phase 3 PK study report PB-06-001 in type 1 Gaucher patients for review in this submission.

General clinical pharmacology/Biopharmaceutics
The PK parameter values of taliglucerase alfa were determined in Gaucher patients at the proposed indicated dose of 60 U/kg every other week, and 30 U/kg every other week using a non-compartmental method (see Table 1).

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

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

(copied from clinical pharmacology review, I.J. Lee, page 3)

The clinical pharmacology reviewer noted that the PK parameters for taliglucerase alfa do not appear to be dose-proportional based on the doses studied. The AUC values for the 60 U/kg dose compared to the 30 U/kg dose increased by 178% and 200% on Day 1 and Week 38. Additionally, CL values were reduced by 30% and 35% on Day 1 and Week 38, respectively. The clinical pharmacology reviewer also noted that the design of this PK study did not collect samples at or around 90 minutes (the length of the infusion), and therefore, Cmax could not be measured based on this study.

The applicant also performed a phase 1 study in healthy subjects. The utility of the information obtain in this study is unclear because the PK and PD findings in healthy human subjects who presumably have normal glucocerbrosidase activity would like be different than Gaucher patients. The clinical pharmacology reviewer noted that the AUC_{last} and clearance of taliglucerase alfa were both higher (2.6 and 2.8-fold higher, respectively) in healthy subjects compared to Gaucher patients. Additionally, t½ values were longer in Gaucher patients compared to healthy subjects.

The clinical pharmacology reviewer also noted that there appears to be no significant exposure-response relationship based on the two doses of taliglucerase studied (30 U/kg and 60 U/kg) in the primary efficacy endpoint, spleen volume. There was a statistically significant decrease in spleen volume at the end of the study for both doses studied (see section 8: Clinical/Statistical: Efficacy).

<u>Drug-drug interactions</u>
No drug-drug interaction studies were conducted for this submission.

Pathway of elimination
Taliglucerase alfa, a therapeutic protein product, is likely cleared by absorption into macrophages. Therefore, metabolism, excretion, and mass balance studies were not required or performed.

Demographic interactions/intrinsic factors, special populations
The applicant did not explore the impact of intrinsic factors on taliglucerase alfa exposure-efficacy or safety response relationships in the submission. Specifically, the submission did not include studies evaluating geriatric or pediatric or pediatric age groups. The effect of gender, race, and presence of renal or hepatic impairment on PK was also not specifically evaluated in any study.

QT assessment
A thorough QT assessment was not performed nor required because as a therapeutic protein product, taliglucerase alfa, like other ERTs, would not be expected to affect hERG channels. Blockade of hERG channels can result in significant alterations in ventricular repolarization, potentially resulting in torsades de pointe which can degenerate into fatal ventricular arrhythmias. Additionally, ECG results at all visits were normal in a PK study (P-01-2005) in healthy subjects.

Other issues: Immunogenicity
The effect of immunogenicity on PK and PD parameters could not be reviewed during this review cycle because the formation of anti-taliglucerase alfa antibodies could not be adequately determined based on the review of the CMC immunogenicity reviewer (see section 3.C: CMC, above). Additionally, the effect of neutralizing antibodies to enzyme uptake could not be evaluated because the applicant has not yet developed an assay for this specific inhibitory antibody. Information requests regarding the impact of immunogenicity on PK and efficacy of taliglucerase were conveyed to the applicant on November 23 and December 21, 2010. However, there was insufficient time in during the current review cycle to adequately review this information. Furthermore, a clear determination of the anti-taliglucerase antibody assay cut-points has not been established. Therefore, the effect of immunogenicity of PK parameters and efficacy cannot be determined until these assay cut-points have been established.

The following comments will be provided to the applicant in the complete response letter, and represent deficiencies that must be addressed in their complete response.

1. The immunogenic potential of taliglucerase alfa and its impact on the pharmacokinetic and pharmacodynamic (PK and PD) parameters cannot be adequately evaluated.
    a. Propose an acceptable confirmatory cut-point for your anti-product IgG antibody assay and submit a re-analysis of the impact on PK and PD parameters in patients treated with taliglucerase alfa.
    b. Develop an acceptable neutralizing antibody assay and submit a re-analysis of the impact on PK and PD parameters in patients treated with taliglucerase alfa.

Conclusions and Recommendations
The clinical pharmacology reviewer concluded that a complete review of the information was not possible during the current review cycle. Major outstanding issues include the development of a validated assay to assess for neutralizing antibodies for enzyme uptake, and the establishment of anti-taliglucerase antibody confirmatory assay cut-points that can be used to establish the effect of immunogenicity on PK parameters and efficacy. I agree with the clinical pharmacology reviewer's conclusions and recommendations. These issues must be addressed by the applicant in their Complete Response.

7. Clinical Microbiology

Clinical microbiology considerations do not apply to this application because taliglucerase alfa is not intended as an antimicrobial product.

8. Clinical/Statistical- Efficacy

The reader is referred to the clinical review by C. Epps, dated February 22, 2011, and the statistical review by B. Vali, dated February 24, 2011, for complete information.

The data submitted to support the efficacy of Taliglucerase alfa was contained in a single phase 3 trial, PB-06-001. Additional preliminary supportive efficacy data from two on-going studies were also submitted. Study PB-06-002 is a multicenter, open-label, switch over study in stable Gaucher patients receiving imiglucerase (Cerezyme). The applicant submitted preliminary data on six patients currently enrolled in this study. Study PB-06-003 is an open-label extension study for patients previously enrolled in either study PB-06-001 or PB-06-002. However, the efficacy data from these two studies is insufficient to provide any real conclusions because of the limited number of patients with data provided by the applicant at the time of the submission. Additionally, these studies are on-going and only interim data could be provided. Therefore, the discussion of efficacy will be limited in this review to results from study PB-06-001.

Study PB-06-001
Study PB-06-001 was a multicenter, randomized, double-blind, parallel-dose study of 33 adult patients with type 1 Gaucher disease.

Eligibility, treatment and assessments
Enrollment was restricted to patients 18 years of age and older who were naïve to enzyme replacement therapy had a spleen volume as measured my MRI of at least 8 times normal, and thrombocytopenia. Patients were randomized 1:1 to receive taliglucerase at a dose of either 30 units/kg or 60 units/kg every other week for nine months.

Endpoints

The pre-specified primary endpoint was the percent change from baseline in spleen volume as measured by MRI after nine months. The primary efficacy analysis was based on two one-sample t-tests (one for each treatment group) using an alpha level of 0.025.

Major secondary endpoints included the change from base line in hemoglobin, liver volume as measured by MRI as a percent change, and platelet count. Additionally, change from baseline in Gaucher disease biomarkers, chitotriosidase, and PARC/CCL18 were also evaluated. These secondary endpoints were analyzed in a sequential (step-down) approach based on the statistical significance of the primary endpoint and each secondary endpoint in the order presented (i.e., hemoglobin, liver volume, and platelet count) using a one-sample t-test. For both the primary and major secondary endpoint analyses, a mixed effects model was fit to examine whether any differences were noted between dose groups at month 6 and month 9. Patients who withdrew early from the study were analyzed using the last observation carried forward (LOCF) approach. However, if the patient withdrew due to a serious adverse event, no-change from baseline was imputed.

Results

The applicant reports that 33 patients were enrolled and randomized into the study. All but one patient received at least one dose of study drug, and 29/33 patients completed all 20 study visits. Three patients discontinued the study; two withdrew due to adverse events (one each in the 30 unit/kg and 60 unit/kg groups), and one withdrew due to pregnancy (60 unit/kg group). There were 24 patients with reported protocol deviations. Of these, 16 patients had 31 protocol deviations that were approved by the Medical Director, including visits outside the scheduled window or other study procedures that were not performed according to the protocol schedule. Eight patients had protocol deviations that were not approved by the Medical Director including antibody testing that was not done, improper dilution of study drug, positive urine pregnancy test (see above). Additionally, there were 4 patients included in the study that did not meet inclusion criteria but were included by the Medical Director (2 patients with glucuocerebrosidase activity levels that were > 3 nmol/mg*hr, and 2 patients with platelet counts > 120,000 mm^3. None of these deviations appear to have affected the outcome of the study results.

The applicant provided demographic data analyses for 31 patients who comprised their intent to treat (ITT) population, defined as patients who received at least one dose of medication and had at least the screening/baseline MRI evaluation. Two patients were excluded from the applicant's ITT population; one patient who withdrew for personal reasons prior to receiving any study medication, and one patient who developed anaphylaxis during the first dose of taliglucerase alfa. It should be noted, however, that the statistical reviewer analyzed the efficacy data using a "corrected intent-to-treat" population (all patients who were randomized into the study), or a corrected intent-to-treat population of 33 patients (16 patients in the 30U/kg arm and 17 patients in the 60U/kg arm). There were no significant differences in mean or median results between treatment groups for age, gender, race, or weight. The majority of patients enrolled were Caucasian (100% for the 30 unit/kg group and 94% for the 60 unit/kg group).

The primary efficacy endpoint was evaluated for both treatment groups at 6 months and at 9 months. Treatment with either 30 U/kg or 60 U/kg was associated with a statistically significant decrease in the percent change in mean spleen volume at 6 months and at 9 months (see Table 2). Both treatment arms demonstrated a decline in spleen volume of greater than 20% (the pre-specified definition of a clinically meaningful change in spleen volume) at both 6 months and 9 months. Furthermore, when these dose arms are compared utilizing a two independent sample t-test in the "corrected in-to-treat" population as defined by the statistical reviewer, a significant difference between the arms is also recognized. The p-value from this two independent sample t-test, which assumes equal variance between the two arms, equals 0.01. The mean difference between these dosing arms (60 units/kg – 30 units/kg) in percent change from baseline in spleen volume is -10.6 with corresponding 95% C.I.(-18.82, -2.27). Although the result from this dose comparison is exploratory in nature, this analysis suggests greater effectiveness of the 60 unit/kg dose (see Figure 1). There were no substantive differences in the analysis when these two patients are included in the analysis.

Table 2: Mean change in spleen volume by treatment group based on applicant's ITT population

Treatment Group	**Length of Treatment**	
	6 months	**9 months**
30U/kg Group (n=15) Mean Percent Change±SD (Min-Max)	-22%±5 (-12 to -29) p<0.0001* 95% CI (-24.3, -19.7)	-27%±8 (-16 to -43) p<0.0001* 95% CI (-30.9, -23.1)
60 U/kg Group (n=16) Mean Percent Change±SD (Min-Max)	-30%±13 (+3 to -53) p<0.0001* 95% CI (-36.2, -23.8)	-38%±9 (-21 to -56) p<0.0001* 95% CI (-42.6, -33.4)
All Treatment Groups (n=31) Mean Percent Change±SD	-26%±10	-33%±10

* p-value obtained from one-sample t-test (combined)
(table modified from clinical review by C. Epps)

Figure 1: Change in spleen volume by treatment group*

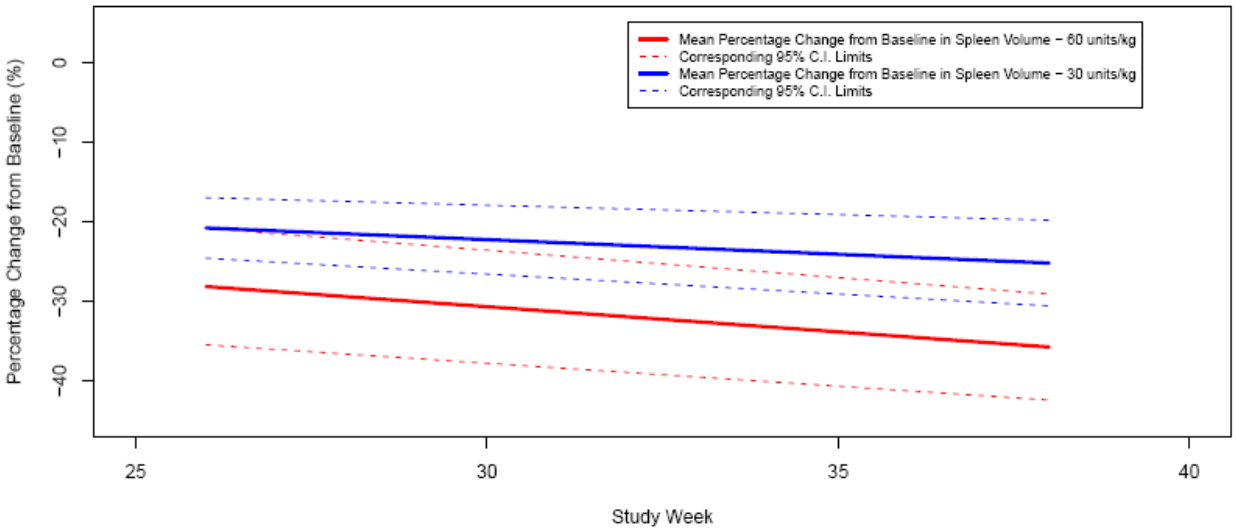

*Figure based on data from "corrected ITT" population
(copied from statistical review by B. Vali)

The clinical and statistical reviewer both concluded that the data demonstrated a clinically meaningful and statistically significant difference in spleen volume in both treatment groups at the end of the study.

Key secondary endpoints for the study include change in liver volume, platelet count, hemoglobin and chitotriosidase levels (see Table 3). There was a statistically significant decrease in the percent change in liver volume compared to baseline for both treatment groups at the end of the study (-11% in the 30 U/kg group and -11% in the 60 U/kg group). Additionally, improvements in mean platelet count and hemoglobin were also demonstrated in both treatment groups at the end of the 9-month treatment period. Finally, decreases in a relevant Gaucher biomarker, chitotriosidase, were also noted in both treatment groups at the end of the study. It should be noted that the improvement in platelet count was only modest in the 30 U/kg group at the end of the study. This difference bordered on statistical significance (p=0.046), however the clinical significance of this differences is not clear. The difference in platelet count in the 60 U/kg group appears to be both clinically meaningful and statistically significant. The clinical relevance of an improvement of 1.6-2.2 g/dL in mean hemoglobin could also be questioned; however, baseline hemoglobin levels for patients in both treatment groups was near normal (12.2 g/dL for the 30 U/kg group and 11.4 g/dL in the 60 U/kg group) and therefore, improvements would be expected to be modest. Overall, these results support the effect of taliglucerase in patients with type 1 Gaucher disease and are consistent with the findings demonstrated in the primary endpoint.

Table 3: Results of key secondary endpoints at 9 months

Secondary Endpoints	30 U/kg Group	60 U/kg Group	All Treatment Groups
Mean percent change in Liver volume	**-11±11 (p=0.0041)**	**-11±7 (p<0.0001)**	**-11±9**
Mean change in platelet count	**11K±20K (p=0.046)**	**41K±47K (p=0.0031)**	**27K±39K**
Mean change in hemoglobin (g/dL) ± SD	**1.6±1.4 (p=0.001)**	**2.2±1.4 (p<0.0001)**	**1.9±1.4**
Mean change in chitotriosidase level	**-13264±8378 (p<0.0001)**	**-12165±12064 (p=0.016)**	

p-values obtained from one-sample t-test
(table modified from clinical review by C. Epps)

Effect of Immunogenicity on Efficacy

An important consideration with all enzyme replacement therapies for lysosomal storage diseases is the development of immune responses to the infused enzyme replacement therapy. These immune responses can be associated with the development of allergic/hypersensitivity reactions as well as altered effectiveness of treatment. All patients were tested for development of anti-taliglucerase antibody formation during the study. The applicant noted that only two patients developed anti-taliglucerase IgG antibodies during the study. Both of the patients completed the study and there was no apparent association between the development of anti-taliglucerase IgG antibodies and changes in efficacy outcome. It should also be noted that the immunogenicity reviewer noted five patients (not two, as the applicant stated) with positive anti-taliglucerase IgG antibodies (see immunogenicity reviewer's review for details). However, due to the small numbers of patients reported and the relatively lack of long-term efficacy data, it is not possible to draw clear conclusions regarding the effect of IgG antibody development and long-term efficacy.

Additionally, the immunogenicity reviewer disagrees with the criteria used by the applicant to identify patients who develop anti-taliglucerase IgG antibodies. The cut-point used by the applicant in the confirmatory immunodepletion assay was determined to be unacceptable. Furthermore, the applicant included patients as having developed IgG antibodies only if the assay was positive at the end of the study. This is inconsistent with the definition used in other ERT applications. The Agency has consistently defined patients who develop IgG antibodies as any patient who developed a positive antibody titer *at any time point in the study*, not only the last time point. It is likely that a change in the criteria used to define patients who develop anti-taliglucerase IgG antibodies will increase the number of patients that have developed IgG antibodies and re-analysis of the efficacy and safety data will be warranted. The immunogenicity reviewer notes that in a preliminary analysis of the immunodepletion assay results submitted by the applicant, if a cut-point for the assay consistent with other ERT approvals is used, the number of patients identified as anti-taliglucerase antibody positive increases to 10-13 patients. This increase could have an important effect on the review of the

safety and efficacy data for the product. Furthermore, the applicant has not completed the development and validation of an assay to evaluate for neutralizing antibodies for enzyme uptake by macrophages. IgG antibodies for enzyme uptake appear to be the main mechanism for neutralization of activity of ERTs based on data from other approved ERTs. Therefore, development and validation of this assay should be required to fully assess the immunogenicity of taliglucerase alfa.

Therefore, due to inability to adequately assess the immunogenicity of taliglucerase because of the lack of an acceptable IgG anti-taliglucerase IgG antibody cut-point for the confirmatory immunodepletion assay, lack of an acceptable definition for patients who develop anti-taliglucerase IgG antibodies, and the lack of a validated assay to identify neutralizing antibodies for enzyme uptake, the efficacy and safety of the product cannot be adequately established and I agree with the immunogenicity reviewer recommendation that a complete response action should be taken. Recommendations for the applicant in the complete response letter will include a requirement to reassess the effect of immunogenicity on efficacy and safety after an acceptable criteria for use of the anti-taliglucerase IgG antibody assay are determined.

Conclusions and Recommendations

The data from this single pivotal trial demonstrate that treatment with taliglucerase alfa produced a statistically significant and clinically meaningful decrease in spleen volume at 6 and 9 months. Additionally, important secondary endpoints including decrease in liver volume, and improvements in hemoglobin and platelet count were also demonstrated. Indeed, as was noted in the primary clinical review, the magnitude of the treatment effect for decrease in spleen volume was similar to that of a recently approved ERT for Gaucher disease, velaglucerase. Thus, despite the reliance on a single pivotal trial, the data demonstrate a clear and robust treatment effect that would not have been expected to occur without treatment. In the Guidance for Industry, "Providing clinical Evidence of Effectiveness for Human Drug and Biological Products," specific recommendations regarding the quality and quantity of evidence required to substantiate effectiveness of a product based on a single pivotal trial are discussed. These factors include consistency across study subsets, multiple endpoints involving different events that all demonstrate a statistically persuasive effects, and statistically very persuasive findings in the primary endpoint that would be highly inconsistent with the null hypothesis. All of these factors have been demonstrated in support of the efficacy of taliglucerase alfa based on the single pivotal trial, PB-06-001.

However, the guidance also discusses the important caveats to the reliance of a single pivotal study, including that even a strong result can represent an isolated or biased result. Additionally, the applicant did not perform a head-to-head comparison between taliglucerase and other approved ERTs for Gaucher disease. Therefore, it is not possible to draw clear conclusions about the relative effectiveness of taliglucerase alfa in the treatment of Gaucher disease compared to other approved ERTs. Because Gaucher disease is a life-threatening condition for which there are already approved products in the U.S., lack of clear data demonstrating the relative effectiveness of taliglucerase compared to these approved products is a significant weakness in this application. Furthermore, the clinical reviewer noted two recent publications that suggest that clinical parameters of Gaucher disease remained stable or

did not deteriorate precipitously up to 6 months after treatment withdrawal.[1,2] In the earlier survey, some patients were clinically stable after more than two years without ERT treatment. These data suggest that a trial to evaluate the relative efficacy of taliglucerase compared with other approved ERTs must include data for at least 6-12 months. Additionally, in the approval for VPRIV, the reviewer noted that a head-to-head trial was conducted comparing efficacy and safety of VPRIV compared to Cerezyme in a trial lasting 12 months.

Additionally, the effect of immunogenicity on efficacy could not be fully evaluated during this review cycle because the criteria used by the sponsor to define patients with anti-taliglucerase IgG antibodies was unacceptable. Furthermore, development of neutralizing antibodies to enzyme uptake is a major mechanism by which efficacy can be affected in ERTs. The applicant has not yet developed a validated assay to measure the development of neutralizing antibodies for enzyme uptake for taliglucerase.

I agree with the primary clinical reviewer and statistical reviewer that demonstration of efficacy compared to other approved ERTs has not been established and precludes approval of this product during this review cycle. However, I do not agree with the clinical reviewer and statistical reviewer's recommendation that an additional clinical study must be performed using a head-to-head design to establish the relative efficacy and safety of taliglucerase alfa to other approved ERTs as a condition for resubmission. I recommend that data from study PB-06-002 and PB-06-003 be carefully evaluated to assess the clinical outcome of patients switched from Cerezyme to taliglucerase alfa who have received treatment for at least 12 months. These data may be sufficient to demonstrate the relative effectiveness of taliglucerase alfa compared to Cerezyme. However, if these data are not sufficient to conclude that the efficacy and safety of taliglucerase alfa is similar to Cerezyme, then additional clinical studies may be required in the future. Additionally, a re-analysis of information regarding the immunogenicity of the product and its effect on efficacy and safety must also be included in a re-submission.

9. Safety

The safety data for taliglucerase alfa comes from the experience in Study PB-06-001, as well as interim data from Study PB-06-002 (imiglucerase switch study), PB-06-003 (phase 3 extension study), and PB-06-004 (expanded access protocol). The interim data from Studies PB-06-002 and PB-06-003 were minimal, and therefore, the safety data from each study were reviewed separately by the clinical reviewer. Additionally, this product is a new molecular entity and has not been approved outside the U.S. Therefore, there are no postmarketing data available for the safety review.

The safety database consisted of 83 patients with type 1 Gaucher disease. Of the 83 patients, 39% (32/83) were treatment naïve patients who received taliglucerase alfa, and 30% were

1 Elstein D, Abrahamov A et al, Withdrawal of enzyme replacement therapy in Gaucher's disease, *Br. J Haematol* 2000; 110(2):488-492.
2 Zimran A, Altarescu G, Elstein D, Nonprecipitous changes upon withdrawal from imiglucerase for gaucher disease because of a shortage in supply, *Blood Cells Mol Dis* 2011: 46 (1):111-114.

switched from imiglucerase to taliglucerase. Additionally, 44% (27/83) patients completed 12 months of treatment; and only 8% (7/83) completed 24 months of treatment (see Table 4).

Table 4: Total patient exposure to taliglucerase alfa

			Months of Treatment											
Study	0*		3	6	9	12	15	18	21	24	27	30	33	36
PB-06-001	32		31	29	29									
PB-06-002	25		24	20	8									
PB-06-003						27	26	20	11	7	3	2	1	
PB-06-004	26		16	6										
Total	83		71	55	37	27	26	20	11	7	3	2	1	

*Number of subjects enrolled and treated as of June 30, 2010

(copied from Clinical Review by C. Epps)

No deaths were reported. The applicant reported three serious adverse events. These adverse events included one episode each of epistaxis, immune thrombocytopenic purpura (ITP), and nephrolithiasis. The clinical reviewer agreed with the applicant's assessment that these serious adverse events were not likely related to treatment with taliglucerase alfa. However, it is not clear whether the patient with ITP could have developed an immune response during treatment with taliglucerase alfa that could have precipitated this adverse event.

Anaphylaxis, acute and chronic immune reactions, and infusion reactions are the most serious adverse events related to treatment with ERTs for lysosomal storage diseases. The applicant reported only one patient has having developed anaphylaxis. However, the clinical reviewer independently assessed the adverse events and recoded these events based on the clinical definition of anaphylaxis as published by Sampson et al. Based on the clinical reviewer's assessment, 9% (3/32) patients definitely met criteria for anaphylaxis. One patient who developed a "hypersensitivity reaction" may have also had anaphylaxis, but there was insufficient information provided to clearly determine whether this patient sustained a clinical episode of anaphylaxis. In the clinical review for VPRIV, there was one case of anaphylaxis identified in the phase 3 trials. The incidence of anaphylaxis in Cerezyme is estimated to be less than 1% based on a review of the post-marketing experience. It appears that the incidence of anaphylaxis may be slightly higher for taliglucerase alfa, but no clear conclusions can be drawn regarding the relative incidence of anaphylaxis between these products because the data are limited.

Infusion reactions (adverse reactions that occurred during or within 2 hours of the completion of the infusion) were seen commonly with taliglucerase treatment. The clinical reviewer noted that 41-48% of patients across studies PB-06-001, PB-06-002, and PB-06-003 developed infusion reactions. These reactions included abdominal/epigastric discomfort, arthralgia, asthenia chest pain/discomfort, dizziness, drug eruption, dyspnea, erythema, fatigue, feeling

hot, flushing, infusion related reaction, headache, hyperglycemia, hyperhidrosis, hypersensitivity, hypertension, lethargy, nausea, pain, palpitations, presyncope, pruritis, pyrexia, rash/skin irritation, swelling, tachycardia, and vomiting (see Table 6).

Table 5: Commonly reported infusion reactions across trials for taliglucerase alfa

System Organ Class Preferred Term	**PB-06-001 N=32**	**PB-06-002 N=25**	**PB-06-003 N=29**
General Disorders and Administration Site Conditions (N=13)			
Infusion related reaction	0	4 (16%)	2 (7%)
Asthenia	0	2 (8%)	0
Chest pain/discomfort	2 (6%)	0	0
Fatigue	0	1 (4%)	2 (7%)
Nervous System Disorders (N=13)			
Headache	5 (16%)	2 (8%)	1 (3%)
Hypoesthesia/paresthesia	1 (3%)	1 (4%)	1 (3%)
Dizziness/Presyncope	1 (3%)	0	1 (3%)
Skin and Subcutaneous Tissue Disorders (N=10)			
Erythema	1 (3%)	1 (4%)	2 (7%)
Urticaria/rash/drug eruption	0	1 (4%)	3 (10%)
Pruritis	1 (3%)	1 (4%)	0
Gastrointestinal Disorders (N=8)			
Abdominal/Epigastric discomfort	1 (3%)	1 (4%)	1 (3%)
Diarrhea	1 (3%)	1 (4%)	1 (3%)
Vomiting	1 (3%)	0	1 (3%)
Musculoskeletal and Connective Tissue Disorders (N=7)			
Arthralgia/back pain	2	2 (8%)	3 (10%)
Vascular Disorders (N=6)			
Flushing	2 (6%)	1 (4%)	0
Hypertension/increased blood pressure	1 (3%)	0	2 (7%)
Immune System Disorders (N=3)			
Hypersensitivity*	2 (6%)	0	1 (3%)

(copied from clinical review, C. Epps)

Common adverse events, defined as occurring in >5% of treated patients, were classified by the clinical reviewer for Study PB-06-001. The most common adverse events included upper respiratory infections/colds (22%) pharyngitis /throat infection, headaches (each 19%), and influenza/flu and arthalgia/back pain (13%) (see Table 6). It should be noted that this study was not placebo-controlled and therefore clear associations between treatment and adverse events are difficult to assess. However, I agree with the clinical reviewer's assessment that adverse reactions could reasonably be defined as those adverse events occurring at an incidence of >5% of treated patients. Common adverse events for studies PB-06-002 and PB-06-003 were similar.

Table 6: Common Adverse Events (>5% of treated patients)

System Organ Class	Preferred Term	30 U/kg group N=16	60 U/kg group N=16	All treatment groups N=32
Infections and Infestations				
	URI/Cold	3 (19%)	4 (25%)	7 (22%)
	Pharyngitis/Throat infection	4 (25%)	2 (13%)	6 (19%)
	Eye infection	1 (6%)	1 (6%)	2 (6%)
	Influenza/Flu	1 (6%)	3 (19%)	4 (13%)
	UTI/Pyelonephritis	1 (6%)	2 (13%)	3 (9%)
	Gastroenteritis	1 (6%)	1 (6%)	2 (6%)
	Otitis externa	1 (6%)	2 (13%)	2 (6%)
Musculoskeletal and Connective Tissue Disorders				
	Arthralgia/back pain	1(6%)	3 (19%	4 13%)
Nervous System Disorders				
	Headache	1 (6%)	5 (32%)	6 (19%)
	Dizziness	2 (13%)	1 (6%)	3 (9%)
Gastrointestinal Disorders				
	Nausea	1 (6%)	2 (13%)	3 (9%)
	Vomiting	2 (13%)	0 (0%)	2 (6%)
	Abdominal pain	2 (13%)	0 (0%)	2 (6%)
General Disorders and Administration Site Conditions				
	Fatigue/tiredness	1 (6%)	2 (13%)	3 (9%)
	Warmth	1 (6%)	1 (6%)	22 (6%)
Skin and Subcutaneous Tissue Disorders				
	Itching	1 (6%)	1 (6%)	2 (6%)
	Skin mycosis	1 (6%)	1 (6%)	2 (6%)
Vascular disorders				
	Facial flushing	1 (6%)	1 (6%)	2 (6%)
	Hypertension/high BP	2 (13%)	0 (0%)	2 (6%)
Blood and Lymphatic System Disorders				
	Enlarged lymph nodes	1 (6%)	1 (6%)	2 (6%)
Immune System Disorders				
	Hypersensitivity	1* (6%)	1* (6%)	2 (6%)
Respiratory, Thoracic, and Mediastinal Disorders				
	Epistaxis	2 (13%)	0 (0%)	2 (6%)

*Patient was discontinued from the trial
(copied from clinical review, C. Epps)

The clinical reviewer evaluated the incidence of abnormal laboratory findings, abnormal vital sign reports, and abnormal ECG and echocardiogram reports. There was no pattern or apparent safety signal uncovered with any of these parameters.

The effect of immunogenicity is also an important concern for all ERTs. The applicant reported that only two patients developed anti-taliglucerase IgG antibodies in Study PB-06-001. As noted above (section 8: Clinical/Statistical: Efficacy; Immunogenicity), the antibody assay cut-off that the applicant used was not acceptable by the immunogenicity reviewer. Therefore, it was not possible to fully assess the effect of immunogenicity of the safety of the

product during this review cycle. Of two patients that developed IgG antibodies to taliglucerase as reported by the applicant, neither of the patients developed anaphylaxis, allergic reactions, or immune-mediated reactions. A complete review of the effect of immunogenicity must be re-evaluated after the applicant provides an acceptable antibody assay.

Conclusions and Recommendations

Overall, the clinical reviewer concluded that the size of the safety database was acceptable because of the rarity of the disease. I agree with the reviewer's assessment. However, there were very few patients in the safety database with data on longer-term treatment (i.e., more than 12 months). Immune-mediated reactions and chronic allergic reactions may be seen in ERTs with continued long-term treatment. Therefore, I would recommend that additional longer-term safety data from study PB-06-003 should be required as part of the Complete Response. Additionally, I would recommend that a complete study report for Study PB-06-002 be required as part of the Complete Response to assess safety in patients who switched from imiglucerase to taliglucerase more fully.

Additionally, the impact of immunogenicity could not be fully assessed during this review cycle because the applicant did not provide an adequate cut-point for the confirmatory immunodepletion assay for anti-taliglucerase alfa antibody formation. Therefore, I recommend that an acceptable cut-point for the confirmatory immunodepletion assay for anti-taliglucerase alfa antibodies be required as a part of the Complete Response, and that the applicant must reanalyze all available safety data based on the revised assay.

Postmarketing safety requirements were not negotiated because the safety data could not be completed reviewed during this review cycle.

Overall recommendations

Based on the overall review of the safety and efficacy of taliglucerase alfa, significant questions remain unanswered. Therefore, I recommend that a Complete Response action be taken for this submission. The following comments will be provided to the applicant in the complete response letter, and represent deficiencies that must be addressed in their complete response.

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

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

2. There are insufficient data provided to assess the efficacy and safety of taliglucerase alfa in patients switched from other enzyme replacement therapies. Submit the final

study report from PB-06-002, and a minimum of 12 months of efficacy and safety data from PB-06-003 for patients switched from other enzyme replacement therapies to taliglucerase alfa.

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

10. Advisory Committee Meeting

This product is considered a new molecular entity. However, it shares similarity with previously approved ERTs for Gaucher disease; Ceredase, Cerezyme, and Velaglucerase. Additionally, no new or unique concerns were identified during the review of this product compared to other drugs in this class. Therefore, no advisory committee meeting convened for this product during this review cycle.

11. Pediatrics

Taliglucerase alfa received orphan designation on September 3, 2009. Therefore, the regulations that pertain to the Pediatric Equity in Research Act (PREA) do not apply to taliglucerase alfa. The submission was not presented to the Pediatric Review Committee (PeRC).

12. Other Relevant Regulatory Issues

A. DSI audits and Financial Disclosures

All of the study sites for the single pivotal trial were conducted at foreign sites. The Division of Scientific Investigations (DSI) performed clinical site inspections at two foreign sites (Site #30, Clinical Center of Serbia, Belgrade, Serbia and Site #10, Shaare Zedek Medical Center, Jerusalem, Israel). The DSI inspector found that the data from the two clinical study sites inspected are reliable and can be used in support of the BLA. Additionally, an inspection of the applicant, Protalix Biotherapeutics was performed by DSI because taliglucerase is a new molecular entity. The inspection of the applicant revealed no significant deficiencies and the DSI inspector noted that the applicant adequately monitored the studies conducted in the application.

Financial disclosures were submitted by the applicant for one investigator, (b) (6) [redacted] This site underwent DSI audit (see above) and the inspection did not note any

significant deficiencies. Thus, despite the significant financial relationships between the (b) (6) and the applicant, the conduct of the studies does not appear to have been affected by these financial arrangements.

B. Clinical Consults

There were no clinical consults obtained for the current review.

C. Drug shortage

There are currently two approved ERT products for Type 1 Gaucher disease in the U.S.; Cerezyme (imiglucerase) and VPRIV (velaglucerase). U.S. production of Cerezyme was temporarily suspended in June 2009 due to manufacturing issues at Genzyme's Allston Landing facility, where Cerezyme is manufactured. Although Velaglucerase alfa was made available through a treatment protocol in July 2009 and received U.S. approval in February 2010, there was an on-going drug shortage at the time of submission of this application. Genzyme issued a statement on January 11, 2011 that the supply of Cerezyme had been restored for all patients currently receiving therapy and that Cerezyme will be available to new Gaucher patients. We have not received any reports of any U.S. Gaucher patients that are unable to access ERT at the present time. Therefore, it appears that the drug shortage for U.S. Gaucher patients has resolved at the time of this review.

13. Labeling

Proprietary name

During this review cycle, the originally proposed trade name of (b) (4) was submitted for review. A review of the trade name was performed by Z. Oleszczuk in the Division of Medication Errors Prevention and Analysis (DMEPA). The proposed name, (b) (4) was rejected by DMEPA (b) (4) The applicant subsequently submitted a new proposed name, Elelyso. A review of this trade name was performed by Z. Oleszczuk, DMEPA. The trade name, Elelyso, was found to be acceptable. However, this proposed name must be reviewed again with the applicant's complete response submission.

Physician labeling/ Carton and immediate container labels

Final product labeling, as well as carton and container labeling were not satisfactorily negotiated during the current review cycle because deficiencies in the submission leading to a Complete Response action precluded a complete review and negotiation of final labeling with the applicant. The applicant will be required to submit proposed physician labeling and carton and container labeling with their Complete Response.

Patient labeling/Medication guide (if considered or required)

A final determination of the requirement for patient labeling and/or medication guide was not made during this review cycle. However, other approved products in this class have not included a medication guide because ERTs are intended to be administered by specialized infusion staff. Taliglucerase, like other ERTs for Gaucher disease would not be directly supplied to the patient. Therefore, it is unlikely that a medication guide will be required.

14. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
The current application contains deficiencies that have not been satisfactorily addressed. These include serious CMC, immunogenicity, product quality microbiology, clinical pharmacology, and clinical issues that have not been resolved. Therefore, I recommend that a Complete Response (CR) action be taken for this application.

Risk Benefit Assessment
The benefit of taliglucerase alfa in the treatment of Gaucher disease appears to have been demonstrated based on a single study. However, the relative benefit of the product compared to two products already approved in the same class of biologic products to treat Gaucher disease has not yet been clearly demonstrated. Furthermore, the risk of immunogenicity for this product could not be evaluated during this review cycle because the immunogenicity assays used by the applicant to determine the immunogenicity of the product were not acceptable. Finally, it should be noted that at the present time, the drug shortage for Gaucher patients appears to have eased. Genzyme reported in January 2011 that Cerezyme supplies were improved and that new Gaucher patients would be able to access the product. Additionally, VPRIV has been available since February 2010 and we have not received any reports of any U.S. Gaucher patients that are unable to access ERT at the present time. It appears that the drug shortage for U.S. Gaucher patients has resolved at the time of this review. Therefore, the risk benefit assessment is currently unacceptable and precludes approval of the product during this review cycle.

Additionally, the clinical and statistical reviewer both recommended that an additional study must be performed to establish the relative efficacy and safety of taliglucerase alfa compared to other approved ERT products because the current submission contained inadequate information to assess this. I agree that additional information must be included in the resubmission to address this deficiency. However, I do not agree that an additional clinical study must be performed as a condition for resubmission. I recommend that data from study PB-06-002 and PB-06-003 be carefully evaluated to assess the clinical outcome of patients switched from Cerezyme to taliglucerase alfa who have received treatment for at least 12 months. If these data are sufficient to demonstrate the relative effectiveness of taliglucerase alfa compared to Cerezyme, then an additional study may not be necessary. This was discussed with both the clinical and statistical reviewer who both agree that this recommendation was reasonable. However, the reviewers continue to express concern that the data contained in PB-06-002 and PB-06-003 may not sufficient, and if not, they agree that an additional clinical study should be required at that time.

Recommendation for Postmarketing Risk Evaluation and Management Strategies
Postmarketing risk management activities were not reviewed extensively during this review cycle because a Complete Response action is recommended. However, during the review of the application, no special issues that would require postmarketing risk management activities were identified. Therefore, the Complete Response action will not include recommended risk management strategies to be included in a Complete Response.

Recommendation for other Postmarketing Requirements and Commitments
Postmarketing requirements and commitments were not reviewed extensively during this review cycle because a Complete Response action is recommended. Therefore, the Complete Response action will not include recommended specific recommendations for postmarketing requirements and commitments to be included in a Complete Response.

Recommended Comments to Applicant

Clinical
The following recommended comments regarding further clinical information to be included in the complete response are as follows:

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

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

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

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

Clinical Pharmacology
The following recommended comments regarding further clinical pharmacology information to be included in the complete response are as follows:

4. The immunogenic potential of taliglucerase alfa and its impact on the pharmacokinetic and pharmacodynamic (PK and PD) parameters cannot be adequately evaluated.

    a. Propose an acceptable confirmatory cut-point for your anti-product IgG antibody assay and submit a re-analysis of the impact on PK and PD parameters in patients treated with taliglucerase alfa.
    b. Develop an acceptable neutralizing antibody assay and submit a re-analysis of the impact on PK and PD parameters in patients treated with taliglucerase alfa.

Product Quality
The following recommended comments regarding further product quality information to be included in the complete response are as follows:

Specifications and Assay Validation

5. Results of USP <788> particulate testing and appearance testing on reconstituted drug product have not been submitted to the NDA. Both tests provide a useful measure of product quality that is not monitored by other tests you have proposed. Add these tests to the release and stability specifications and provide available results for release and stability testing of the three conformance lots and any additional results you may have.

6. A potency assay that quantitatively measures specific receptor binding and/or high affinity internalization into cells is required since internalization is a critical component of taliglucerase alfa's mechanism of action and it is not fully assessed in your current potency assay. The assay should use multiple taliglucerase alfa concentrations to generate a complete dose-response curve in order to calculate the half-maximal effective concentration (EC_{50app}). Develop and implement this assay for use in release and stability testing.

7. Some SE-HPLC chromatographs exhibit a [redacted (b) (4)]. Because this [redacted (b) (4)] may reflect variability in a product-related variant, it should be identified and, if necessary, controlled. Characterize the protein [redacted (b) (4)] and determine whether a control strategy that better monitors this product attribute(s) should be implemented. Provide the results of your analyses and any proposed changes to your specifications.

8. RP-HPLC chromatograms suggest that taliglucerase alfa variants [redacted (b) (4)]. The risk to product quality is expected to vary depending on the nature of the variant. Thus, in order to establish an appropriate control strategy, you should identify and control for the quantity of these variants, if present. It may be useful to alter assay conditions or gradients to [redacted (b) (4)]. Provide information on the presence of unresolved variants and, if present, provide a revised specification that more accurately quantitates and controls these variants together with supporting data.

9. Enzyme kinetic parameters and specific activity are measured using synthetic p-nitrophenyl-glucopyranoside (pNP-Glc) substrate. [redacted (b) (4)] may be less sensitive in detecting changes to product quality. Provide enzyme kinetic data to determine the enzyme kinetic parameters, Km and kcat. [redacted (b) (4)] Include a detailed description of the assay, supporting assay qualification data, as well as a justification for why this test should not be added to the release and stability specifications.

10. Stability testing of diluted drug product in infusion bags did not include USP <788> particulate testing or information on the impact of dilution on subvisible particulates that are between [redacted]. USP <788> testing results are critical to mitigate the risk associated with occlusion of small blood vessels and small subvisible particles may pose an immunogenicity risk. Provide USP <788> particulate testing data for in-use stability studies and an analysis of particulates between [redacted].

11. The mannose content specification is based on a MALDI-TOF analysis of taliglucerase alfa. However, the property that is being measured in the MALDI-TOF analysis is mass to charge ratio, not mannose content. Thus, the acceptance criterion should be set around the mass to charge ratio and the mannose content acceptance criterion should be removed from the MALDI-TOF specification. Provide the new specification together with supporting data.

12. The acceptance criterion for moisture content in drug product is [redacted] for both release and stability testing. Release and stability testing results consistently show moisture content to be below [redacted] and no data were submitted indicating that a [redacted] moisture content would not have an adverse impact on product stability throughout the product's dating period. Amend the moisture content acceptance criterion to reflect your manufacturing capability and consideration of any additional knowledge you may have concerning the impact of moisture on product stability and provide the new specification, if appropriate, together with supporting data.

13. Monosaccharide content and glycan structure analysis submitted in the characterization section of the NDA contained inconsistent results. Monosaccharide content analysis on two batches indicated that the [redacted] whereas the glycan analysis data determined that [redacted] of the glycan structures have a [redacted] Provide an explanation for these results or submit data that identify the more accurate analysis using batches made in [redacted]

14. The acceptance criteria for the enzyme kinetic parameters K_m and V_{max} are [redacted] respectively. An analysis of 40 drug substance batches resulted in mean and standard deviations for K_m and V_{max} equal to [redacted] respectively. Consequently, the acceptance criteria appear too wide and should be amended to reflect process capability and clinical experience. Provide the revised specification for enzyme kinetic parameters or your justification as to why your proposal ensures reproducible product potency.

15. In a [redacted] vial drug product fill, the sampling plan calls for [redacted] to be collected for moisture content testing. [redacted] vials are tested and the mean value is reported on the certificate of analysis. Because the moisture content in an individual vial will vary within any given lot, the proposed sampling plan should provide a reasonable assessment of the variability of the results within a lot. While data from a robust validation study will

provide a basis for establishing the sampling plan for the moisture specification, your current sample size and the mean value set as the reportable result are insufficient to assess the moisture content of the final drug product. Submit the revised specification for moisture content with these considerations in mind and provide a justification for your proposal.

16. Chromatograms for drug substance and drug product RP-HPLC analyses contain data from (b) (4). Perform the RP-HPLC analysis such that data from (b) (4) and from (b) (4) (b) (4) is included so that all potential impurities and contaminants can be detected and controlled if necessary. Provide chromatograms where all data are shown (b) (4) minutes) on lots evaluated in the (b) (4) comparability studies.

17. The isoelectric focusing (IEF) assay has acceptance criteria of (b) (4) in a pI range of (b) (4) reportedly because of assay variation. This level of assay variability is not consistent with the expected validation characteristics for this type of assay. Develop, implement, and provide data on a validated IEF method in which the reference standard always produces the same number of bands in a consistent pI range. In addition, each gel should have a quantity of reference standard loaded near the limits of detection to verify the sensitivity of the analysis.

18. The (b) (4) assay results are rounded off to the nearest integer which can mask significant differences in (b) (4) between lots. Report all (b) (4) assay results to two significant digits without rounding off to the nearest integer, revise the acceptance criterion accordingly and submit the revised specification.

19. (b) (4)

20. The peptide map specification calls for (b) (4) peptide peaks where a countable peak is defined as (b) (4) Justify the use of this acceptance criterion in light of the potential amounts of impurities and contaminants that would be acceptable, or revise the criteria for countable peaks. Also, include a revision of the acceptance criteria such that relative peak areas on several selected peptides are specified. Provide the new specification together with supporting data.

21. A host cell protein standard curve is used to determine the levels of host cell proteins in the drug substance. The data from the standard curve is fit to a four parameter logistic regression model even though the data do not reach a plateau and the fitted curve is not

fully determined. However, there is a simple linear relationship between host cell protein and assay response. Provide a justification for the use of a four parameter logistic regression model or use a linear regression model to generate a host cell protein standard curve. Submit the revised specification along with the supporting analytical method validation data.

Comparability

22. The relative amounts of the individual glycans in the glycan profile shifted upon the switch to (b) (4). Since the glycan structures are critical to taliglucerase alfa's mechanism of action, a change in the concentration of the glycan structures has the potential to adversely impact clinical performance. Using a potency assay that quantitatively measures specific receptor binding and/or high affinity internalization into cells (see previous comment), perform a head-to-head comparison of three drug substance lots of taliglucerase alfa manufactured in (b) (4)

23. Results for SE-HPLC data provided in the NDA are reported as (b) (4). As (b) (4) may represent a different risk to product quality, they should be independently monitored and controlled. To support your revised acceptance criteria, provide all SE-HPLC data available to date in the application with (b) (4) reported separately. For comparison purposes, provide tabulated drug product stability SE-HPLC data separating drug product lots that were manufactured with drug substance made exclusively in (b) (4)

24. Your SE-HPLC test method employed a UV detector. However, use of a light scattering detector may allow (b) (4) that migrate in the void volume to be observed following SE-HPLC. This provides a much more sensitive qualitative method for monitoring this product attribute. Perform a head-to-head comparison of three drug product lots manufactured exclusively from drug substance made in (b) (4) using light scatter detection and provide the results in your resubmission.

Process Validation

25. The time limits for individual manufacturing steps and for the complete manufacturing process are not clearly defined in the NDA. For example, strict limits for (b) (4) Provide this information and relate it to the processes used to manufacture clinical study lot PB-06-001, commercial validation lots and the genomic stability sequencing study.

26. Process validation reports indicate that vials containing drug product were put on (b) (4) lyophilizer shelves. Validation of the lyophilization process should

include assessment of vials [redacted] and in different positions within a shelf to confirm consistency of the lyophilization process. Provide a revised validation protocol and report including the results for moisture content testing.

27. [redacted]

Control of Impurities

28. The testing to demonstrate that the master cell bank was free of plant specific viruses tabulated the results without providing data on the suitability of the PCR methods to detect viruses. In order to interpret the results you provided, the suitability of methods for their intended purpose needs to be assessed. Provide the assay qualification data and a description of the system suitability controls for each PCR method used to detect plant specific viruses.

29. The compound [redacted] is a component [redacted] levels in drug substance or drug product were not determined. [redacted] may exhibit toxicity to humans [redacted] and is therefore viewed as a [redacted] impurity that should be well controlled. Provide a control strategy to either include a limit on [redacted] to a level that will not impact product quality as it may relate to safety or efficacy, or validate that the process can clear [redacted] to an appropriate level.

30. [redacted], but its final concentration in drug product has not been determined. The label should accurately describe the final concentration of all excipients which should be confirmed at release. Provide the results on the [redacted] concentration for three drug product lots and provide your justification for not implementing the determination of [redacted] as a drug product release test.

Product Quality Immunogenicity

The following recommended comments regarding further immunogenicity information to be included in the complete response are as follows:

31. The concentration of rabbit anti taliglucerase alfa IgG antibodies (b) (4)) that you used for the positive control-1 (PC-1) for the anti-product IgG assay quality assessment (binding assay) was high. The agency recognizes that the limit of detection may be different due to affinity differences of the antibodies in the assay. However, in order to ensure reliable performance of the assay, a lower concentration for the positive control that will produce a signal close to the established cut-point of the assay should also be used. Confirm that your assay contains a low concentration positive control that can reproducibly produce a response closer to the established cut-point of your assay.

32. You set the cut-point at (b) (4) for the immunodepletion assay to confirm the antibody status of patients. The agency recommends that the confirmatory cut-point be set based on assay precision. Re-establish the immunodepletion assay cut-point based on assay precision using serum from healthy human subjects and from treatment-naïve patients, if available.

33. In your drug tolerance study, you used control antibodies at a concentration of (b) (4) to assess drug tolerance. Your assay is insufficient to address drug tolerance at low concentrations of anti-product antibodies. Repeat your drug tolerance study in the presence of low concentrations of control antibodies.

34. Develop appropriate quality controls in the neutralizing antibody assay and establish acceptance criteria based on these controls.

35. The specificity assessment should be designed to show that the drug product specifically binds to the antibodies induced by the product in human serum in the presence of exogenously added interfering molecules of similar size and charge (e.g., inclusion of IgG in IgE assay development).

36. We recognize that an alternative control for the anti-product IgE antibody assay may be required if a human positive control is not available, and that the detection limit may vary depending on antibody affinity. However, an estimation of assay sensitivity expressed in mass units is necessary to ensure assay suitability and performance for the intended purpose. Determine assay sensitivity and report the results.

Product Quality Microbiology

The following recommended comments regarding further product quality microbiology information to be included in the complete response are as follows:

37. With regard to the validation of (b) (4) provide a bioburden data summary to justify this (b) (4).

38. For the [redacted] Lyophilizer, provide summary data from three consecutive successful [redacted] runs with acceptable [redacted] results.

[redacted]

39. Provide validation summary reports for sterility and bacterial endotoxin test methods.

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/s/

LYNNE P YAO
02/24/2011

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	022-458
Priority or Standard	Standard
Submit Date(s)	April 26, 2010
Received Date(s)	April 26, 2010
PDUFA Goal Date	February 26, 2011
Division / Office	DGP/ODE III
Reviewer Name(s)	Carla Epps, MD, MPH
Review Completion Date	
Established Name	Taliglucerase alfa
(Proposed) Trade Name	Elelyso
Therapeutic Class	Enzyme Replacement Therapy
Applicant	Protalix
Formulation(s)	Lyophilized powder for solution for infusion
Proposed Dosing Regimen	(b) (4) 60 units/kg once every 2 weeks
Proposed Indication(s)	Long-term enzyme replacement therapy for patients with Gaucher disease
Proposed Intended Population(s)	Gaucher patients with anemia,thrombocytopenia, hepatomegaly or splenomegaly, bone disease and/or bone crisis

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend a Complete Response action for this application due the lack of sufficient data to adequately assess the relative risks and benefits of taliglucerase alfa compared to other enzyme replace products that are already available for the treatment of Gaucher type 1 disease.

For reasons discussed in my review of the supporting Phase 3 trials (i.e., differences in patient populations, duration of treatment effect after withdrawal from ERT treatment, and lack of interpretable immunogenicity data), I have concerns that the Applicant's ongoing open-label switchover trial (PB-06-002) may not provide sufficiently robust evidence of a similar treatment effect and safety profile compared to other available ERTs. It is not in the best interest of patients with Gaucher disease to approve taliglucerase before these comparative data are available because there are two approved ERTs and a drug shortage does not exist at the present time. Therefore, I recommend that the Applicant conduct one or more additional studies to evaluate effect of treatment with taliglucerase compared to another approved ERT (e.g., active comparator control, randomized add-on or withdrawal). In addition, the Applicant should provide complete trial data for the supporting Phase 3 trials (PB-06-002 and PB-06-003).

1.2 Risk Benefit Assessment

Treatment with taliglucerase alfa appears to have resulted in clinically and statistically significant improvements in major clinical features of Gaucher disease. Clinical studies have evaluated doses ranging from 9 U/kg to 60 U/kg. Based on the data available for review, taliglucerase alfa appears to have a similar safety profile to other ERT products. However, additional data is needed to assess the impact of immunogenicity on its safety profile, particularly long-term data on chronic immune-mediated adverse events that are typically associated with enzyme replacement therapies, and Gaucher disease-specific bone events. Evidence of safety is based on a database of 83 adult patients with type 1 Gaucher disease; fewer than 10 patients have completed two or more years of treatment with taliglucerase alfa.

The risk benefit of taliglucerase alfa will need to include an evaluation of its safety and effectiveness relative to other enzyme replacement therapy products that are already available for treatment of Gaucher Type 1 patients. I recommend that the Applicant provide complete study data for PB-06-002, the study evaluating the efficacy of taliglucerase alfa compared to Cerezyme. If data from Study PB-06-002 are insufficient

to clearly establish the effect of taliglucerase alfa compared to other approved ERTs, then additional clinical studies may be required. In addition, the Applicant will need to submit long-term safety data and more comprehensive data on the immunogenicity of the product, including data on neutralizing IgG antibodies. Therefore, as stated above, the Applicant should conduct one or more additional studies to evaluate the comparative efficacy and safety of taliglucerase alfa to currently approved ERT products.

Finally, although Gaucher type 1 disease has orphan status, there are adequate therapies available for treatment at this time. At the time of submission of this application, there was a drug shortage due to manufacturing issues with Cerezyme, which was then the sole approved ERT product for Gaucher type 1 disease. In the interim, VPRIV received approval in February 2010. Genzyme, the manufacturer of Cerezyme, reported in January 2011 that Cerezyme supplies were improved and that new Gaucher patients also would be able to access Cerezyme. As a result, lack of access to treatment no longer appears to be a major factor in determining the risk benefit of taliglucerase alfa.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Recommendations for postmarketing risk management activities were deferred because a Complete Response action is being taken.

1.4 Recommendations for Postmarket Requirements and Commitments

Recommendations for postmarketing requirements and commitments were deferred because a Complete Response action is being taken.

2 Introduction and Regulatory Background

A. Gaucher Disease

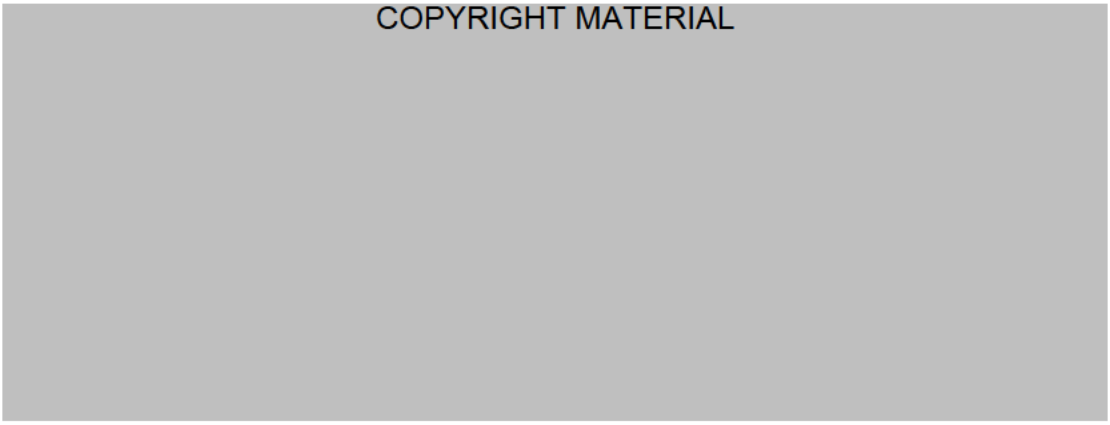
Gaucher disease is the most common of the lysosomal storage diseases. It is inherited as an autosomal recessive trait and is caused by a deficiency of β-glucocerebrosidase activity. This enzyme deficiency results in accumulation of glucosylceramide in tissue macrophages, particularly in the liver, spleen, bone marrow, and lungs. These lipid-filled macrophages are the so-called "Gaucher cells" characteristic of the disease.

Gaucher disease is a clinically heterogeneous disorder, with three main phenotypes based on the presence or absence of primary neurologic disease and severity of neurologic disease. Type 1 Gaucher disease is the most common variant and accounts for about 94% of all Gaucher cases. Type 1 Gaucher disease does not involve the CNS. Typical manifestations of type 1 Gaucher disease include hepatomegaly, splenomegaly, thrombocytopenia, bleeding tendencies, anemia, hypermetabolism, skeletal pathology, growth retardation, pulmonary disease, and decreased quality of life. The estimated worldwide incidence of type 1 Gaucher disease is 1 in 50,000 to 100,000.[1]

Patients with type 2 and type 3 Gaucher disease have neurologic disease in addition to hematologic, visceral, and bone disease. Patients with type 2 Gaucher disease present with acute neurological deterioration; death usually occurs by two years of age. Neurologic findings include spasticity, head retraction, and oculomotor palsy. Type 3 disease typically follows a more subacute neurological course, with progression occurring over three to four decades. Neurologic findings include horizontal nuclear palsy, ataxia, dementia, and spasticity. The different types of Gaucher disease are summarized in Table 1:

1 Cox TM, Aerts JMFG et al, Management of non-neuronopathic Gaucher disease with special reference to pregnancy, splenectomy, bisphosphonate therapy, use of biomarkers and bone disease monitoring, *J. Inherit Metab Dis* 2008; 31:319-336.

Table 1: Clinical features of the three types of Gaucher disease



Electronically copied and reproduced from: Mehta A, Epidemiology and natural history of Gaucher's disease, *European Journal of Internal Medicine* 2006; 17(Supp 1):S2-S5.

Most research effort to date has focused on strategies for augmenting enzyme levels to compensate for the underlying enzyme deficiency. These strategies include bone marrow transplantation (BMT), gene therapy, substrate reduction therapy (SRT), chaperone-mediated enzyme enhancement therapy, and enzyme replacement therapy (ERT).[2]

ERT is the first-line treatment of Gaucher type 1 disease, and reverses or improves important disease manifestations. SRT is an alternative therapy for patients who do not tolerate ERT. Zavesca (miglustat), an inhibitor of glucosylceramide production, is the only approved SRT for Gaucher disease. ERT and SRT are not approved for neuropathic Gaucher disease. For patients with severe Gaucher disease, primarily those with chronic neurologic involvement (Gaucher Type 3), bone marrow transplantation can be of benefit. However, with the advent of ERT, bone marrow transplantation has become a secondary therapy due to its high risk of morbidity and mortality. Supportive care for all Gaucher patients may include blood transfusions for severe anemia and bleeding, analgesics for bone pain, joint replacement or other orthopedic intervention for chronic pain and restoration of skeletal function, and bisphosphonates and calcium for osteopenia.

Prior to the availability of ERT, splenectomy was a common procedure to treat patients with massive splenomegaly and thrombocytopenia. Due the effectiveness of ERT in reducing organomegaly, splenectomy is rarely indicated in treated patients.[3] Similarly, a majority of patients (90%) achieve normal hemoglobin levels within two years of

2 Pastores GM, Barnett NL, Current and emerging therapies for the lysosomal storage disorders, *Expert Opin Emerging Drugs 2005*: 10(4):891-902.
3 Cox TM, Aerts JMFG et al, Management of non-neuronopathic Gaucher disease with special reference to pregnancy, splenectomy, bisphosphonate therapy, use of biomarkers and bone disease monitoring, *J Inherit Metab Dis* 2008; 31:319-36.

initiation of ERT.[4] Although, ERT has been demonstrated to reduce bone pain, other manifestations of bone involvement has been more refractory to ERT.

B. Natural History of Type 1 Gaucher Disease

The clinical expression of Gaucher disease is variable within all three subtypes, especially within type 1 Gaucher disease. Pediatric type 1 Gaucher disease is common, with more than 50% of type 1 Gaucher cases in the International Collaborative Gaucher Group (ICGG) Gaucher Registry reporting an onset of disease manifestations in childhood or adolescence. Infants with type 1 Gaucher disease are clinically normal; in severe cases, organomegaly becomes evident after the first year or two of life, and may progress for some years after. The primary clinical manifestations of the disease, hepatomegaly, anemia, and thrombocytopenia, have been related to splenic dysfunction. In an analysis of 1028 type 1 Gaucher patients in the ICGG Gaucher Registry, 637/677 (94%) patients "with spleen" (i.e., had an intact spleen) had hepatomegaly, anemia, or thrombocytopenia (or a combination of these three abnormalities), compared with 172 (62%) of the 277 patients who had undergone splenectomy ($P<0.01$).[5] Systematic follow-up of a number of patients over age 15 years shows that Gaucher disease-related changes in untreated patients, if they occur at all, are noted over decades. Hematologic measures of anemia and decreased platelet counts as well as spleen and liver sizes exhibit little or no change. Progressive osteopenia and occasional development of new fractures may be observed; however, bone disease usually occurs later than visceral disease. Pediatric-onset disease may represent a more aggressive form of type 1 Gaucher disease. However, in adults, rapid progression of previously quiescent disease is unusual. In an analysis of survival data of type 1 Gaucher patients enrolled in the ICGG Gaucher Registry, the estimated life expectancy at birth for type 1 Gaucher patients was about 9 years less than the general US population.[6]

Hematologic Effects

Anemia and thrombocytopenia are almost universal in untreated Gaucher disease and may present together or separately in the course of the disease. The pattern of anemia and thrombocytopenia in Gaucher disease is dependent on the degree of splenic dysfunction. Thrombocytopenia is the most common peripheral blood abnormality in patients with Gaucher disease and may result from hypersplenism, splenic pooling of platelets, or marrow infiltration or infarction. Early in the course of the disease, it is usually due to splenic sequestration of platelets and responds to splenectomy. Later,

4 Weinreb NJ, Charrow J et al, Effectiveness of enzyme replacement therapy in 1028 patients with type 1 Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher Registry. *Am J Med* 2002; 113: 112–9.
5 Weinreb NJ, Charrow J et al, Effectiveness of enzyme replacement therapy in 1028 patients with type 1 Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher Registry. *Am J Med* 2002; 113: 112–9.
6 Weinreb NJ, Deegan P et al, Life expectancy in Gaucher disease type 1, *Am J Hematol* 2008;83:896-900.

replacement of the marrow by Gaucher cells may be more important etiologically in patients who have undergone splenectomy. Thrombocytopenia may be associated with easy bruising or overt bleeding, particularly with trauma, surgery, or pregnancy.

Anemia may result from hypersplenism. In advanced disease, decreased erythropoiesis is a result of bone marrow failure from Gaucher cell infiltration or medullary infarction. As a result, hemoglobin concentrations and platelet counts are routinely monitored in patients to determine disease burden. Leukopenia is rarely severe enough to require treatment.

Organomegaly
Enlargement of the liver is a hallmark in Gaucher patients. In severe cases, the liver may fill the entire abdomen. Minor abnormalities of liver enzymes, consisting of increases in plasma transaminase and gammaglutyl transferase activities, are commonly present, even in mildly affected patients. Similarly, splenic enlargement is present in all but the most mildly affected patients with type 1 Gaucher disease. In patients who are otherwise asymptomatic, splenic enlargement is commonly the presenting sign. As in other diseases in which splenomegaly occurs, splenic infarctions frequently result. In an analysis of 400 patients in the ICGG Gaucher Registry, 116 patients with data available prior to ERT had a mean enlargement of the spleen 19-fold normal. Liver and spleen size /volume are also routine measures of disease burden in patients. Changes over time in liver occur very slowly, with a slight downward trend in untreated patients with type 1 Gaucher disease.

Bone disease
Bone involvement results in skeletal abnormalities and deformities, bone pain crises, and is a frequent presenting feature of Gaucher disease in children. Bone marrow infiltration and splenic sequestration lead to clinically significant anemia and thrombocytopenia respectively. Bone disease occurs in 70-100% of patients with type 1 Gaucher disease and is the greatest source of morbidity and long-term disability. Bone pain and bone crises were reported by 63% and 33% respectively in all Gaucher patients with available information from the ICGG Gaucher Registry. Bone disease may not correlate with the severity of hematologic or visceral involvement. Skeletal abnormalities secondary to bone disease contribute to the chronic growth failure observed in children with inadequately treated disease.

Lung disease
Only 1-2 % of type 1 Gaucher patients exhibit lung disease, which manifests as interstitial lung disease, pulmonary hypertension, or hepatopulmonary syndrome. Pulmonary hypertension is an important cause of early mortality in type 1 Gaucher disease; development of pulmonary hypertension may be prevented by avoidance of splenectomy. The spleen serves as the primary reservoir of Gaucher storage cells.

Removal of the spleen promotes migration of storage cells to other tissue macrophage pools, including the lungs, liver, and bones.[7]

C. Current Therapy

To date, ERT has been the cornerstone of treatment for Gaucher disease. Data from the ICGG demonstrate that approximately 90% of all patients should achieve normal hemoglobin concentration within two years of initiation of treatment. ERT has been shown to reduce organomegaly and improve hematological parameters. Although there is some evidence of the benefit of ERT on the bone-related complications of Gaucher disease, longstanding complex osseous complications of Gaucher disease may remain refractory to ERT**.** Similarly, the effect of ERT on lung disease is uncertain. In vivo studies indicate that exogenous enzyme delivery is lower in lung tissue compared to other target tissues.[8] Furthermore, since ERT has not been shown to pass the blood brain barrier, it is not indicated for the treatment of patients with type 2 and type 3 Gaucher disease.

2.1 Product Information

Taliglucerase alfa is a new molecular entity. It is a recombinant human glucocerebrosidase (GCB) produced from genetically modified carrot plant root cells. Uptake of exogenous glucocerebrosidase into the target cells of Gaucher disease (reticuloendothelial cells) occurs through binding to mannose receptors on the cell surface. Plant-derived glucocerebrosidase contains exposed terminal mannose residues. Production of Cerezyme requires a deglycosylation process to expose mannose residues. Taliglucerase alfa differs from native human glucocerebrosidase by two amino acids at the N-terminal and 7 amino acids at the C-terminal. The molecular weight of taliglucerase alfa protein is approximately 60,800 Daltons.

The proposed indication for taliglucerase alfa is for long-term ERT for patients with Gaucher disease. It is administered intravenously with a proposed dosing of 60 U/kg every other week.

7 Mostry PK, Sirrs S et al, Pumonary hypertension in type 1 Gaucherr's disease: genetic and epigenetic determinants of phenotype and response to therapy*, Mol Genet Metab* 2002; 77:91-98.
8 Mistry PK, Sirrs S et al, Pulmonary hypertension in type 1 Gaucher's disease: genetic and epigenetic determinants of phenotype and response to therapy, *Mol Genet Metab* 2002; 77: 91-98.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 2: Currently Available Treatments for Proposed Indications

Drug	Formulation	Indication	Dosage
Cerezyme (imiglucerase)	IV formulation of recombinant DNA using CHO cells culture.	Long-term ERT for pediatric and adult patients with type 1 Gaucher with anemia, thrombocytopenia, bone disease, or hepatomegaly or splenomegaly	2.5 U/kg three times per week to 60 U/kg every two weeks
VPRIV (velaglucerase alfa)	IV formulation of recombinant DNA using CHO cells culture.	Long-term ERT for pediatric and adult patients with type 1 Gaucher with anemia, thrombocytopenia, bone disease, or hepatomegaly or splenomegaly	60 Units/kg every other week
Zavesca (miglustat)	Capsule for oral administration	Treatment of adult type 1 Gaucher patients for whom ERT is not an option.	100 mg three times daily

Cerezyme (imiglucerase)
ERT has been commercially available for the treatment of Type 1 Gaucher disease since 1991, when Ceredase (alglucerase), placentally-derived GCB, received approval as the first enzyme for the treatment of Gaucher disease. Cerezyme (imiglucerase), a recombinant product, received approval in the U.S. for the treatment of Gaucher disease in 1994. Cerezyme has replaced Ceredase. Warning information for Cerezyme includes hypersensitivity and anaphylactic reactions. There are also precautions related to pulmonary hypertension and pneumonia. The pregnancy category is C. See Section 2.4 for other adverse reactions.

VPRIV (velaglucerase alfa)
Velaglucerase alfa was approved in the U.S. in February 2010 for the treatment of type 1 Gaucher disease. Velaglucerase differs from Cerezyme by one amino acid, and has an identical amino acid sequence to Ceredase. Warning information for VPRIV includes hypersensitivity and anaphylactic reactions. The pregnancy category is B. See Section 2.4 for other adverse reactions.

Zavesca (miglustat)
Zavesca is an inhibitor of the enzyme glucosylceramide synthase, which is a glucosyl transferase enzyme responsible for the first step in the synthesis of glucosylceramide and other glycosphingolipids. An important warning included in product labeling is that Zavesca may cause fetal harm when administered to a pregnant woman (Pregnancy Category X). There is also a warning for potential development of peripheral neuropathy. Patients receiving Zavesca should have neurological evaluations every six months. Other precautions from product labeling include tremor, diarrhea and weight loss, and effect on male fertility. Other common adverse events are: flatulence, abdominal pain, headache, and influenza-like symptoms.

2.3 Availability of Proposed Active Ingredient in the United States

There are currently two approved ERT products for Type 1 Gaucher disease in the U.S.; Cerezyme (imiglucerase) and VPRIV (velaglucerase). U.S. production of Cerezyme was temporarily suspended in June 2009 due to manufacturing issues at Genzyme's Allston Landing facility, where Cerezyme is manufactured. Although Velaglucerase alfa was made available through a treatment protocol in July 2009 and received U.S. approval in February 2010, there was an on-going drug shortage at the time of submission of this application. Genzyme issued a statement on January 11, 2011 that the supply of Cerezyme had been restored for all patients currently receiving therapy and that Cerezyme will be available to new Gaucher patients.[9]

2.4 Important Safety Issues With Consideration to Related Drugs

The labeling for Cerezyme notes the following:

1. Approximately 14% of patients experienced AEs related to Cerezyme administration.

2. Some of the AEs were related to the route of administration such as discomfort, pruritus, burning, swelling, or sterile abscess at the site of venipuncture (each reported in <1% of the patient population).

3. Anaphylactoid reaction has been reported in <1% of the patient population. Further treatment with imiglucerase should be conducted with caution. Most patients have successfully continued therapy after a reduction in rate of infusion and pretreatment with antihistamines and/or corticosteroids.

4. Symptoms suggestive of hypersensitivity (e.g., pruritus, flushing, urticaria, angioedema, chest discomfort, dyspnea, coughing, cyanosis, and hypotension)

9 http://supplyupdate.genzyme.com/weblog/cerezyme/

have been noted in approximately 6.6% of patients. (Onset of such symptoms has occurred during or shortly after infusions.)

5. Approximately 15% of patients treated and tested have developed IgG antibody to Cerezyme during the first year of therapy. Patients who developed IgG antibody did so largely within 6 months of treatment, and rarely developed antibodies to Cerezyme after 12 months of therapy.

6. Approximately 46% of patients with detectable IgG antibodies experienced symptoms of hypersensitivity. Patients with antibody to Cerezyme have a higher risk of hypersensitivity, but not all patients with symptoms of hypersensitivity have detectable IgG antibody.

The labeling for Ceredase also notes AEs related to route of administration, symptoms suggestive of hypersensitivity, and a higher risk of hypersensitivity reactions in patients with antibody to Ceredase. As per the Ceredase labeling, approximately 13% of patients treated and tested developed antibody to Ceredase.

The labeling for VPRIV notes the following:

1. The most serious AEs in patients treated with VPRIV were hypersensitivity reactions

2. The most commonly reported AEs were infusion-related reactions. (b) (4)

3. Other AEs affecting more than one patient (>3% of treatment-naïve patients and >2% of patients switched from Cerezyme) were bone pain, tachycardia, rash, urticaria, flushing, hypertension, and hypotension.

4. Adverse reactions more commonly seen in pediatric patients compared to adult patients include (>10% difference): upper respiratory tract infection, rash, aPTT prolonged, and pyrexia.

5. 1 of 54 (2%) treatment-naïve patients treated with VPRIV developed IgG class antibodies to VPRIV. Antibodies were neutralizing in this patient. No infusion-related reactions were reported for this patient.

6. In treatment-naïve patients, onset of infusion-related reactions occurred mostly during the first 6 months of treatment and tended to occur less frequently with time.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Jun 30, 2004: Pre-IND meeting held to discuss design of Phase 1 trial (PB-06-001). Agreement was made that a single Phase 3 trial to support NDA claim could be sufficient if results were sufficiently robust and statistically significant and if the safety profile were adequate.

Jun 15, 2005: The initial IND for taliglucerase alfa (IND 069,703) was submitted.

Jul 15, 2005: The IND was placed on Partial Hold due to missing nonclinical animal studies (chronic toxicity and reproductive toxicology studies or a single bridging study comparing taliglucerase alfa to Cerezyme).

Feb 21, 2007: Type B meeting held to discuss partial clinical hold. Agreement was made that 9-month chronic toxicity study in monkeys could serve as the basis to remove partial clinical hold; the study did not have to demonstrate similarity to Cerezyme.

Mar 28, 2007: Protalix submitted a special protocol assessment (SPA) for a proposed phase 3 clinical trial. No agreement was reached on the SPA due to deficiencies in MRI methodology and the statistical analysis plan.

Apr 16, 2007: The Partial Hold was removed after review of the 9-month chronic toxicity data. The Division recommended additional nonclinical studies (reproductive toxicology studies) be conducted prior to Phase 3 trials.

May 21, 2009: Pre-NDA meeting to discuss contents of NDA submission (see Meeting Minutes archived in DARRTS June 29, 2009). Agreement was made that the NDA would consist of a full study report for PB-06-001 and abbreviated study reports with interim safety data for studies PB-06-002 and PB-06-003.

Aug 14, 2009: Expanded access treatment protocol was allowed to proceed.

Aug 24, 2009: Fast Track Designation was granted for "*the investigation of taliglucerase for treatment of type 1 Gaucher disease."

Sep 3, 2009: Orphan Designation granted for taliglucerase alfa.

May 26, 2010: The NDA was submitted.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This was an electronic submission. Overall, the submission was well organized. Two major amendments to protocol criteria were issued during the trial:

- Patients experiencing progressive or severe hypersensitivity were to be withdrawn from the trial (Version 5- dated April 2, 2008)
- Female patients (or female partners of male patients)of child-bearing potential were required to use two methods of contraception (Version 6- dated May 19, 2008)

These amendments were made during the course of the study to improve safety. They did not impact my review of the submission. Additional clinical information is needed to complete a comprehensive review of the submission, including updated safety data from the two ongoing Phase 3 extension trials and clinical pharmacology information related to immunogenicity status. The Applicant has responded to information requests for these data; however, the response was not received in time to be included in this review.

3.2 Compliance with Good Clinical Practices

According to the Applicant, these trials were conducted pursuant to the following International Conference on Harmonisation (ICH) guidelines: Good Clinical Practice (ICH E6), Statistical Principles for Clinical Trials (ICH E9), and Choice of Control Group and Related Issues in Clinical Trials (ICH E10).

The Division of Scientific Investigations (DSI) was consulted to determine the reliability of data by evaluating clinical sites with most enrolled patients. Two clinical sites were inspected: The Gaucher Clinic at the Shaare Zedek Medical Center, Israel and Clinical Center of Serbia, Serbia. The DSI reviewer reported that there were no significant deficiencies noted and that the study appears to have been conducted adequately. The DSI reviewer concluded that the data appear to be reliable to support the application.

3.3 Financial Disclosures

Protalix disclosed financial arrangements with one investigator, (b) (6)

(b) (6)

This financial arrangement does not appear to have impacted the trial's integrity as there were no discrepancies in trial conduct or trial results between sites noted during this review.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Taliglucerase alfa drug substance is a single polypeptide chain containing the exact amino acid sequence to human glucocerebrosidase with [redacted] the plant cell expression vector. The [redacted] an N-terminal and a C-terminal. The molecular weight is ~ 60,800 Da with [redacted]

Taliglucerase alfa is expressed in carrot cells. The Applicant notes that use of a plant system affords advantages in producing glucocerebrosidase. One advantage is the elimination of issues with mammalian adventitious viral agents. Another advantage is that the glycosylation process in carrot cells results in naturally exposed terminal mannose residues. Production of currently available glucocerebrosidase products, which are produced in mammalian cell systems, includes a deglycosylation process to expose terminal mannose residues.

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

Product quality review
CMC data have been reviewed by the Product Quality Reviewer (Richard Ledwidge, Ph.D.); please see the CMC review for the complete review of the product data. Dr. Ledwidge recommended a Complete Response action on the application. Quality issues identified in the CMC review include:

- Testing for presence of particles not in place for routine release and stability testing
- Provision of separate reporting for [redacted] stability data for drug product lots
- Insufficient data in order to evaluate comparability of drug product lots
- Inadequate risk assessment on drug product sampling
- Imprecisely defined time of manufacturing

- Provision of control strategy for several compounds used in manufacturing process
- Incomplete assay validation process for some assays
- Inadequate testing performed in in-use and stress stability studies.
- Incomplete manufacturing process validation

Facility review/inspection
Ten facilities are involved in the manufacturing of taliglucerase alfa. The Office of Compliance noted serious deficiencies in two facilities- Protalix, Ltd. (b) (4) (b) (4) The Protalix facility is involved in the manufacturing Documented deficiencies at the Protalix facility included inadequacies in control of the manufacturing process, risk assessments regarding bioburden contamination, assay validation, and procedures for documenting investigations. The (b) (4) facility is involved in the manufacture (b) (4) (b) (4) Documented deficiencies at the (b) (4) facilty include the presence of (b) (4). The Applicant provided adequate responses to the deficiencies and the Office of Compliance has classified the facility as VAI (Voluntary Action Indicated) and has recommended an approval action.

Microbiology product quality
Microbiology product quality data were reviewed by Vinayak Pawar, Ph.D. Dr. Pawar noted outstanding issues to be addressed at (b) (4) the two drug product manufacturing facilities for this product. Dr. Pawar noted three deficiencies at the (b) (4): lack of validation of (b) (4) hold time; incomplete validation data for sterilization of the lyophilizer; deficient (b) (4) rubber stoppers used for container closure. Dr. Pawar noted that the (b) (4) facility needed to provide validation summary reports for sterility and bacterial endotoxin test results. Dr. Pawar stated that approval of this application in regards to microbiology product quality was contingent upon resolution of these outstanding issues.

Immunogenicity
The immunogenicity assays used by the Applicant for the clinical trials were reviewed by Faruk Sheikh, Ph.D. Dr Sheikh identified several issues with the immunogenicity assays that need to be addressed by the Applicant. Dr. Sheikh noted that the cut-point in the confirmatory anti-drug antibody assay is unacceptable and therefore the incidence of immunogenicity may have been underestimated in the phase 3 clinical trial. In addition, although the Applicant developed a neutralizing antibody assay to assess for antibodies that interfere with enzymatic activity, the Applicant does not have an assay to assess for antibodies that neutralize drug uptake. The Applicant submitted additional data regarding the assays in response to a 74-day letter issued by the

Division. However, these data were received too late for review during this review cycle. Therefore, Dr. Sheikh recommended a Complete Response action for the application.

4.2 Clinical Microbiology

Clinical microbiology considerations do not apply to this application because taliglucerase alfa is not an antimicrobial agent.

4.3 Preclinical Pharmacology/Toxicology

The preclinical pharmacology/toxicology data were reviewed by Tamal K. Chakraborti, Ph.D. The following nonclinical studies were conducted:

1. In vitro studies
In vitro studies were conducted in mouse and human macrophages to compare the enzymatic activity of taliglucerase alfa to Cerezyme. Overall, the studies demonstrated that taliglucerase alfa had similar activity as Cerezyme.

2. Single-dose and repeat- dose toxicity studies
In single-dose studies in mice and monkeys, taliglucerase alfa was non-lethal in doses up to 18 mg/kg in both species. In a repeat-dose study (non-GLP) in Marmoset monkeys with doses of 11 and 55 mg/kg/day, the NOAEL was considered to be 11 mg/kg/day (about 6 times the applicant's proposed clinical dose). The target organ appeared to be the spleen (increase in spleen weight, extramedullary hematopoiesis and macrophage aggregates) and lymph node (hypercellullarity in mandibular lymph node). In chronic toxicology studies in cynomolgus monkeys, the NOAEL appeared to be the highest tested dose of 27.8 mg/kg/day. The target organ of toxicity could not be identified in the absence of any significant histopathological findings.

Anti-drug antibody formation was observed in repeat dose toxicology studies in monkeys; however, these antibodies were not considered neutralizing antibodies.

3. Reproductive toxicity
A Segment I fertility and early embryonic development study was conducted in male and female rats. No significant treatment related adverse effects were observed in either sex. In a Segment II teratology study conducted in rats and in rabbits, taliglucerase was not teratogenic at doses up to 55 mg/kg and 27.8 mg/kg, respectively.

Based on the nonclinical pharmacology and toxicology review, there were no additional nonclinical studies recommended and the reviewer's final recommendation is for approval of the product.

4.4 Clinical Pharmacology

The clinical pharmacology data were reviewed by Jang-Ik Lee, Ph.D. Based on a preliminary review of the clinical pharmacology data, Dr. Lee noted that there appears to be a difference in PK parameters in patients who develop anti-product antibodies. However, an in-depth analysis of the impact of immunogenicity status on PK parameters was not done for this review cycle due to insufficient information on the immunogenicity assays used in the clinical trials.

4.4.1 Mechanism of Action

The rationale for enzyme replacement is that exogenous administration of glucocerebrosidase (GCD) should mitigate the deficiency of endogenous enzyme in Gaucher disease. Exogenous GCD must be taken up by target cells via mannose receptors; the enzyme is then taken up by lysosomes where it undergoes conversion to a more active form. The active ingredient of the drug product is taliglucerase alfa, which contains the same amino acid sequence as the naturally occurring human enzyme, glucocerebrosidase (GCD). Taliglucerase alfa naturally contains exposed terminal mannose residues. The Applicant proposes that this structural characteristic will facilitate internalization of taliglucerase alfa by target cells.

4.4.2 Pharmacodynamics

In humans, glucosylceramide-laden tissue macrophages in Gaucher patients secrete large quantities of chitotriosidase and chemokine ligand 18 (CCL18), resulting in markedly increased plasma levels. These two substances are being used as biomarkers to monitor disease progression or response to treatment. Chitotriosidase and CCL18 levels were measured as secondary efficacy endpoints in the pivotal study (PB-06-001) for this drug product.

4.4.3 Pharmacokinetics

The pharmacokinetic (PK) profiles of six healthy volunteers and 31 type 1 Gaucher patients were studied. The data were analyzed using a non-compartmental method. In the Phase 1 trial (PB-01-2005), healthy volunteers were administered escalating doses of 15, 30, and 60 U/kg once weekly. In the Phase 3 trial (PB-06-001), Gaucher patients were administered doses of 30 or 60 U/kg. The PK findings from PB-06-001 are summarized in Table 3.

Table 3: Pharmacokinetic parameters (mean ± standard deviation) of taliglucerase alfa determined in Gaucher patients (Study PB-06-001)

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

Electronically copied and reproduced from Clinical Pharmacology review by I-J Lee, Ph.D., p. 3.

PK parameters did not appear to be dose proportional at the doses studied. The inter-subject variability of PK parameters in volunteers and patients was in the range of 34% to 72%. In the Phase 3 trial, exposure increased slightly over time for both dose groups (8% for the 30 U/kg group and 17% for the 60 U/kg group from Day 1 until the end of the study). C_{max} could not be measured in the Phase 3 trial because samples were not collected at the end of the drug infusion. PK metrics differed between volunteers and Gaucher patients. Clearance (CL) in Gaucher patients was 2.9 fold larger than the CL in healthy volunteers. Mean $t_{1/2}$ values in Gaucher patients were slightly longer (25 minutes versus 20 minutes).

No specific analyses of age, race or gender were conducted for the application.

5 Sources of Clinical Data

Submitted for review are the following: full clinical study reports for PB-06-001 (first-in-human trial) and abbreviated safety summaries for Studies PB-06-002 (switch trial) and PB-06-003 (follow-on trial). I also completed a literature review (See Section 9.1).

Trials PB-06-002 and PB-06-003 are ongoing. PB-06-002 is a Phase 3, open-label trial evaluating the safety and efficacy of taliglucerase in patients previously treated with imiglucerase (Cerezyme). PB-06-003 is a Phase 3, open-label extension trial, evaluating the long term safety and efficacy of taliglucerase (30 to 60 U/kg) in patients who completed PB-06-001 and PB-06-002. Therefore, the data submitted in support of the efficacy of taliglucerase rely exclusively on the information contained in Study PB-06-001, the only completed Phase 3 clinical trial submitted by the Applicant.

5.1 Tables of Studies/Clinical Trials

In addition to the Phase 3 trials submitted in the application, the clinical program includes a phase 1 trial (PB-01-2005) and a treatment protocol (PB-06-004). The phase 1 trial investigated the safety of taliglucerase in six healthy volunteers. The treatment protocol was opened in August 2009 in response to a world-wide shortage of imiglucerase that began in June 2009 and is ongoing. Twenty-six patients were enrolled in the treatment protocol at the time of submission of this application. To date, no pediatric patients have been enrolled any of the clinical trials for taliglucerase alfa. Pediatric patients were excluded from PB-06-001. See Table 4 for a list of taliglucerase clinical trials.

Table 4: Taliglucerase Clinical trials

Trial (# Sites) Country	Phase	N (# pediatric pts)	Design	Dosing	Inclusion Criteria --- Exclusion Criteria	Duration	Status
P-01-2005 (**)	1	6	Safety	IV once/wk		3 weeks	completed
PB-06-001 (10**) Canada Chile Israel Italy Mexico Serbia South Africa Spain UK	3	33 (pediatric patients excluded)	R/DB Safety /Efficacy	30 U/kg EOW;60 U/kg EOW	•Gaucher pts ≥ 18 yrs •Spleen > 8X normal size •Thrombocytopenia •No anti-GCD antibodies --- •Gaucher-related neurologic disease •Pregnant/lactating women •Allergic to carrots •Allergic to Cerezyme/Ceredase	9 months	completed
PB-06-002 (9) Australia, Canada Israel (2) Serbia Spain UK US(2)	3	30 (24 enrolled to date; no pediatric patients)	OL Safety /Efficacy	IV over 2 hrs EOW	•Gaucher pts ≥ 2 years old with stable disease •Prior treatment w/ Cerezyme ≥2 yrs & regimen unchanged in past 6 mos --- •Pregnant/lactating women criterion removed •No anti-GCD antibodies criterion removed	9 months	ongoing
PB-06-003 (15) Australia Canada Chile Israel (2) Italy Mexico (2) Serbia South Africa Spain UK (2) US (2)	3	60 (29 enrolled to date; no pediatric patients)	OL Safety /Efficacy	30 U/kg EOW;60 U/kg EOW	•Completion of PB-06-001 or 002 ----	15 months	ongoing

Table 4: Taliglucerase Clinical Trials (cont'd.)

Trial (# Sites) Country	Phase	N	Design	Dosing	Inclusion Criteria --- Exclusion Criteria	Duration	Status
PB-06-004	3	Up to 200 (26 enrolled to date)	Expanded Access	Same dose as previous ERT	N/A	unspecified	ongoing
PB-06-005	3	10 (enrollment pending)	Pediatric Trial	30 U/kg EOW;60 U/kg EOW		12 months	pending

5.2 Review Strategy

The development program for taliglucerase was reviewed, subject to certain limitations, as best possible. An integrated review of data for PB-06-001, PB-06-002 and PB-06-003 was not performed because the efficacy data submitted as part of the ongoing studies were severely limited. However, this review of the efficacy of taliglucerase includes a post-hoc comparison of results from clinical studies for the two currently available enzyme replacement therapies, Cerezyme (imiglucerase) and VRIV (velaglucerase).

Additional information requests were sent to the Applicant regarding clinical pharmacology and immunogenicity results for PB-06-001. Information submitted by the Applicant in response to these information requests was received late in the review cycle and will not be reviewed in this document.

5.3 Discussion of Individual Clinical Trials

5.3.1 PB-06-001-Single Pivotal Phase 3 Trial

A. General Design and Objectives

This was a multicenter, randomized, double-blinded trial designed to evaluate the PK, efficacy, and safety of taliglucerase every other week (EOW) over 9 months in 33 treatment naïve patients with type 1 Gaucher disease.

A parallel group approach (30 U/kg and 60 U/kg) was selected to evaluate whether there is a difference in treatment effect or rate of onset of treatment effect. As noted by the Applicant, at the time of the start of the trial, there was no objective information on the dose response of glucocerebrosidase in initial or maintenance treatment of Gaucher patients; available data consisted solely of data from case series studies.

Patients were to have been treatment naïve or were to have not been treated for Gaucher disease within 12 months prior to trial entry. The primary efficacy endpoint point was change in spleen volume as assessed by MRI. Additional efficacy endpoints assessed included change in hemoglobin, platelet count, and liver volume. This trial was conducted in nine countries: Israel, South Africa, United Kingdom, Spain, Italy, Canada, Serbia, Mexico, and Chile. The trial period was from August 5, 2007, to September 11, 2009.

Two major amendments to protocol criteria were issued during the trial:

- Patients experiencing progressive or severe hypersensitivity were to be withdrawn from the trial (Version 5- dated April 2, 2008)

- Female patients (or female partners of male patients)of child-bearing potential were required to use two methods of contraception (Version 6- dated May 19, 2008)

B. Inclusion Criteria

1. Patients ≥18 years old with Gaucher disease diagnosed by leukocyte GCD activity
2. Splenomegaly (> 8X normal volume)
3. Thrombocytopenia (<120K/mm^3)
4. No history of enzyme replacement or substrate reduction therapy in the past 12 months
5. No history of presence of anti-glucocerebrosidase antibodies

C. Exclusion Criteria

1. Severe neurological signs secondary to Gaucher disease
2. History of hypersensitivity to Cerezyme or Ceredase
3. History of carrot allergy

D. Endpoints

Primary Efficacy Endpoint

1. Percent change from baseline of spleen volume after 9 months

Secondary Efficacy Endpoints

1. Change from baseline in:
    - Mean change in hemoglobin
    - Percent change in liver volume
    - Mean change in platelet counts
2. Biomarkers: chitotriosidase and PARC/CCL18
3. Proportion of patients with > 10% reduction in spleen volume at 9 months

Other Endpoints

1. Change in bone mineral density measured with dual-energy x-ray absorptiometry (DEXA)
2. Quantitative Chemical Shift Imaging (QCSI) in a subpopulation of patients

E. Treatment

This trial was comprised of three periods:
1. Screening: Day –25 ±10
2. Baseline: Day 1
3. Treatment: Week 2 through Week 38

Screening evaluations included a medical history and physical examination, medications, MRI measurements of spleen and liver volumes, laboratory assessments, echocardiogram, chest X-ray (CXR), pulmonary function tests (PFTs), and bone mineral density (DEXA scan). Optional Quantitative Chemical Shift Imaging (QCSI) measurements of bone marrow fat content in the lumbar spine were also performed in a subset of patients. Patients exposed to ERT prior to trial enrollment were tested for anti-human taliglucerase alfa antibodies.

Baseline assessments included physical examination, concomitant medications, laboratory assessments, electrocardiogram (ECG), and full skeletal x-ray series. In addition, anti-human taliglucerase antibody titers and biomarker levels (chitotriosidase or PARC/CCL18) were obtained. Following baseline evaluations, patients were randomized in a 1:1 ratio to receive either taliglucerase 30 U/kg or 60 U/kg using a computer-generated randomization schedule.

During the treatment period, patients received up to a total of 20 IV infusions of double-blind trial medication at the clinical site once every other week for a total of 38 weeks. Safety and efficacy assessments were made at regular intervals during the treatment period. The final assessments of safety and efficacy were to be performed at the Week 38 visit.

Concomitant Medications
Patients were allowed to take medications for allergic reactions, anemia, bone disease, and analgesia. All medications taken during the trial were recorded.

Prohibited Medications
Patients were prohibited from taking Zavesca, Ceredase, or Cerezyme. Patients also were prohibited from taking another experimental drug for any condition.

Safety Considerations/Monitoring
Safety was assessed by adverse events (AEs), concomitant medication use, and vital signs. Table 5 details the assessments protocol for PB-06-001. Additional safety assessments included: echocardiograms, ECGs, physical examinations, pulmonary function tests, and clinical laboratory tests (hematology, serum chemistry, and urinalysis). Anti-taliglucerase alfa antibodies were assessed at every visit for the first five visits and then every other visit for the rest of the trial. All events of a hypersensitivity reaction also were recorded.

Safety results were reviewed by the trial Investigator. In addition, an independent Data Monitoring Committee (DMC) was chartered to conduct scheduled interim safety analyses and *ad hoc* safety analyses as requested. The DMC conducted three blinded interim safety data reviews during the course of the trial. Stopping rules were created to ensure patient safety. If two or more patients experienced a WHO Grade 3 toxicity or if any patient experienced a WHO Grade 4 toxicity that was considered possibly or

probably related to the trial drug, the trial would be stopped and the safety data reviewed by the DMC.

Hemoglobin concentration and platelet counts were assessed at every infusion. Hemoglobin was analyzed at a central laboratory and platelet counts were measured in local laboratories. Quantitative abdominal MRI of the liver and spleen using a standardized protocol was performed at the trial sites for the determination of changes in liver and spleen volumes at screening, Month 6, and Month 9. Images were collected and sent to two central radiographic reviewers who remained blinded to the trial medication and the order in which the images were taken. A third reader was available for adjudication of reading results; no adjudication review was required during the trial.

Exploratory efficacy assessments included biomarkers (plasma chitotriosidase and/or PARC/CCL18) and bone disease assessments (DEXA scans and optional QCSI).

Safety Measurements
Safety was evaluated through the assessment of AEs, vital signs, physical examination, and electrocardiogram. Clinical safety laboratory analyses included serum chemistry with transferrin, folic acid and Vitamin B12 monitoring, urinalysis, hematology, and the presence of anti-taliglucerase alfa antibodies. Pregnancy screening was performed for female patients of childbearing potential.

Table 5: PB-06-001 Schedule of Trial Assessments

Activity	Screening	Visit 1 Baseline	Visits 2-6	Visit 7 Month 3	Visits 8-13	Visit 14 Month 6	Visits 15-19	Visit 20 Month 9
Physical Examination	X	X		X		X		X
Adverse Events		X	X	X	X	X	X	X
Current/Concomitant Medications	X	X	X	X	X	X	X	X
β-HCG	X			X		X		X
Serology	X							
TSH, transferrin, B12 and folic acid	X							
Glucocerebrosidase activity	X							
Mutation analysis		X						
X-ray Skeletal Evaluation		X						X
Laboratory		X		X		X		X
ECG		X		X		X		X
CXR, Echo, PFTs, DEXA, QCSI	X							X
Organ volumes	X					X		X
Biomarkers		X		X		X		X
Anti-human taliglucerase alfa antibodies	X	X	X	X	X	X	X	X
PK Profile		X						

F. Statistical Analysis Plan

The Statistical Reviewer, Behrang Vali, MS, did not identify any issues with the analytical assumptions or models used in the trial.

Analysis populations

Three trial populations were reviewed in the data analyses:

- Intent-to-Treat (ITT): patients who received at least one dose of medication and had at least the Screening/Baseline MRI evaluation.
- Per Protocol (PP): all ITT patients who completed 9 months and had no major protocol violations.
- Safety population: patients who received at least one dose of trial medication.

The Applicant performed all efficacy analyses using the ITT and PP populations.

Comment: The Applicant's definitions of the analysis populations are consistent with the definitions for analysis sets contained in ICH E9 "Statistical Principles for Clinical Trials." The Statistical Reviewer noted that the most appropriate term for the Applicant's ITT analysis set would be a modified-ITT set since it did not include all randomized patients.

Table 6: PB-06-001 Data Sets Analyzed

Patient Population	30 U/kg N (%)	60 U/kg N (%)	Total N (%)
Patients randomized	16 (100)	17 (100)	33 (100)
ITT	15 (94)	16 (94)	31 (94)
PP	14 (88)	15 (88)	29 (88)
Safety	16 (100)	16 (94)	32 (97)

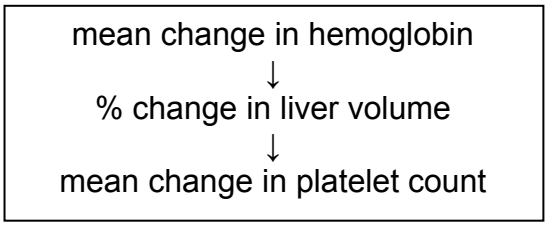
Determination of Sample Size

The sample size for this trial was chosen to have power to detect a clinically significant difference in percent change in spleen volume from baseline to nine months. As agreed upon with the Division during a Type A meeting on July 24, 2007, the Applicant pre-specified a 20% change in spleen volume at 9 months as a clinically significant change. A total of 12 patients per treatment arm were required for the primary analysis. This number is based on the assumption that the standard deviation (SD) for the percent change in spleen volume was 12%. With 12 patients, using a two-sided alpha level of 0.05, the Applicant estimated that there would be greater than 95% power to detect a change of 20% or more. If the actual SD was at least 19%, then the Applicant estimated that there would be greater than 83% power to detect a change of 20% or more. To ensure that at least 12 patients completed trial assessments, the Applicant planned to enroll at least 15 patients in each treatment group.

The Applicant noted that the standard deviations for change in the secondary parameters of mean change in hemoglobin (16%), percent change in liver volume

(10%), and mean change in platelet count (47%) were also estimated based on the results of previous unspecified studies. A published review of clinical trial results comparing the efficacy of Ceredase and Cerezyme cites similar values for the standard deviations for these parameters.[10] Based on these SD estimates, the applicant estimated that a sample size of 12 patients would provide 84% power to detect a change in hemoglobin, 86% power to detect a change in liver volume, and 81% power to detect a change in platelet count. The pre-specified changes for these parameters, as agreed upon with the Division, were hemoglobin 12% change, liver 8% change, and platelets 33% change.

The effect of taliglucerase on mean change from baseline within treatment was tested for the following efficacy parameters: spleen volume, hemoglobin concentration, platelet count, and liver volume. P-values were computed using a one-sample t-test (alpha=0.025, 2-sided test to allow for each group to be tested separately). The primary efficacy analysis of percent change in spleen volume was performed using a multiple imputation approach at the 0.05 level of significance. .Secondary analyses were performed at each dose level in a step-down fashion in the following order:



The standard error was also reported for any efficacy parameter for which inferential statistics were calculated.

A mixed effect model that included dose and time, with subject as a random effect was used for both the primary and secondary efficacy endpoints to determine whether there was a difference between dose groups.

Additional Analyses
For the primary efficacy endpoint, sensitivity analyses for missing data were performed using a last observation carried forward (LOCF) approach. In addition, MRI results were analyzed by individual reader. The intraclass correlation coefficient was estimated to describe reader agreement and a paired t-test was estimated to compare reader scores to determine whether there was a significant difference between readers.

10 Grabowski GA, Barton NW, Enzyme Therapy in Type 1 Gaucher Disease: Comparative Efficacy of Mannnose-terminated Glucocerebrosidase from Natural and Recombinant Sources, *Ann Intern Med* 1995; 122:33-39.

Analysis of Primary Endpoint

As noted earlier in the overview of the natural history of Gaucher disease, spleen and liver size are important measures of disease burden in patients. Clinical trials of both Cerezyme and VPRIV evaluated change in organ volume, along with changes in hemoglobin and platelet count, as measures of treatment efficacy. The pivotal trial for Cerezyme evaluated all of these parameters as primary endpoints, while the pivotal trial for VPRIV evaluated hemoglobin and platelet count as primary endpoints and organ volumes as secondary endpoints. Current therapeutic goals for treatment of Gaucher disease include improvement in these parameters, as well as improvement in pulmonary and bone disease. Additionally, growth is considered an important clinical measure in pediatric patients.[11]

The trial design for PB-06-001 meets the regulatory requirements for adequate and well-controlled trials as delineated in 21 CFR 314.126. The study objectives are clearly defined. The trial design (randomized, double-blind, dose-comparison concurrent control) is appropriate for evaluation of Gaucher type 1 disease, since the natural history of the disease is well-characterized. The trial design includes appropriate measures to minimize bias, including blinding, randomization, and a prospective statistical analysis.

The design provides a reasonable assessment of treatment benefit versus placebo in treatment-naïve patients because spontaneous improvement in the pre-specified clinical endpoints (e.g., spleen volume, liver volume, hemoglobin, and platelet count) are not expected to occur based on the known natural history of the disease. However, the use of a randomized, double-blind, active comparator control study design would have potentially allowed for a direct comparison of the treatment effect of taliglucerase alfa to currently available enzyme replacement therapies. Clinical trials for VPRIV included a head-to-head study of VRIV compared to Cerezyme that demonstrated that VPRIV was non-inferior to Cerezyme. Additionally, currently there are no data for review in pediatric patients. As noted earlier, pediatric patients were not included in this trial and no pediatric patients have been enrolled in the other phase 3 trials to date. Therefore, results from this study cannot be used to evaluate treatment effect differences in different age groups. The Applicant has proposed a pediatric study to evaluate the efficacy and safety of taliglucerase alfa in this population, but this study has not yet been initiated.

11 Pastores GM, Weinreb NJ, Aerts H, et al.,Therapeutic goals in the treatment of Gaucher disease, *Semin Hematol* 2004;41 (Suppl. 5):4-14.

G. Patient Disposition

Patient Disposition

Of the 44 patients screened in this trial, 11 patients (25%) were not eligible. The most common reason (6/11) for not being eligible for randomization was that a patient did not meet the inclusion criterion of spleen size of at least 8-times normal. A total of 33 patients were randomized to one of the two treatment groups, including 16 to the 30 U/kg group and 17 to the 60 U/kg group. One patient (patient 30-023) randomized into the 60 units/kg treatment group withdrew from the trial for unspecified personal reasons prior to treatment.

Of the randomized patients, one patient who withdrew from the study prior to dosing and one patient who was discontinued after receiving a partial single dose of study drug were excluded from the ITT analysis (one patient in each treatment group). A total of four patients (the two patients excluded from the ITT analysis and two additional patients who were discontinued early from the study for safety reasons) were excluded from the PP analysis.

Discontinuations

Three patients discontinued from the trial after initiating treatment. Two patients (one from each treatment group) were discontinued after experiencing an adverse event of an allergic reaction. One patient in the 30 U/kg group withdrew from the trial after Week 18 due to pregnancy.

Table 7: PB-06-001 Patient Disposition

Disposition	30 U/kg Treatment Group	60 U/kg Treatment Group	Total N (%)
Patients randomized	16 (100)	17 (100)	33 (100)
Completed	14 (88)	15 (88)	29 (88)
Discontinued	2 (12)	1 (6)	3 (9)
Withdrew consent	0	1 (6)	1 (3)

Three patients (all patients who were discontinued from the trial) did not receive all 20 scheduled infusions of study drug. One patient experienced an allergic reaction during the initial infusion and only received a single partial dose of trial drug. A second patient was discontinued due to an allergic reaction after receiving 10 infusions. The third patient was discontinued due to pregnancy after receiving 12 infusions. The remaining 29 patients who were treated received all scheduled infusions.

Patient Compliance

All patients who completed the study received all 20 scheduled infusions of study drug. The only patients who did not receive all 20 scheduled infusions were patients that discontinued the study as described above.

Protocol Deviations and Compliance

There were a total of 21 patients with protocol deviations. One patient (patient 10-012) had a major protocol violation of pregnancy. Four patients did not meet the eligibility criteria but were approved for randomization into the trial by the Medical Director:

- Patent 10-006, randomized to the 30 U/kg group, had a platelet count higher than the criterion of < 120K/mm^3
- Patient 30-009, randomized to the 60 U/kg group, had a platelet count higher than the criterion of < 120K/mm^3
- Patient 11-007, randomized to the 60 U/kg group, had a GCD activity level higher than the criterion of $\leq$ 3 nmol/mg*hr
- Patient 12-024, randomized to the 60 U/kg group, had a GCD activity level higher than the criterion of $\leq$ 3 nmol/mg*hr

The remaining 16 patients primarily had deviations from schedule windows for trial visits or procedures; 12 of these patients had exempted protocol deviations.

5.3.1 Review of PB-06-001 Study Results

A. Demographics

The treatment groups were balanced for age, gender, race, and weight. No pediatric patients were included in this trial. The age range was 19-74 years old (see Table 8), with a median age of 35 years and 33 years for the low dose and high dose treatment groups, respectively. The demographic characteristics of the per protocol (PP) population were similar to those of the intent to treat (ITT) population, as only two patients (one patient from each treatment group) were excluded from the PP population.

Table 8: PB-06-001 Patient Demographics at Screening

Baseline Data	**30 U/kg prGCD (N=16)**	**60 U/kg prGCD (N=17)**	**Total Patients (N=33)**
Age (yrs) Mean Min-Max	 **36** 19-74	 **37** 19-58	 **37** 19-74
Age at Diagnosis (yrs) Mean Min-Max	 **19** 0-61	 **28** 7-48	 **23** 0-61
Sex Male Female	 8 M (50%) 8 F (50%)	 9 M (53%) 8 F (47%)	 17 M 52%) 16 F (48%)
Race	White-16 (100%)	White-16 (94%) South African Black-1 (6%)	White-32 (97 %) South African Black-1 (3%)
Country Canada Chile Israel Italy Mexico Serbia South Africa Spain United Kingdom	 1 (3%) 1 (3%) 6 (18%) 1 (3%) 4 (12%) 2 (6%) 1(3%) 0 0	 1 (3%) 1 (3%) 6 (18%) 1 (3%) 2 (6%) 3 (9%) 1 (3%) 1 (3%) 1 (3%)	 2 (6%) 2 (6%) 12 (36%) 2 (6%) 6 (18%) 5 (15%) 2 (6%) 1 (3%) 1 (3%)
Weight (kg) Males Females	67.9 75.2 60.5	68.4 72.6 63.7	68.1 73.8 62.1

The treatment groups were balanced for baseline disease severity, with similar measurements of chitotriosidase levels and organ volumes. The high dose group had a slightly lower mean platelet count value than the low dose group (65K and 74K

respectively); however, the difference in platelet count was not clinically significant. The high dose group had a borderline low mean hemoglobin (11.4 g/dL) compared to a normal mean hemoglobin (12.2 g/dL) in the low dose group (see Table 9); however, the difference in hemoglobin was not clinically or statistically significant.

Table 9: PB-06-001 Baseline Gaucher Disease Severity

Baseline Data	**30 U/kg prGCD (N=16)**	**60 U/kg prGCD (N=17)**	**Total Patients (N=33)**
Prior Treatment for Gaucher > 12 months ago None	 2 (12%) 14 (88%)	 2 (12%) 15 (88%)	 4 (12%) 29 (88%)
Chitotriosidase levels (nmol/hr/mL) Mean Min-Max (normal: 0-150 nmol/hr/mL)	 28158 (7791-50254) **188X NML**	 24702 (4639-66628) **165X NML**	 26430 (4639-66628) **176X NML**
Screening Spleen Volume (mL) Mean Min-Max (normal: 120 mL)	 2131 (886-4901) **18X NML**	 2117 (973-5418) **18X NML**	 2124 (886-5418) **18 X NML**
Screening Liver Volume (mL) Mean Min-Max (normal: 1500 mL)	 2880 (2282-5096) **1.9X NML**	 2481 (1758-3297) **1.7X NML**	 2675 (1758-5096) **1.8X NML**
Screening Hemoglobin (g/dL) Mean Min-Max (normal: > 11.5-12.0 g/dL)	 **12.2** (7.9-14.6)	 **11.4** (5.5-15.3)	 **12.0** (5.5-15.3)
Platelet Count (_/mm3) Mean Min-Max (normal: > 120K)	 **74K** (26K-163K)	 **65K** (21K-122K)	 **70K** (21K-163K)

B. Concomitant Medications

Concomitant medications were recorded using standardized WHO Anatomical Therapeutic Chemical (ATC) classification codes. The majority (79%) of randomized patients received at least one concomitant medication. The most common (>10% overall) therapeutic classes of concomitant medications in the trial were analgesics (33%), antibacterials for systemic use (30%), antihistamines for systemic use (15%), anti-anemic preparations (12%), and anti-inflammatory and anti-rheumatic products (12%). The most common concomitant medication administered overall in both treatment groups was acetaminophen (30% overall).

C. Review of Efficacy

Efficacy Summary

The efficacy data submitted from this single trial appear adequate to demonstrate the efficacy of taliglucerase alfa for treatment of adult patients with Gaucher disease. Clinically meaningful improvements were observed in organ volume, hemoglobin concentration, and platelet count at both doses evaluated (30 U/kg and 60 U/kg given IV every other week). The 60 U/kg dose shows a statistically significant greater response compared to the 30 U/kg dose for spleen volume and platelet count. A statistically significant difference in dose groups was observed for spleen volume using a true ITT analysis set but not the Applicant's modified-ITT analysis set. Otherwise, the Statistical Reviewer noted that statistical results were consistent between the true ITT, modified-ITT, and PP analysis sets. The Statistical Reviewer did not identify any errors or discrepancies in the statistical analysis performed by the Applicant. Therefore, except where specifically noted in my discussion of results for spleen volume, the efficacy results presented in this review are results from the modified-ITT analysis.

Taliglucerase appears to have similar efficacy to currently available ERT products, based on a comparison of data from clinical trials for these products. However, due to the trial's design (i.e., no active comparator arms) and differences in trial populations, it is difficult to determine if taliglucerase alfa is fully comparable to currently approved products. The Statistical Reviewer determined that the single pivotal trial PB-06-001 did not provide sufficient statistical evidence to support approval. He asserted that the clinical development program for VPRIV, which included a parallel dose trial and a non-inferiority trial comparing VPRIV and Cerezyme established a precedent for the level of statistical evidence for approval of additional ERT products for Gaucher disease. In addition, he noted that only interim results were presented for the supportive trials PB-06-002 and PB-06-003. He recommended that the Applicant conduct at least one additional trial to evaluate comparability, using a randomized, controlled, and properly powered 'head-to-head' study comparing taliglucerase alfa with at least one of the currently approved ERT products. He also recommended that the Applicant submit final clinical study report for the two supportive trials.

From a clinical perspective, I do not feel that the efficacy data from the single pivotal trial are sufficient to support approval of taliglucerase alfa because the trial was not a designed to establish the efficacy and safety of taliglucerase compared to other approved ERTs. I concur with the Statistical Reviewer that the Applicant must submit data establishing the safety and efficacy of taliglucerase compared with currently approved ERT products. Therefore, I recommend that the Applicant conduct at least one or more additional studies to evaluate comparability (e.g., active comparator control, randomized add-on or withdrawal). In addition, the Applicant should submit the completed trial data for PB-06-002 and PB-06-003 for review as part of its Complete Response.

Analysis of Primary Endpoint

1. **Spleen Volume**

Table 10 summarizes the primary endpoint, the percent change from baseline in spleen volume at 9 months for the ITT population. In the ITT population, the percent change was -27% and -38% in the low dose and high dose groups, respectively; the overall percent change was -33%. The percent change at 6 months and 9 months was statistically significant (p<0.0001) for both dose groups. Analyses on the PP population and using the LOCF approach on the ITT population produced similar results. No adjudication review was required during the evaluation of MRI results because the differences between readers were negligible; the majority of readings showed less than 1% difference (range was 0% to 2.6% difference), which was below the pre-specified 5% margin of agreement that would trigger an adjudication review.

There were statistically significant differences in mean percent change in spleen volume observed between the two treatment groups at 6 months and 9 months (in the true ITT analysis p=0.014) but not in the modified-ITT analysis (p=0.060).

Table 10: PB-06-001- Change in Spleen Volume (MRI%) by Treatment Group

Treatment Group	Length of Treatment	
	6 months	9 months
30U/kg Group		
Mean Percent Change±SD	-22%±5	-27%±8
(Min-Max)	(-12 to -29)	(-16 to -43)
Mean Volume (mL)	1675	1566
(Min-Max)	(630-4117)	(606-3894)
p-value	<0.0001	<0.0001
95% C.I.	(-24.3, -19.7)	(-30.9, -23.1)
60 U/kg Group		
Mean Percent Change±SD	-30%±13	-38%±9
(Min-Max)	(+3 to -53)	(-21 to -56)
Mean Volume (mL)	1544	1377
(Min-Max)	(522-3582)	(541-4220)
p-value	<0.0001	<0.0001
95% C.I.	(-36.2, -23.8)	(-42.6, -33.4)
All Treatment Groups		
Mean Percent Change±SD	-26%±10	-33%±10
Mean Volume (mL)	1607	1468

Analysis of Secondary Endpoints
Table 11 summarizes the key secondary efficacy endpoints (change from baseline in liver volume, platelet count, hemoglobin, and biomarkers).

Table 11: PB-06-001- Summary Table of Key Secondary Endpoints

Secondary Endpoints	30 U/kg Group	60 U/kg Group	All Treatment Groups
Liver (mL) ± SD (Min-Max)	2564±560 (2000-4122)	2190±377 (1654-2894)	2371±502 (1654-4122)
Percent Change	**-10±11 (p=0.0041)**	**-11±7 (p<0.0001)**	**-11±9**
Platelet (_/mm3) ± SD (Min-Max)	88K±51K (20K-168K)	107K±53K (25K-241K)	97K±52K (20K-241K)
Mean Change	**11K±20K**	**41K±47K**	**27K±39K**
Hemoglobin (g/dL) ± SD (Min-Max)	14.0±1.4 (12.2-16.9)	13.6±2.0 (8.6-16.5)	13.8±1.7 (8.6-16.9)
Mean Change	**1.6±1.4**	**2.2±1.4**	**1.9±1.4**
Chitotriosidase (nmol/hr/mL) ± SD (Min-Max)	14548±8026 (5318-34528)	12538 ±14489 (619-53283)	13508±11659 (619-53283)
Percent Change	**-47±19**	**-58±33**	**-53±27**

1. **Liver volume**

The mean liver volume decreased from baseline in both treatment groups at Month 6 (7.6% in 30 U/kg group, p=0.0020; 7.5% in 60 U/kg group, p=0.0022) and Month 9 (10.5% in 30 U/kg group, p=0.0041; 11.1% in 60 U/kg group, p<0.0001). There were no significant differences observed in mean percent change in liver volume between the two treatment groups at either time point (p=0.349).

2. **Platelet count**

A mean increase in platelet count from baseline was observed for both treatment groups by 6 months, with a mean increase of 13K in the low dose group and 41K in the high dose group. No further increase was observed at 9 months. At 9 months, the increase in platelet count only reached statistical significance for the high dose group (p=0.0031). There was a statistically significant difference in increases in mean platelet count between the two treatment groups at 6 months and 9 months (p=0.042), which suggests a dose-effect for this parameter.

3. Hemoglobin

In contrast to the other baseline disease parameters, the mean hemoglobin at baseline for both treatment groups was within the normal range although the mean value was slightly lower in the high dose group compared to the dose group (11.4 vs. 12.24 g/dL). Mean hemoglobin increased in both treatment groups at Month 6 (1.6 g/dL in 30 U/ kg group, p=0.0002; 1.7 g/dL in 60 U/kg group, p=0.0002) and Month 9 (1.6 g/dL in 30 U/ kg group, p=0.0010; 2.2 g/dL in 60 U/kg group, p<0.0001.). There were no significant differences in mean hemoglobin observed between the two treatment groups at either time point (p=0.719). Because the mean baseline values were normal for the two treatment groups, it is difficult to assess the treatment effect of taliglucerase for this clinical parameter. Note that patients enrolled in trials for earlier ERT products had low mean baseline hemoglobin values.

4. Biomarkers

A mean decrease in chitotriosidase levels was observed at the end of the trial in both treatment groups (47% in the low dose group and 58% in the high dose group). One patient did not have elevated chitotriosidase levels at baseline but did have an elevated PARC/CCL18 level which decreased at the end of the trial.

5. Proportion of patients with > 10% reduction in spleen volume at 9 months

Spleen volume reduction of > 10% was observed in all patients by the end of the trial. One patient had an increased spleen volume (3% increase) at 6 months but had a > 10% decrease in spleen volume at 9 months (20% decrease).

Other Endpoints

As noted earlier, effective treatment of bone disease in Gaucher patients remains a therapeutic challenge. Gaucher disease affects both cortical bone and bone marrow and can result in focal or diffuse clinical findings in either bone compartment. The burden of Gaucher disease in bone may not correlate with the burden of Gaucher disease in other tissues. Bone disease, as measured by DEXA scans and QSCI, were evaluated as exploratory endpoints. No formal statistical analyses were performed.

1. DEXA scans

Lumbar spine, femoral neck and total hip DEXA scans were obtained at the screening visit and at the end of the trial, with measurements of T-score, Z-score, and bone mineral density (BMD). The mean baseline values were within the normal range (not lower than -1) in both treatment groups, with the exception of lumbar spine T- and Z-scores. At 9 months, the lumbar spine T-score in the high dose group improved by 0.1 from -1.2 to -1.1; the Z-score improved by 0.2 from -1.2 to -1.0 (normal). At 9 months, the total hip T-scores in both treatment groups declined from a baseline score of -0.7 to -1.2 in the low dose group and -1.1 in the high dose group (See Table 12).

Table 12: DEXA Scan Shift Table

DEXA Measurement	30 U/kg Group n=15		60 U/kg Group n=16	
	Screening	Month 9	Screening	Month 9
Lumbar Spine				
Mean T Score	Normal n=13	Normal n=13	Abnormal (-1.2) n=14	Abnormal (-1.1) n=14
Mean Z Score	Normal n=14	Normal n=14	Abnormal (-1.2) n=15	Normal n=15
Mean BMD	Normal n=11	Normal n=11	Normal n=13	Normal n=13
Femoral Neck				
Mean T Score	Normal N=13	Normal N=13	Normal N=15	Normal N=15
Mean Z Score	Normal N=14	Normal N=14	Normal N=15	Normal N=15
Mean BMD	Normal N=11	Normal N=11	Normal N=15	Normal N=15
Total Hip				
Mean T Score	Normal N=4	Abnormal (-1.2) N=4	Normal N=6	Abnormal (-1.1) N=6
Mean Z Score	Normal N=5	Normal N=5	Normal N=6	Normal N=6
Mean BMD	Normal N=5	Normal N=5	Normal N=6	Normal N=6

The study population appears to have had essentially normal bone parameters at baseline and at the end of the study. Based on prior ERT treatment experience, bone mineral density parameters do no appear to change significantly within the first year of treatment. Therefore, the trial period may not have been long enough to evaluate this parameter.

Comment: DEXA scans have been used to predict risk factor for fractures in other populations (post-menopausal women). However, the relationship of osteoporosis (i.e., bone mineralization) to fracture risk in Gaucher patients has not been established. General limitations in using DEXA scans to assess therapeutic response include false normal or high values with certain bone abnormalities, and lack of normative data for the pediatric population.[12]

12 Cox TM, Aerts JMFG, et al, Management of non-neuronopathic Gaucher disease with special reference to pregnancy, splenectomy, bisphosphonate therapy, use of biomarkers and bone disease monitoring, *J Inherit Metab Dis* (2008) 31:319–336

2. QCSI

Quantitative chemical shift imaging (QCSI) was used to measure bone marrow fat fraction content as an exploratory endpoint. QCSI was performed at the screening visit for 10 patients (5 patients from each treatment group) and at the end of trial visit for nine patients. Due to technical issues, one screening reading was not evaluable and therefore only eight patients (4 patients from each treatment group) had QCSI performed at the end of the trial.

The QSCI data are summarized in Table13. The Applicant notes that a fat fraction of $\leq$ 0.23 has been associated with a higher risk for bone complications in Gaucher patients (Maas M. et al 2002). At baseline, 2/8 patients (both in the high dose group) had a fat fraction > 0.23. At 9 months, 6/8 patients (2 patients in the low dose group, 4 patients in the high dose group) had a fat fraction > 0.23. 8/8 patients were observed to have an increase in fat fraction, with increases from baseline ranging from 0.02 to 0.19. The mean increase in fat fraction was higher in the high dose group (0.12) compared to the low dose group (0.07). The clinical significance of these results is unclear. This reviewer notes that no patient experienced a bone-related complication (e.g., osteonecrosis or fracture) during the trial period. The trial duration may not have been long enough to evaluate bone disease events. The larger mean increase in fat fraction observed in the high dose group suggests a dose-related effect on this clinical parameter. However, interpretation of these results is limited by the small number of patients evaluated.

Comment: Fat fraction content is a recognized parameter for invasion of bone marrow by Gaucher disease. In a published study by Maas et al, the authors note that although QCSI is the state of the art modality for assessing bone marrow disease, its use is limited because it is not widely available. In addition, QCSI has not been validated for the Gaucher population.

Table 13: PB-06-001- QCSI Summary Table

Patient ID Number	Baseline	9 Month	Change from Baseline
Taliglucerase alfa 30 units/kg			
10-006	0.11	0.13	0.02
10-028	0.11	0.17	0.06
15-015	0.23	0.26	0.03
30-008	0.22	0.39	0.17
Mean	**0.1675**	**0.2375**	**0.0700**
Taliglucerase alfa 60 units/kg			
10-005	0.35	0.42	0.07
15-016	0.33	0.43	0.10
30-009	0.14	0.27	0.13
30-011	0.13	0.32	0.19
Mean	**0.2375**	**0.3600**	**0.1225**

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Subpopulations
No difference in efficacy by age or gender was noted.

Analysis of Clinical Information Relevant to Dosing Recommendations
Dose-Response
For the primary endpoint, there was a statistically significant difference between the two treatment groups at 6 months and 9 months using a true ITT analysis set (p=0.014) but not the Applicant's modified-ITT analysis set (p=0.060). For the secondary endpoint platelet count, there was a statistically significant difference in increases in mean platelet count between the two treatment groups at 6 months and 9 months (p=0.042) that was also clinically significant. For the secondary endpoints liver volume and hemoglobin, here was no statistically significant difference observed between the two treatment groups at 6 months and 9 months. Based on the dose-effect observed on spleen volume and platelet count, the 60 U/kg dose appears to be more effective than the 30 U/kg dose as an initial treatment dose.

Additional Efficacy Issues/Analyses

Immunogenicity
An important safety consideration with all enzyme replacement therapies for lysosomal storage diseases is the development of immune responses to the infused enzyme. These immune responses can be associated with the development of allergic/hypersensitivity reactions as well as altered effectiveness of treatment. Three patients developed anti-GCD antibodies during the study (See Table 14). One patient (10-003 from the 30 U/kg group) had a positive IgE antibody pre-infusion on Day 1. The patient experienced an allergic reaction within a few minutes after the start of his initial infusion and was discontinued from the trial. Two other patients (10-001 from the 30 U/kg group and 12-024 from the 30 U/kg group) developed IgG antibodies but did not experience any allergic reactions and completed the trial. No patients developed inhibitory antibodies.

Table 14: PB-06-001- Patients with Positive Antibodies

Initial IgG Titer	Highest IgG Titer	End of Trial IgG Titer	IgE Antibody	Adverse Events	Hypersensitivity reaction?
5403 (Week 34)	8094 (Week 38)	8094 (Week 38)	negative	vomiting facial flushing fever/flu enlarged lymph nodes hypertension	No
172 (Week 4)	1467 (Week 14)	1361 (Week 38)	negative	glucosuria nfluenza	No
negative (Day 1)	NA	negative (Week 6)	positive (Day 1)	mmediate hypersensitivity rxn	Yes

Both patients with positive IgG antibodies experienced improvement in organ volume, hematologic and biomarker parameters (See Table 15). Both patients had significant baseline thrombocytopenia (10-001 had baseline platelet count of 28K; 12-024 had baseline platelet count of 48k). Patient 12-024 had a smaller increase in platelet count compared to other patients in the 60 U/kg group (mean change of 41K±47K) or other patients with a platelet count < 50K (mean change 15K±29K). Otherwise, there did not appear to be a difference in treatment response in these patients compared to patients in the same treatment group or patients overall. As noted earlier, the impact of immunogenicity on the efficacy of taliglucerase alfa will need to be re-evaluated and based on data obtained from confirmatory assays using an appropriate cut-point and enzyme activity and cellular uptake inhibitory antibody assays.

Table 15: PB-06-001- Efficacy Results in Patients with Positive Antibodies

Efficacy Endpoints	30 U/kg Group		60 U/kg Group		All Treatment Groups
	Pt 10-001	Group Mean	Pt 12-024	Group Mean	Group mean
Spleen Volume - % Change	-29	-27%±8	-38	-38%±9	-33%±10
Liver Volume - % Change	-8	-10±11	-15	-11±7	-11±9
Platelet (_/mm^3)- Mean Change	10K	11K±20K	5K	41K±47K	27K±39K
Hemoglobin (g/dL)- Mean Change	2.6	1.6±1.4	1	2.2±1.4	1.9±1.4
Chitotriosidase- % Change	-31	-47±19	-67	-58±33	-53±27

Conclusions for Study PB-06-001

Based on the trial characteristics for a single adequate and well-controlled study described in the guidance for industry, "*Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*," the efficacy data submitted from this single trial appear adequate to support an efficacy claim. Specifically, the guidance notes that a single trial that includes multiple "important, prospectively identified primary or secondary endpoints, each of which represents a beneficial, but different, effect."[13] Prior experience has demonstrated that ERT results in significant clinical improvement in organ volume and hematologic parameters in Gaucher patients. In contrast, no spontaneous improvement in these parameters is expected in individuals with untreated disease. Clinical trials for earlier ERT products all evaluated organ volume, hemoglobin, and platelet count. These parameters are objective, easily measured, and

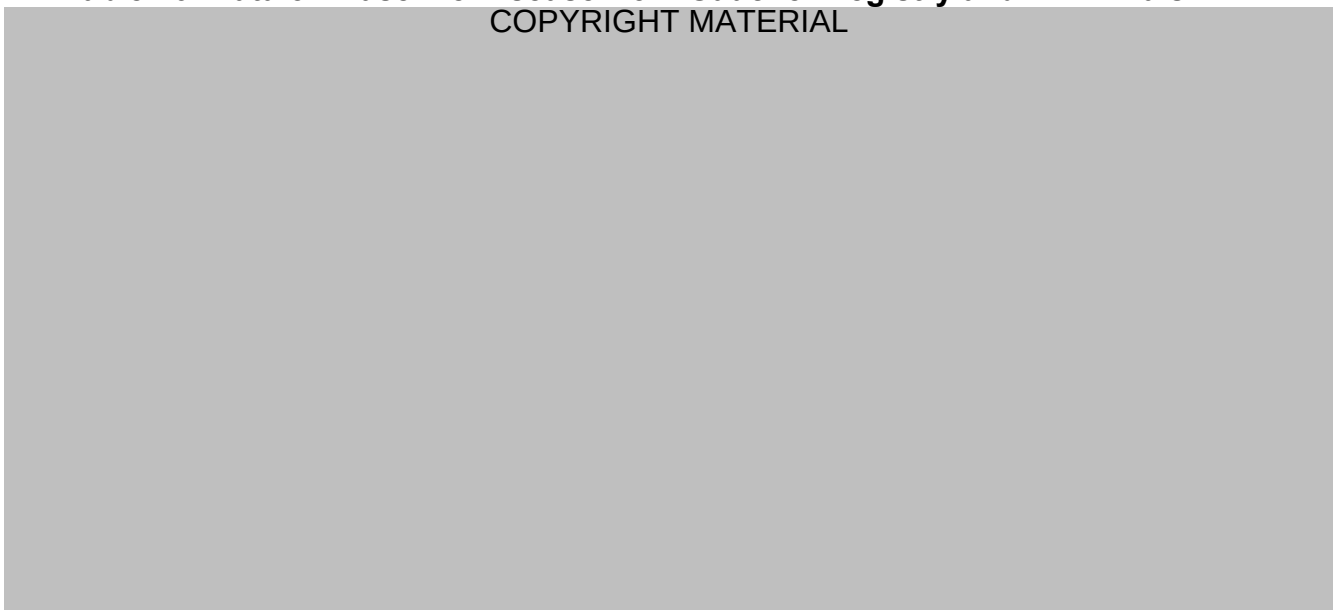
13 http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064981.htm

correlate closely to significant clinical conditions or events (i.e., hypersplenism, anemia, and bleeding).

As noted earlier, the changes in clinical parameters selected by the Applicant as clinical meaningful differences (30% decrease in spleen volume, 12% increase in hemoglobin, 8% decrease in liver volume, and 33% increase in platelet count) are consistent with the changes observed in clinical trials for Ceredase and Cerezyme. The European Medicines Agency included a responder analysis as part of its evaluation of the clinical efficacy of VPRIV, with a "good response" being defined as a hemoglobin increase > 1.5 g/dL, a platelet count increase > 30K, and spleen and liver volume reduction > 30%.[14]

Efficacy results for taliglucerase are similar to those for other ERT products. The mean decrease in spleen and liver volumes for patients treated with taliglucerase were 33% and 11%, respectively, compared to decreases of 42 and 16% for Ceredase, and decreases of 47 and 21%, respectively, for Cerezyme (see Table 16). Similarly, the mean increase in hemoglobin from baseline for taliglucerase patients was1.6 g/dL compared to increases of +2.3 g/DL for Ceredase and +2.5g/dL for Cerezyme. The mean increase in platelet count was +30K compared to increases of +53K for Ceredase and +44K for Cerezyme.

Table 16: Data on Baseline Disease from Gaucher Registry and ERT Trials



* Data from: Grabowski et al. Enzyme Therapy in Type1 Gaucher Disease: Comparative Efficacy of Mannose Terminated Glucocerebrosidase from Natural and Recombinant Sources, *Ann Intern Med* 1995;122:33-29.

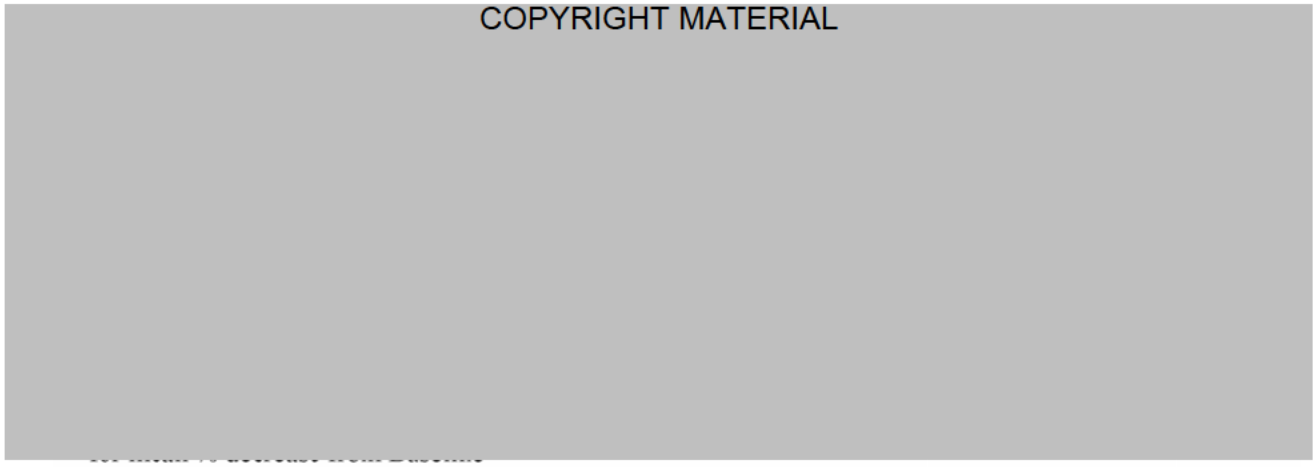
14 http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001249/WC500096489.pdf

The magnitude of treatment response for hematologic parameters appears to depend on baseline disease severity. In a stratified analysis of 1028 patients from the Gaucher Registry, patients with a baseline hemoglobin <10 g/dL achieved a mean hemoglobin increase of 2.6 g/dL after one year of treatment; patients with a baseline hemoglobin >10 g/dL achieved a mean hemoglobin increase of 2.0 g/dL. Hemoglobin levels normalized (hemoglobin > 11.0 g/dL in females and > 12.0 g/dL in males) in approximately 90% of all Gaucher patients within two years of starting ERT treatment. Patients with a baseline platelet count of 60K or higher achieved a 1.5- to 2.0-fold increase after one year of treatment; patients with a baseline platelet count of < 60K achieved a 1.5-fold increase.[15] Based on the clinical experience with ERT, therapeutic goals for ERT treatment were established for treatment of Gaucher type 1 disease in 2003 (See Section 9.4).[16]

Baseline values for clinical parameters for patients in this trial are similar to those for untreated patients in the general Gaucher population and in the trial populations for other ERT products, with the exception of hemoglobin concentration (see Table 17). However, patients in this trial were older (mean age was 37 years) at the time of initiation of treatment compared to patients in the general Gaucher population (mean age was 30 years) or patients in earlier ERT trial (mean age was 26 years in the VPRIV pivotal study; mean age was 28 years in the Ceredase-Cerezyme comparison trial). The reason for this age difference is not clear. The normal baseline hemoglobin observed in patients in this trial suggests that the patients had relatively less severe disease. However, it is difficult to make comparisons of disease severity among Gaucher patient populations due to the lack of validated quantitative assessment disease severity indices for this disease.[17] Patient selection bias, such as enrollment of patients who had no other access to ERT therapy (due to financial or other barriers), could also result in a difference in the age demographic. Also of note, the clinical trials for Ceredase, Cerezyme and VPRIV all included pediatric patients. As noted earlier, pediatric-onset disease may represent a more aggressive (i.e., more severe) form of type 1 Gaucher disease, based on the degree and rate of disease progression that has been observed in pediatric patients.

15 Weinreb NJ, Charrow J et al, Effectiveness of enzyme replacement therapy in 1028 patients with type 1 Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher Registry. *Am J Med* 2002; 113: 112–9.
16 Pastores GM, Weinreb NJ, Aerts H, et al. Therapeutic goals in the treatment of Gaucher disease. *Semin Hematol* 2004;41 (Suppl. 5):4-14.
17 Weinreb NJ, Cappellini MD, et al, A validated disease severity scoring system for adults with type 1 Gaucher disease, *Genet Med* 2010:12(1):44 –51.

Table 17: Comparison of Efficacy Results for Ceredase and Cerezyme



Electronically reproduced and copied from: Grabowski et al. Enzyme Therapy in Type1 Gaucher Disease: Comparative Efficacy of Mannose Terminated Glucocerebrosidase from Natural and Recombinant Sources. Ann Intern Med 1995;122: 33-29.

The Statistical Reviewer noted that the robustness of the efficacy results was weakened by the lack of an active comparator control arm. He did not identify any errors or discrepancies in the statistical analysis performed by the Applicant. Only two patients were randomized but did not complete the study; therefore, conclusions based on efficacy findings were not impacted by missing data.

As noted earlier, the effect of immunogenicity on efficacy results cannot be determined at this point. The effect of immunogenicity on efficacy will need to be re-evaluated and based on data obtained from confirmatory assays using an appropriate cut point and enzyme activity and cellular uptake inhibitory antibody assays.

In summary, although the data from PB-06-001 support the efficacy of taliglucerase in patients with type 1 Gaucher disease, a comparison of the efficacy of taliglucerase with currently available ERT products cannot be directly determined because the study did not include an active comparator arm. Therefore, only cross-study comparisons can be made, and these types of comparisons are prone to bias (e.g., selection bias) that may lead to erroneous conclusions. Additional studies using an active comparator control design and/or a randomized add-on or withdrawal design would allow a direct comparison of efficacy of taliglucerase with other ERT products. The Statistical Reviewer recommended that the Applicant conduct one or more additional studies to evaluate the effect of treatment with taliglucerase compared to another approved ERT (e.g., active comparator control, randomized add-on or withdrawal). Therefore, I concur with this recommendation. For reasons discussed in my review of the supporting Phase 3 trials (Section 5.3.2), I have concerns that the Applicant's ongoing open-label switchover trial potentially will not provide sufficiently robust evidence of a similar treatment effect and safety profile compared to other available ERTs.

5.3.2 Supporting Phase 3 Trials (PB-06-002 and PB-06-003)

A. PB-06-002- Phase 3 Switchover Trial

PB-06-002 is a multicenter, open-label, switchover trial designed to evaluate the efficacy and safety of taliglucerase every other week (EOW) for 9 months in 30 type 1 Gaucher patients who had previously been treated with Cerezyme (imiglucerase). Patients were required to have been on ERT with Cerezyme for at least 2 years, judged to be clinically stable (see below), and on a stable maintenance regimen (defined as no dose change within the past 6 months).

Stable Gaucher disease at baseline was defined as no change in the following parameters within the past year:

- hemoglobin (no value >mean $\pm$ 15%)
- platelet count ($\geq$120K:no value >mean $\pm$ 40%; <120K: no value >mean $\pm$ 40%)
- no spleen or liver volume increase (as measured by MRI)
- no major surgery
- no transfusions or major bleeding episode
- no acute avascular necrosis event

Patients received a starting dose of taliglucerase alfa equivalent to their stable Cerezyme dose. For patients whose Cerezyme treatments have been discontinued due to drug shortage, the starting taliglucerase dose was based on their usual dose prior to drug shortage. During the treatment period, the dosage could be increased to a maximum dose of 60 U/kg if the patient experienced Gaucher disease deterioration as defined by a pre-specified decline in organ volume, hemoglobin, or platelet count.

Efficacy was evaluated by monitoring the following parameters for evidence of clinical deterioration:

- platelet count (> 120K-40% decrease; $\leq$ 120K-20% decrease)
- hemoglobin (20% decrease)
- spleen volume (20% increase)
- liver volume (10% increase)

Other efficacy endpoints included biomarkers (chitotriosidase and CCL18). Growth and development parameters (change in growth and development, height and weight, Tanner stage, bone age) were evaluated as exploratory endpoints for pediatric patients (patients < 18 years old).

The safety monitoring for Trial PB-06-002 included the same safety measurements as performed in PB-06-001. In addition, clinical deterioration in hemoglobin or platelet

count, defined as three consecutive measures of declining values, was monitored as a safety variable.

An abbreviated trial report with interim safety and efficacy data was included in the NDA because the trial was ongoing at the time of the NDA submission. Currently, 24 patients have been enrolled; no pediatric patients were enrolled at the time of the NDA submission. Fourteen patients have completed 6 months of treatment; four patients have completed 9 months of treatment. The abbreviated study report includes safety data up to a database freeze date of April 30, 2010. The safety data for this study will be reviewed in Section 7.

Review of Efficacy

Efficacy Summary

Long-term data on the efficacy of taliglucerase alfa in patients switched from Cerezyme are limited. One of four patients (25%) experienced clinical deterioration after 9 months of treatment with taliglucerase alfa. Hemoglobin and platelet count appear to remain stable after 6 months of treatment with taliglucerase alfa. However, clear conclusions regarding the efficacy of taliglucerase from this trial cannot be made because of the small number of patients and the short time period of treatment with taliglucerase. In addition, two retrospective surveys of patients withdrawn from ERT treatment for various reasons (e.g., medical complications, financial constraints, drug shortage) indicated that clinical parameters of Gaucher disease remained stable or did not deteriorate precipitously up to 6 months after treatment withdrawal.[18,19] In the earlier survey, some patients were clinical stable after more than two years without ERT treatment. Therefore, it is difficult to apportion the contributions of Cerezyme and taliglucerase alfa to clinical stability in the earlier months after a switchover. The open-label design of this study also limits the ability to draw clear conclusions from these data.

1. Spleen and Liver Volume

Three of the four patients who completed the trial did not experience clinical deterioration in organ volume or hematologic parameters. One patient (10-203) experienced a greater than 20% increase in spleen volume from baseline to 9 months. Dosing for the four patients ranged from 9 U/kg to 50 U/kg. None of the four patients had a dose adjustment during the trial.

18 Elstein D, Abrahamov A et al, Withdrawal of enzyme replacement therapy in Gaucher's disease, *Br. J Haematol* 2000; 110(2):488-492.
19 Zimran A, Altarescu G, Elstein D, Nonprecipitous changes upon withdrawal from imiglucerase for gaucher disease because of a shortage in supply, *Blood Cells Mol Dis* 2011: 46 (1):111-114.

Table 18: PB-06-002- Organ Volume and Percent Change at Baseline and Month 9

Patient ID	Visit	Spleen		Liver	
		Volume (ml)	% Change	Volume (ml)	% Change
10-202	Baseline Month 9	(b) (4)			
10-201	Baseline Month 9				
10-203	Baseline Month 9				
10-204	Baseline Month 9				

2. Hemoglobin

All patients maintained stable mean hemoglobin levels at Month 3 or Month 6. The mean change in hemoglobin at 6 months was -0.2 g/dL + 0.6. The percent change in mean hemoglobin ranged from -10% to +6% at Month 3 and -12% to +7% at Month 6.

Table 19: PB-06-002- Hemoglobin (g/dL) at Baseline, Month 3, and Month 6

Baseline (n=24)	Month 3 (n=23)	Month 6 (n=14)
13.5±1.6 (10.7-16.1)	13.3±1.5 (10.6-15.6)	13.3±2.0 (10.0-16.2)

3. Platelet Count

The mean change in platelet count at 6 months was -3K/mm^3 +3K. Nine of 24 patients (38%) had a platelet count of < 120K at baseline. The mean platelet count decreased in 2/14 patients (10-201 and 10-203) at Month 6. Both patients had a baseline platelet count of < 120K.

Table 20: PB-06-002- Platelet Count (_/mm3) at Baseline, Month 3 and Month 6

Baseline (n=24)	Month 3 (n=23)	Month 6 (n=14)
160K±80K (38K-310K)	148K±75K (33K-283K)	161K±90K (47K-316K)

B. PB-06-003- Phase 3 Extension Trial

PB-06-003 is a multicenter, extension trial to assess the safety and efficacy of taliglucerase alfa in Gaucher disease patients who completed 9 months of treatment in studies PB-06-001 and PB-06-002. Patients are being continued on their previous dose of taliglucerase alfa (maximum dose of 60 U/kg).

Efficacy variables are spleen and liver volume, platelet count, hemoglobin, and biomarkers. Safety variables are adverse events, clinical laboratory, anti-prGCD antibodies, ECG, echocardiogram, PFTs, and hypersensitivity reactions.

The original duration of the trial was at least 15 months, however, the protocol was amended to extend the trial until marketing approval is obtained or for a maximum of 30 months. The trial is ongoing and is being conducted in 15 sites across Australia, Canada, Chile, Israel (2 sites), Italy, Mexico (2 sites), Serbia, South Africa, Spain, UK (2 sites), and the US (2 sites). The first patient was enrolled on June 9, 2010.

An abbreviated trial report with interim safety data was submitted to the NDA as the trial is ongoing. Currently, 29 patients have been enrolled, including 26 patients enrolled from trial PB-06-001 and 3 patients enrolled from trial PB-06-002. No pediatric patients were enrolled at the time of the NDA submission.

The abbreviated study report includes safety data for 29 patients up to a database freeze date of April 30, 2010. No efficacy data were submitted for review. The safety data for this study will be reviewed in Section 7.

6 Review of Efficacy

6.1 Indication

The Applicant proposes the following indication:

(b) (4)

(b) (4)

I recommend that the indication be revised to be consistent with the labeled indication for other ERT products for Gaucher disease:

"Taliglucerase alfa is indicated for long-term enzyme replacement therapy (ERT) for pediatric and adult patients with type 1 Gaucher disease."

Labeling negotiations with the Applicant were not conducted during this review cycle because a Complete Response action is being taken.

Efficacy is discussed in Section 5 of this review.

7 Review of Safety

Safety Summary

Taliglucerase alfa is generally well tolerated in adult treatment-naïve patients with Type 1 Gaucher disease. Only eight patients transitioned from imiglucerase to taliglucerase (PB-06-002) have completed all study safety assessments; however, early data suggest that taliglucerase alfa also is well tolerated in this population. Most treatment emergent adverse events (TEAEs) were mild or moderate in severity. There were no deaths in any of the clinical trials. Additionally, none of the serious adverse events (SAEs) appear to be directly related to taliglucerase treatment. The most common AEs (>10%) reported among all patients were upper respiratory infections/colds (22%) pharyngitis /throat infection, headaches (each 19%), and influenza/flu and arthalgia/back pain (13%). The Applicant reported that 31/83 (37%) patients experienced events considered to be related to the use of taliglucerase. Adverse reactions considered related to the use of taliglucerase as reported by the Applicant include infusion related reaction, headache, hypersensitivity, fatigue, pruritis, and erythema. The Applicant did not report any events of anaphylaxis. Based on my independent analysis of reported adverse events, 3/32 patients (9%) in PB-06-001 definitely or possibly experienced anaphylactic reactions; insufficient information was available to definitively determine whether one of the patients had experienced an anaphylactic reaction. In addition to the adverse reactions listed by the Applicant, arthralgia/back pain and urticaria/rash/drug eruption were other common adverse reactions. According to the Applicant's analysis, three patients in the development program thus far have developed antibodies to taliglucerase. Safety results do not appear to be different for these patients. However, the ability to interpret immunogenicity data for this product is hampered by inadequacies in the immunogenicity assays (i.e., inappropriate cut-point for the confirmatory anti-product IgG antibody assay and lack of an assay for cellular uptake neutralizing antibodies) used for the clinical trials. The impact of immunogenicity on the safety profile of this product will need to be re-evaluated once adequate immunogenicity assays and evaluation criteria have been established. Based on review of the safety data available for this review cycle, my independent safety analysis did not uncover major discrepancies compared with the Applicant's analysis.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety information for this clinical review includes compete study data from PB-06-001 and interim safety data for PB-06-002 and PB-06-003. The database cut-off date for the interim safety data was April 30, 2010. The Applicant also included adverse event data from PB-06-004 in an integrated safety summary.

7.1.2 Categorization of Adverse Events

The Applicant coded AEs by System Organ Class (SOC) and AE preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). I revised AE preferred terms and SOC terms so that AE terms were clustered together to allow for a more meaningful description of the AE profile of taliglucerase alfa. For example, urinary tract infection and pyelonephritis were grouped as urinary tract infection.

Reporting of adverse events included information such as classification of AE using standard medical terminology (MedDRA Version 10.1), system organ class (SOC), timing of AE in relationship to the infusion, classification of relationship to study medication, classification of severity of AE, and date of onset and resolution of AE. These appear to be adequate to assess the safety profile of taliglucerase alfa.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data from the various studies were not pooled as the type and quality of data collected and the duration of data collection varied. Only data from PB-06-001, PB-06-002, and PB-06-003 were submitted in electronic datasets.

7.2 Adequacy of Safety Assessments

Safety parameters for the three trials reviewed included ECG, echocardiogram, PFT, DEXA, QCSI, clinical chemistry, hematology, and urinalysis, and determination of anti-taliglucerase alfa antibodies, including enzyme activity neutralizing antibodies).

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The safety database includes 83 patients with type 1 Gaucher disease (treatment-naïve or transitioning from imiglucerase) treated with taliglucerase alfa every other week with doses from 9 to 60 U/kg (see Table 21).

As of June 30, 2010, 27/83 (44%) patients had completed 12 months of treatment with taliglucerase alfa and 7/83 (8%) had completed 24 months of treatment. Eight of 25 patients (32%) who were transitioned from imiglucerase to taliglucerase have completed nine months of treatment.

Table 21: Total Patient Exposure to Taliglucerase Alfa

			Months of Treatment											
Study	0*		3	6	9	12	15	18	21	24	27	30	33	36
PB-06-001	32		31	29	29									
PB-06-002	25		24	20	8									
PB-06-003						27	26	20	11	7	3	2	1	
PB-06-004	26		16	6										
Total	83		71	55	37	27	26	20	11	7	3	2	1	

*Number of subjects enrolled and treated as of June 30, 2010
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The demographic data for the three studies reviewed were similar (See Tables 22 and 23). The Applicant noted that the mean age for patients in the switch-over trial and treatment protocol was about 10 years older than the mean age for patients in PB-06-001 (i.e., treatment naïve patients). The Applicant suggested that this difference could be explained by the fact that previously treated patients likely had received ERT for many years prior to trial enrollment; however, the submission did not include individual patient information regarding length of prior ERT treatment. Therefore, this assertion could not be substantiated.

Table 22: Base Demographics for Safety Population

Baseline Characteristics		Study		
		PB-06-001 N=32	PB-06-002 N=25	PB-06-004 N=26
Age	Mean±SD Min-Max	36.2±11.8 19 to 74	47.4±13.0 18 to 66	50.0±17.2 25 to 85
Sex	Male Female	16 (50%) 16 (50%)	13 (52%) 12 (48%)	14 (58%) 12 (46%)
Race	White Native American Other	31 (97%) 0 1 (3%)	25 (100%) 0 0	23 (89%) 1 (4%) 0

Table 23: PB-06-003- Summary Patient Demographic Information

Baseline Characteristics		PB-06-003 N=29		
		PB-06-001 30U/kg N=12	PB-06-002 60 U/kg N=14	PB-06-002 prGCD N=5
Age	Mean±SD Min-Max	38.9±12.1 24 to 74	35.6 ±12.0 19 to 58	40.6±18.7 18 to 66
Sex	Male Female	7 (58%) 5 (42%)	8 (57%) 6 (43%)	2 (40%) 3 (60%)
Race	White Native American Other	12 (100%) 0 0	13 (93%) 0 1 (7%)	5 (100%) 0 0

7.2.2 Explorations for Dose Response

Relationship between dose and response was evaluated in PB-06-001. There was no clear dose response relationship in terms of safety signals seen. See Section 7.5.1 for evaluation of AEs and various dosages of taliglucerase treatment.

7.2.4 Routine Clinical Testing

Routine safety laboratory studies were performed for trials PB-06-001, PB-06-002, and PB-06-003. Local laboratory facilities were used for measurements of platelet count, erythrocyte sedimentation rate, and urinalysis due to the instability of these measurements associated with shipping time and conditions. All other safety laboratory studies were performed in a single central laboratory center. Laboratory results are discussed in Section 7.4.2.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adequate evaluation for potential adverse events for the other ERTs for type 1 Gaucher disease was performed through a literature search by the Applicant. The literature review included analyses of a pharmacovigilance database. The most common events reported in adults and adolescents were headache, pruritis, and rash; the most common events reported in children included dyspnea, fever, nausea, flushing, vomiting, and coughing.

All ERT products have the potential to produce anaphylaxis, severe allergic reactions, and immune-mediated reactions. The labeling for Cerezyme notes that an anaphylactoid reaction has been reported in less than 1% of the patient population. The labeling for Lumizyme includes a box warning noting the risk for development of

immune-mediated reactions. These reactions occurred several weeks to three years after initiation of Lumizyme infusions. Diminished therapeutic response due to the development of neutralizing antibodies has also been reported with the use of ERT products.

7.3 Major Safety Results

The major safety results reviewed in this section are from PB-06-001 except where noted otherwise. Safety data from other studies submitted to this application are also reviewed and are presented in Section 7.4.

7.3.1 Deaths

No deaths have been reported in this development program to date.

7.3.2 Nonfatal Serious Adverse Events

Three SAEs were reported for the safety population, including two SAES in two patients in PB-06-002 (epistaxis and nephrolithiasis) and one SAE in PB-06-003 (immune thrombocytopenia). An additional event of pelvic pain in one patient was reported in error as a SAE and subsequently corrected in the database. None of these SAEs were considered by the investigator to be related to treatment. Table 24 describes the specific serious adverse events reported in the clinical trials for taliglucerase.

Table 24: Summary of Serious Adverse Events in Taliglucerase Trials

PB-06-001	PB-06-002	PB-06-003	PB-06-004
0/32	2/25 (8%) • Epistaxis (previous history of epistaxis) • Nephrolithiasis	1/29 (3%) • Idiopathic immune thrombocytopenia	0/26

Narratives for the reported SAEs:

Patient 10-202 (PB-06-002)
SAE: Epistaxis- right nostril due to perforation of septum
The patient is a 36 year-old white female with a history of bleeding (hematoma, bleeding from gums, and epistaxis) diagnosed in 1978 and a history of a deviated nasal septum

treated surgically in 1993 with perforation treated surgically in 1996 and 1999. Her medical history included cardiac valve disease (minimal mitral and tricuspid valve incompetence), bilateral deafness, osteopenia, wrist, shoulder and back pain, dysuria, heartburn, and non-specific gastritis. The patient was treated with imiglucerase since 1974 and started treated with taliglucerase alfa on March 9, 2009 with doses of 800 units alternating with 1000 units every other week. She was taking no other medication at the time of the SAE.

On (b) (6), the patient experienced epistaxis which required hospitalization for chemical cauterization and packing. She was discharged on (b) (6) and chemical cauterization was repeated on (b) (6). The event was reported as being resolved.

Comment: This reviewer agrees that the event does not appear to be treatment-related.

Patient 11-007 (PB-06-002)
SAE: Immune Thrombocytopenia
The patient is a 25 year-old South African black female. Her medical history included anemia, hyperuricemia, urinary tract infection, systolic heart murmur, backache, tiredness, and pyrexia. The patient completed PB-06-001 and received her first infusion under PB-06-003 on January 27, 2009 with taliglucerase 60 U/kg every other week. Her last infusion prior to the SEAE was on September 22, 2009. The patient's concomitant medications at the time of the SAE were allopurinol, Vitamin B12, and acetaminophen.

On September 22, 2009, the patient was noted to have persistent low platelet values, despite response in hemoglobin, liver and spleen size. A diagnostic work-up was significant for positive platelet antibody tests and normal bone marrow biopsies. The patient was diagnosed with idiopathic thrombocytopenic purpura (ITP) and was started on a course of high dose corticosteroids on October 9, 2009 which was slowly reduced. Treatment was ongoing at the time of the SAE report.

Comment: This reviewer agrees that the event does not appear to be treatment-related.

Patient 18-219 (PB-06-003)
SAE: Nephrolithiasis
The patient is a 65 year-old male diagnosed with Gaucher disease in 1960. His medical history included bone disease, anemia, thrombocytopenia, and iron overload, hypertension, hepatomegaly with cirrhosis and fibrosis, asymptomatic gallstones, and incisional hernia. Related to this event, he had left hydronephrosis treated with surgery in 1964. The patient started treatment with imiglucerase in December 1997 with a dose of 800 units every 2 weeks. Due to the drug shortage, his dose was decreased to 400

units and then discontinued. He started treatment with taliglucerase on December 14, 2009 with 800 units every 2 weeks.

On June 3, 2010, the patient had an acute onset of hematuria. An ultrasound performed on June 7, 2010 suggested renal stones. The diagnosis was confirmed by cystoscopy and CT scan on June 24, 2010. The patient was admitted on (b) (6) and underwent insertion of a right ureteric stent. He was discharged on (b) (6) on a 5-day course of antibiotics. He was readmitted on (b) (6) for lithotripsy. The procedure was incomplete and he was scheduled for further stone fragmentation for (b) (6).

Comment: This reviewer agrees that the event does not appear to be treatment-related.

7.3.3 Dropouts and/or Discontinuations

A total of eight patients were withdrawn from treatment, including 3 patients withdrawn from PB-06-001 for safety reasons (one patient with an anaphylactic reaction, one patient with an allergic reaction, and one patient who became pregnant) and 5 patients who voluntarily withdrew from PB-06-004 for reasons not related to safety. No further information was provided on the dropouts from PB-06-004.

7.3.4 Significant Adverse Events

The Applicant reported hypersensitivity reactions in five patients. Based on my review of the AE reports, one patient (10-002 and) in PB-06-001 and one patient (30-009) in PB-06-003 who were reported as having hypersensitivity reactions experienced anaphylactic reactions; both patients were in the high dose treatment group. Two patients (10-001 and 10-003) reported as experiencing a hypersensitivity reaction did not meet the criteria for anaphylaxis. There was insufficient information for one patient (74-4022) in PB-06-004 to determine if he had developed anaphylaxis. See Section 7.3.5 for my review of these events.

There were no other significant AEs reported for PB-06-001 or PB-06-002. One patient (40-018) in PB-06-003 developed diabetes mellitus requiring treatment with insulin. One patient (71-4011) in PB-06-004 with a history of bone disease developed severe back pain. Both of these AEs were categorized as severe and unrelated to treatment.

7.3.5 Submission Specific Primary Safety Concerns

Anaphylaxis and Severe Allergic Reactions
The Applicant performed standardized MedDRA queries on the safety data for the following: anaphylactic reactions, anaphylactic shock, angioedema, toxic septic shock, asthma and bronchitis, pulmonary hypertension, and extravasation events.

There were no cases found under anaphylactic shock, toxic septic shock, or asthma and bronchitis. All events of anaphylactic reaction, angioedema, pulmonary hypertension, and extravasation were classified as mild or moderate.

I reviewed reported hypersensitivity AEs and the patient narratives provided by the Applicant using the criteria developed by the national Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) to diagnose anaphylaxis (see Table 25). Based on these criteria, I assessed 3/5 patients reported as experiencing hypersensitivity reactions as having experienced anaphylactic reactions.

Table 25: Clinical Criteria for Diagnosing Anaphylaxis

From: Sampson HA, Muñoz-Furlong A et al, Second symposium on the definition and management of anaphylaxis: Summary report- second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium, *J Allergy Clin Immunol* 2006; 117: 391-7.

Narratives for the reported hypersensitivity AEs:

Patient 10-002 (PB-06-001)
The patient developed symptoms of feeling warm, palpitation, chest tightness, nausea and facial flushing during infusion 11. The infusion was temporarily suspended and then resumed at a lower rate without further symptomatology. During the 12th infusion, the patient experienced facial flushing, nausea, chest tightness, urticaria, wheezing, and prickling feeling in the hands. The infusion was permanently discontinued and the patient was administered a corticosteroid and antihistamine.

Comment: The patient's symptoms during the 12th infusion meet anaphylaxis criteria.

Patient 10-003 (PB-06-001)
The patient developed symptoms of rash with itching, redness, urticaria, chills and tremor, and swelling of the right eyelid within minutes of the start of his initial infusion. The patient was administered a corticosteroid and antihistamine. The patient was discontinued from the study. An antibody sample obtained pre-infusion was positive for IgE antibody. The patient had a history of a reaction of pruritis and urticaria with Cerezyme.

Comment: The patient's symptoms do not meet anaphylaxis criteria. .

Patient 30-009 (PB-06-003)
The patient developed symptoms of dizziness, nausea, vomiting, urticaria, and hypotension 70 minutes after his 23rd infusion (20 of the infusions were received during PB-06-001). The patient had no reported AEs during his treatment in PB-06-001. The infusion was discontinued and the patient was administered a adrenaline, methylprednisolone, and chloropiramine. Infusions were resumed at a lower infusion rate and the patient is receiving premedication before infusions. He is reported as tolerating infusions well. He has completed 24 months of treatment.

Comment: The patient's symptoms meet anaphylaxis criteria.

Patient 10-001 (PB-06-003)
The patient presented with a whitish indurated area on his left cheek and no other signs or symptoms during his 32nd infusion ((20 of the infusions were received during PB-06-001) on November 23, 2008. The lesion resolved within a few hours after the end of the infusion and was thought to be due to an insect bite. The patient presented with the same finding during several subsequent infusions. No changes were made to his treatment and the skin lesion resolved each time without sequelae. The patient was referred to a dermatologist for evaluation and was diagnosed on August 20, 2009 as having a fixed drug eruption due to the enzyme treatment. The patient has continued on an unchanged treatment regimen and has continued to have intermittent skin eruptions. The patient tested positive for IgG antibodies during PB-06-001

Comment: The patient's symptoms do not meet anaphylaxis criteria.

Patient 74-4022 (PB-06-004)
The patient was treatment-naïve prior to enrollment in PB-06-004. The patient's allergy history is significant for multiple medication and environmental allergies but no allergies to food, including carrots. The patient tested positive for anti-taliglucerase alfa IgG antibodies but negative for IgE antibodies during baseline antibody testing. The Applicant stated: "Because there is only a weak connection between positive antibodies and the development of signs or symptoms of hypersensitivity, the decision was made to enroll the patient into the trial due to the shortage of Cerezyme."

The patient developed hives with no change in vital signs during the first infusion. The infusion rate was decreased and the patient was treated with an antihistamine with improvement of his symptoms. The infusion rate was increased again and the patient completed the infusion with total recovery of his symptoms.

The patient received premedication (acetaminophen and diphenhydramine) before the second infusion. The patient is reported to have "experienced signs of a hypersensitivity reaction" during this infusion but completed the infusion. The patient received premedication before his third and fourth infusion; he experienced hives and watery, itchy eyes during the third infusion, and itchy eyes during the fourth infusion. He has received 9 infusions to date and continue to receive premedication for hypersensitivity.

Comment: There is insufficient information to assess whether this patient experienced an anaphylactic event during his second infusion. The Applicant did not provide details of this particular hypersensitivity reaction and no patient data listings or datasets were available for review.

Infusion reactions
Infusion reactions were defined by the Applicant as any AE that occurred during the infusion and was possibly related to the study drug. At the request of DGP, the Applicant submitted datasets on the timing of the AE in relationship to the infusion and divided the AEs into 3 categories: 1) AE onset during the infusion or within 2 hours of completion of infusion 2) AE onset between 2-24 hours post- infusion 4) AE onset greater than 24 hours post- infusion. Table 26 is a summary table of adverse events during or after an infusion submitted by the Applicant. I revised the Applicant's table to mark hypersensitivity reactions meeting the criteria for anaphylaxis. Twenty-five individual patients experienced 66 events during or within 2 hours of completion of infusion in PB-06-001, PB-06-002, and PB-06-003. The Applicant also reported 39 adverse events occurring during or after an infusion (time period not specified) in 10 patients for PB-06-004.

Table 26: Adverse Events During or After an Infusion

Study/Drug Dose	**PID**	**Infusion**[a]	**Adverse Events (AEs)**[b]	**Treatment Relationship**
PB-06-001				
30 U/kg	10-001	1	Vomiting and facial flushing	Probably not
		12E	Fixed drug eruption on left cheek of face	Possibly
		21E	Fixed drug eruption on left cheek of face	Possibly
		30E	Redness under left eye	Possibly
		31E	Fixed drug eruption on left cheek of face	Possibly
		32E	Fixed drug eruption on left cheek of face	Possibly
		36E	Mild swelling under left eye	Definitely
		37E	Mild swelling under left eye	Definitely
		38E	Mild swelling over right eye	Definitely
		39E	Fixed drug eruption above right eye	Definitely
		40E	Fixed drug eruption under left eye	Definitely
		41E	Mild swelling under left eye	Definitely
	10-003	1	Hypersensitivity	Definitely
	10-028	15E	Infusion site problem- needle went para to vein	Definitely not
	11-014	23E	Dry mouth post infusion (intermittent)	Possibly
	17-032	1E	Arthralgia localized at legs	Probably
	40-017	3	Hypertension	Definitely not
	41-021	1	Vessel puncture site hematoma	Definitely not
	41-022	1	Hypoaesthesia	Probably not
		12	Headache	Possibly
	42-025	1	Dizziness and feeling hot	Possibly
		5	Dizziness	Possibly
		11	Muscle spasms	Possibly
60 U/kg	10-002	11	Chest discomfort, feeling hot, nausea, palpitations	Probably not
		12	Hypersensitivity/ (**Anaphylaxis)**	Probably
	10-005	2E	Dizziness during infusion	Possibly
		27E	Nausea during infusion as before	Possibly
	10-013	1	Nausea	Definitely not
		2	Headache	Definitely not
		18	Headache/skin irritation	Definitely not/Possibly
		13E	Itching	Probably not
		22E	General pain	Probably not
		23E	Worsening of pre-existing rash under adhesive	Probably not
		29E	Rash at infusion site	Definitely not
	10-029	3	Headache	Definitely not
		4	Headache	Definitely not
		5	Headache	Definitely not
		9	Headache	Definitely not
		10	Headache	Possibly
		12	Headache	Possibly
		15	Headache	Possibly
		4E	Headache	Possibly
		19E	Headache	Possibly
	15-016	9	Arthralgia and chest pain	Probably not
	22-030	4E	Fatigue	Probably not
	30-009	3E	Hypersensitivity reaction(**Anaphylaxis)**	Probably

Table 26: Adverse Events During or After an Infusion (cont'd)

Study/Drug Dose	PID	Infusion[a]	Adverse Events (AEs)[b]	Treatment Relationship
PB-06-002				
11.3 U/kg	10-202	3	Mild worsening of Baseline condition of headaches	Definitely not
		5	Mild worsening of Baseline condition of headaches	Possibly
		6	Headache during infusion	Probably not
		10	Fatigue during infusion	Definitely not
13.2 U/kg	10-203	11	Headache during infusion	Possibly
12.6 U/kg	10-205	10	Slightly elevated temperature from prior to and throughout the infusion and follow-up	Definitely not
14.5 U/kg	10-218	1	Itching between thumb and index finger on left hand	Possibly
		2	Itching between thumb and index finger on left hand	Possibly
		3	Itching between thumb and index finger on left hand	Probably
		4	Itching between thumb and index finger on left hand	Probably
		6	Itching between thumb and index finger on left hand	Definitely
		7	Itching between thumb and index finger on left hand	Definitely
		10	Itching between thumb and index finger on left hand	Definitely
		12	Itching between thumb and index finger on left hand	Definitely
17.1 U/kg	15-222	3	Numbness on left hand	Definitely not
16.8 U/kg	18-221	1	Red area of skin at infusion site in shape of the dressing	Probably not
59.5 U/k	20-211	1	Complained that she was very tired after the infusion	Possibly
		2	Feeling weak after the infusion	Possibly
56.8 U/kg	23-206	1	Flushing on forearms, upper chest and feet	Possibly
18.4 U/kg	60-208	1	Lethargy	Possibly

Table 26: Adverse Events During or After an Infusion (cont'd)

Study/Drug Dose	**PID**	**Infusion**[a]	**Adverse Events (AEs)**[b]	**Treatment Relationship**
PB-06-004				
18.0 U/kg	03-4008	1	Very mild hand erythema	Possibly
		2	Face flushing	Possibly
		3	Mild throat pain, face flushing, very mild hand erythema	Possibly
		8	Very mild hand erythema	Possibly
		12	Lips swelling	Possibly
14.4 U/kg	04-4012	8	Headache	Definitely not
34.1 U/kg	20-4026	1	Sneezing, runny nose, throat congestion	Possibly
59.4 U/kg	23-4005	2	Headache	Possibly
30.6 U/kg	71-4001	2	Chest pressure, heart racing	Definitely not
26.3 U/kg	71-4007	9	Left calf stabbing pain	Probably not
20.2 U/kg	71-4011	1	Nausea	Possibly
		2	Nausea	Possibly
		3	Nausea	Possibly
		3	Fatigue	Probably not
		4	Nausea	Possibly
		7	Headache	Possibly
		7	Fatigue	Probably
		8	Headache	Possibly
		10	Headache	Probably
		10	Fatigue	Possibly
		11	Headache, Fatigue	Possibly
		12	Headache, Fatigue	Probably
		13	Headache, Fatigue	Probably
43.6 U/kg	71-4014	1	Burning sensation (chest, throat, back), Nausea	Possibly
		1	Redness and edema under eyes, Itching and scaling on eye lids	Probably
		2	Burning (chest), Back pain	Possibly
		2	Redness and edema under eyes, Itching and scaling on eye lids	Probably
		3	Esophageal burning	Possibly
		3	Redness and edema under eyes, Itching and scaling on eye lids	Probably
		4	Esophageal burning	Probably
		4	Redness and edema under eyes, Itching and scaling on eye lids	Probably
		6	Esophageal burning	Possibly
19.0 U/kg	71-4023	1	Fatigue	Possibly
31.6 U/kg	71-4022	1	Hypersensitivity	Definitely
		2	Hypersensitivity	Definitely
		3	Hypersensitivity	Definitely
		4	Hypersensitivity	Definitely
		5	Hypersensitivity	Definitely

[a]E=Extension trial PB-06-003
[b] Hypersensitivity reactions meeting criteria for anaphylaxis are listed as Hypersensitivity **(Anaphylaxis)**
Table modified from Applicant's Submission

I independently re-evaluated the relationship of the AE to the study drug. Many AEs that occurred during the infusion or within two hours after completion of the infusion were classified as unlikely related to the study medication by the Applicant. I analyzed the clinical context of the AEs and recoded them as possibly related to the study drug if the event occurred during the infusion or within 24 hours after completion of the infusion. The preferred terms that were recoded as possibly related included: abdominal/epigastric discomfort, arthralgia, asthenia chest pain/discomfort, dizziness, drug eruption, dyspnea, erythema, fatigue, feeling hot, flushing, infusion related reaction, headache, hyperglycemia, hyperhidrosis, hypersensitivity, hypertension, lethargy, nausea, pain, palpitations, presyncope, pruritis, pyrexia, rash/skin irritation, swelling, tachycardia, and vomiting. Table 27 summarizes the number of infusion reaction AEs and number of patients experiencing infusion reaction AEs based on recoding of AEs.

Table 27: Summary of Infusion Reaction Events by Trial

PB-06-001 Events/Patients (%)	**PB-06-002** Events/Patients (%)	**PB-06-003** Events/Patients (%)
39/14 (44%)	37/12 (48%)	40/12 (41%)

Table 28 describes the most commonly reported infusion reaction AEs (infusion reaction AEs reported in two or more patients). The reported number of patients with hypersensitivity reactions in the table includes patients with reactions that met the criteria for anaphylaxis. The most commonly reported infusion reactions were infusion-related reaction, headache, arthralgia/back pain, and urticaria/rash/ drug eruption. Overall, infusion reaction AEs were mild in severity and did not impact the patient's ability to receive their scheduled infusions.

Table 28: Most Commonly Reported Infusion Reactions (occurring during or up to 24 hours post-infusion) in All Trials

System Organ Class Preferred Term	**PB-06-001** **N=32**	**PB-06-002** **N=25**	**PB-06-003** **N=29**
General Disorders and Administration Site Conditions (N=13)			
Infusion related reaction	0	4 (16%)	2 (7%)
Asthenia	0	2 (8%)	0
Chest pain/discomfort	2 (6%)	0	0
Fatigue	0	1 (4%)	2 (7%)
Nervous System Disorders (N=13)			
Headache	5 (16%)	2 (8%)	1 (3%)
Hypoesthesia/parasthesia	1 (3%)	1 (4%)	1 (3%)
Dizziness/Presyncope	1 (3%)	0	1 (3%)
Skin and Subcutaneous Tissue Disorders (N=10)			
Erythema	1 (3%)	1 (4%)	2 (7%)
Urticaria/rash/drug eruption	0	1 (4%)	3 (10%)
Pruritis	1 (3%)	1 (4%)	0
Gastrointestinal Disorders (N=8)			
Abdominal/Epigastric discomfort	1 (3%)	1 (4%)	1 (3%)
Diarrhea	1 (3%)	1 (4%)	1 (3%)
Vomiting	1 (3%)	0	1 (3%)
Musculoskeletal and Connective Tissue Disorders (N=7)			
Arthralgia/back pain	2	2 (8%)	3 (10%)
Vascular Disorders (N=6)			
Flushing	2 (6%)	1 (4%)	0
Hypertension/increased blood pressure	1 (3%)	0	2 (7%)
Immune System Disorders (N=3)			
Hypersensitivity*	2 (6%)	0	1 (3%)

*Includes patients with hypersensitivity reactions meeting criteria for anaphylaxis.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Overall, the frequency of AEs was similar across trials with nasopharyngitis/URI, arthralgia/back pain, and headaches being included in the most commonly reported AEs in all three studies.

PB-06-001
23/32 (72%) of enrolled patients experienced at least one AE. The occurrence of AEs was similar in the two treatment groups (12 patients in the low dose group; 11 patients in the high dose group). Eight patients (25%) experienced an AE that was assessed by the investigator as treatment-related (3 patients in low dose group; 5 patients in high dose group). All AEs were mild and moderate in intensity. Four patients experienced AEs that were ongoing at the end of the trial; none of these AEs were considered to be treatment related.

The most common AEs (>10%) reported among all patients were upper respiratory infections/colds (22%) pharyngitis /throat infection, headaches (each 19%), and influenza/flu and arthalgia/back pain (13%). Adverse events reported by at least 10% of the 16 patients in the high dose group were headache (32%), upper respiratory infections/colds (25%), influenza/flu and arthalgia/back pain (each 19%), pharyngitis /throat infection, urinary tract infection/pyelonephritis, otitis externa, , nausea, and fatigue/tiredness (each 13%). Adverse events reported by at least 10% of the 16 patients in the low dose group were pharyngitis /throat infection (25%), upper respiratory infections/colds (19%), dizziness, vomiting, abdominal pain, hypertension/high blood pressure, and epistaxis (each 13%). Table 29 lists adverse events reported by two or more patients in PB-06-001.

Table 29: PB-06-001- Most Commonly Reported Adverse Events (>5% of treated patients)

System Organ Class	Preferred Term	30 U/kg group N=16	60 U/kg group N=16	All treatment groups N=32
Infections and Infestations				
	URI/Cold	3 (19%)	4 (25%)	7 (22%)
	Pharyngitis/Throat infection	4 (25%)	2 (13%)	6 (19%)
	Eye infection	1 (6%)	1 (6%)	2 (6%)
	Influenza/Flu	1 (6%)	3 (19%)	4 (13%)
	UTI/Pyelonephritis	1 (6%)	2 (13%)	3 (9%)
	Gastroenteritis	1 (6%)	1 (6%)	2 (6%)
	Otitis externa	1 (6%)	2 (13%)	2 (6%)
Musculoskeletal and Connective Tissue Disorders				
	Arthralgia/back pain	1(6%)	3 (19%	4 13%)
Nervous System Disorders				
	Headache	1 (6%)	5 (32%)	6 (19%)
	Dizziness	2 (13%)	1 (6%)	3 (9%)
Gastrointestinal Disorders				
	Nausea	1 (6%)	2 (13%)	3 (9%)
	Vomiting	2 (13%)	0 (0%)	2 (6%)
	Abdominal pain	2 (13%)	0 (0%)	2 (6%)
General Disorders and Administration Site Conditions				
	Fatigue/tiredness	1 (6%)	2 (13%)	3 (9%)
	Warmth	1 (6%)	1 (6%)	22 (6%)
Skin and Subcutaneous Tissue Disorders				
	Itching	1 (6%)	1 (6%)	2 (6%)
	Skin mycosis	1 (6%)	1 (6%)	2 (6%)
Vascular disorders				
	Facial flushing	1 (6%)	1 (6%)	2 (6%)
	Hypertension/high BP	2 (13%)	0 (0%)	2 (6%)
Blood and Lymphatic System Disorders				
	Enlarged lymph nodes	1 (6%)	1 (6%)	2 (6%)
Immune System Disorders				
	Hypersensitivity	1* (6%)	1* (6%)	2 (6%)
Respiratory, Thoracic, and Mediastinal Disorders				
	Epistaxis	2 (13%)	0 (0%)	2 (6%)

*Patient was discontinued from the trial

PB-06-002

At the time of database freeze, 21/24 (88%) patients had experienced 97 AEs. Seven patients (29%) experienced 19 AEs that were considered treatment related by the investigator. All AEs were mild or moderate in intensity. AEs reported in more than 1 patient included infusion reaction (5 patients, 21%), nasopharyngitis (4 patients, 17%), spleen disorder, urinary tract infection (each 3 patients, 13%), diarrhea, arthralgia, back pain, osteopenia, headache, and cough (each 2 patients, 8%).

The most commonly experienced AEs were infusion reactions (5 patients, 21%) and nasopharyngitis (4 patients, 17%). Infusion reaction symptoms included headache, itching, fatigue/tiredness, flushing, lethargy, and feeling weak. Table 30 lists adverse events reported by two or more patients in PB-06-002.

Table 30: PB-06-002- Most Commonly Reported Adverse Events (>5% of treated patients)

System Organ Class	Preferred Term	Number of patients N=32
Infections and Infestations		
	URI/nasopharyngitis	5 (21%)
	UTI/	3 (13%)
Musculoskeletal and Connective Tissue Disorders		
	Arthralgia/back pain/ extremity pain	4 (17%)
Nervous System Disorders		
	Headache	2(8%)
Gastrointestinal Disorders		
	Diarrhea	2 (8%)
General Disorders and Administration Site Conditions		
	Infusion reaction	5 (21%)
	Pain	2 (8%)
Blood and Lymphatic System Disorders		
	Spleen disorder	3 (13%)
Respiratory, Thoracic, and Mediastinal Disorders		
	Cough	2 (8%)

PB-06-003
There were no AE events reported for the 3 patients enrolled from PB-06-002. The most common AEs (≥10%) reported in all patients were arthralgia/back pain and nasopharyngitis/URI (8 patients each, 28%), headache (5 patients (17%), and fatigue, pyrexia, erythema, pruritis, and pharyngolaryngeal pain (3 patients each, 10%). Table 31 lists adverse events reported by two or more patients in PB-06-003.

Table 31: PB-06-003- Most Commonly Reported Adverse Events (>5% of treated patients)

System Organ Class	Preferred Term	PB-06-001 N=26		PB-06-002 N=3	All Pts N=29
		30 U/kg N=12	60 U/kg N=14		
Infections and Infestations					
	Nasopharyngitis/URI	4 (17%)	4 (14%)	0	8 (14%)
Musculoskeletal and Connective Tissue Disorders					
	Arthralgia/back pain	4 (33%)	4 (29%)	0	8 (28%)
Nervous System Disorders					
	Headache	3 (25%)	2 (14%)	0	5 (17%)
General Disorders and Administration Site Conditions					
	Fatigue	1 (8%)	2 (14%)	0	3 (10%)
	Pyrexia	0	3 (21%)	0	3 (10%)
Skin and Subcutaneous Tissue Disorders					
	Erythema	3 (25%)	0	0	3 (10%)
	Pruritis	1 (8%)	2 (14%)	0	3 (10%)
Respiratory, Thoracic, and Mediastinal Disorders					
	Pharyngolaryngeal pain	1 (8%)	2 (14%)	0	3 (10%)

7.4.2 Laboratory Findings

In PB-06-001, there were four laboratory AEs reported (elevated ALT, hyperuricemia, glycosuria, hypertriglyceridemia) in three patients (all in the high dose group). Two patients in the high dose group had elevated ALT levels. One patient had an elevated ALT level of 4 times the upper limit of normal (ULN); the level decreased to just outside the normal range by the end of trial and was not reported as an AE. The other patient had an ALT level of 2 times ULN at Week 16 that was reported as an AE.

In PB-06-002, there were five laboratory AEs reported (prolonged PTT, increased cholesterol, increased glucose, decreased folate and abnormal UA) in five patients.

In PB-06-003, hypertriglyceridemia was reported in one patient in the 60 U/kg treatment group.

For all three trials, the majority of laboratory hematology and biochemistry parameter remained at normal baseline levels or improved to normal levels by the end of the trial. All reported laboratory AEs were classified as mild in severity.

Comment: There does not appear to be any pattern in the laboratory findings concerning for a possible safety signal.

7.4.3 Vital Signs

Vitals signs were measured at each infusion visit for 210 minutes- prior to infusion, every 15 minutes up to 2 hours during the infusion, and three additional measurements every 30 minutes. No AEs were reported associated with patients' vital sign measurements for the three trials. Changes in vitals signs during taliglucerase alfa infusions were not analyzed, but no adverse events were reported for significant changes not related to hypersensitivity reactions.

7.4.4 Electrocardiograms (ECGs) and echocardiograms

In PB-06-001, no clinically significant electrocardiogram changes from baseline were observed at Visits 7, 14, and 20. Nine patients had abnormal echocardiogram results during screening. Six patients had normal results by the end of the trial while three patients (1 patient in the low dose group with minimal tricuspid incompetence; 2 patients in the high dose group [1 patient with congenital valve anomaly and 1 patient with minimal tricuspid incompetence]) continued to have abnormal results.

There were insufficient data to assess electrocardiogram and echocardiogram results for PB-06-002 and PB-06-003.

7.4.6 Immunogenicity

Based on the Applicant's original antibody assays, there were three patients, all of whom were treatment naïve, who developed antibodies to taliglucerase. In addition, one patient enrolled in the treatment protocol (PB-06-004), also treatment naïve, tested positive for antibodies to taliglucerase during baseline screening. Three of the four patients with positive antibodies experienced an allergic or anaphylactic event. See patient narratives in Section 7.3.5 for further details on patients who experienced anaphylactic or allergic events.

PB-06-001
Three patients developed anti-GCD antibodies during the trial. One patient (10-003 from the 30 U/kg group) had a positive IgE antibody pre-infusion on Day 1. He experienced an allergic reaction within a few minutes after the start of his initial infusion and was discontinued from the trial. Two other patients (10-001 from the 30 U/kg group and 12-024 from the 30 U/kg group) developed IgG antibodies but did not experience any allergic reactions and completed the trial. One patient (10-002) experienced an anaphylactic reaction but did not develop antibodies; he was discontinued from the study No patients developed inhibitory antibodies. Table 32 summarizes immunogenicity testing results for PB-06-001.

Table 32: PB-06-001- Patients with Positive Antibodies

Patient ID	Initial IgG Titer	Highest IgG Titer	End of Trial IgG Titer	IgE Antibody	Adverse Events	Hypersensitivity reaction?
10-001	5403 (Week 34)	8094 (Week 38)	8094 (Week 38)	negative	vomiting facial flushing fever/flu enlarged lymph nodes hypertension	No
12-024	172 (Week 4)	1467 (Week 14)	1361 (Week 38)	negative	glucosuria nfluenza	No
10-003	negative (Day 1)	NA	negative (Week 6)	positive (Day 1)	allergic reaction	Yes

PB-06-002
Antibody testing was performed in the four patients who completed PB-06-002; testing was negative for all four patients. No allergic reactions were reported.

PB-06-003
Patient 30-009 (60 U/kg treatment group) experienced an anaphylactic reaction. The patient has received premedication for subsequent infusions and has tolerated the infusions well. The patient tested negative for antibodies in PB-06-001. The Applicant did not provide information on results of antibody testing performed during PB-06-003.

Patient 10-001 (30 U/kg treatment group) experienced a fixed drug eruption (lesion located on the face). The patient was documented as having positive IgG antibodies during PB-06-001.

Comment: Due to inadequacies in the immunogenicity assays (i.e., inappropriate cut-point for the confirmatory assay and lack of an assay for cellular uptake neutralizing antibodies) used for the clinical trials, I am unable to make a complete assessment of the risks of taliglucerase at this time. The Applicant will need to submit the results of a confirmatory assay using an appropriate cut-point. In addition, the Applicant will need to submit assay results for both cellular uptake and enzyme activity neutralizing antibodies. At the time of the NDA submission, the Applicant had not yet developed an assay for cellular uptake neutralizing antibodies.

7.4.7 Other Safety Parameters

Pulmonary function tests
In PB-06-001, no changes were observed in PFT parameters from baseline to the end of the trial. There were insufficient data to assess PFT results for PB-06-002 and PB-06-003.

Bone disease
No AEs for bone pain or fractures were reported during PB-06-001, PB-06-002, or PB-06-003. The duration of these trials may not have been long enough to capture these types of AEs. One patient in PB-06-004 experienced a severe AE of back pain.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

PB-06-001 and PB-06-003 provide information on this safety analysis in treatment naïve patients. There does not appear to be an obvious dose dependency for adverse events.

7.5.2 Time Dependency for Adverse Events

I reviewed adverse event reporting for infusion reactions for PB-06-001. The time period for reported infusion reactions ranged from Day 1 (initial infusion) to week 34. The initial infusion reaction for 7/8 eight patients who experienced an infusion reaction occurred at Visit 12 (3 months of treatment) or sooner. One patient had an initial infusion reaction (skin irritation) that occurred at Visit 18. Information was not provided for other AEs by treatment visit; therefore, I was unable to directly assess the data for time trends for other events. However, the type and frequency of AEs reported in PB-06-003 (i.e., after 15 months of treatment) were similar to those reported in PB-06-001. Therefore, there does not appear to be a change in occurrence over time.

7.5.3 Drug-Demographic Interactions

There do not appear to be any significant differences in adverse events based on gender. No safety subgroup analyses were performed for race or age since the vast majority of patients were white and there are no pediatric patients enrolled in the trials to date.

7.5.4 Drug-Disease Interactions

No data are available for drug-disease interactions.

7.5.5 Drug-Drug Interactions

No drug-drug interactions were examined with regard to safety data.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There was no evidence of human carcinogenicity in the safety evaluation.

7.6.2 Human Reproduction and Pregnancy Data

Cerezyme has a Pregnancy category C. Velaglucerase has a Pregnancy category B. One patient was discontinued from the trial due to pregnancy after receiving 10 doses of trial drug. She was followed through her pregnancy and delivered a term, healthy baby girl. The spouse of a male patient became pregnant while the patient was being treated. The spouse delivered a healthy baby girl. There are insufficient data to assess the impact of taliglucerase alfa on pregnancy. The Division will consult Pediatric and Maternal Health Staff during the next review cycle regarding labeling recommendations.

7.6.3 Pediatrics and Assessment of Effects on Growth

No pediatric patients participated in the development program.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No data are available. Taliglucerase is unlikely to be of drug abuse potential given the mechanism of action and because treatment is administered by trained medical personnel.

7.7 Additional Submissions / Safety Issues

Information requests were sent to the Applicant on November 23 and December 21, 2010 regarding additional PK data related to immunogenicity status. These data were not available for review during this review cycle.

8 Postmarket Experience

None.

9 Appendices

9.1 Literature Review/Reference

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9.2 Labeling Recommendations

Labeling negotiations with the Applicant were not conducted during this review cycle because a Complete Response action is being taken.

9.4 Therapeutic Goals for Treatment of Gaucher Type 1 Disease

Specific therapeutic goals for treatment of GD1 (from 23 October 2003 Global Experts Meeting on Therapeutic Goals for the Treatment of Gaucher Disease)[20]

Bone

- Lessen or eliminate bone pain within 1-2 years
- Prevent bone crises
- Prevent osteonecrosis and subchondral joint collapse
- Improve BMD
  - Pediatric patients
    - Attain normal or ideal peak skeletal mass
    - Increase cortical and trabecular BMD by year 2
  - Adult patients
    - Increase trabecular BMD by 3-5 years

Anemia

- Increase hemoglobin levels within 12-24 months to $\geq$ 11 g/dL for women and children and $\geq$12 g/dL for men
- Eliminate blood transfusion dependency
- Reduce fatigue, dyspnea, angina
- Maintain improved hemoglobin values achieved after the first 12 -24 months of therapy

Thrombocytopenia

- Increase platelet count during Year 1 sufficiently to prevent surgical, obstetrical and spontaneous bleeding
- Patients with splenectomy: normalization of platelet count by 1 year of treatment
- Patients with an intact spleen:
  - Moderate baseline thrombocytopenia: increase 1.5-2.0 fold by Year 1
  - Severe baseline thrombocytopenia: increase 1.5 fold by Year 1 and continue to increase slightly during Years 2-5 (doubling by Year 2) but normalization is not expected
  - Avoid splenectomy
  - Maintain stable platelet counts to eliminate risks of bleeding after a maximal response has been achieved

20 Pastores GM, Weinreb NJ, Aerts H, et al. Therapeutic goals in the treatment of Gaucher disease. *Semin Hematol* 2004;41 (Suppl. 5):4-14.,

Specific therapeutic goals for treatment of GD1 (from 23 October 2003 Global Experts Meeting on Therapeutic Goals for the Treatment of Gaucher Disease)- cont'd.

Hepatomegaly

- Reduce and maintain liver volume to 1-1.5 times normal
- Reduce volume by 20-30% within Year 1 and by 30-40% by Year 3-5

Splenomegaly

- Reduce and maintain spleen volume to 2-8 times normal
- Reduce spleen volume by 30-50% within Year 1 and by 50-60% by year 2-5
- Alleviate symptoms due to splenomegaly: abdominal distension, early satiety, new splenic infarction
- Eliminate hypersplenism

Growth (Pediatric Patients)

- Normalize growth such that patient achieves a normal height according to population standards within 3 years of treatment
- Achieve normal onset of puberty

Pulmonary

- Reverse hepatopulmonary syndrome and dependency on oxygen
- Ameliorate pulmonary hypertension (ERT plus adjuvant therapies)
- Improve functional status and quality of life
- Prevent rapid deterioration of pulmonary disease and sudden death
- Prevent pulmonary disease by timely initiation of ERT and avoidance of splenectomy

Functional Health and Well-being

- Improve or restore physical function for carrying out normal daily activities and fulfilling functional roles
- Improve scores from baseline of a validated quality-of-life instrument within 2-3 years or less depending on disease burden

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/s/

CARLA L EPPS
02/22/2011
NDA 022-458 Clinical Review
Recommendation: Complete Response

LYNNE P YAO
02/22/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 022-458 **Applicant: Protalix** **Stamp Date: April 26, 2010**

Drug Name: prGCD **NDA/BLA Type: NDA**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?		X		
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: P-01-2005 Study Title: A Phase 1, Non Randomized, Open Label, Single Dose-Escalation Safety Study of Recombinant Human Glocuocerebrosidase (prGCD) in Healthy Volunteers Sample Size: 6 Arms: 1 Location in submission: 5.3.3.1	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1- PB-06-001	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Indication: long-term enzyme replacement therapy in patients with a confirmed diagnosis of Gaucher disease Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			Division agreed that number of patients/length of exposure in study was adequate
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	new drug belongs?				
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Exempt from PREA (orphan product designation) but a pediatric study (PB-06-005) in pts ages 2-17 yrs will be conducted
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			Clinical Overview 2.5.1.5

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Application is fileable.

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

Carla Epps, M.D.	June 24, 2010	
Reviewing Medical Officer		Date
Lynne Yao, M.D.	June 25, 2010	
Clinical Team Leader		Date

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

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/s/

CARLA L EPPS
06/25/2010
NDA022-458 Clinical Filing Checklist
Application Fileable

LYNNE P YAO
06/25/2010