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APPLICATION NUMBER:

22-575

MEDICAL REVIEW(S)

CLINICAL REVIEW ADDENDUM

Application Type	NDA
Application Number(s)	22-575
Priority or Standard	Priority
Submit Date(s)	August 31, 2009
Received Date(s)	August 31, 2009
PDUFA Goal Date	February 26, 2010
Division / Office	DGP/OND
Reviewer Name(s)	Ii-Lun Chen, MD
Review Completion Date	February 12, 2010
Established Name	Velaglucerase alfa
(Proposed) Trade Name	VPRIV
Therapeutic Class	Enzyme Replacement Therapy
Applicant	Shire
Formulation(s)	Lyophilized powder for solution for infusion
Dosing Regimen	60 units/kg every other week
Indication(s)	Long-term enzyme replacement therapy
Intended Population(s)	Type 1 Gaucher patients

This is an addendum to the clinical review of velaglucerase alfa, dated February 5, 2010. The addendum contains:

1. Trial 039 secondary efficacy evaluation on spleen volume which was previously not included.
2. Additional individual patient data from Trial 034 on the primary and key secondary efficacy endpoints to provide more detailed dosing information for patients previously treated on a stable dose of imiglucerase transitioning to velaglucerase treatment.

Spleen Volume Data from Trial 039

Trial 039 was a randomized, double-blind, parallel-group study of velaglucerase compared with imiglucerase in 34 patients with type 1 Gaucher disease.

All analyses for changes in spleen volume are normalized by body weight to adjust for the variation in organ volumes between patients 2 to 17 years old and ≥18 years old. Only the results for adjusted spleen volume are currently available. Twenty splenectomized patients (10 per group) were excluded.

The baseline mean normalized spleen volume was 2.53% and 4.24% of body weight for the velaglucerase and imiglucerase groups, respectively. The median normalized spleen volumes were similar between treatment groups 1.90% and 1.40% of body weight in the velaglucerase and imiglucerase groups, respectively. Reduction in spleen volume occurred during treatment, and at the Week 41 mean normalized spleen volume was 1.19% and 1.79% body weight for velaglucerase and imiglucerase, respectively. The Week 41 assessment median normalized spleen volume was 1.00% and 0.90% body weight for velaglucerase and imiglucerase, respectively. The unadjusted mean change was -1.34% and -2.46% for the velaglucerase alfa and imiglucerase groups, respectively. The model-based estimated mean treatment difference between velaglucerase and imiglucerase for the mean change was 0.08% body weight. The 95% confidence interval was (-0.52, 0.68), demonstrating that there was no significant difference in normalized spleen volume decrease from Baseline between the two treatment groups.

Table 1: Normalized Spleen Volume from Baseline to Week 41 by Treatment in Trial 039

Normalized Spleen Volume (%BW)	Velaglucerase (n=7)		Imiglucerase (n=7)	
	Baseline	Week 41	Baseline	Week 41
Mean Observed Value (±SE) Min to Max	2.53±0.64 1.4 to 6.3	1.19±0.22 0.8 to 2.5	4.24±1.5 0.6 to 8.9	1.79±0.57 0.5 to 4.3
Change from Baseline* (±SE) Min to Max	—	-1.34±0.42 -3.8 to -0.6	—	-2.46±0.97 -5.5 to -0.1

*The estimated mean treatment difference between velaglucerase and imiglucerase at Week 41 is 0.08 (95% CI= -0.52 to 0.68).

Additional Patient Data from Trial 034

Trial 034 was an open-label, 12-month trial evaluating the safety and efficacy of velaglucerase in 40 patients who had received imiglucerase therapy for type I Gaucher disease for at least 30 consecutive months. Patients were to receive the same dose of imiglucerase during the six months prior to study enrollment. Eligible patients were to receive the same dose (U/kg) of velaglucerase every other week as their imiglucerase dose, which ranged between 15 U/kg and 60 U/kg.

I requested Shire to provide additional data that could be helpful in providing appropriate dosing instructions for patients previously treated on a stable dose of imiglucerase. Individual patient data by dose cohort on hemoglobin concentration across the trial were reviewed. In addition, the mean results for each dose cohort were analyzed for hemoglobin concentration, platelet counts, liver volume, and spleen volume over 51 weeks.

As seen in Figures 1 through 4, patients switched to velaglucerase on the same dose of imiglucerase appear to be able to maintain treatment effect over the course of the year without a significant loss of effect in the first months after the transition. Given that no dosage adjustments were necessary during Trial 034, it appears reasonable that non-naïve patients do not need to start with the recommended dosage of 60 Units/kg of velaglucerase, but should rather transition to velaglucerase on the previous lower dosage that was effective on imiglucerase.

Figure 1: Mean Hemoglobin (g/dL) ±SE by Visit per Dose Cohort in Trial 034

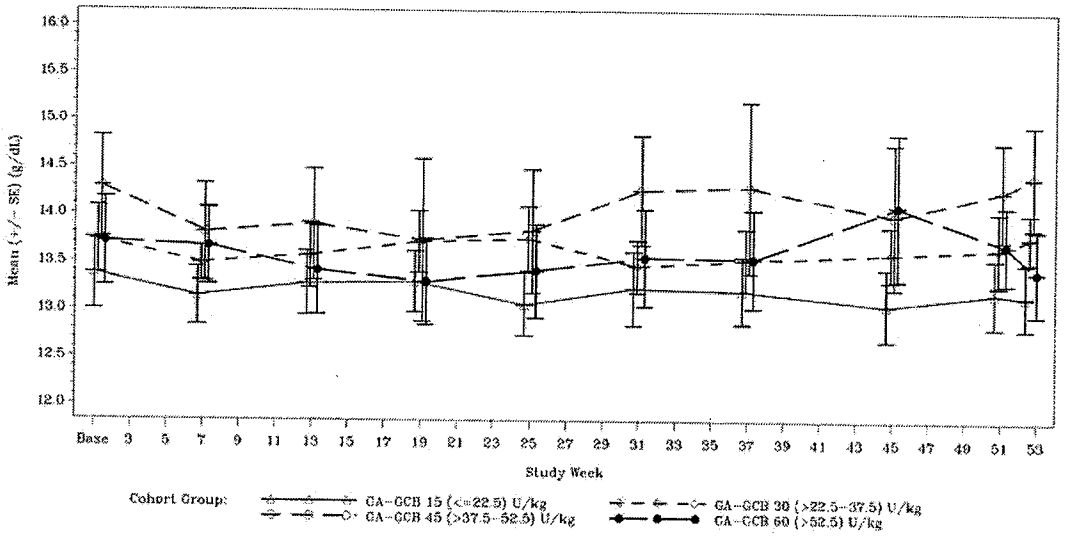


Figure 2: Mean Platelet Count (x10^9/L) ±SE by Visit per Dose Cohort in Trial 034

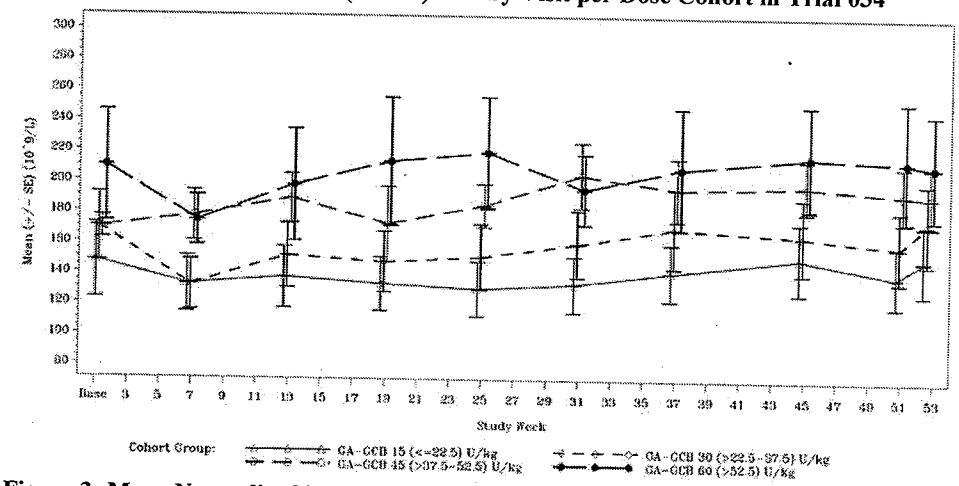


Figure 3: Mean Normalized Liver Volume (% Body Weight) ±SE by Visit per Dose Cohort in Trial 034

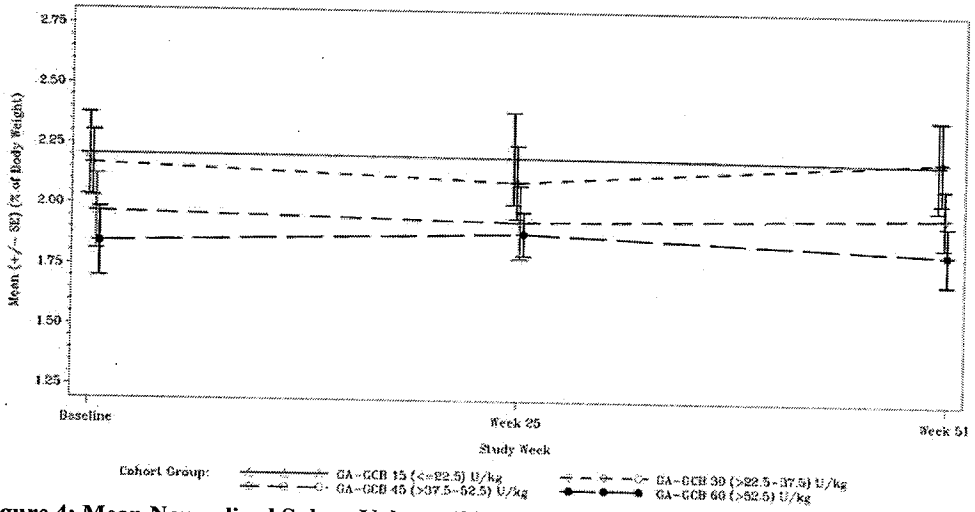
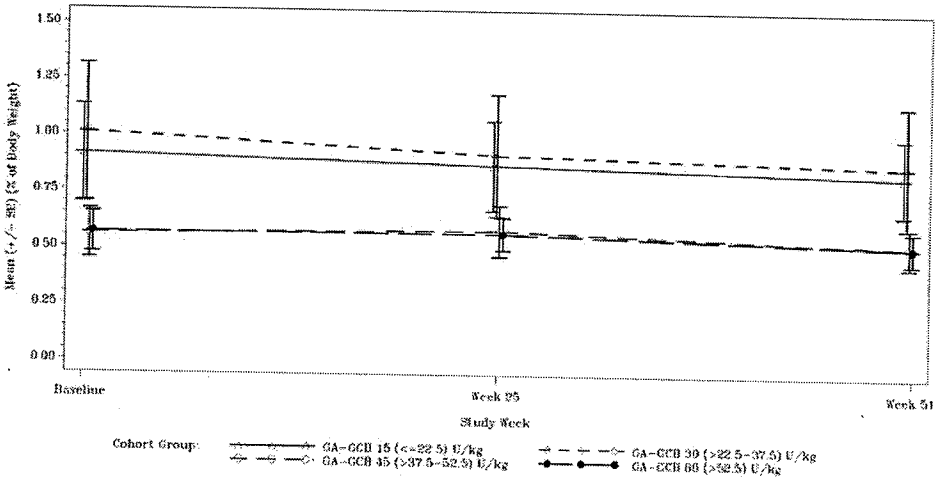


Figure 4: Mean Normalized Spleen Volume (% of Body Weight) ±SE by Visit per Dose Cohort in Trial 034



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

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/s/

II-LUN CHEN
02/23/2010

JOHN E HYDE
02/23/2010

CLINICAL REVIEW

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of VPRIV for the treatment of type 1 Gaucher disease. The recommended dosage is 60 U/kg every other week as a 60-minute intravenous infusion. Dosage adjustments can be made on an individual basis based on achievement and maintenance of therapeutic goals. Clinical studies have evaluated doses ranging from 15 U/kg to 60 U/kg.

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 approximately 100 pediatric and adult patients with type 1 Gaucher disease, which is an orphan indication.

1.2 Risk Benefit Assessment

Overall, VPRIV is well-tolerated, and the benefits from treatment appear appropriate in comparison to the risk of treatment.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Routine surveillance for adverse events is recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

Clinical:
No PMR or PMCs recommended.

Clinical Pharmacology:
Dr. Fang, the Clinical Pharmacology reviewer, recommends that the Applicant should either reanalyze archived PK samples for 032 using adequate in-process quality controls and standard curves or conduct a new PK study as a PMC study. Briefly, only duplicates (rather than the standard ≥ 3 replicates) of the quality control samples were included in patient PK sample runs. The intra-assay accuracy and precision could not be adequately determined. The PK parameters characterized by the Applicant and reviewed may not be accurate for labeling. Considering the supply shortage of marketed imiglucerase (see Section 2.3) and the apparent clinical efficacy and safety of velaglucerase, the definitive PK parameter characterization is being deferred.

Chemistry, Manufacturing, and Controls:
Dr. Lacana, the CMC reviewer, made draft recommendations for the Applicant to develop improved:

1. Potency assays
2. Drug substance/product release and stability protocols.

Dr. Mill, the Immunogenicity Reviewer, made draft recommendations for the Applicant to develop:

1. A cutpoint for the anti-velaglucerase and anti-imiglucerase antibody screening assay that yields a false positive rate in the range of 5 % of pre-immune patient serum samples, and to revise the cutpoint for the confirmatory anti-velaglucerase and anti-imiglucerase screening assays so that they are consistent with a revised cutpoint in the antibody screening assay.
2. An assay for detection of anti-velaglucerase and anti-imiglucerase IgE that has a sensitivity commensurate with the expected range of IgE responses.
3. An assay that will measure the ability of patient antibodies to block the uptake of velaglucerase and imiglucerase into target cells.

2 Introduction and Regulatory Background

Gaucher Disease
Gaucher disease is a potentially serious and life-threatening disease. Approximately 1 in 40,000 people in the general population are thought to be affected.[1] This pan-ethnic disease occurs when an inherited deficiency of the lysosomal enzyme glucocerebrosidase (GCB) causes an accumulation of glucocerebroside within macrophages. This leads to cellular engorgement and multi-organ system dysfunction with clinical features reflective of the distribution of abnormal macrophages (Gaucher cells) in the liver, spleen, bone marrow, skeleton, and lungs. Glucocerebroside in the liver and spleen leads to organomegaly. Bone involvement results in skeletal abnormalities and deformities as well as bone pain crises. Deposits in the bone marrow by Gaucher cells and splenic sequestration lead to clinically significant anemia and thrombocytopenia respectively. In a minority of patients, central nervous system (CNS) involvement leads to progressive neurological decline.

The disease has been classified into three clinical subtypes, based on the presence or absence of neurological symptoms and severity of neurological disease. Type 1 Gaucher disease accounting for more than 90% of all cases does not involve the CNS. Type 1 Gaucher disease affects approximately 30,000 patients around the world, and is the most common glycoshingolipid storage disorder. 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. Patients with Type 2 Gaucher disease present with acute neurological deterioration, and those with Type 3 disease typically display a more subacute neurological course. Most research effort to date has focused on strategies for augmenting enzyme levels to compensate for the underlying defect; these strategies include bone marrow transplantation (BMT), gene therapy, inhibition of glucosylceramide synthase, and enzyme replacement therapy (ERT).

Natural History of Type 1 Gaucher Disease
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 spleen status. In an analysis of 1028 patients with type 1 Gaucher disease in the International Gaucher Disease Registry, 637/677 (94%) patients "with 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 ($P<0.01$). Systematic follow-up of a number of patients over age 15 years shows that Gaucher disease-

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

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 lesions usually occur later than visceral disease. In adults, rapid progression of previously quiescent disease is unusual.

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 spleen status. Low platelet count may result from hypersplenism, splenic pooling of platelets, or marrow infiltration or infarction. Thrombocytopenia may be associated with easy bruising or overt bleeding, particularly with trauma, surgery, or pregnancy. Anemia may result from hypersplenism, hemodilution (e.g., pregnant status), iron deficiency or B12 deficiency and, in advanced disease, decreased erythropoiesis as a result of bone marrow failure from Gaucher cell infiltration or medullary infarction. As a result, hemoglobin concentrations and platelet counts are routinely followed in patients to determine disease burden.

Thrombocytopenia is the most common peripheral blood abnormality. 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.

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 gammaglumyl 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, it is commonly the presenting sign. The bulk of the spleen may interfere with normal food intake and may cause dyspareunia in women. As in other diseases in which splenomegaly occur, splenic infarctions frequently result. In an analysis of 400 patients in the International Collaborative Gaucher Group Registry (ICGG), 116 patients with data available prior to ERT had a mean enlargement of the spleen 19-fold normal. Liver and spleen size 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.

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 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. Furthermore, since ERT has not been shown to pass the blood brain barrier, it has limited ability to improve neurological etiology.

2.1 Product Information

Velaglucerase alfa is a new molecular entity. It is a glucocerebrosidase (GCB) produced by insertion of regulatory and structural DNA sequences into the human GCB locus (i.e., gene activation) in a human continuous cell line. Velaglucerase is a monomeric glycoprotein (63kDa) containing 497 amino acids and has an identical amino acid sequence to naturally occurring GCB; however velaglucerase has undergone post-manufacturing processing (high mannose type N-linked glycans) so that velaglucerase can be effectively taken up into phagocytic cells.

The proposed indication for velaglucerase is for long-term ERT for patients with type 1 Gaucher disease ages two years and older. It is administered intravenously with a proposed dosing of 60 U/kg every other week.

2.2 Tables of Currently Available Treatments for Proposed Indications

Drug	Formulation	Indication	Dosage
Cerezyme (imiglucerase)	IV formulation of recombinant DNA using CHO cell culture.	Long-term ERT for pediatric and adult patients with type 1 Gaucher with anemia, thrombocytopenia, bone disease, or heptomegaly or splenomegaly	2.5 U/kg three times per week to 60 U/kg every two weeks
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
ERT has been commercially available for the treatment of Type 1 Gaucher disease since 1991; Ceredase (alglucerase), placentally-derived GCB, was the first enzyme to receive approval for the treatment of Gaucher disease. Cerezyme (imiglucerase), a recombinant product, received approval from the Agency for the treatment of Gaucher disease in 1994. Cerezyme production has replaced Ceredase, which was extremely costly to produce because it is derived from human placenta. Velaglucerase differs from Cerezyme by one amino acid, and has an identical amino acid sequence to Ceredase. Warning information for Cerezyme include 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.

Zavesca
Zavesca is an inhibitor of the enzyme glucosylceramide synthase, which is a glucosyl transferase enzyme responsible for the first step in the synthesis of most glycosphingolipids. An important warning 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 include: tremor, weight loss, diarrhea, and problems with 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

The only currently marketed ERT for Type 1 Gaucher disease is Cerezyme (imiglucerase). US production of Cerezyme has been temporarily suspended as of June 2009 due to CMC issues at Genzyme's Allston Landing facility, where Cerezyme is manufactured. As a result, an immediate drug shortage has occurred, and adult patients may be asked to interrupt their usual therapy by missing infusions, or receiving treatment at a lower dose. Availability of velaglucerase through a treatment protocol was approved on July 30, 2009, and is intended to allow access to treatment for Gaucher patients without the need to skip doses or receive lower doses.

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) 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.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Nov 18, 2003: Pre-IND meeting held to discuss design of Phase 1/2 Trial 025.
Dec 31, 2003: The initial IND for Velaglucerase alfa (IND 61,220) was submitted.
Jan 11, 2006: An End-of-Phase 2 meeting was held between Shire and DGP for discussion on the future direction of the drug development program.
Nov 20, 2006: The IND was placed on Clinical Hold, primarily due to CMC issues. Shire was required to demonstrate the comparability of drug substance by two manufacturing processes.
Nov 30, 2006: Shire submitted a Complete Response to the Clinical Hold. Review of this Complete Response led to lifting of the Full Clinical Hold.
Dec 7, 2006: The IND was placed on Partial Hold on Dec 7, 2006, until outstanding deficiencies were resolved which included further characterization and comparison of the drug substances manufactured by different processes.
Dec 21, 2006: The Partial Hold was removed.
June 8, 2009: Orphan Drug Designation granted for "treatment of Gaucher disease" based on a hypothesis of superiority to imiglucerase due to faster clinical response and lower antibody formation.
July 15, 2009: Fast Track Designation granted for "investigation of velaglucerase for treatment of type 1 Gaucher disease".
July 30, 2009: Treatment protocol allowed to proceed.
Aug 10, 2009: Pre-NDA meeting to discuss contents of NDA submission (see Meeting Minutes archived in DARRTS Sept 19, 2009). In brief, agreement was made that the NDA would consist of a full study reports for Trials 025 and 032, and abbreviated study reports with protocols for 034 and 039. A literature review on ERTs used for treatment of type 1 Gaucher disease and evaluation of the natural history of Gaucher disease was also to be included. The three-month safety update would include information from the ongoing extension trials 025Ext and 044.
Aug 11, 2009: Type C meeting held to discuss plans for a new manufacturing facility.
Dec 16, 2009: VPRIV trade name granted by OSE.

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 organized and complete, given the agreements made during the Pre-NDA meeting.

3.2 Compliance with Good Clinical Practices

According to the Applicant, these trials were conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. They were also conducted in accordance with local country regulations and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) E6 guidelines.

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 Sociedad Espanola de Socorros Mutuos, Paraguay. The Israeli site participated in all of the trials included in the submission (31 patients total), and the Paraguayan site participated in Trials 032 and 039 (16 patients total). The preliminary analysis of DSI reports that although there were some deviations in compliance with Good Clinical Practices, the data appear to be reliable to support the application.

In addition, to the routine audit request of the two clinical sites, Shire was inspected as velaglucerase is a new molecular entity and Shire had not been previously inspected. The CRO, , was also inspected when it was discovered that was solely responsible for MRI interpretations, generating the secondary efficacy endpoint data (changes in liver and spleen volumes) for all phase 3 studies submitted. During the audits of the clinical investigators, it was discovered that the source records and media (MRI images) were not retained at the sites, but instead forwarded to this CRO for interpretation and archiving. The reliability of the secondary efficacy endpoint data for liver and spleen volumes for the phase 3 studies could only be verified by audit of this CRO. Preliminary discussions with DSI are that the inspections of Shire and found that records and procedures were complete and well organized. Reporting of AEs/SAEs appeared adequate, and a review of monitoring reports found no major issues. b(4)

3.3 Financial Disclosures

Shire has disclosed financial arrangements with clinical investigators for trials As there were several investigators who were paid significant consultant fees (approximately $570,000 from over $1 million b(6)

. Efforts were made to ensure unbiased results by taking particular b(6)
steps:

- Treatment assignment blinded to investigators and staff, patients and families, all Shire and CRO staff directly involved with the blinded conduct of the study.
- MRI, wrist radiographs, PK, GA-GCB antibodies, liver and spleen sizes were collected and sent to a CRO who conducted a blinded analysis of the data. These results have not been disclosed to the investigators.
- Protocol adherence through monitoring by blinded and unblinded monitors.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

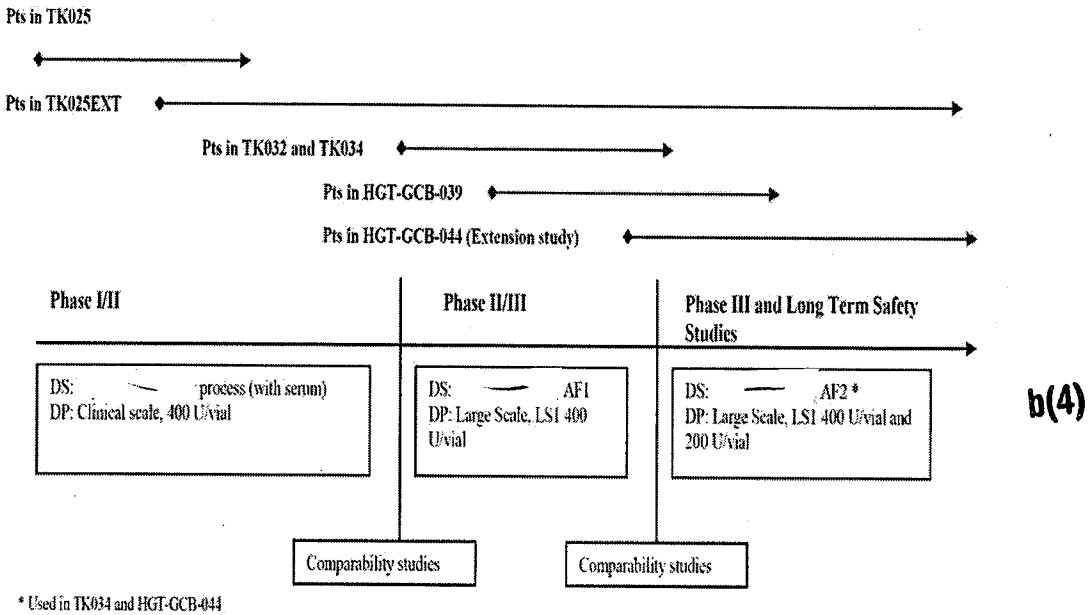
Preliminary review by Dr. Emanuela Lacana reports that velaglucerase alfa is manufactured to specifically facilitate internalization of the enzyme by the phagocytic target cells via the mannose receptor. The manufacture of velaglucerase alfa drug substance consists of

b(4)

manufacturing consists of
lyophilization . The final formulation of the drug product is
2.5 mg/mL velaglucerase alfa in Na citrate, containing sucrose and
vol/vol polysorbate 20, at pH 6.0. b(4)

The following figure describes the various drug lots used during the clinical development of velaglucerase.

Figure 1: Development of Velaglucerase Alpha (from Shire)



b(4)

According to the preliminary review by Dr. Lacana, patients in 025 have been treated with a clinical study supply of velaglucerase, ——— which was found not to be comparable with AF1, ——— process, used in other trials (032 and 034). Preliminary data show that AF1 and AF2 (to-be-marketed) are chemically comparable. Thus, the results of trials using the —— supply are reviewed but can not directly be used to represent safety and efficacy of the AF2 drug product which has been used in 034 and 025Ext. b(4)

4.2 Clinical Microbiology

There do not appear to be any issues related to sterility assurance, endotoxin, and container closure for velaglucerase drug product from a microbiology standpoint according to the preliminary review by Dr. Denise Miller.

4.3 Preclinical Pharmacology/Toxicology

Dr. Tamal Chakraborti is the pharmacology reviewer for velaglucerase. His preliminary report confirms that velaglucerase has been evaluated in a comprehensive nonclinical program and determined to be safe for use in clinical studies. Specifically, nonclinical studies were conducted to determine pharmacodynamic profiles in a D409V/null mouse model of Gaucher disease, pharmacokinetic profiles in Sprague-Dawley (S-D) rats, beagle dogs, and rhesus monkeys, tissue biodistribution in rats, acute toxicity in rats. Additionally, three- and six-month toxicity studies in rats, as well as a six-month toxicokinetic study in rhesus monkeys, were performed. The route of administration for all studies was intravenous (IV), consistent with the mode of administration in the clinical trials.

In an acute rat toxicity study, the highest dose of 23 mg/kg was nonlethal and well tolerated. In a three-month repeat-dose toxicity study in rats, there were no toxicologically-significant findings related to dosing with velaglucerase up to the highest dose given: 17 mg/kg. Additionally, there were no velaglucerase-related adverse effects noted in rats or monkeys dosed every two weeks for six months. Velaglucerase given IV was well tolerated at the injection site in rats and monkeys. There were transient dosing reactions attributed to velaglucerase in the three- and six-month rat studies, but these were not considered adverse, were rat-specific, and related to release of histamine.

The NOAEL in the six-month rhesus monkey study and the three- and six-month rat studies was 17 mg/kg, the highest dose evaluated, which provides safety margins (on a mg/kg basis) of approximately 44-fold for the human dose of 15 U/kg (0.38 mg/kg) and 11-fold for the human dose of 60 U/kg (1.5 mg/kg).

Developmental and reproductive toxicology studies were conducted in S-D rats and NZW rabbits in parallel with the phase III clinical trials. No meaningful toxicological

findings on developmental or reproductive parameters were noted in these studies. The no observed effect level (NOEL)/no observed adverse effect level (NOAEL) values in each of these studies corresponded to the highest dose evaluated in both species tested (17 mg/kg/dose in rats and 20 mg/kg/dose in rabbits; 11- and 13- fold the highest tested human dose of 1.5 mg/kg/dose [60U/kg], respectively). Since velaglucerase was given as two doses per week (IV bolus) in the DART studies, but is intended as an every other week IV infusion in the clinic, the safety margin could be adjusted based on frequency.

A mouse model of Gaucher disease, D409V/null Mouse (9V/null), was developed. The 9V/null mice demonstrate features most similar to the human type 1 Gaucher disease with accumulation of Gaucher cells in the lung, liver, and spleen. There is appearance of storage cells early in the pathogenic process and lack of pathology in the brain. The data from the 9V/null mouse model showed a similar pharmacodynamic action of imiglucerase and velaglucerase where both enzymes restored normal lipid content in the liver and to a lesser extent in the spleen; neither enzyme affected the lipid content of the lung. Additionally, the numbers of storage cells in the liver were also reduced; no effect was observed in the spleen or lung.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The active ingredient of the drug product is velaglucerase alfa, which contains the same amino acid sequence of the naturally occurring human enzyme, glucocerebrosidase. Velaglucerase alfa is manufactured to specifically facilitate internalization of the enzyme by the phagocytic target cells via the mannose receptor. Velaglucerase supplements or replaces the deficient GCB enzymes in the lysosomes to reduce the amount of accumulated glucocerebroside substrate.

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.

Exploratory analysis from the pivotal Trial 032 show that velaglucerase treatment appears to decrease Gaucher cells in the body:
Plasma Chitotriosidase: Only two patients in the 60 U/kg group and seven patients in the 45 U/kg group were evaluated for changes in chitotriosidase, as the remainder of the 16 patients were deficient in chitotriosidase activity (i.e., had baseline values below 5700 nmol/mL/h, the upper limit of normal [ULN]) and were excluded from the analysis.

Median Baseline plasma chitotriosidase levels were 44,208 nmol/ml/h in the 60 U/kg group and 47,166 nmol/mL/h in the 45 U/kg group. Mean plasma chitotriosidase activity decreased over one year of treatment. Decreases from baseline in mean plasma chitotriosidase activity were evident in both treatment groups at Week 13, the first evaluation time point. Mean plasma chitotriosidase activity decreased from Baseline by 70% (-27,413 nmol/mL/h; p=0.1324) in the 60 U/kg group and by 61% (-24,499 nmol/mL/h; p=0.0038) in the 45 U/kg group following one year of treatment.

CCL18: All randomized patients had CCL18 levels evaluated. Mean CCL18 levels decreased over one year of treatment. Decreases from baseline were evident in both treatment groups at Week 13, the first evaluation time point. By Week 53, the mean decrease from baseline in CCL18 was significant at the 0.05 level in both treatment groups although there was no adjustment for multiple testing: 66% (-1380 ng/mL, p=0.0001) in the 60 U/kg group and 47% (-1215.4 ng/mL, p=0.0005) in the 45 U/kg group.

4.4.3 Pharmacokinetics

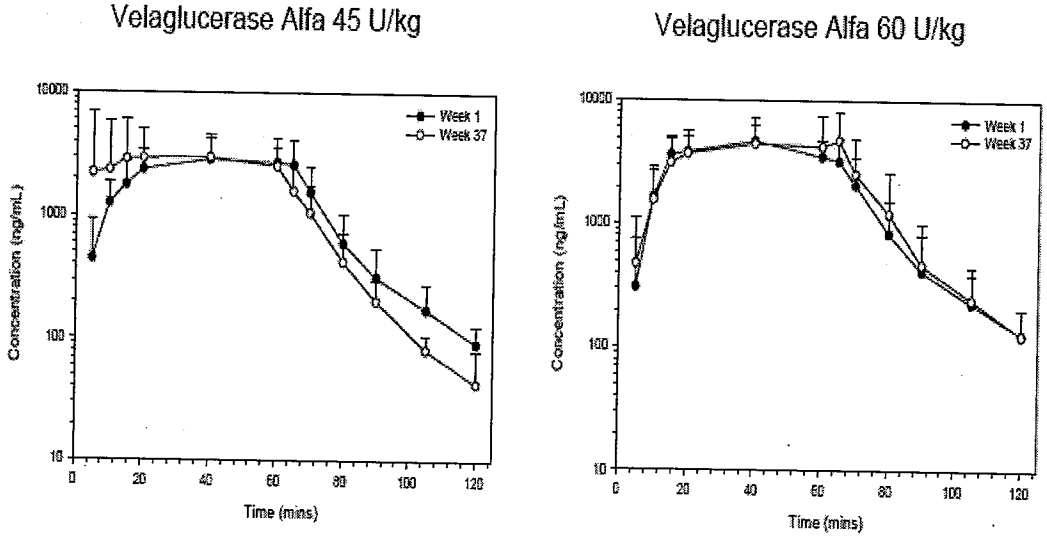
Table 1 describes the three clinical trials that contained PK components. Note that Trial 025 used a drug supply that is not chemically equivalent to the to-be-marketed AF2 supply. The clinical pharmacology review focused on data from 032.

Table 1: Clinical Trials with PK Components

Trial	Treatment	Number of Patients
025	15 U/kg	3
	60 U/kg	9
025 EXT	60 U/kg	10
032	45 U/kg	13
	60 U/kg	12

In Trial 032, pediatric (≥ 2 years old) and adult patients with type 1 Gaucher disease (actual age range: 4 to 62 years old), were randomized to receive either 45 or 60 U/kg velaglucerase administered as one-hour infusions EOW for 51 weeks. Serum samples were analyzed for both velaglucerase protein content by ELISA assay (ng/mL) and velaglucerase activity by colorimetric assay (mU/mL) at Week 1 and Week 37. The pharmacokinetic analysis was based on the velaglucerase protein content data. At all dose levels, serum concentrations rose rapidly for the first 20 minutes of the one-hour infusion before leveling off, and Cmax typically was attained between 40 to 60 minutes after the start of the infusion. After the end of the infusion, serum concentrations fell rapidly in a monophasic or biphasic fashion with a mean $t_{1/2}$ ranging from 7 to 12 minutes for the 30, 45, and 60 U/kg doses in these studies.

Figure 2: Mean (± SD) Serum Concentrations of Velaglucerase After Single IV Infusion (45 or 60 U/kg) at Week 1 and Multiple IV infusions at Week 37 (032 from Shire)



In Trial 025, velaglucerase Cmax and AUC increased approximately linearly proportional to dose in the two patients with PK evaluation at 15, 30, and 60 U/kg, compared to study TKT032 in which the Cmax and AUC increased slightly more than proportional to dose between the 45 U/kg and 60 U/kg groups. Overall, velaglucerase exhibited approximately linear dose proportionality over a dose range of 15 to 60 U/kg.

Table 2: PK Parameters post 1-hour Infusion of Velaglucerase in 032 (from Shire)

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

In Trial 032, the mean CL and Vss were similar for 45 and 60 U/kg between Week 1 and Week 37 (mean CL ranged from 6.7 to 7.6 mL/min/kg, and mean Vss ranged from 8% to 11%). For those who started with 60 U/kg in 025, the mean serum CL changed from 12.6 mL/min/kg at Week 1 to 5.6 mL/min/kg at Week 37/39 and to 6.5 mL/min/kg at Week 65 in the open-label extension study. Similarly, mean Vss changed from 18% at Week 1 to 5% at Week 37/39 and to 8% at Week 65. Additionally, the mean disposition $t_{1/2}$ ranged from 6.8 to 9.8 minutes for Trials 025 and 025EXT compared to 11.4 to 12.4 minutes in 032.

The rapid clearance of velaglucerase from serum (mean 6.7 to 7.6 mL/min/kg in 032) is consistent with the uptake of velaglucerase into macrophages via mannose receptors. The PK results from 032 (Week 1 and Week 37) are consistent with the Week 37/39 PK results from study 025, but the Week 1 CL and Vss values are lower in 032 than the Week 1 values in 025. In Trial 032, there was no apparent trend for velaglucerase AUC or CL to change with increasing age in the 45 U/kg dose group (age range 6 to 62 years old). However, in the 60 U/kg group (age range 4 to 42 years old), there was an apparent trend for lower AUC values and higher CL values in patients below 10 years of age compared to the adults. However, if the two dose groups are combined, the range of CL values in the children is completely contained within the range of values in the adults.

Shire concludes that systemic clearance represents the distribution of velaglucerase from the intravascular circulation into the intracellular target location, a desired and necessary step for the enzyme to exert its clinical benefit. It is unlikely that a difference in systemic clearance between children and adults would significantly alter the overall tissue biodistribution of the administered velaglucerase, and, therefore, pediatric and adult patients should receive the same weight-normalized dose of velaglucerase (e.g., 60 U/kg administered EOW). Preliminary review by the Clinical Pharmacology Reviewer, Dr. Lucy Fang, showed that there was no apparent trend for AUC or CL to change with increasing age. Therefore, the same body weight-normalized dose of velaglucerase is recommended for dosing in pediatric and adult patients, and that there are no apparent differences in PK parameters between male and females patients.

Dr. Fang's review states that the in-process velaglucerase alfa assay performance was insufficient, since duplicates (rather than triplicates or more replicates as is standard) of quantity control (QC) samples were included in patient PK sample runs. As such, the PK parameters characterized by the Applicant and reviewed by the Clinical Pharmacology team may not be accurate and reliable for labeling purposes. However, considering the supply shortage of the currently marketed imiglucerase and the demonstrated clinical efficacy and safety of velaglucerase alfa, a post-marketing commitment (PMC) will recommended to fill this gap in data.

Immunogenicity/Anti-Velaglucerase Alfa Antibodies
Prior to enrolling in 025 or 032, patients were confirmed to be negative for anti-imiglucerase antibodies.

For Trial 025, a baseline serum sample was collected from all patients and additional samples were collected at Weeks 13, 25, 37, and 41. In 025EXT, samples are being collected at Weeks 1, 13, 25, 37, 49/51, 65/67, 77, 89, 101/103, 117, 129, 141, 153/155, 169, 181, 193, 205/207, 219, 233, 245, 257/259, 271, 285, 297, 309/311, 323, 337, 349, and 365. For both studies, serum samples were available and analyzed up through Month 51 (Week 205) of cumulative treatment across studies 025 and 025EXT. No patients in these studies have developed antibodies to velaglucerase alfa to date.

For study 032, serum samples were collected from all patients for evaluation of anti-velaglucerase antibodies at Week 7, 13, 19, 25, 31, 37, 43, 49, and 53. There was one positive antibody response. This patient was positive for anti-velaglucerase IgG type antibodies at Week 53 (end of study), but was negative for IgE antibodies at this time. The neutralizing antibody assay result was reported as 42% inhibition. No one was positive for anti-velaglucerase antibodies on the days of pharmacokinetic evaluation. Therefore, it is not possible to correlate the antibody response with the observed velaglucerase pharmacokinetic parameters.

Preliminary review by Dr. Fred Mills, the Immunogenicity Reviewer, shows that the cut-points for anti-velaglucerase and anti-imiglucerase screening assays create a 99.9%

expectation that values above the cut-point are positive. Conversely, there would be very small expectations that values below the cut-point are actually positive. In other words, there are likely to be no false positives, the assay is very specific but not sensitive. The Division of Therapeutic Proteins recommends that a revised approach be used that allows for approximately 5% false positives in screening assays. There is insufficient data at this time to fully evaluate if velaglucerase is less immunogenic than imiglucerase or if the assay is too stringent to detect all possible patients with positive anti-body titres.

5 Sources of Clinical Data

Submitted for review are the following: full clinical study reports for Trials 025 (first-in-human) and 032 (pivotal, dose-ranging), an abbreviated safety summary with key efficacy results for Trial 034 (switch), and a top-line efficacy report for 039 (head-to-head). Trials 034 and 039 have recently been completed and analyses are ongoing.

Two follow-on clinical trials are ongoing. Trial 025EXT is a Phase 2/3, open-label extension trial, evaluating the long term safety and efficacy of velaglucerase in patients who completed Trial 025. Trial 044 is a Phase 3, open-label extension trial, evaluating the long term safety and efficacy of velaglucerase (15 to 60 U/kg) in patients who completed 032, 034, or 039.

The clinical program has investigated the safety and efficacy velaglucerase via evaluation of:

- Two different treatment doses (032)
- Switch to velaglucerase in patients previously treated with imiglucerase (034)
- A head-to-head comparison of velaglucerase and imiglucerase in treatment-naïve patients (039)

5.1 Tables of Studies/Clinical Trials

Study	Phase	N	Design	Dosed (U/Kg) every other week	Duration
025*^	1/2	12 Adults only	OL, Dose escalation, Safety and PK	15, 30, or 60	9 months
032*	3	25	R, DB, Dose ranging, Safety, Efficacy, and PK	45 or 60	12 months
034	2/3	41	OL, Safety, and Efficacy (on Cerezyme prior)	15 to 60	12 months
039*	3	35	R, DB, parallel, Safety, and Efficacy	60 velaglucerase or imiglucerase	9 months

*Treatment naïve patients studied in these trials
^Patients treated with the —— drug supply (not comparable to the to-be-marketed AF2 supply) b(4)

Extension Studies	N planned	Design	Dose (U/Kg EOW)
025 ext*	11	OL from 025, PK	30, 45, or 60
044^	101	OL from 032, 034 and 039	15 to 60

*Median duration of exposure is 4.6 years (cumulative)
^Median duration of exposure is 1.4 years (cumulative)

5.2 Review Strategy

The development program for velaglucerase was reviewed, subject to certain limitations, as best possible. As the patient population is small, each trial has a distinct and specific purpose and efficacy results are difficult to integrate between trials. However, safety was pooled when possible to evaluate for safety signals. Full clinical study reports were available for only 025 and 032. An abbreviated safety summary with key efficacy results for 034 and an abbreviated efficacy result report for 039 were submitted. Trials 034 and 039 have recently been completed and analyses are ongoing; full clinical study reports for these studies will be submitted when analyses are complete. Safety evaluation included available information from 025, 032, 034, 039, and the extension trials 025Ext and 044.

One further restriction in reviewing the data is that patients in 025 have been treated with a clinical study supply which was found not to be comparable with the drug supply used in other trials (see Section 4.1). Thus, the results of 025 are reviewed but can not directly be used to understand safety and efficacy of the to-be-marketed drug product.

In Section 5.3, I describe and review in detail the individual protocol and data for the trials submitted for this NDA. Whereas in Sections 6 and 7, I pool together the information from the various trials to develop a "big picture" understanding of the safety and efficacy of velaglucerase treatment in type 1 Gaucher patients.

For a pharmacovigilance evaluation, an AERS Database search for post marketing safety reports on Cerezyme and other enzyme replacement therapies was conducted. The large majority of Cerezyme AERS reports appear to be related to the underlying disease.

5.3 Discussion of Individual Studies/Clinical Trials

Trial 032 - Single Pivotal Phase 3 Trial

5.3.1 General Design and Objective

This was a multicenter, randomized, double-blinded trial designed to evaluate the PK, efficacy, and safety of velaglucerase every other week (EOW) over 12 months in 24 treatment naïve patients with type 1 Gaucher disease.

A parallel group approach (45 U/kg and 60 U/kg) was selected to maximize patient exposure to velaglucerase, as the global patient population is relatively small and there is currently an approved ERT for Gaucher disease in some countries, including but not limited to the United States and European Union. Patients were to have been treatment naïve or were to have not been treated for Gaucher disease within 30 months prior to study entry. Efficacy was primarily assessed via hemoglobin concentration, platelet count, and liver and spleen volume by MRI. This trial was conducted in five countries: Israel, Tunisia, Paraguay, Argentina, and Russia. The trial period was from Feb 15, 2007, to April 1, 2009.

The protocol was amended on June 22, 2007. Major changes in Protocol Amendment 1 were:

- Removal of the Six Minute Walk test as a result of feedback from Investigators regarding the relevance of this test as an efficacy measure.
- Addition of a Week 25 MRI of the liver and spleen to make the schedule consistent with time points of the Phase 1/2 study.
- Addition of chitotriosidase genotyping during Screening, because it was considered relevant to know the patients' chitotriosidase gene mutation to evaluate the observed response.
- Folic acid and vitamin B12 assessments were added at Screening.
- CCL18 and Chitotriosidase evaluation frequency was reduced from every infusion to every 12 weeks based on the rate of change of these markers determined in the Phase 1/2 study.

5.3.2 Inclusion

1. Male or female two years of age or older with documented diagnosis of type 1 Gaucher disease, as determined by deficient GCB as measured in leukocytes or by genotype analysis.
2. Gaucher disease-related anemia, defined as: hemoglobin levels of at least 1 g/dL below the lower limit of normal for age and gender and

1 OR MORE OF THE FOLLOWING 3 CRITERIA

The patient had at least moderate splenomegaly (2 to 3 cm below the left costal margin) by palpation.

OR

The patient had Gaucher disease-related thrombocytopenia, defined as a platelet count <90 x 10^9 platelets/L.

OR

The patient had a Gaucher disease-related readily palpable enlarged liver.

3. Not received treatment for Gaucher disease (investigational products, miglustat, or imiglucerase) within 30 months prior to study entry.

5.3.3 Exclusion

1. Type 2 or 3 Gaucher disease.
2. Splenectomy.
3. Antibody-positive to imiglucerase during Screening or the patient had experienced an anaphylactic reaction to imiglucerase.
4. Treatment with any non-Gaucher disease-related investigational drug or device within the 30 days prior to study entry; such use during the study was not permitted.
5. Currently receiving red blood cell growth factor, (e.g., erythropoietin), chronic systemic corticosteroids, or had been on such treatment within the previous six months.
6. Positive for HIV, hepatitis B and/or C
7. Presented with exacerbated anemia at Screening (due to iron, folic acid, and/or vitamin B12 deficiency, or infectious/immune-mediated causes).
8. Significant comorbidity(ies) that might affect study data or confound the study results (e.g., malignancies, primary biliary cirrhosis, autoimmune liver disease).
9. Pregnant or lactating female and those not willing to use birth control.

5.3.4 Treatment

This trial was comprised of five phases as follows:

1. Screening: Day –21 through Day –4
2. Baseline: Day –3 through Day 0 (prior to first dose)
3. Treatment Phase: Week 1 (Day 1; first dose) through Week 51, with a total of 26 infusions planned per patient
4. End of Study Visit: Week 53
5. Follow-up: 30 days after the final infusion (for patients who discontinued or withdrew prior to the Week 53 evaluation, or for patients who completed this study but did not elect to enroll in the follow-on Trial 044)

Following Baseline evaluations, patients were randomized in a 1:1 ratio to receive either velaglucerase 45 U/kg or 60 U/kg via a computer-generated randomization schedule. A

minimization or covariate-adaptive randomization algorithm was used to balance across a number of prognostic factors such as age and gender. Patients received up to a total of 26 IV infusions of double-blind study medication at the clinical site once EOW for a total of 51 weeks. Safety and efficacy assessments were made at regular intervals during the treatment period. The final assessments of safety and efficacy were to be made at the Week 51 and Week 53 visits.

Concomitant Medications
Patients were allowed supportive Gaucher treatment (e.g., treatments for bone disease or hematologic symptoms such as iron and vitamin supplements).

Prohibited Medications
Patients were not to have received treatment with red blood cell growth factor, chronic systemic steroids, or investigational drugs during the trial or within 30 days after the last infusion.

5.3.5 Safety Considerations/Monitoring

Safety was assessed by adverse events (AEs), concomitant medication use, and vital signs. Table 3 details the schedule of assessments in Trial 032. Additional safety assessments included: ECGs, physical examinations, and clinical laboratory tests (hematology, serum chemistry, and urinalysis).

Presence of anti-velaglucerase alfa antibodies and enzyme neutralizing antibodies was assessed approximately every six weeks. Safety results were reviewed by an internal Safety Review Team, consisting of the Medical Monitor and members of Shire's Biostatistics and Pharmacovigilance departments. Stopping rules were created to ensure patient safety. If any patient experienced a life-threatening (Grade 4) SAE or a death occurred that was considered possibly or probably related to the study drug, the study would be stopped and the safety data reviewed.

Hemoglobin concentration and platelet counts were assessed at every infusion; assessments by the central laboratory were used for efficacy analyses. Quantitative abdominal MRI of the liver and spleen was performed at the trial sites for the determination of changes in liver and spleen volumes at Baseline, Week 25 (after Amendment 1 only), and Week 51. Images were collected and sent to a single independent reviewer who remained blinded to the study medication and the order in which the images were taken.

Other efficacy assessments included plasma concentrations of chitotriosidase and CCL18. Patients' QoL was evaluated at Baseline and at Week 53 using validated questionnaires. The CHQ-PF50 was completed by the patient's caregiver for patients 5 to 17 years old, while for patients ≥18 years old, the Short Form 36 (SF-36) was completed by the patient. Both questionnaires assess quality of life using multi-item

scales. The CHQ-PF50 yields a 14-health concept/domain profile as well as two summary component scores. The SF-36 standardized scoring system yields a profile of eight health concepts (domains).

Additional efficacy measures for patients 2 to 17 years old include growth velocity, skeletal growth, and Tanner stages of puberty. At each visit, height measurements were collected three times for each patient using a calibrated stadiometer. Growth velocity was calculated using these height and weight measurements. Patients had radiography of the left hand and wrist at Baseline and Week 51 for evaluation of skeletal age. Images were collected and independent interpretation was performed — b(4)

Safety Measurements
Safety was evaluated through the assessment of AEs, vital signs (every infusion week), physical examination, and electrocardiogram (Weeks 13, 25, 37, and 53). Clinical safety laboratory analyses included serum chemistry with iron monitoring, urinalysis, hematology and coagulation, and the presence of anti-velaglucerase alfa antibodies or anti-imiglucerase antibodies.

For patients enrolled under Amendment 1, AEs were monitored from informed consent/assent while for patients enrolled under the original protocol AEs were monitored from the first infusion. AEs were monitored through 30 days after the last infusion. For patients who completed this trial (032) and elected to enroll in the long-term clinical trial (044), AEs were monitored through the Week 53 visit.

The schedule from Baseline to Week 25 is below. There was an additional follow-up visit 30-days after the end of study, during which time concomitant medication and adverse event information was collected.

Table 3: Trial032 Study Schedule

Procedure	Screen Day -21 to Day -4	Baseline Day -3 to Day 0	Study Week												
			1	3,5	7	9,11	13	15, 17	19	21, 23	25	27-35*	37	39-51*	53
Med History, Gaucher and Chitotriosidase Genotype Analysis, anti-imiglucerase Ab, HIV and Hep B/C testing	X														
Concomitant Meds, AEs, Vitals, CBC Pregnancy test	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X					X				X		X		
Height, Weight, ECG		X					X				X		X		
UA, Chemistries, Hematology	X	X					X				X		X		
Serum anti-velaglucerase		X			X		X		X		X		X		
Iron testing	X	X					X				X		X		
Plasma chitotriosidase, CCL18		X					X				X		X		
PK testing			X										X		
Liver/Spleen MRI		X									X			X^	
Additional Procedures for Adult Patients															
DXA Spine and Femoral neck, Serum NTx and CTx, PFT, QoL		X												X#	
Additional Procedures for Pediatric Patients															
MRI of femoral neck and spine, wrist x-ray, QoL		X												X+	
Growth velocity Tanner staging		X					X				X				X

* Visits occurred every 2 weeks ^Week 51 only #PFT and QoL only +x-ray and QoL only

5.3.6 Endpoints

Primary Efficacy Endpoint

- The primary objective of this study was to determine the efficacy of EOW dosing of velaglucerase at a dose of 60 U/kg. The primary efficacy endpoint was measured by increases in hemoglobin concentration from baseline to Week 53.

Secondary Efficacy Endpoints

- Safety of EOW doses of 45 and 60 U/kg
- Efficacy of EOW 45 U/kg by increases in hemoglobin concentration
- Efficacy of EOW 60 and 45 U/kg by assessing increases in platelet counts, decreases in spleen and liver volumes, and decreases in levels of plasma chitotriosidase and Chemokine ligand 18 (CCL18)
- Effect of EOW 60 and 45 U/kg on overall quality of life (QoL), as measured by the Short Form-36 (SF-36) for patients ≥18 years old and the Childhood Health Questionnaire (CHQ, PF50) for patients 5 to 17 years old
- Single- and repeat-dose pharmacokinetics of EOW 45 and 60 U/kg

Other Endpoints

- Determine the time from Baseline to achieve a hemoglobin response, defined as an increase in hemoglobin concentration of ≥1g/dL
- Pulmonary function tests (PFTs) in patients ≥18 years old
- Growth velocity and Tanner staging in patients between 2 and 17 years old
- Changes in skeletal age in patients between 2 and 17 years old by radiography of the left hand and wrist
- Establish a Baseline from which to evaluate bone disease in patients between 2 and 17 years old by MRI of the lumbar spine and femoral neck
- Establish a Baseline from which to evaluate the long-term effect of velaglucerase therapy on Gaucher-related local and systemic bone disease in patients ≥18 years old by:
  a) Dual energy x-ray absorption (DXA) of the lumbar spine and femoral neck
  b) Serum alkaline phosphatase, N-Telopeptide cross-links (NTx), and C-Telopeptide cross-links (CTx)

5.3.7 Data Analysis

Analysis Populations

The primary dataset for efficacy analyses was the intent-to-treat (ITT) patient population, defined as all randomized patients who received at least one study drug infusion (or partial infusion). In the ITT population, patients were analyzed according to randomized treatment. The primary efficacy analysis of the change in hemoglobin concentration for patients receiving 60 U/kg of velaglucerase (primary endpoint) was to be repeated in a per-protocol (PP) population but this analysis was only to be conducted

if the PP population was less than 90% of the ITT population in the 60 U/kg arm. The PP patient population was defined as all patients who received ≥80% of the scheduled infusions at 60 U/kg of velaglucerase (≥21 out of 26 infusions; not including partial infusions), qualified for enrollment, and who had non-missing hemoglobin assessments at Baseline and Week 53. Patients who did not meet the eligibility criteria but received an exemption (prior to the date of the first infusion) to participate were to be included in the PP patient population analysis dataset.

A supportive analysis of the primary and secondary endpoints (change from Baseline to Week 53 in hemoglobin concentration, platelet count, organ volumes, and plasma biomarkers) was performed within a modified intent-to-treat (MITT) patient population. The MITT patient population was defined as all of the patients in the ITT population who qualified for enrollment. Patients who did not meet the eligibility criteria but received an exemption (prior to the date of the 1st infusion) to participate were to be included in the MITT patient population.

Determination of Sample Size
The sample size for this study was chosen to have power to detect a clinically significant difference in mean change in hemoglobin concentrations from Baseline to 12 months (per protocol 1g/dL was determined to be clinically significant). A total of 10 patients per treatment arm were required for the primary analysis. This number is based upon the results from 025, examining the within patient change from Baseline results. It was observed that at Week 25, the mean hemoglobin increase from Baseline was 1.9 g/dL with a standard deviation of 0.8. The assumption was that the standard deviation of the mean change from Baseline to 12 months would be approximately the same. Using a two-sided alpha level of 0.05 and assuming a one-unit change from Baseline to 12 months in hemoglobin concentration is clinically significant and the standard deviation of the change from Baseline is 0.8, then 10 total patients was needed to have a power of 90%. Assuming a 20% drop out rate, a total of 12 patients per group (24 total) was needed.

Efficacy Parameters - Statistical method for efficacy endpoints
Formal statistical tests were not used for between treatment comparisons but were used for within group changes from Baseline at selected follow-up time points.

The effect of velaglucerase on mean change from Baseline within treatment was tested for the following efficacy parameters: hemoglobin concentration, platelet count, liver and spleen volume, plasma chitotriosidase, and CCL18. P-values were computed using the paired t-test. All hypothesis testing was two-sided and was performed at the 0.05 level of significance. The 95% confidence intervals around the means were computed to further support the results of the two-sided hypothesis tests. The standard error was also reported for any efficacy parameter for which inferential statistics were calculated.

Outliers were defined as any extreme observation. No outliers were to be excluded from the main analysis. Outliers were to be assessed carefully, as they might convey clinically meaningful information. In the case of putative outliers, a sensitivity analysis was to be performed that excluded outliers, to understand the impact that these outliers might have on estimates and statistical tests. A method that was to be employed to identify potential outliers was to examine whether the observed data fell outside the outer fences. The α preserving plan for secondary endpoints was use of stepwise Holm Procedure.

Additional Efficacy Analysis
Following review of the Phase 1/2 Trial 025 at the Scientific Advice Meeting in 2006, the European Medicines Evaluations Agency (EMEA) recommended an analysis of response categories, based on minimum clinically meaningful response, to be performed on changes in hemoglobin concentration, platelet count, liver volume, and spleen volume during this trial.

Analyses of response categories were performed for change in hemoglobin, platelet count, liver volume, and spleen volume at Weeks 13, 25, 37, and Week 53 (hemoglobin and platelet count) or Week 51 (organ volume). The EMEA suggested the following response criteria:

For hemoglobin	
No response	*Increase of ≤0.5 g/dL*
Moderate response	*Increase from Baseline >0.5 g/dL, but ≤1.5 g/dL*
Good response	*Increase from Baseline >1.5 g/dL*
For platelet count	
No response	*Increase from Baseline of ≤15 x 10^9/L*
Moderate response	*Increase of >15 x 10^9/L but ≤30 x 10^9/L*
Good response	*Increase from Baseline of >30 x 10^9/L*

Patients with normal platelet counts (≥150 x 10^9/L) at Baseline were to be excluded from the analysis of response categories. However, the same analysis was repeated within the ITT patient population, namely, to include the two remaining patients (1 on 60 U/kg; 1 on 45 U/kg) with normal platelet counts at Baseline; the results were similar and the conclusions unchanged.

For normalized liver and spleen volume:	
No response	*Reduction from Baseline of <10%*
Moderate response	*Reduction from Baseline of ≥10% but <30%*
Good response	*Reduction from Baseline of ≥30%*

Patients without a readily palpable enlarged liver at Baseline were excluded from the analysis of liver volume response categories (two patients on the 45 U/kg group and

one patient on the 60 U/kg group). Patients without moderate splenomegaly (2 to 3 cm below the left coastal margin) by palpation at Baseline were excluded from the analysis of spleen volume response categories (no patients on the 45 U/kg group and one patient on the 60 U/kg group). Patients who underwent a splenectomy during the study were to be excluded from the analysis of spleen volume.

Safety Parameters
All patients who received at least one dose of study drug (or partial dose) were assessed for clinical safety and tolerability. No formal statistical tests were performed on the safety parameters. Vital signs, ECG, clinical chemistry, hematology, and urinalysis safety monitoring were summarized. For categorical variables, such as AEs, the number and percentage of patients experiencing each AE were tabulated. AEs were summarized by severity of event. The number and percentage of patients experiencing drug-related AEs and infusion-related AEs, as well as AEs that were not considered related to study drug were also displayed. Clinical laboratory evaluations (hematology, serum chemistry, urinalysis, and determination of anti-velaglucerase alfa and anti-imiglucerase alfa antibodies including enzyme neutralizing antibodies) were used to assess the safety of velaglucerase alfa.

5.3.8 Number of Patients and Disposition

Of the 39 patients screened in this study, 14 patients (36%) were not eligible. The most common reason (11/14) for not being eligible for randomization was that a patient did not meet inclusion for Gaucher disease-related anemia and either moderate splenomegaly, platelet count $<90x10^9$/L, or palpable enlarged liver).

A total of 25 patients were randomized to one of the two treatment groups, including 13 to the 45 U/kg group and 12 to the 60 U/kg group. All 25 patients (100%) received study drug and completed the study. No patient was prematurely discontinued/withdrawn from this study for any reason.

Discontinuations
None.

Protocol Deviations and Compliance
Two patients (one patient in each group) had protocol deviations that met the definition of a protocol violation (deviation from the eligibility criteria for which no exemption was obtained) as follows:

- Patient 032-152-0010, randomized to the 60 U/kg group, did not meet the hemoglobin criterion of 1 g/dL below the LLN at Screening and Baseline.
- Patient 032-152-0008, randomized to the 45 U/kg group, did not meet the hemoglobin criterion of 1g/dL below the LLN at Screening and Baseline.

Table 4: Data Sets Analyzed for Trial032

Patient Population	45 U/kg N (%)	60 U/kg N (%)	Total N (%)
Patients randomized	13 (100)	12 (100)	25 (100)
ITT	13 (100)	12 (100)	25 (100)
MITT	12 (92)	11 (92)	23 (92)
Safety	13 (100)	12 (100)	25 (100)

ITT=Intent-to-treat: all randomized patients who received at least one study drug infusion (full or partial).
MITT=Modified Intent-to-Treat; a subset if the ITT patient population that only includes those patients who met the eligibility criteria.

There was a high degree of patient compliance with the treatment infusions. All patients received a median of 26 infusions. Only one patient in the 45 U/kg group, missed any infusions (2 infusions). All randomized patients had ≥80% of the 26 required infusions.

5.3.9 Demographics

Patients in this trial were mostly adults (72%), with an even distribution between males and females. The demographic characteristics of the MITT were similar to those of the ITT population, as only two patients (one in each group) were excluded from the MITT population.

Table 5: Demographics for Trial032

Baseline Characteristics		velaglucerase		
		45 U/Kg=13	60 U/Kg=12	Total=25
Age (years)	2-4	0	1 (8%)	1 (4%)
	5-17	3 (23%)	3 (25%)	6 (24%)
	≥18	10 (77%)	8 (67%)	18 (72%)
	Mean±SD Min-Max	31±17 6-62	21±12 4-42	26±15 4-62
Sex	Male	8 (62%)	7 (58%)	15 (60%)
	Female	5 (39%)	5 (42%)	10 (40%)
Race	Caucasian	13 (100%)	12 (100%)	25 (100%)
Ethnicity	Hispanic/Latino	6 (46%)	5 (42%)	11 (44%)
	Non- Hispanic	7 (54%)	7 (58%)	14 (56%)
Country	Argentina	1 (8%)	0	1 (4%)
	Israel	1 (8%)	6 (50%)	7 (28%)
	Paraguay	6 (46%)	5 (42%)	11 (44%)
	Russia	3 (23%)	0	3 (12%)
	Tunisia	2 (15%)	1 (8%)	3 (12%)
Height (cm)	Mean±SD Min-Max	161±18 116-194	150±28 106-175	156±23 106-194
Weight (Kg)	Mean±SD Min-Max	58±20 21-95	47±20 16-70	53±21 16-95

Table 6: Gaucher Disease Characteristics for Trial032

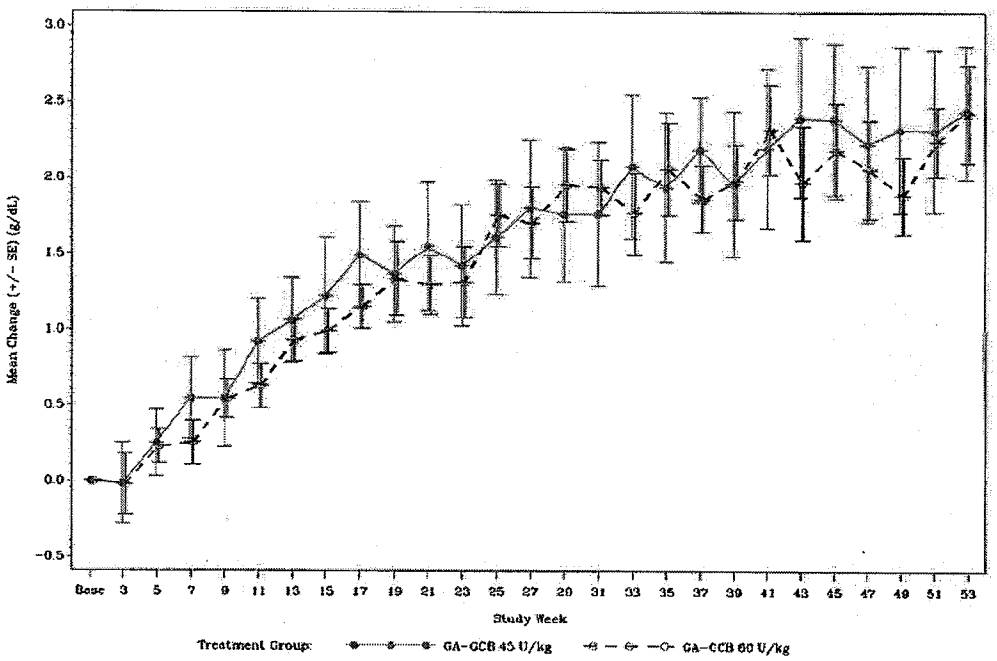
Baseline Characteristics		Velaglucerase		
		45U/Kg	60U/Kg	Total
Gaucher disease genotype	N370S/N370S	3 (23%)	4 (33%)	7 (28%)
	N370S/84GG	0	0	0
	N370S/L44P	1 (8%)	0	1 (4%)
	L444P/L44P	0	0	0
	N370S/Other	6 (46%)	3 (25%)	9 (36%)
	L444P/Other	2 (15%)	2 (17%)	4 (16%)
	Other/Other	1 (8%)	3 (25%)	4 (16%)
Chitotriosidase Gene 24bp	Duplication	5 (39%)	10 (83%)	15 (60%)
	No duplication	10 (62%)	2 (17%)	10 (40%)
Treatment for Gaucher	>30 months	0	1 (8%)	1 (4%)
	None previous	13 (100%)	11 (92%)	24 (96%)
Time to diagnosis (yrs)	Mean±SD	6.5±8	4.9±6.1	5.7±7
	Min-Max	0.1-27	0.1-19	0.1-27
Hemoglobin at Baseline (g/dL)	Mean±SD	10.6/1.4	10.7±1.4	10.6±1.3
	Min-Max	8.5-12.6	6.8-12.2	6.8-12.6
Platelets at Baseline ($x10^9$)	Mean±SD	84±60	113±112	97±87
	Min-Max	12-201	40-438	12-438

Concomitant Medications
The majority (88%) of randomized patients received at least one concomitant medication. The most common (>20% overall) therapeutic classes of concomitant medications in the study were anilides (60%), glucocorticoids (28%), mucolytics (28%), fluoroquinolones (24%), pyrazolones (24%), yellow fever vaccines (24%), ascorbic acid, plain (20%), propionic acid derivatives (20%), substituted alkylamines (20%), and vitamin B12 (20%), all administered for "other" indications. The most common concomitant medication administered overall in both treatment groups was acetaminophen (52% overall).

5.3.10 Efficacy Evaluation

Primary Efficacy
Hemoglobin levels increased from Baseline across 53 weeks of treatment with velaglucerase alfa 60 U/kg administered IV once every other week. The mean increase from Baseline to Week 53 in hemoglobin (2.4 g/dL±0.3 [SE, CI=1.7-3.1], 23%) in the 60 U/kg group was clinically meaningful (i.e., ≥1 g/dL) and statistically significant ($p<0.0001$). The greatest mean increase in this group was observed at Week 53, the last evaluation in this study. The baseline mean hemoglobin was 10.7 (Std. Err.=0.4) and the Week 53 hemoglobin was 13.1 (Std. Err.=0.5).

Figure 3: Velaglucerase 45 & 60 U/kg Mean Hemoglobin Change from Baseline (g/dL) ±SE inTrial032 – ITT Population (from Shire)



As recommended by the EMEA, the hemoglobin response by category is summarized in Table 7.

Table 7: Hemoglobin Response Category for Treatment Groups in 032 (from Shire)

	Week 13		Week 25		Week 37		Week 53	
	Velaglucerase alfa		Velaglucerase alfa		Velaglucerase alfa		Velaglucerase alfa	
Hemoglobin Concentration Endpoint	45 U/kg	60 U/kg	45 U/kg	60 U/kg	45 U/kg	60 U/kg	45 U/kg	60 U/kg
Response category[a] (n[%])								
Good response	3 (23.1)	1 (8.3)	7 (53.8)	7 (58.3)	10 (76.9)	7 (58.3)	8 (61.5)	10 (83.3)
Moderate response	6 (46.2)	9 (75.0)	3 (23.1)	5 (41.7)	3 (23.1)	5 (41.7)	5 (38.5)	2 (16.7)
No response	4 (30.8)	2 (16.7)	3 (23.1)	0	0	0	0	0

Note: Imputation was applied to missing data.

a A good response is defined as an increase from baseline of >1.5 g/dL; a moderate response is defined as an increase of >0.5 g/dL, but ≤1.5 g/dL; no response is defined as an increase from baseline of ≤0.5 g/dL.

Secondary, Tertiary and Other Efficacy Endpoints

1. Hemoglobin concentration change from baseline (45 U/kg group)

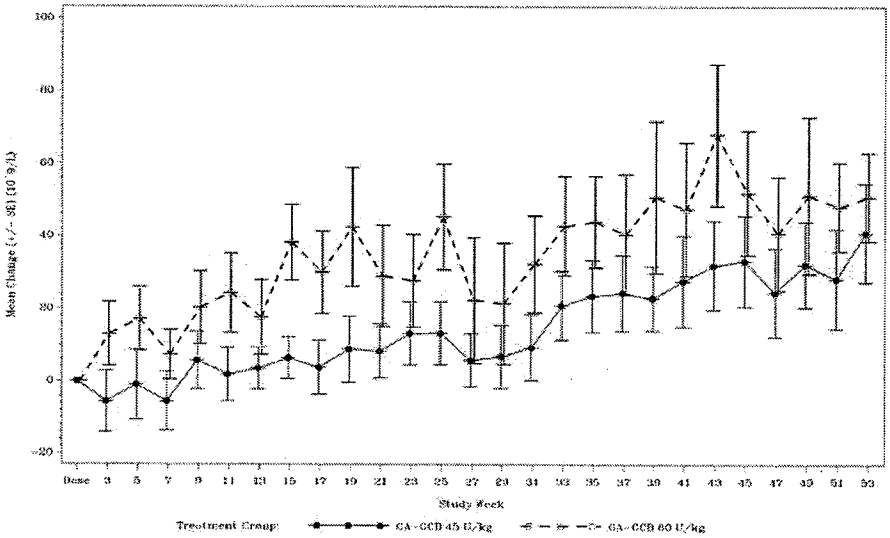
Hemoglobin levels increased from Baseline across 53 weeks of treatment. A similar improvement was seen as compared to the 60 U/kg group with a mean change of 2.4 g/dL±0.4 [SE, CI=1.5-3.4] (24%) with a p value=0.0001 as detailed in Figure 3.

2. Platelet counts

Mean and median platelet counts at Baseline were 108 x 10^9/L and 67 x 10^9/L in the 60 U/kg group and 84 x 10^9/L and 58 x 10^9/L in the 45 U/kg group. The mean and median

platelet counts at Week 53 were 159 x 10^9/L and 126 x 10^9/L in the 60 U/kg group and 125 x 10^9/L and 139 x 10^9/L in the 45 U/kg group The mean and median increases in platelet counts were higher in the 60 U/kg group than in the 45 U/kg group from Week 3 to 51; however, by Week 53, the mean percent changes from Baseline was similar in both treatment groups (approximately 66%).

Figure 4: Mean Platelet Count Change from Baseline ±SE in 032 (from Shire)



A dose-related effect in favor of 60 U/kg was observed by a platelet count response (moderate to good), defined as an increase of at least 15 x 10^9/L in patients with below normal platelet counts at Baseline (<150 x 10^9/L), of 82% by Week 53 versus 58% seen within the 45 U/kg group. There were 2 out of 11 (18%) patients receiving 60 U/kg who did not experience a platelet count response by Week 53, while 5 out of 12 (42%) patients in the 45 U/kg group did not experience a platelet count response by Week 53 as seen in Table 8.

Table 8: Platelet Response Category for All Treatment Groups in 032 (from Shire)

	Week 13		Week 25		Week 37		Week 53	
Platelet Count Endpoint	GA-GCB 45 U/kg	GA-GCB 60 U/kg	GA-GCB 45 U/kg	GA-GCB 60 U/kg	GA-GCB 45 U/kg	GA-GCB 60 U/kg	GA-GCB 45 U/kg	GA-GCB 60 U/kg
Response category[a] [n (%)]								
Good response	2 (15.4)	3 (25.0)	2 (15.4)	6 (50.0)	5 (38.5)	6 (50.0)	6 (46.2)	6 (50.0)
Moderate response	1 (7.7)	2 (16.7)	4 (30.8)	2 (16.7)	3 (23.1)	1 (8.3)	1 (7.7)	3 (25.0)
No response	10 (76.9)	7 (58.3)	7 (53.8)	4 (33.3)	5 (38.5)	5 (41.7)	6 (46.2)	3 (25.0)

a A good response is defined as an increase from baseline of > 30x10^9/L; a moderate response is defined as an increase of > 15x10^9/L, but <= 30x10^9/L; no response is defined as an increase from baseline of <= 15x10^9/L.

3. Change in liver volume

All analyses for changes in liver volume were presented for actual liver volume and for liver volume normalized by body weight to adjust for the variation in organ volumes between patients 2 to 17 years old and ≥18 years old. Only the volume normalized for body weight results are discussed.

At Baseline, median normalized liver volume was 3.7% and 3.5% of body weight in the 60 U/kg and 45 U/kg treatment groups, respectively. There were only two patients, one in each treatment group, with normal liver size, defined as 2.5% of body weight at Baseline (2.3% of body weight in the 45 U/kg group and 2.4% of body weight in the 60 U/kg group). Normalized liver volume decreased over one year of treatment. By Week 51, a mean reduction in normalized liver volume of 17% from baseline (-0.8% body weight, p=0.028) was seen in the 60 U/kg group. By Week 51, a mean reduction in normalized liver volume of 6% from Baseline (-0.3% body weight; p=0.3149) was seen in the 45 U/kg group.

Prior to protocol Amendment 1, abdominal MRIs of the liver and spleen were only collected at Baseline and Week 51. As a result, caution should be used when interpreting the Week 25 data, as one third of all patients had liver volume data imputed due to the low number of MRIs performed at this visit; no patients were missing the Week 51 MRIs.

Table 9: Liver Response Category for All Treatment Groups in 032 (from Shire)

Normalized Liver Volume Endpoint	Week 25		Week 51	
	GA-GCB 45 U/kg	GA-GCB 60 U/kg	GA-GCB 45 U/kg	GA-GCB 60 U/kg
Response category[a] [n (%)]				
Good response	2 (18.2)	2 (18.2)	1 (9.1)	1 (9.1)
Moderate response	3 (27.3)	4 (36.4)	6 (54.5)	8 (72.7)
No response	6 (54.5)	5 (45.5)	4 (36.4)	2 (18.2)

Note: Imputation was applied to missing data.
a A good response is defined as a reduction from baseline of >= 30%; a moderate response is defined as a reduction from baseline of >= 10%, but < 30%; no response is defined as a reduction from baseline of < 10%. Patients without a readily palpable enlarged liver at baseline are excluded.

4. Change in spleen volume

Analyses for changes in spleen volume are presented for actual and normalized by body weight to adjust for the variation in organ volumes between patients 2 to 17 years old and ≥18 years old. Prior to protocol Amendment 1, abdominal MRIs of the liver and spleen were only collected at Baseline and Week 51, thus caution should be used when interpreting the Week 25 data as one third of all patients had spleen volume data imputed due to the low number of MRIs performed at this visit; no patients were missing the Week 51 MRIs.

There were no patients with normal spleen size at Baseline, defined as 0.2% of body weight. At Baseline, median normalized spleen volume was 2.9% and 2.8% of body weight in the 45 U/kg and 60 U/kg treatment groups. Mean normalized spleen volume decreased over 51 weeks with a mean decrease of 50% from baseline (-1.9% body weight, p=0.0032) was seen in the 60 U/kg group and a mean decrease of 40% from Baseline (-1.9% body weight; p=0.0085) was seen in the 45 U/kg group. The changes for both groups were statistically significant. Table 10 summarizes an exploratory analysis for responses in spleen size at Weeks 25 and 51.

Table 10: Change in Spleen Response Category for All Treatment Groups in 032 (from Shire)

	Week 25		Week 51	
Normalized Spleen Volume Endpoint	GA-GCB 45 U/kg	GA-GCB 60 U/kg	GA-GCB 45 U/kg	GA-GCB 60 U/kg
Response category[a] [n (%)]				
Good response	8 (61.5)	8 (72.7)	10 (76.9)	10 (90.9)
Moderate response	1 (7.7)	1 (9.1)	2 (15.4)	1 (9.1)
No response	4 (30.8)	2 (18.2)	1 (7.7)	0

Note: Imputation was applied to missing data.
There are no splenectomized patients excluded.
a A good response is defined as a reduction from baseline of >= 30%; a moderate response is defined as a reduction from baseline of >= 10%, but < 30%; no response is defined as a reduction from baseline of < 10%. Patients without moderate splenomegaly (2 to 3 cm below the left coastal margin) by palpation at baseline are excluded.

5. Biomarkers
Chitotriosidase and CCL18 levels decreased over the treatment period. See Section 4.4.2 for discussion and results.

6. Time to first hemoglobin response in both treatment groups
The cumulative incidence of first hemoglobin responses (increase of ≥1 g/dL) was slightly greater in the 45 U/kg group than the 60 U/kg group from Weeks 3 (8% vs 0%) to 15 (77% vs 75%). However, the cumulative incidence of responses was slightly greater in the 60 U/kg group from Weeks 17 (77% vs. 83%) to 35 (85% vs. 100%). From Week 37, both groups had a 100% incidence of first responses. A cumulative incidence of 100% first response was reached 10 weeks earlier (at Week 27) in the 60 U/kg group than in the 45 U/kg group (Week 37).

7. Quality of Life
No definitive conclusions were made on the effect on treatment on either individual health concepts or on overall score of the quality of life evaluations due to the small number of patients evaluated in each group (n=3 for CHQ-PF50, n=6 for SF6v2).

8. Pulmonary Function
Only one center had spirometry equipment to evaluate PFTs resulting in a small number of patients ≥18 yrs being evaluated. However, there was a trend toward improvement by apparent increases in FVC, FEV, and residual volume at Week 53 compared to Baseline in the 60 U/kg group.

Drug-Dose Relationship to Response
No direct statistical comparisons of the 60 U/kg and 45 U/kg groups were conducted; however, changes from baseline in several secondary, tertiary, and exploratory efficacy endpoints suggested a possible trend in favor of the 60 U/kg dose as follows:

- 100% of patients in the 60 U/kg group had a hemoglobin first response (increase of ≥1 g/dL) 10 weeks earlier (by Week 27) than patients in the 45 U/kg group
- At Week 53, 83% of patients had a good hemoglobin response (increase >1.5 g/dL) and 17% had a moderate (increase >0.5 but <1.5 g/dL) hemoglobin response in the 60 U/kg group compared with 62% with a good and 39% with a moderate response in the 45 U/kg group.
- A dose-related effect in favor of 60 U/kg was observed by a platelet count response (moderate to good), defined as an increase of at least 15 x 10^9/L in patients with below normal platelet counts at Baseline (<150 x 10^9/L), of 82% by Month 12 versus 58% seen in the 45 U/kg group.
- By Week 51, although the mean reduction from Baseline in normalized liver volume within each of the treatment groups was not statistically significant after adjusting for performing multiple tests, a reduction of 17% was seen in the 60 U/kg group compared with a mean reduction of 6% in the 45 U/kg group.

5.3.11 Safety Evaluation

Exposure
There were 23 patients (92%) who experienced at least one AE, including 12/12 (100%) in the 60 U/kg group and 11/13 (85%) in the 45 U/kg group. The majority of patients experienced mild or moderate AEs; only 2 of 25 patients (8%), both in the 45 U/kg group, reported severe AEs (syncope and thrombocytopenia). No life-threatening AEs were reported in this trial.

Deaths
None.

Serious Adverse Events
One patient (4% of total), 032-152-0006, in the 60 U/kg group, experienced a serious adverse event (SAE) of seizure that is likely unrelated to treatment. See Section 7.3.2 for the full narrative.

Adverse Events

The most common (at least 20%) AEs reported among all 25 patients were headache (48%), nasopharyngitis (36%), injury, arthralgia (each 32%), cough, pyrexia (each 28%), dizziness (24%), influenza, nasal congestion, vomiting, bone pain, and aPTT prolonged (each 20%).

Adverse events reported by at least 20% of the 12 patients in the 60 U/kg group were nasopharyngitis (50%), headache (42%), bone pain (33.3%), cough, rash, pyrexia, cheilitis, and aPTT prolonged (each 25%). Adverse events reported by at least 20% of the 13 patients in the 45 U/kg group were headache (54%), injury, arthralgia (each 46%), pyrexia, cough, dizziness (each 31%), nasopharyngitis, influenza, nasal congestion, productive cough, vomiting, petechiae, back pain, and myalgia (each 23%).

Overall, 60% (15/25) of patients, including 6/12 (50%) in the 60 U/kg group and 9/13 (69%) in the 45 U/kg group, had at least one AE considered by the Investigator to be drug-related (i.e., possibly or probably related). Among all 25 patients, the drug-related AEs reported by more than one patient were headache (4/25, 16%), hypotension, petechiae (each 3/25, 12%), thrombocytopenia, dizziness, somnolence, tachycardia, hypertension, arthralgia, back pain, and feeling cold (each 2/25, 8%). In the 60 U/kg group, the drug-related AEs reported in more than one patient were headache and hypotension (each 2/12, 17%) and, in the 45 U/kg group, the only drug-related AEs reported by more than one patient were headache, petechiae, arthralgia, and back pain (each 2/13, 15%).

Infusion-related AE was defined as any AE occurring within 12 hours of the start of infusion and possibly or probably related to study drug. Infusion-related AEs were reported for 14 patients (56%), including 6 (50%) in the 60 U/kg group and 8 (62%) in the 45 U/kg group. Infusion-related AEs reported by at least 10% of patients overall were headache and hypotension (each 3/25, 12%). Infusion-related AEs reported by more than one patient in each of the treatment groups were hypotension (2/12, 17%) in the 60 U/kg group and headache, arthralgia, and back pain (each 2/13, 15%) in the 45 U/kg group.

Table 11: Summary of TEAEs for 032 (from Shire)

DESCRIPTION	Patients n(%) Velaglucerase alfa 45 U/kg N=13	60 U/kg N=12	Total N=25
Experienced No Adverse Events	2 (15.4)	0	2 (8.0)
Experienced At Least 1 Adverse Event	11 (84.6)	12 (100.0)	23 (92.0)
Experienced At Least 1 Drug-Related Adverse Event	9 (69.2)	6 (50.0)	15 (60.0)
Experienced At Least 1 Infusion-Related Adverse Event	8 (61.5)	6 (50.0)	14 (56.0)
Experienced At Least 1 Severe Or Life-Threatening Adverse Event	2 (15.4)	0	2 (8.0)
Experienced At Least 1 Serious Adverse Event	0	1 (8.3)	1 (4.0)
Discontinued Due To An Adverse Event	0	0	0
Deaths	0	0	0

Safety Related Discontinuations
None.

ECG
In the 60 U/kg group, ten patients had normal Baseline ECG of which three were determined to have abnormal status at Week 53 (but not clinically significant). There were two patients with abnormal ECG status at Baseline of which one patient was abnormal and one patient was normal at Week 53. In the 45 U/kg group, there were eight patients with normal Baseline ECG, one of whom then was reported to have an abnormal ECG at Week 53 (but not clinically significant). Among the five patients with abnormal ECG status at Baseline, four were normal and one was abnormal at Week 53. There was no apparent increased safety risk with velaglucerase alfa treatment as determined by changes in overall 12-lead ECG status.
Comment: Specifically, QTc does not appear to be adversely affected by treatment. None of the abnormalities was deemed clinically significant or related to treatment by the Investigator. There were no consistent abnormalities between study visits for a patient (such as an incomplete right bundle branch block at a mid-trial visit which was resolved by end of study ECG) or between patients.

Vital Signs
Symptomatic abnormalities in vital signs considered clinically significant and reported as adverse events included two cases of mild hypertension, one case of mild hypotension, and four cases of mild pyrexia.

Laboratory Results
Anti-velaglucerase alfa antibodies
Only 1/25 patients (4%) developed anti-velaglucerase antibodies late in the one-year trial. These were IgG and neutralizing. This was a Russian male who was administered the 45 U/kg dose. He was naïve to ERT for Gaucher disease. The patient

did have clinically meaningful increases in hemoglobin and platelet values at the end of the trial and did not report any adverse events.

Chemistry and Hematology Labs
The majority of clinically significant hematology, serum chemistry and urinalysis test results were reported as mild AEs. Among the clinically significant hematology tests in the 60 U/kg group at Week 53, the one case of thrombocytopenia was reported as a moderate AE considered related and not serious. In the 45 U/kg group, one clinically significant low platelet count at Week 53 was reported as a severe AE of thrombocytopenia (not drug-related per the investigator). There do not appear to be clinically significant trends in adverse post-baseline shifts in laboratory parameters.

Growth
There were seven patients in the pediatric age range (2-17 years; 4 on 60 U/kg and 3 on 45 U/kg). By Week 53, the mean growth velocity was 8.3 in the 60U/kg and 7.8 in the 45 U/kg group. The patients were also evaluated for skeletal age. At Baseline and Week 51, the patients in the 60 U/kg group, respectively, had mean skeletal ages of 2.2±0.9 years and 1.7±1.1 years younger than their chronological age. Therefore, these patients had improved the difference between skeletal and chronological ages by 0.4±0.3 years following 12 months of treatment. No improvement from baseline (-1.4±1.0 years at Baseline, -2.0±0.9 at Week51) in the difference between skeletal and chronological age was seen in the patients evaluated in the 45 U/kg group.
Comment: Normal growth velocity is dependent on the specific age of each patient. Thus, comparison of mean growth velocity between two groups with small patient numbers and large age range is not very meaningful. Overall, it does appear that treatment does not negatively impact growth.

5.3.12 Conclusions

A. Efficacy Conclusions
Velaglucerase alfa 45 and 60 U/kg given IV every other week is effective in improving systemic parameters affected by type 1 Gaucher disease, including hemoglobin concentration, platelet count, and spleen volume. The 60 U/kg dose shows a greater increase (not statistically significant) response compared to the 45 U/kg dose, in particular when considering the EMEA recommended analysis of response categories.

B. Safety Conclusions
There were no deaths reported. There was one SAE reported that appears unrelated to treatment. The most common adverse reactions were signs and symptoms related to infusion of the treatment drug. These reactions tended to be more frequent at the beginning of therapy and tapered off with time. There were no patients with infusion-related AE requiring interruption or discontinuation of treatment. Among the pediatric patients, there were no SAEs or severe AEs. Overall, velaglucerase alfa appears to be well tolerated by the patients.

Trial 039 Phase 3 Trial

A Multicenter, Randomized, Double-Blind, Parallel-Group Study of Gene Activated Human Glucocerebrosidase (GA-GCB) Enzyme Replacement Therapy Compared with Imiglucerase in Patients with Type 1 Gaucher Disease

Trial period: January 2008 - May 2009

NOTE Only a top line efficacy report and narratives for serious adverse events with raw safety data were submitted originally to the NDA as the trial was recently completed and analysis is ongoing.

5.3.13 General Design and Objective

Primary Objective

- Compare the effects of velaglucerase alfa and imiglucerase on hemoglobin concentration in patients with type 1 Gaucher disease.

Secondary Objective(s)

- Compare the effects of velaglucerase alfa and imiglucerase on platelet count
- Compare the effects of velaglucerase alfa and imiglucerase on liver and spleen volumes (by MRI)
- Compare the effects of velaglucerase alfa and imiglucerase on Gaucher disease-specific biomarkers (plasma chitotriosidase and CCL18 levels)

The plan was to analyze 28 treatment-naïve patients two years of age and older with type 1 Gaucher disease and who have disease-related anemia (defined as hemoglobin below the lower limit of normal for age and gender). Patients were not to have received any treatment for Gaucher disease within 12 months of study entry and were to have tested negative for anti-imiglucerase antibodies.

5.3.14 Inclusion

Each patient had to meet the following criteria to be eligible for the study:

1. Two years or older with a diagnosis of type 1 Gaucher disease, as determined by deficient glucocerebrosidase (GCB) activity relative to normal, as measured in leukocytes or by genotype analysis.
2. Has Gaucher-disease-related anemia, defined as a hemoglobin concentration below the lower limit of normal for age and gender and

   1 OR MORE OF THE FOLLOWING 3 CRITERIA:

   The patient had at least moderate splenomegaly (2 to 3 cm below the left costal margin) by palpation.

OR

The patient had Gaucher-disease-related thrombocytopenia (defined as a platelet count ≤120 x $10^3/mm^3$).

OR

The patient had a Gaucher-disease-related readily palpable enlarged liver.

3. The patient had not received treatment for Gaucher disease within 12 months prior to study entry.
4. Female patients of child-bearing potential must have agreed to use a medically acceptable method of contraception at all times during the study. Male patients must have used a medically acceptable method of birth control throughout their participation in the study and were required to report pregnancy of a partner.

5.3.15 Exclusion

Patients who met any of the following criteria were excluded from the study:

1. The patient was antibody-positive to imiglucerase or velaglucerase alfa at Screening, or the patient had experienced an anaphylactic or anaphylactoid reaction to imiglucerase or velaglucerase alfa, or the patient required routine premedication use to manage infusion reactions to ERT therapy.
2. Receiving red blood cell growth factor or had received chronic systemic corticosteroids within the last six months.
3. Known to be positive for HIV, HBV, or HCV.
4. Presented with serum transferrin saturation <20 and serum ferritin <50 ng/mL.

5.3.16 Treatment and Monitoring

Double-blind study medication was administered as a continuous one-hour IV infusion of velaglucerase alfa or imiglucerase. All infusions were administered at the clinical site. Velaglucerase alfa was administered at a dose of 60 U/kg every other week (± 3 days) over 60 minutes for 39 Weeks (20 infusions). Imiglucerase was administered at a dose of 60 U/kg every other week (± 3 days) over 1 to 2 hours for 39 Weeks (20 infusions).

Permitted Therapies
Patients could receive supportive Gaucher treatment (treatments for bone disease or hematologic symptoms). For drug interactions of imiglucerase, the investigators were to take the precautions in consideration of the Prescribing Information for imiglucerase.

Prohibited Therapies
Patients were not to receive treatment with red blood cell growth factor or investigational drug(s) or device(s) at any point during this study or within 30 days after the last infusion.

A computer-generated randomization schedule was used to allocate patients to treatment groups. The randomization plan also aimed to obtain treatment groups that

were comparable in certain prognostic variables: age, hemoglobin concentration, and whether the patient had undergone splenectomy. Patients received a total of 20 intravenous (IV) infusions of double-blind study medications at the clinical site once every other week for a total of 39 weeks. Safety and efficacy assessments were made at regular intervals during the treatment phase. The final assessments of safety and efficacy were made at Week 41 (two weeks after final infusion).

Safety was assessed throughout the study by assessments of adverse events (AEs), including infusion-related AEs, concomitant medication use, and vital signs. Additional safety assessments, including ECG, physical examinations, clinical laboratory tests (hematology, serum chemistry, and urinalysis), were made at Weeks 13, 25, and 41. Determination of the presence of anti-velaglucerase alfa or anti-imiglucerase antibodies and enzyme neutralizing antibodies were conducted approximately every six weeks until Week 41.

Efficacy was assessed via hemoglobin concentration and platelet count, liver and spleen volume, and plasma chitotriosidase and CCL18 levels. Additional efficacy assessments included growth velocity and Tanner staging, quality of life indicators, and skeletal growth. Immune and inflammatory response (as measured by selected cytokine parameters) was also measured in adult patients (≥18 years of age at study entry).

5.3.17 Endpoints

Primary Efficacy Variable
The primary efficacy endpoint was the difference of the mean change from Baseline to Week 41 in hemoglobin concentration between the two treatment groups.

Secondary Efficacy Variables
For the secondary efficacy parameters (platelet counts, liver, and spleen volumes, chitotriosidase, and CCL18) statistical tests evaluated if the mean changes from Baseline to Week 41 between the two treatment groups were significant (p-value <0.05).

5.3.18 Data Analysis

Statistical and Analytical Plans
Two data sets are considered for the statistical analyses of efficacy: 1) the intent-to-treat (ITT) data set and 2) the per-protocol (PP) data set. The ITT data set is all randomized patients who received at least one full or partial dose of study drug. The PP data set is a subset of the ITT data set, which includes patients who have completed 41 weeks of the study, have had both the Baseline and the Week 41 measurements of the primary efficacy variable collected, have not had any protocol violation, and have received at least 80% of their scheduled treatments.

Primary Efficacy Analysis
This is a non-inferiority randomized controlled trial designed to demonstrate that velaglucerase alfa is non-inferior to imiglucerase in terms maintaining hemoglobin concentration. Non-inferiority is demonstrated by either a one-sided confidence interval or a hypothesis test for testing the null hypothesis that the treatment difference is less than or equal to the lower equivalence margin in hemoglobin (-1 g/dL) versus the alternative that imiglucerase treatment difference is greater than the lower equivalence margin. A one-sided, 97.5% confidence interval was used.

Secondary Efficacy Analyses
For the secondary efficacy parameters (platelet counts, liver, and spleen volumes, chitotriosidase, and CCL18) comparing changes from Baseline between treatment groups, statistical tests were used to evaluate if the difference in mean changes from Baseline to Week 41 in the two treatment groups is statistically significant.

Determination of Sample Size
With a sample size in each treatment group of 14, a two-group, 0.025 one-sided t-test would have an 80% power to reject the null hypothesis that the difference in means for hemoglobin is less than −1 g/dL in favor of the alternative hypothesis that the difference in means is greater than −1 g/dL, assuming that the expected difference in means is 0, and the common standard deviation is 0.90. A 15% dropout was assumed, therefore a total of 32 patients (16 patients per treatment arm) were to be enrolled into the study.

Changes in the Conduct of the Study
Noteworthy changes were implemented in Version 3 (dated June 10, 2008):

- The language describing the primary endpoint was modified to: The primary endpoint of this study is to measure the mean change from Baseline to Week 41 in hemoglobin concentration between the two treatment groups. Previously it was not specified that the change was to Week 41.
- The analyses of secondary endpoints were originally planned as an ANCOVA model. To further consider the correlation of within-subject measurements, the analyses were amended to use the mixed model.

5.3.19 Number and Disposition of Patients

Table 12 summarizes patient disposition by treatment group and for treatment groups combined. Of the 42 patients screened, 7 (17%) were not eligible for randomization. The most common reason (4/7 patients) for ineligibility was failure to meet inclusion criteria. In addition, one patient each did not provide written informed consent, was unable to comply with the protocol, or had transferrin saturation <20% and serum ferritin <50 ng/mL. All 17 randomized patients in the velaglucerase alfa group received at least one infusion and were included in the safety analysis population. One of the 18 patients randomized to the imiglucerase treatment group did not meet all the eligibility criteria and thus was terminated prior to any infusion (the patient was found to have antibodies

to imiglucerase during screening). One patient in the velaglucerase alfa group discontinued after 17 weeks of treatment as she was lost to follow-up following an SAE of convulsion. One patient in the imiglucerase treatment group withdrew consent after 23 weeks of treatment due to infusion-associated reactions.

Table 12: Patient Disposition for 039

Disposition	velaglucerase N (%)	imiglucerase N (%)	Total N (%)
Patients randomized	17 (100)	18 (100)	35 (100)
Completed	16 (94)	16 (89)	32 (91)
Discontinued	1 (6)	2 (11)	3 (9)
Withdrew consent	0	1 (6)	1 (3)
Investigator decision	0	1 (6)	1 (3)
Lost to follow-up	1 (6)	0	1 (3)

Data Sets Analyzed
All randomized patients, with the exception of the patient on imiglucerase treatment who was antibody positive at study entry, were included in the ITT analysis. Two patients in the velaglucerase alfa and in the imiglucerase groups did not meet criteria for inclusion in the PP population.

5.3.20 Demographics

The treatment groups were balanced for gender, race, height, and weight. The number of patients ≥18 years of age were similar between the two groups; however, the two treatment groups are dissimilar in the distribution of children between these two additional age groups. The velaglucerase group included only older children; in contrast, the imiglucerase group had 4 of 5 children (80%) in the 2 to 4 year group.

The two treatment groups were balanced with respect to splenectomy status. Modified Baseline was defined as the average of the parameter measured at Screening and Baseline visits. Median hemoglobin concentration at Modified Baseline appeared to be greater in the velaglucerase alfa treatment group: 11.4 g/dL and 10.6 g/dL in the velaglucerase alfa and imiglucerase treatment group, respectively. Median platelets were 172 and 188 x 10^9 cells/L in the velaglucerase alfa and imiglucerase treatment groups, respectively. The PP population consisted of 30 patients (30 of 34, 88%) included in the ITT population, as such the demographics were similar between the two populations.

Table 13: Demographics for Trial 039

Baseline Characteristics		Treatment		
		Velaglucerase N=17	Imiglucerase N=17	Total=34
Age (years)	2-4	0	4 (24%)	4 (12%)
	5-17	4 (24%)	1 (6%)	5 (15%)
	≥18	13 (76%)	12 (70%)	25 (73%)
	Mean±SD Min-Max	31±17 7-60	28±20 3-73	30±18 3-73
Sex	Male	8 (47%)	8 (47%)	16 (47%)
	Female	9 (53%)	9 (53%)	18 (53%)
Race	Caucasian	12 (71%)	10 (59%)	22 (65%)
	Asian	4 (24%)	4 (24%)	8 (24%)
	Other	1 (6%)	2 (12%)	3 (9%)
Ethnicity	Hispanic/Latino	5 (30%)	4 (24%)	9 (26%)
	Non- Hispanic	12 (70%)	13 (76%)	25 (74%)
Height (cm)	Mean±SD Min-Max	157±19 111-173	143±34 83-181	150±28 83-181
Weight (Kg)	Mean±SD Min-Max	53±18 16-84	47±27 10-110	50±23 10-11
Splenectomy	Yes	10 (59%)	10 (59%)	20 (59%)
Hemoglobin	mean±SD(g/dL)	11.5±1.2	10.5±1.4	11.0±1.4
Platelets	mean±SD($x10^9$/L)	161±91	181±101	171±95

Measurements of Treatment Compliance
In the velaglucerase alfa treatment group 11 (65%) patients received all 20 infusions while in the imiglucerase group 14 (82%) patients received all scheduled infusions. Overall treatment compliance was high in both treatment groups: 96% in the velaglucerase alfa group, and 99% in the imiglucerase group.

Five patients from the same site (3 velaglucerase alfa, 2 imiglucerase) missed one infusion each because vials of study drug were refrigerated below the recommended temperature. The missed infusion occurred while waiting for replacement vials. One patient in the velaglucerase alfa group missed two infusions during a SAE of allergic dermatitis, but received additional treatment and completed the study after resolution of this SAE. One patient in the velaglucerase group missed the last infusion due to an unspecified technical reason. One patient in the velaglucerase group experienced a SAE of convulsions, and had not returned for nine weeks before she was considered lost to follow-up; all scheduled infusions until the date of discontinuation (>4) were considered missed. One patient in the imiglucerase group missed one infusion and later withdrew consent to participate in the study.

Table 14: Exposure to Treatment by Group in 039 (from Shire)

Parameter	GA-GCB 60 U/kg N = 17	imiglucerase 60 U/kg N = 17
Number of infusions received		
n	17	17
Mean	19.0	19.4
Std. Dev.	2.65	1.94
Median	20.0	20.0
Minimum	9	12
Maximum	20	20
Number of missed infusions [n (%)][a]		
None	11 (64.7)	14 (82.4)
1	4 (23.5)	3 (17.6)
2 to 4	1 (5.9)	0
> 4	1 (5.9)	0

5.3.21 Efficacy Evaluation

Primary Endpoint

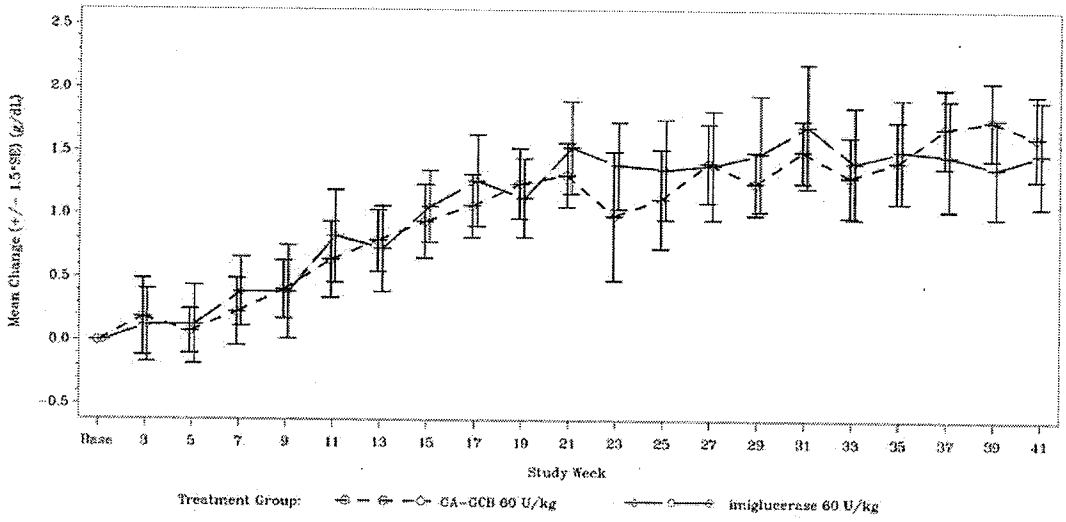
Table 15 summarizes the primary endpoint, the mean absolute change from Baseline in hemoglobin at Week 41 for the ITT patient population. In the ITT population, mean absolute change was 1.6 and 1.5 g/dL in the velaglucerase alfa and imiglucerase groups, respectively. The estimated mean treatment difference (n=34) was 0.13 g/dL with a lower bound of the 97.5% one-sided confidence interval of -0.6 g/dL. The estimated mean treatment difference in the PP population (n=30) was 0.16 g/dL with a lower bound of the confidence interval of -0.6 g/dL. The lower bounds in both ITT and PP population are greater than the pre-defined non-inferiority margin of -1 g/dL although the 11.4 g/dL median baseline hemoglobin concentration of the velaglucerase alfa group was 0.8 g/dL higher than that of imiglucerase group (10.6 g/dL). Figure 5 depicts the mean hemoglobin change from baseline to each week comparing velaglucerase and imiglucerase treatment.

Table 15: Hemoglobin Results by Treatment Group in 039

Hemoglobin (g/dL)	Velaglucerase (N=17)		Imiglucerase (N=17)	
	Baseline	Week 41	Baseline	Week 41
Mean Observed Value (±SE) Min-Max	11.5±0.3 9.7 – 14.4	13.1±0.4 10.9 – 15.9	10.5±0.3 8.1 – 13.1	11.9±0.3 8.7 – 13.6
Change from Baseline* (±SE) Min-Max	—	1.6±0.2 -0.2 – 3.6	—	1.5±0.3 -0.6 – 3.5

*The estimated mean treatment difference (vela-imi)=0.13 g/dL with a lower bound of the 97.5% one-sided confidence interval of -0.6 g/dL.

Figure 5: Mean Hemoglobin Change from Baseline ±SE by Study Week for 039 (from Shire)



Secondary Endpoints

Platelet Counts

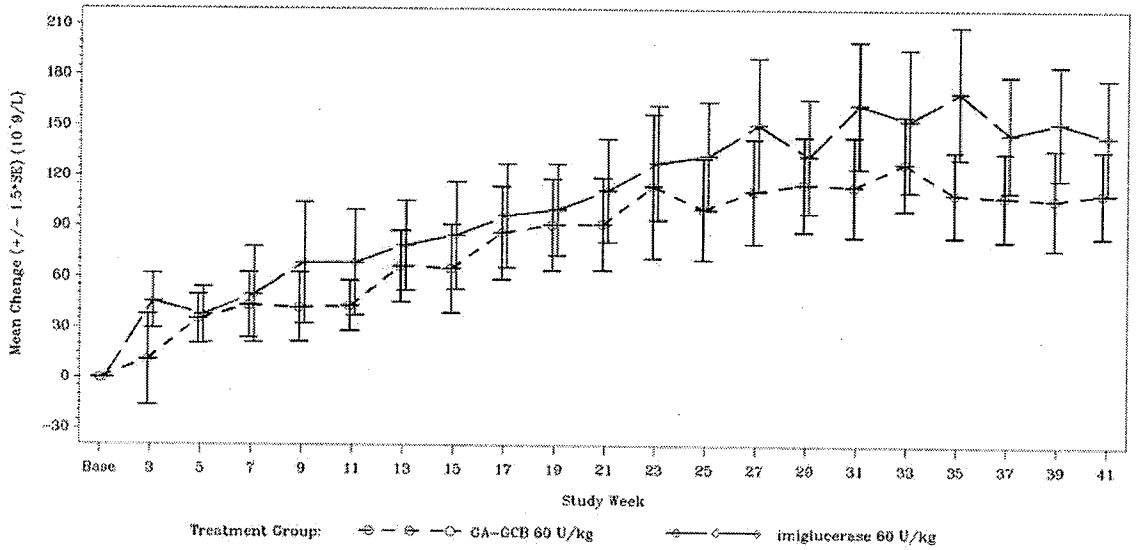
Mean platelet counts increased over the treatment period with both velaglucerase and imiglucerase ERT. The mean platelet count at Baseline was greater in imiglucerase compared to velaglucerase (181 vs. 161 x 10^9/L). The difference was not clinically meaningful, as determined by Shire, and the standard errors of the means overlapped. The mean platelet count was greater for imiglucerase than velaglucerase at each assessment throughout the study and the treatment difference appeared to increase in the latter half of the trial. At Week 41, the mean change was 110 x10^9/L in the velaglucerase alfa group and 144 x10^9/L in the imiglucerase group. The model-based estimated treatment difference in mean change at Week 41 was -39 x 10^9 cells/L and the 95% confidence interval (-88, 10.99) included zero. There were no statistically significant differences in change from Baseline between treatment-naïve patients treated with 60 U/kg of velaglucerase alfa to those seen for patients treated with 60 U/kg of imiglucerase after nine months of treatment, meeting this secondary efficacy endpoint.

Table 16: Platelet Count Results by Treatment Group 039 (ITT)

Platelet Count (x10^9/L)	Velaglucerase (N=17)		Imiglucerase (N=17)	
	Baseline	Week 41	Baseline	Week 41
Mean Observed Value (±SE) Min-Max	161±22 44 – 311	272±32 64 – 464	181±25 63 – 431	326±32 135 – 519
Change from Baseline* (±SE) Min-Max	—	110±17 20 – 271	—	144±23 32 – 314

*The estimated mean treatment difference (vela-imi)=-39x10^9 cells/L and 95%CI (-88, 11).

Figure 6: Mean Platelet Change from Baseline to Each Study Week in 039 (from Shire)



Liver Volume
All analyses for changes in liver volume are presented for baseline liver values, splenectomy status, and liver volume normalized by body weight to adjust for the variations in organ volumes between patients 2 to 17 years old and ≥18 years old. Table 17 summarizes the results of liver volume change on treatment. The model-based estimated mean treatment difference at Week 41 is -0.07% of body weight with a 95% CI (-0.43, 0.29) percent that includes zero.

Table 17: Normalized (% of Body Weight) Liver Volume Results by Treatment Group in 039 (ITT)

Normalized Liver Volume (%BW)	Velaglucerase		Imiglucerase	
	Baseline	Week 41	Baseline	Week 41
Mean Observed Value (±SE) Min-Max	4.4±0.6 1.9 – 12.2	3.1±0.2 1.6 – 4.7	4.2±0.3 1.7 – 7	3.1±0.2 1.8 – 4.6
Change from Baseline* (±SE) Min-Max	—	-1.3±0.3 -6.5 – 0.1	—	-1.1±0.2 -2.4 – 0.4

*The estimated mean treatment difference at Week 41 is -0.07% of body weight (95% CI= -0.43 to 0.29).

Spleen Volume information was not provided in the Applicant's abbreviated report.

Plasma Biomarkers:
There were 21 patients who had chitotriosidase levels measured (10 patients in the velaglucerase alfa group and 11 patients in the imiglucerase group). In 12 of 13 patients where chitotriosidase was not detected there was 24bp duplication; the remaining patient had a different mutation. Baseline median chitotriosidase level was 45,534 nmol/mL/h in the velaglucerase alfa group and 50,077 nmol/mL/h in the

imiglucerase group, and chitotriosidase levels decreased over the 40 weeks of treatment (normal range approximately < 80 nmol/hr/ml). At Week 41, the unadjusted mean decrease in the velaglucerase alfa group was 34,712 nmol/mL/h, while the unadjusted mean decrease in the imiglucerase group was 35,110 nmol/mL/h. Using a linear mixed model adjusting for Baseline chitotriosidase values, splenectomy status, and age at informed consent (2 to 17 vs ≥18 years old), the estimated mean treatment difference was -704 nmol/mL/h with a 95% confidence interval (-11762, 10355) that included zero.

The Baseline median CCL18 level was 1637 ng/mL for the velaglucerase alfa and 1849 ng/mL for the imiglucerase group. CCL18 levels decreased over the 40 weeks of treatment. At Week 41 there was an unadjusted mean change of -926 ng/mL (-55%) for the velaglucerase group and an unadjusted mean change of -1153 ng/mL (-49%) for the imiglucerase group. Using a linear mixed model adjusting for Baseline CCL18 values, splenectomy status and age at informed consent (2 to 17 vs ≥18 years old), the estimated mean treatment difference was 146 ng/mL with a 95% CI (-189, 480) that included 0.

5.3.22 Safety Evaluation

A brief safety report was submitted as a response to an Information Request. The Applicant's analysis is ongoing. There were no deaths. There are five case narratives for serious adverse events (SAEs), one of which was considered probably related to treatment by the investigator (allergic dermatitis) and four of which were considered unrelated to treatment by the investigator. The two SAEs reported for imiglucerase treated patients both occurred prior to treatment (sepsis and thrombocytopenia) and are not described. See Section 7.3.2 for narratives of the SAEs reported for this trial.

Adverse events were reported in 16 of 17 patients in both treatment groups. The only preferred term for which there was a discrepancy between treatment groups of more than two patients was for "peripheral edema," which was reported in three velaglucerase patients and no imiglucerase patients.

In both treatment groups, most patients reported AEs that were mild or moderate in severity. The AEs rated as severe are described in Table 18. There does not seem to be a pattern in the type of severe AE reported in either treatment group.

Table 18: Severe Adverse Events by Treatment Group for 039 (as assessed by Shire)

Patient No/ Gender/Baseline Age	Preferred Term/ AE Description	SAE	Severity	Investigational Product Action	Relation to Study Drug	Outcome
velaglucerase alfa						
039-165-0001/Female/49	Back pain/ worsening of lumbar pain	N	Grade 3	Unchanged	Not related	Not resolved
039-165-0001/Female/49	Allergic dermatitis/ Skin allergic reaction	Y	Grade 3	Temporarily Withheld	Probably related	Resolved
039-180-0001/Male/14.2	Activated partial thromboplastin time[a] prolonged/ high aPTT	N	Grade 3	Unchanged	Probably related	Unknown
039-185-0001/Female/9.1	Convulsion/ convulsion	Y	Grade 4	Unchanged	Not related	Resolved
imiglucerase						
039-094-0004/Female/34	Arthralgia/worsening of inflammatory left hip pain	N	Grade 3	Unchanged	Not related	Resolved
039-167-0001/Male/73	Chills/Rigors	N	Grade 3	Temporarily Withheld	Probably related	Resolved

a: This patient had prolonged aPTT of 36.6 seconds at Screening that was out of range high but not considered clinically significant. From Week 1 through Week 25 aPTT ranged from 33.9 to 38.4 seconds. At the Week 41 visit aPTT was reported to be 129.6 seconds and was reported as an adverse event. Prothrombin time was also prolonged (17.2 seconds). Liver function tests (ALT, AST, and GGT) were normal throughout the study and the patient continued velaglucerase alfa treatment in the extension protocol. Data Source: Table 10.3.1.5, CDISC Data Sets

Finally, analysis of infusion-related AEs shows that there were similar outcomes for both groups. There were 5 of 17 velaglucerase patients and 4 of 17 imiglucerase patients with infusion related AEs.

Using the raw safety data provided, I conducted my own evaluation of adverse events between velaglucerase and imiglucerase treated patients. There were no adverse events for which there was a difference of more than two patients. Thus, it appears that in this trial, no significant difference in safety can be detected between the two treatment groups with the exception of "peripheral edema."

5.3.23 Conclusion

From the abbreviated information available, it appears that the efficacy of velaglucerase is similar to imiglucerase in the endpoints measured. In terms of safety, the overall number of patients reporting AEs is equal in both groups; however, there were no SAEs reported for imiglucerase while on treatment compared to three for velaglucerase. Also, there were four severe AEs reported in velaglucerase compared to two for imiglucerase. Review of these events do not show any apparent pattern and the patients numbers are too small to make any definitive conclusion regarding the difference in safety profile between these two ERT treatments.

Trial 034 (Phase 2/3 Trial)

A Multicenter, Open-Label Study of Gene-Activated Human Glucocerebrosidase Enzyme Replacement Therapy in Patients with Type 1 Gaucher Disease Previously Treated with Imiglucerase

*Of note, results for safety, hemoglobin concentrations, and platelet counts were submitted in an abbreviated clinical study report, given the trial recently concluded.

Trial period: July 25, 2007 – June 26, 2009
Sites: 15 sites across Israel, Poland, Spain, UK, and US (11 sites)

5.3.24 General Design and Objective

Primary Objective

- The primary objective of this study was to evaluate the safety of every other week (EOW) dosing of velaglucerase alfa in patients previously treated with imiglucerase.

Secondary Objective(s)

The secondary objectives of this study were:

- Evaluate changes from Baseline in hemoglobin concentration
- Evaluate changes from Baseline in platelet count
- Evaluate changes from Baseline in liver and spleen volumes by abdominal MRI a

This was a one-year, multicenter, open-label, "switch" trial to evaluate the safety of velaglucerase alfa therapy for patients receiving imiglucerase therapy for type 1 Gaucher disease. Patients previously treated with imiglucerase were to be enrolled, including those patients who tested positive for anti-imiglucerase antibodies at Screening. The previous imiglucerase dose was to range between 15 and 60 U/kg with an EOW dosing regimen. For each patient, the same imiglucerase dose was to have been administered by one-hour IV infusion for at least six months prior to enrollment. A patient's velaglucerase alfa dose was to be the same dose as the previous imiglucerase dose received.

5.3.25 Inclusion Criteria

Patients two years of age and older, with type 1 Gaucher disease who had received consistent treatment with imiglucerase for a minimum of 30 consecutive months (with the same dose of treatment for at least six months prior to screening), were eligible for the study.

5.3.26 Exclusion Criteria

- Both a hemoglobin concentration ≤10 g/dL and a platelet count ≤80 x 10^3 platelets/mm^3.
- Unstable hemoglobin concentration during the six months prior to Screening
- Unstable platelet count during the six months prior to Screening
- Type 2 or 3 Gaucher disease
- Treatment with any investigational drug or device within the 30 days prior to study entry
- Positive for HIV, Hep B or C
- Presented with sustained iron, folic acid or vitamin B12 deficiency-related anemia
- Significant comorbidity that might have affected study data or confounded the study results (e.g., malignancies, primary biliary cirrhosis, autoimmune liver disease)
- Experienced an anaphylactic or anaphylactoid reaction with imiglucerase.
- Received miglustat during the six months prior to study enrollment.
- Receiving red blood cell growth factor or chronic systemic corticosteroids in the last six months.
- Clinically significant spleen infarction within 12 months of Screening
- Worsening bone necrosis within 12 months of Screening. Inactive or stable bone necrosis was not excluded.
- Patient was pregnant or lactating.

5.3.27 Treatment

Patients were to receive up to 26 IV infusions of velaglucerase alfa EOW at the same dose that they were treated with imiglucerase. After the first three infusions of velaglucerase alfa therapy, patients who had not experienced a treatment-related SAE or an infusion-related AE were eligible to receive subsequent infusions at home.

Patients were monitored throughout the treatment period for changes in clinical parameters (i.e., hemoglobin concentration, platelet count, and liver and spleen volumes). If a patient demonstrated a clinically significant change in these parameters, the Investigator could increase the patient's dose by 15 U/kg. If the clinical parameters did not return to Baseline within three months, the Investigator would have the option of increasing the dose by increments of 15 U/kg. No dose increase would be offered to patients already receiving 60 U/kg. If the patient failed to respond at a maximum dose of 60 U/kg, the patient could be withdrawn based on the Investigator's clinical judgment.

Permitted Therapies
Patients could receive supportive Gaucher treatment (treatments for bone disease or hematologic symptoms). Patients could receive iron supplement therapy at the Investigator's discretion.

Prohibited Therapies
Patients were not to have received treatment with red blood cell growth factor or investigational drug(s) at any point during this study or within 30 days after the last infusion.

5.3.27 Endpoints

Primary Efficacy Variables
Hemoglobin concentration and platelet counts were used for efficacy analyses. Quantitative abdominal MRI of the liver and spleen (Baseline, Weeks 25, and 51) was performed at the trial sites and read by a central reader for the determination of changes in liver and spleen volume.

The abbreviated report describes the results from the hemoglobin concentration and platelet count measurements only.

Secondary Efficacy Variables
Other efficacy assessments included plasma levels of the biomarkers, chitotriosidase and CCL18, assessment of bone biomarkers, and, for patients 2 to 17 years old only, assessments of growth velocity, skeletal growth, and Tanner stages of puberty.

Primary Safety Variables
Safety was assessed throughout the study by assessments of AEs, concomitant medication use, and vital signs. Additional safety assessments, ECGs, physical examinations (PEs), clinical laboratory tests (hematology, serum chemistry, and urinalysis), were made at Weeks 13, 25, 37, 51, and 53. Determination of anti-velaglucerase alfa antibodies and enzyme neutralizing antibodies was conducted approximately every six weeks. No formal statistical tests were performed.

The abbreviated clinical study report describes the AE assessment, concomitant medication use, and anti-velaglucerase alfa antibody test results only.

5.3.28 Data Analysis

The mean within patient changes from baseline and mean within-patient percent changes from baseline were calculated and presented for hemoglobin concentration and platelet count. For the change from Baseline to Week 53 in hemoglobin concentration and the percent change from Baseline to Week 53 in platelet count, a two-sided 90% confidence interval around the means were computed. If the two-sided 90% confidence interval fell within the corresponding pre-specified clinically meaningful range (±1 g/dL for hemoglobin concentration and ±20% for platelet count) then it was to be concluded that the clinical efficacy parameter is no different from the start of the trial (at the end of imiglucerase therapy) to the end of 12 months of velaglucerase exposure.

Safety analyses were performed on the safety population and efficacy analyses were performed on the intent-to-treat population (ITT). Both the safety and ITT analysis populations were defined as all enrolled patients who received at least one drug infusion. No formal statistical tests were performed on the safety parameters. An overall summary of treatment-emergent adverse events (TEAEs) and a summary of serious adverse events will be presented by velaglucerase dose groups (15 U/kg, 30 U/kg, 45 U/kg, and 60 U/kg). To determine the velaglucerase dose groups, doses were averaged across all infusions for a particular patient.

Determination of Sample Size
This was a safety trial and the sample size selected was based on the efficacy parameters (platelet count, hemoglobin concentration, liver and spleen volume) which were thought to be suitable for the evaluation of less common adverse effects. The inclusion of at least 26 patients was thought to provide basic information on safety and tolerability. A maximum of 40 patients was planned to be enrolled in this study; 40 patients were included in the intent-to-treat (ITT) and safety populations.

Changes in the Conduct of the Study
The protocol was amended once on Oct 19, 2007, significant changes include:

- Inclusion Criteria were changed, requiring male patients to use a medically acceptable method of birth control throughout their participation in the study and to report any pregnancy of a partner.
- Exclusion criterion was rewritten to clarify that exclusion required both a hemoglobin of ≤10 g/dL and a platelet count of ≤80 x 103 platelets/mm3.
- Expanded exclusion of erythropoietin to exclusion of any red cell growth factor and allowed the use of inhaled corticosteroid therapy.
- Clarification that a spleen infarction was required to be active and clinically significant, experienced within 12 months of screening, and radiologically confirmed to be a reason for exclusion from the study. The updated criterion provided clarification that splenectomized patients were not to be excluded.
- Clarification that bone necrosis was to be worsening within 12 months of screening; inactive or stable bone necrosis was not intended to excluded.
- Pregnant or lactating patients were excluded.
- Assessments were added to screening procedures: chitotriosidase genotyping, vital signs, and serum B12 and folic acid concentrations.
- After each of the first three infusions, a safety telephone call from the Investigator to the patient one day after infusion was added to the protocol.
- Infusion time was changed from the same infusion time as the previous imiglucerase dose to a one-hour infusion. Longer infusion times were to be documented.

5.3.29 Number and Disposition of Patients

The table below presents the patient disposition for Study TKT034. Of the 41 patients enrolled, 40 patients (98%) received at least one full or partial dose of study drug and were included in the ITT and safety populations. One patient was not included in the ITT and safety populations because they withdrew from the study prior to receiving study drug. A total of 38 patients (93%) completed the trial, and 3 (7%) discontinued. Two patients in the ITT and Safety populations (both in the 15 U/kg group) discontinued after receiving at least one full or partial dose of study drug. One patient discontinued due to a SAE of anaphylactic reaction during her first infusion with velaglucerase. The other patient withdrew consent at Week 31 due to lack of improvement.

Table 19: Patient Disposition for 034 (from Shire)

Disposition	Total n (%)
Enrolled patients	41 (100.0)
ITT population	40 (97.6)
Safety population	40 (97.6)
Patient status	
Completed	38 (92.7)
Discontinued	3 (7.3)
Reason for discontinuation	
Adverse experience including serious adverse event	1 (2.4)
Withdrawal of consent	2 (4.9)

5.3.30 Demographics

A summary of demographics and baseline characteristics is presented in Table 20. Most patients (31/40, 78%) were 18 years of age or older. There was a balance between male and females. The large majority of patients were Caucasian from the US. The most common Gaucher disease genotype was N370S/N370S (14 patients, 35%) or N370S/Other (13 patients, 33%), although 6 patients (15%) had a genotype of N370S/L444P, 3 patients each (7%) had a genotype of N370S/84GG and Other/Other, and 1 patient (3%) had a genotype of L444P/Other. Three patients (8%) tested positive for anti-imiglucerase alfa antibodies prior to receiving treatment. Patients were treated with imiglucerase for a median of 67 months (range 22 to 192 months) before beginning the study. The median baseline hemoglobin concentration was 13.8 g/dL (range: 10.4 to 16.5 g/dL). The median baseline platelet count was 162×10^9/L (range: 29 to 399 × 10^9/L).

One patient who received 50 U/kg of imiglucerase was categorized in the 15 U/kg velaglucerase dose group. This particular patient was prescribed dose of 50 U/kg; however the patient's first infusion was discontinued after 30 minutes due to an anaphylactic reaction and consequentially only received 13 U/kg of velaglucerase.

Because this patient's actual dose was ≤22.5 U/kg, she has been categorized into the 15 U/kg group for analysis purposes.

Table 20: Demographics for 034

Characteristics		Total n=40
Age (years)	2-4	0
	5-17	9 (23%)
	≥18	31 (78%)
	Mean±SD Min-Max	36±18 9-71
Sex	Male	18 (45%)
	Female	22 (55%)
Race	Caucasian	37 (93%)
	Asian	1 (2%)
	Other	2 (5%)
Ethnicity	Hispanic/Latino	3 (8%)
	Non- Hispanic	37 (92%)
Country	Poland	5 (12%)
	Israel	9 (22%)
	Spain	1 (3%)
	UK	3 (8%)
	USA	22 (55%)
Splenectomy	Yes	4 (10%)
	No	36 (90%)
Anti-imiglucerase	Positive	3 (8%)
	Negative	37 (92%)
Previous imiglucerase dose (U/kg)	15	14 (34%)
	30	12 (30%)
	45	7 (18%)
	60	7 (18%)
Height (cm)	Mean±SD Min-Max	166±11 140-190
Weight (Kg)	Mean±SD Min-Max	69±19 34-117
Hemoglobin (g/dL)	Mean±SD Min-Max	13.7±1.3 10.4-16.5
Platelet ($x10^9$)	Mean±SD Min-Max	169±83 29-399

Measurements of Treatment Compliance

Patients were treated for a median of 50 weeks (range: 0.1 to 52 weeks). Patients received a median of 26 infusions (range: 1 to 26 infusions). No infusions were missed in the 45 and 60 U/kg groups, two patients missed one infusion each in the 15 U/kg group and one patient missed 2 to 5 infusions each in the 15 and 30 U/kg groups. The median percent compliance was 100% overall and for each treatment group. Most

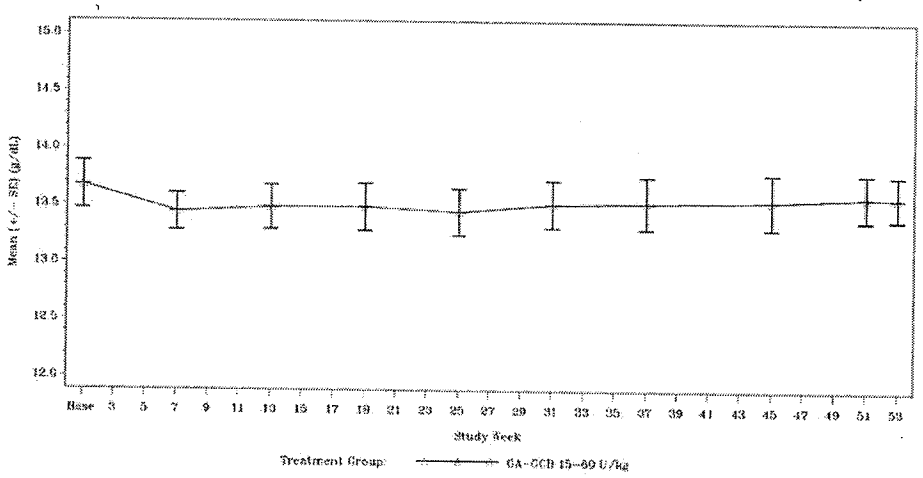
(38/40, 95%) completed 80% or more of their expected infusions; two patients in the 15 U/kg group did not complete 80% or more of their expected infusions. **No dose adjustments were made during the study.**

Concomitant Medications
Most patients (37/40, 93%) received concomitant medications. The most frequently used medications were paracetamol (13, 33%), ibuprofen (12, 30%), omeprazole, multivitamin (7 each, 18%), calcium, and amoxicillin (5 each, 13%). There was only 1 of 40 patients who was administered a pre-infusion medication. This patient was administered dexchlorpheniramine maleate beginning in January 2001, prior to their participation in this trial.

5.3.31 Abbreviated Efficacy Evaluation

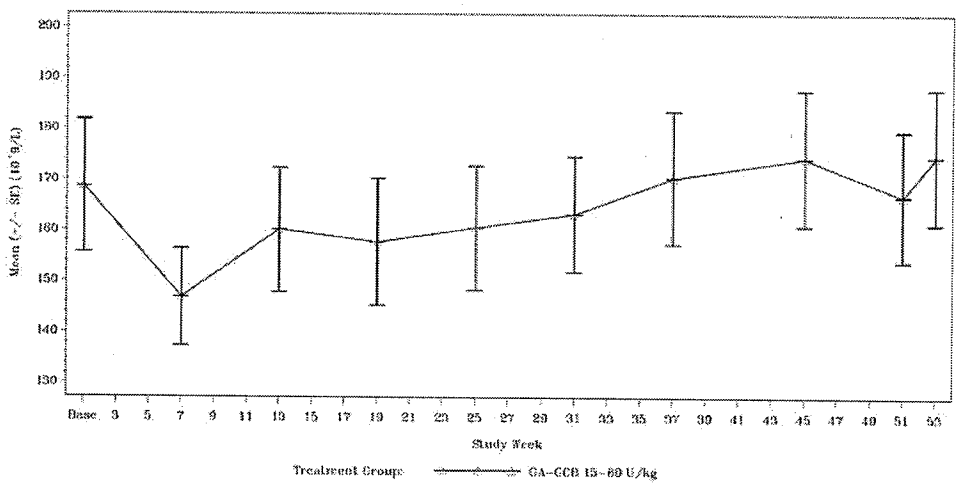
The mean baseline hemoglobin concentration was sustained from Baseline over 12 months of treatment. At Baseline, the median hemoglobin concentration was 13.8 g/dL and after 53 weeks of treatment with velaglucerase, the mean change from Baseline was -0.1 g/dL. The 90% confidence interval for mean change in hemoglobin concentration was -0.27 to 0.07, within the efficacy criterion of ±1 g/dL.

Figure 7: Hemoglobin Concentrations (±SE) Across Visits for 034 (from Shire)



The mean baseline platelet count was also sustained from Baseline over 12 months of treatment. At Baseline, the median platelet count was 162 $\times 10^9$/L. After 53 weeks of treatment, the percent change from Baseline in platelet count was 7%. The 90% confidence interval for percent change in platelet count was 0.5 to 13.5, within the efficacy criterion of ±20%.

Figure 8: Mean Platelet Count (±SE) by Dose Across Visits for 034 (from Shire)



5.3.32 Abbreviated Safety Evaluation

There were no deaths, but, 4 of 40 patients (10%) experienced a total of 5 treatment-emergent SAEs. One patient (15 U/kg) experienced an SAE of anaphylactoid reaction upon receiving their first dose of velaglucerase that led to discontinuation. This is the only reaction of this type across the development program to date. The patient responded to discontinuation of the study drug and to supportive care, recovered without sequelae, and did not develop anti-velaglucerase antibodies (see Section 7.3.2 for narratives).

There were 5 of 40 patients (13%) who experienced adverse events that were severe, and no patient experienced an AE that was life threatening. No patient developed anti-velaglucerase antibodies, including the three patients who had tested positive for anti-imiglucerase antibodies at Screening (Section 4.4.3 for discussion on immunogenicity).

Table 21: Serious Adverse Event Listing in 034 (from Shire)

Velaglucerase alfa Dose	Unique Subject Identifier	Dictionary-Derived Term (Preferred Term)	Reported Term for the Adverse Event	Causality	Severity/ Intensity	Action Taken with Study Treatment
15 U/kg	034-048-0001	Anaphylactoid reaction	Anaphylactoid infusion reaction	Probably related	Moderate	Dose permanently discontinued
30 U/kg	034-154-0003	Swelling face	Swelling - face	Not related	Severe	Dose unchanged
		Urticaria	Hives - bilateral shoulders, neck, forehead, left wrist, and back	Not related	Severe	Dose unchanged
45 U/kg	034-009-0003	Arthralgia	Right ankle pain	Not related	Mild	Dose unchanged
	034-154-0002	Drug hypersensitivity	Allergic reaction to alteplase	Not related	Severe	Dose unchanged

Most patients (34/40, 85%) experienced at least one treatment emergent adverse event (TEAE). The most common TEAEs were headache, arthralgia, nasopharyngitis, back pain, myalgia, cough, pharyngolarnygeal pain, upper abdominal pain, pain in extremity, fatigue, pyrexia, diarrhea, nausea, upper respiratory tract infection, influenza, and

influenza-like illness. Overall, 28% experienced AEs that were considered possibly or probably related to study drug by the investigator. The majority of these events were considered to be infusion related. See the following table for details on the incidence of adverse events reported in this trial separated by treatment dose.

Table 22: Incidence of Adverse Events in 034 by Dose (from Shire)

	Velaglucerase alfa				
	Total N = 40 n (%)	15 U/kg N = 15 n (%)	30 U/kg N = 12 n (%)	45 U/kg N = 6 n (%)	60 U/kg N = 7 n (%)
Experienced No Adverse Events	6 (15.0)	3 (20.0)	1 (8.3)	1 (16.7)	1 (14.3)
Experienced At Least 1 Adverse Event	34 (85.0)	12 (80.0)	11 (91.7)	5 (83.3)	6 (85.7)
Experienced At Least 1 Drug-Related Adverse Event	11 (27.5)	6 (40.0)	3 (25.0)	1 (16.7)	1 (14.3)
Experienced At Least 1 Infusion-Related Adverse Event	9 (22.5)	6 (40.0)	2 (16.7)	0	1 (14.3)
Experienced At Least 1 Severe Or Life-Threatening Adverse Event	5 (12.5)	0	2 (16.7)	1 (16.7)	2 (28.6)
Experienced At Least 1 Serious Adverse Event	4 (10.0)	1 (6.7)	1 (8.3)	2 (33.3)	0
Discontinued Due To An Adverse Event	1 (2.5)	1 (6.7)	0	0	0
Deaths	0	0	0	0	0

5.3.33 Conclusion

Efficacy

Patients who have transitioned from imiglucerase to velaglucerase treatment at doses ranging from 15 to 60 U/kg EOW appear to have sustained clinical stability in hemoglobin concentration and platelet counts through 12 months of velaglucerase treatment. No patients required a dosage adjustment. A more detailed analysis of individual patient results, when the data becomes available, could aid labeling instructions for patients transitioning from a stable dose of imiglucerase.

Safety

From the abbreviated study report, it appears that patients with type 1 Gaucher disease can be safely transitioned from every other week administration of imiglucerase (15 to 60 U/kg) to the same dose of velaglucerase. No deaths or life-threatening AEs were reported. Of the SAEs reported, there is only one SAE that is likely related to study drug. One patient did experience an anaphylactoid reaction upon receiving velaglucerase; however, this is the first adverse reaction of this kind across the development program to date. Patients did not produce antibodies to velaglucerase regardless of their anti-imiglucerase antibody status at Screening indicating that no cross-reactivity was seen.

Trial 025 (Phase 1/2 Trial)

An Open-label, Dose Escalation, Pharmacokinetic, Clinical Activity, and Safety Study of Velaglucerase Alpha (GA-GCB) Replacement Therapy in Patients with Type 1 Gaucher Disease

Trial period: April 24, 2004 to April 18, 2005

This study was conducted at a single clinical site in Israel. The principal investigator was Ari Zimran, MD, . Clinical monitoring was provided by . MRI images were reviewed and echocardiograms were reviewed by a Staff cardiologist . Statistical analyses and report writing were performed by Shire HGT. All clinical laboratory analyses, including tryptase and complement assays, were performed Clinical data management was provided Assays for the measurement of velaglucerase protein concentration by ELISA in serum for pharmacokinetic (PK) analyses and serum antibodies to velaglucerase were performed at Shire HGT. b(4)

Of Note: Patients in Trials 025 and 025EXT have been treated with the clinical study supply of velaglucerase , which was found not to be comparable with AF1 used in TKT032 and TKT039. Thus, the results of these trials are reviewed but can not directly be used to represent safety and efficacy of the to-be-marketed AF2 drug product. Preliminary review of chemistry data show AF1 and AF2 to be comparable. b(4)

5.3.34 General Design and Objective

Primary Objective

- Evaluate the safety of velaglucerase when administered at a dose of 60 U/kg every other week for a total of 40 weeks to patients with type 1 Gaucher disease.

Secondary Objective(s)

The secondary objectives of this study were:

- Evaluate the improvement in hematological parameters and reduction in liver and spleen volume volumes.

This was a single-center, open-label, Phase 1/2 safety study. Velaglucerase was administered intravenously (IV) every other week (EOW) for 40 weeks. A cohort of three patients was first administered velaglucerase in a staggered dose escalation separated by seven days (15, 30, and 60 U/kg). After the third patient had completed velaglucerase dosing at 60 U/kg an additional cohort of nine patients were enrolled and

administered 60 U/kg IV every other week for 20 doses. The initial cohort of three patients who underwent dose escalation received subsequent infusions at 60 U/kg IV EOW.

5.3.35 Inclusion

1. Patients ≥ 18 years with a diagnosis of type 1 Gaucher disease and who had disease-related anemia and thrombocytopenia, deficient GCB enzyme activity (measured in leukocytes), platelet count less than the lower limit of normal (LLN) for age, hemoglobin values at least 1 g/dL below the LLN
2. Negative result for hepatitis B and C antigen and HIV
3. Female patients of child-bearing potential were to use birth control during the study and have a negative serum pregnancy tests
4. Patients who had received imiglucerase were eligible if they received therapy ≥ 12 months prior to enrollment and were imiglucerase antibody-negative at enrollment.
5. Patients enrolled in the dose-escalation phase were to weigh ≥ 50 kg.

5.3.36 Exclusion

Patients who met any of the following criteria were excluded from the study:

1. Previously received an approved or investigational therapy for Gaucher disease within the past 12 months prior to enrolling.
2. Received any investigational therapy within the 30 days prior to enrollment.
3. Patient had type 2 or 3 Gaucher disease.
4. Patient with splenectomy.
5. Patients with anti-imiglucerase antibodies.

5.3.37 Treatment

Velaglucerase was administered as a continuous, one-hour IV infusion at the following dose levels: 15, 30, and 60 U/kg in the initial cohort of three patients. Subsequent dosing in these patients and nine additional patients was to be at 60 U/kg administered EOW (total of 20 infusions).

Permitted and Prohibited Therapies
Additional medications and therapies taken by patients at study entry or during the study were documented on the CRF. Concomitant medications could be given at the discretion of the investigator. Treatment with other investigational drugs or devices during the trial was not allowed.

5.3.38 Endpoints

The primary clinical activity assessments were hemoglobin concentrations, platelet counts, and liver and spleen volumes (pre-specified analysis was to occur at Week 37). Measurements of hemoglobin concentrations and platelet counts were performed at baseline, and Weeks 1, 3, 5, 13, 21, 25, 33, 37, 39 (last infusion), and 41. Liver and spleen volumes were measured using quantitative abdominal MRI at baseline, Week 25, and Week 37.

Secondary Efficacy Variables

- Plasma chitotriosidase levels
- Plasma CCL18 levels
- Exploratory assessments included measurements of pulmonary function (FVC, FEV1, lung volume measurement), echocardiogram, MRI of the femor and lumbar spine, skeletal survey, and bone density assessment of the lumbar spine and femoral neck.

Safety Variables

Safety evaluations performed at every infusion included vital sign measurements and AE assessments. Serum chemistry and hematology laboratory tests were performed at baseline and Weeks 1, 3, 5, 13, 21, 25, 33, 37, 39, and 41. Urinalysis and ECG were performed at baseline and Weeks 1, 5, 13, 21, 25, 33, 37, and 41. Physical examinations were performed at baseline and Weeks 1, 3, 5, 9, 13, 17, 21, 25, 29, 33, 37, 39, and 41. Pregnancy tests were to be performed for females of child-bearing potential at baseline, then periodically as well as at end of study. Testing for serum anti-velaglucerase antibodies was performed at baseline and Weeks 13, 25, 37, and 41. Pulmonary functions tests and cardiac echocardiograms were performed at baseline and Week 37 (echocardiogram) or 41 (pulmonary function).

An infusion-related adverse event was defined prospectively in the protocol as an adverse event that 1) occurred on the day of the infusion, 2) began either during or after the infusion, and 3) was judged as possibly or probably related to study drug.

Pharmacokinetics:
Blood was collected immediately prior to and at specified times during and following specified study drug infusions. Serum samples were evaluated for the presence of administered velaglucerase using a glucocerebrosidase enzyme activity assay.

5.3.39 Data Analysis

For the primary clinical activity parameters of hemoglobin concentration, platelet count, and liver and spleen volumes, the null hypothesis was that there was no difference between the baseline value and the end-of-study (Week 37, 9-month) value. Comparisons were performed using two-tailed hypothesis testing at the 5% level of

significance. The difference between the baseline measurement of the variable and the measurement at the end of study (Week 37) was analyzed using either the Wilcoxon signed rank test (if the data were found to be non-normally distributed) or paired t-test. The change from baseline was calculated and percent change from baseline summarized using descriptive statistics by visit.

For secondary clinical activity parameters, the observed data, change from baseline, and percent change from baseline were summarized by visit using the mean, SD, median, minimum and maximum. No statistical testing was performed on this data.

The intent-to-treat (ITT) patient population was defined as any enrolled patient receiving at least one infusion of velaglucerase (partial of full). The safety population was also defined as all patients receiving at least one full or partial dose; thus the two populations were defined using the same definition. No formal statistical tests were performed on the safety parameters.

Changes in the Conduct of the Study
There were three amended protocols submitted to the IND (Aug 6, 2004, Oct 18, 2004, and Mar 11, 2005) after the initiation of the protocol; however, none of the changes was critical to the efficacy or safety analysis.

5.3.40 Number and Disposition of Patients

In this study, 13 patients were screened; 12 patients were planned, enrolled, and treated; and 11 patients (92%) completed the study. One patient (025-071-0004) was a screen failure and did not receive velaglucease (patient had measurable antibody titers to imiglucerase). One patient discontinued (025-071-0006) for reasons unrelated to velaglucerase administration after receiving her third dose. *(Reviewer Comment: from the CRF, it appears that this patient had psychosocial issues relating to her decision to withdraw from the trial*). No patient was excluded due to a major protocol violation or development of withdrawal criterion.

Three patients did not satisfy all inclusion and exclusion criteria and received an exemption to participate in the study. Patient 025-071-0003 and -0012 were not anemic at the time of enrollment but had genotyping results confirming Gaucher disease. Patient 025-071-0007 had a partial splenectomy in 1987 with Gaucher-related re-growth of the splenic remnant and consequent splenomegaly. In addition, this patient had a history of being anti-hepatitis C virus (HCV) positive. Repeat PCR testing had been shown to be negative.

Table 23: Patient Population and Disposition 025 (from Shire)

Patient Status	Initial GA-GCB Dose		
	15 U/kg n (%)	60 U/kg n (%)	Overall n (%)
Enrolled but not dosed	0	0	1
Patients dosed	3 (100.0)	9 (100.0)	12 (100.0)
Completed the Study	3 (100)	8 (88.9)	11 (91.7)
Withdrew from Study Reason for Withdrawal: Withdrawal of Consent	0 0	1 (11.1) 1 (11.1)	1 (8.3) 1 (8.3)
TKT 025 Patient Populations Intent-to-Treat (ITT) Safety	 3(100.0) 3 (100.0)	 9 (100.0) 9 (100.0)	 12 (100.0) 12 (100.0)

5.3.41 Demographics

The mean age was 42 years (range 19-70 years), and mean weight was 60 kg (50-73 kg). All patients were Caucasian, and 7/12 (58%) were female.

Table 24: Demographics for Patients in 025 (from Shire)

Characteristic	GA-GCB		
	15/30/60 U/kg n = 3	60 U/kg n = 9	All Patients n = 12
Gender, n (%) Male Female	 2 (66.7) 1 (33.3)	 3 (33.3) 6 (66.7)	 5 (41.7) 7 (58.3)
Race, n (%) Caucasian	 3 (100.0%)	 9 (100.0)	 12 (100.0)
Age (years) Mean ± SD Median Range	 47.80 ± 20.17 56.10 24.8 – 62.5	 39.63 ± 17.08 35.60 18.8 – 69.8	 41.68 ± 17.31 39.30 18.8 – 69.8
Weight (kg) Mean ± SD Range	 65.97 ± 11.15 53.1 – 72.8	 57.52 ± 7.85 49.7 – 71.0	 59.63 ± 9.06 49.7 – 72.8
Height (cm) Mean ± SD Range	 167.20 ± 11.15 159.6 – 180.0	 170.07 ± 7.42 161.3 – 184.0	 169.35 ± 8.02 159.6 – 184.0

Percentages are based on total number of patients for each dose group or overall as appropriate.

Concomitant Medications Used
All 12 patients received at least one concomitant medication during the study. The most frequently used (by three or more patients) classes of concomitant medications were vitamin B12 (7, 58%) and anilides (5, 42%), pyrazolones (4, 33%), and coxibs (3, 25%), bisphosphonates (3, 25%), calcium combinations and other drugs (3, 25%), and aluminum/calcium/magnesium combinations (3, 25%). There was no apparent relationship between the concomitant medications and response to treatment.

Measurements of Treatment Compliance
Most (11/12) received all scheduled doses; one patient (025-071-0006) discontinued the study after receiving three doses of study drug for reasons unrelated to GA-GCB (patient withdrew consent). Based on the timing of dosing and safety data collection, the first patient dosed with GA-GCB in the dose-escalation phase received two 15-U/kg doses and then one 30-U/kg escalation dose. The next two patients received one 15-U/kg dose and then one 30-U/kg escalation dose. Based on acceptable safety evaluations, all three of these patients had their doses increased to 60 U/kg.

5.3.42 Efficacy Evaluation

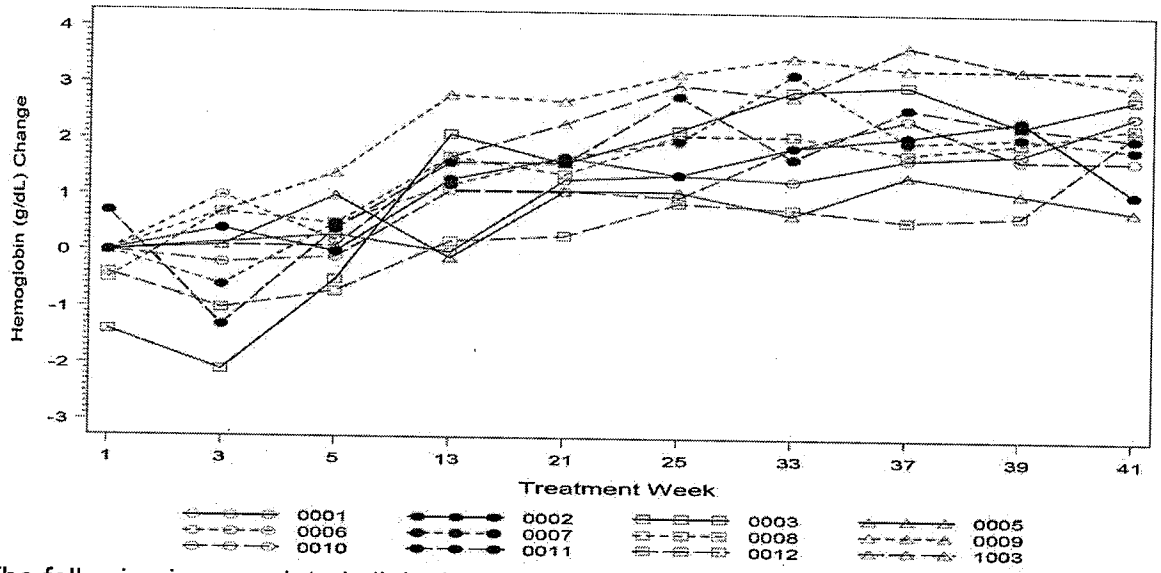
In this nine-month study, clinically and statistically significant mean increases from baseline in hemoglobin concentrations and statistically significant mean increases from baseline in platelet counts were observed three months following initiation of velaglucerase. Additionally, at the first scheduled liver and spleen evaluation at Week 25 (Month 6), statistically significant reductions from baseline were seen in mean liver and spleen volumes. Marked reductions in biomarker values (serum chitotriosidase and CCL18) were observed by Month 3. Overall, mean improvement in all of these parameters was continual during the course of velaglucerase administration.

Primary Efficacy Endpoint
At baseline, mean hemoglobin concentration was 11.6 g/dL. Mean increases from baseline in hemoglobin concentrations were 1.2 g/dL (11%) at Week 13 (Month 3), 1.9 g/dL at Week 25 (16%), and 2.2 g/dL (19%) at Week 37 (Month 9). At the end of the study, 10 of 11 patients experienced normalization of hemoglobin concentration.

Table 25: Mean Hemoglobin Change for 025

Hemoglobin (g/dL)	Baseline N=12	Week 37 N=12
Mean Observed Value (±SD) Min-Max	11.6±1.3 10 – 13.5	13.9±1.8 11.8 – 16.6
Change from Baseline (±SD) Min-Max	–	2.2±0.9 0.6 – 3.7 p<0.001
% Change from Baseline (±SD) Min-Max	–	19%±8 4 – 29% P<0.001

Figure 9: Hemoglobin Data Points for Each Patient During 025 (from Shire)



The following is an updated clinical efficacy figure depicting the mean hemoglobin change from baseline for patient in TKT025 through the extension trial up to 60 months exposure. Improved hemoglobin levels are maintained over time.

Figure 10: Mean Hemoglobin Change(±SE) from Baseline for 025 and Extension (from Shire)

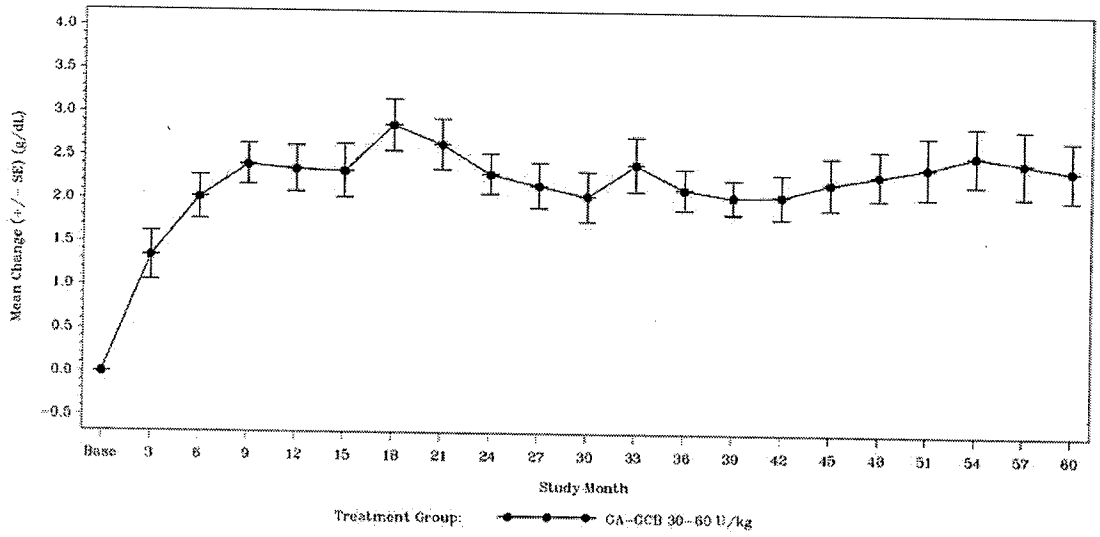


Table 26: Hemoglobin and Platelet Data for Patients in 025 (from Shire)

GA-GCB Dose (U/kg)	Patient Number (Gender)	Baseline Hgb	Hgb Wk 25	Hgb Wk 37	Baseline Platelet Count	Platelet Count Wk 25	Platelet Count Wk 37
		(g\dL)			(x 10^3/ mm^3)		
15/30/60	0001 (Female)	10.8	12.2	12.5	80	123	149
15/30/60	0002 (Male)	12.7	14.1	14.8	69	74	90
15/30/60	1003[a] (Male)	12.9	15.9	16.6	46	40	36
60	0003 (Male)	13.5	15.7	16.5	48	95	128
60	0005 (Female)	10.6	11.7	12.0	52	68	72
60	0006[b] (Female)	10.9	-	-	56	-	-
60	0007 (Female)	10.5	12.5	12.5	37	32	39
60	0008 (Female)	10.0	12.1	11.8	65	137	150
60	0009 (Male)	12.6	15.8	15.9	69	97	120
60	0010 (Female)	10.1	11.1	12.5	48	60	86
60	0011 (Female)	11.0	13.8	13.6	59	98	110
60	0012 (Male)	13.5	14.4	14.1	59	65	99

Hgb = hemoglobin
[a] This patient number was assigned out of sequence but never corrected.
[b] Patient 025-071-0006 discontinued the study (for non drug-related reasons) after receiving the third (Week 5) GA-GCB infusion.

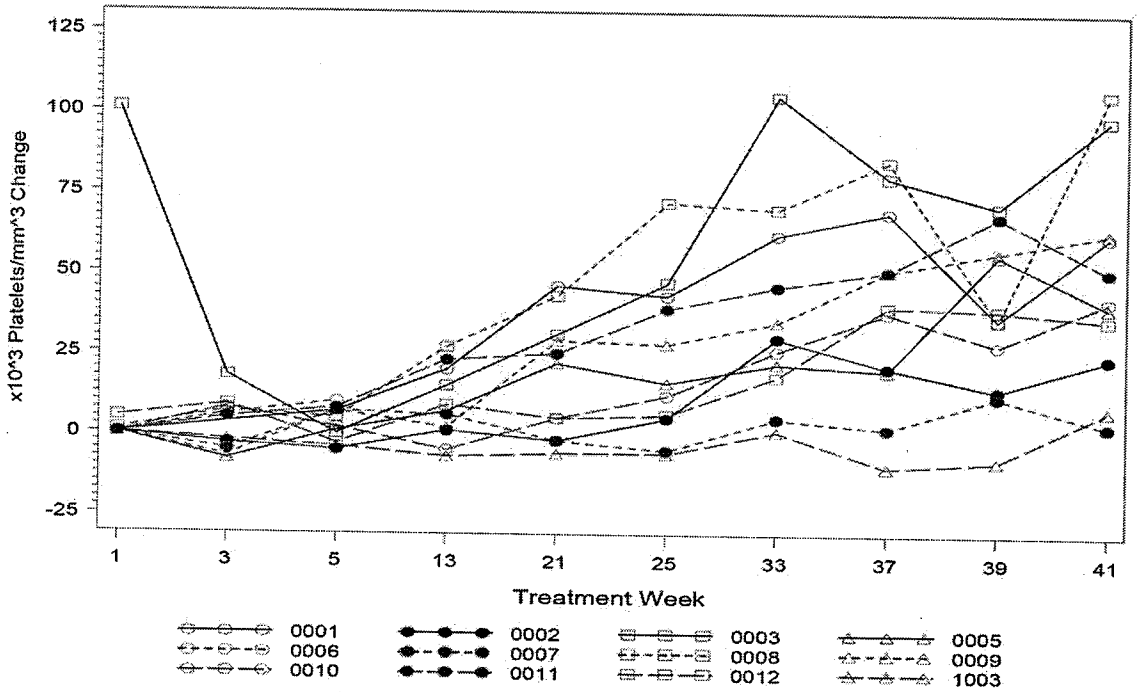
Secondary Efficacy Endpoints

Statistically significant increases from baseline (57 x 10^3/mm^3) in mean platelet counts were observed by Week 13 and continued throughout the study. Platelet counts increased from baseline by 9 x 10^3/mm^3 (15%) at Week 13, by 23 x 10^3/mm^3 (38%) at Week 25, and by 41 x 10^3/mm^3 (68%) at Week 37. Similar results also were observed when hemoglobin and platelet data were analyzed using the last observation carried forward (LOCF) imputation technique.

Table 27: Mean Platelet Change for 025

Platelet Count ($x\ 10^3/mm^3$)	Baseline N=12	Week 39 N=12
Mean Observed Value (±SD) Min-Max	57.3±12 37 – 80	95.4±38.1 36 – 150
Change from Baseline (±SD) Min-Max	–	38.1±31 -10 – 85 P=0.001
% Change from Baseline (±SD) Min-Max	–	64±53% -22 – 167% P=0.002

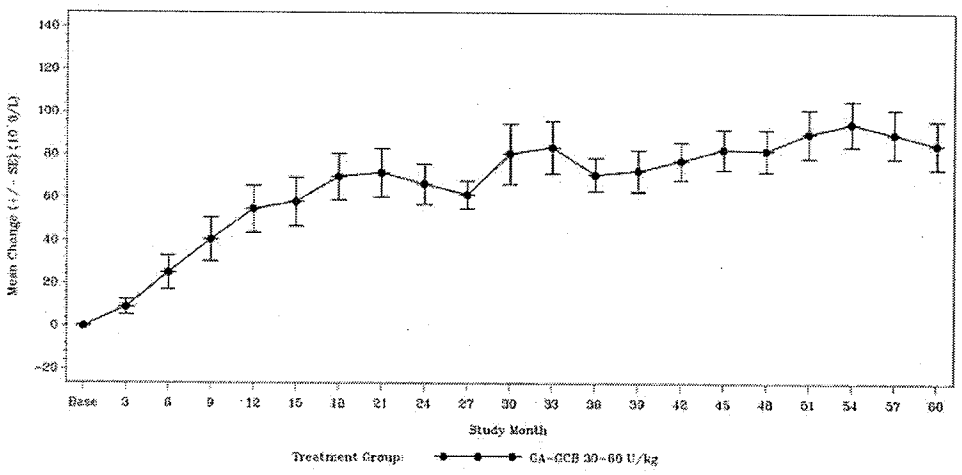
Figure 11: Platelet Count Data Points for Patients in 025 (from Shire)



Of note: Patient 025-071-0003, a 35-year-old male, had a baseline platelet count of 48 x $10^3/mm^3$ with a transient platelet count of 149 x $10^3/mm^3$ observed at Week 1. The investigator attributed these results to a recent bone crisis (occurred approximately one month prior to baseline), as well as acute pain and disability in the left hip joint with possible evidence of acute avascular necrosis.

The following is an updated clinical efficacy figure depicting continued improvement of platelet count from baseline through Month 60 from patients in the 025 and extension trial.

Figure 12: Mean Platelet Count Change (±SE) from Baseline in Trial025 and Extension



Statistically significant decreases from baseline in normalized liver and spleen volumes (corrected by percentage of body weight) were observed at Weeks 25 (Month 6) and 37 (Month 9). At baseline, mean normalized liver volume was 4.2% of body weight (normal volume, 2.5% of body weight), while mean normalized spleen was 3.8% of body weight (normal volume, 0.2% of body weight). At the first scheduled evaluation at Week 25 (Month 6), statistically significant decreases in mean percent changes from baseline in normalized liver volume (-15%, $p = 0.002$) and normalized spleen volume (-41%, $p < 0.001$) were observed. At Week 37 (Month 9), mean percent decreases from baseline in normalized liver volume (-18%, $p < 0.001$) and normalized spleen volume (-50%, $p < 0.001$) were observed.

Table 28: Liver Volume Change for Patients in 025

Liver Volume (% of Body Weight)	Baseline N=12	Week 39 N=11
Mean Observed Value (±SD) Min-Max	4.2±1.2 2.6 – 5.8	3.3±1.9 2.1 – 4.7
Change from Baseline (±SD) Min-Max	–	-0.8±0.5 -1.5 – -0.1 P<0.001
% Change from Baseline (±SD) Min-Max	–	-18±8% -28 – -5% P<0.001

Figure 13: Normalized Liver Volume (% Body Weight) by Patient in 025 (from Shire)

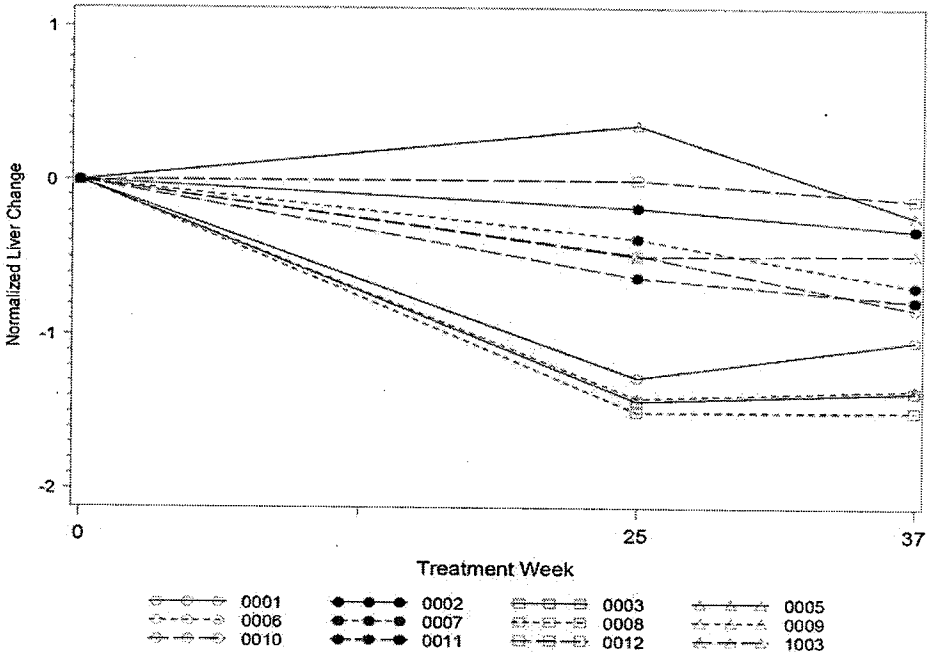


Figure 14: Mean Normalized Liver Volume (±SE) in 025 and Extension

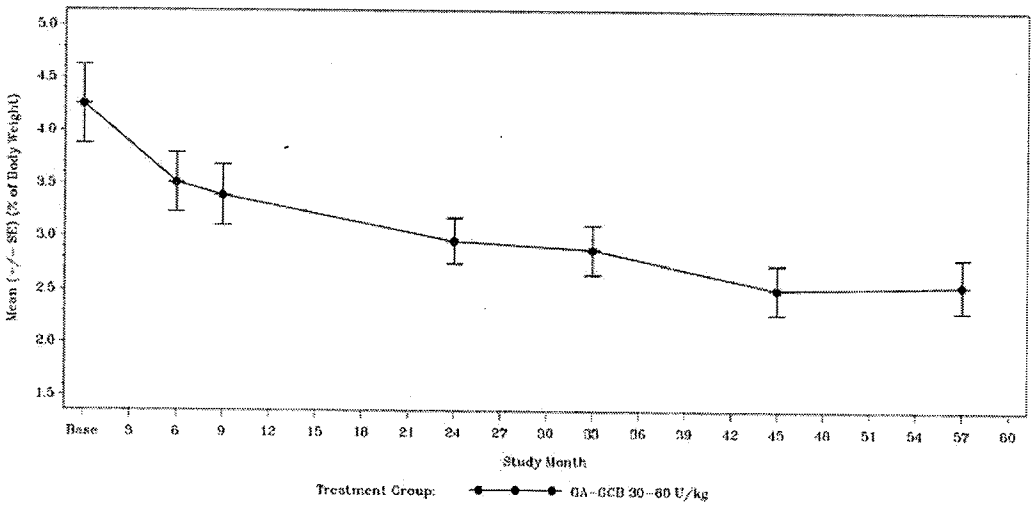


Table 29: Spleen Volume Change for Patients in 025

Spleen Volume (% of Body Weight)	Baseline N=12	Week 39 N=11
Mean Observed Value (±SD) Min-Max	3.8±1.2 2.2 – 6.5	2±1 1.2 – 4.9
Change from Baseline (±SD) Min-Max	–	-1.9±0.7 -3.6 – -1 P<0.001
% Change from Baseline (±SD) Min-Max	–	-49±13% -65 – -24% P<0.001

Figure 15: Normalized Spleen Volume (%Body Weight) by Patient in 025 (from Shire)

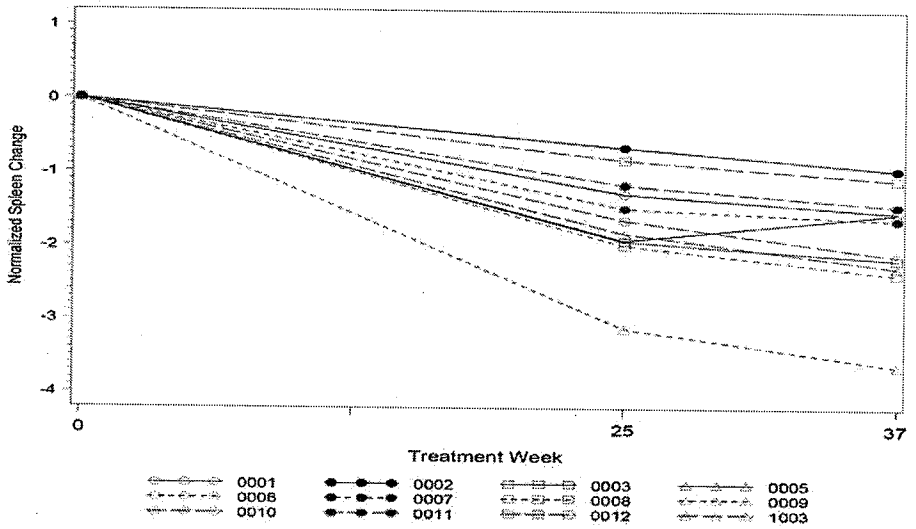
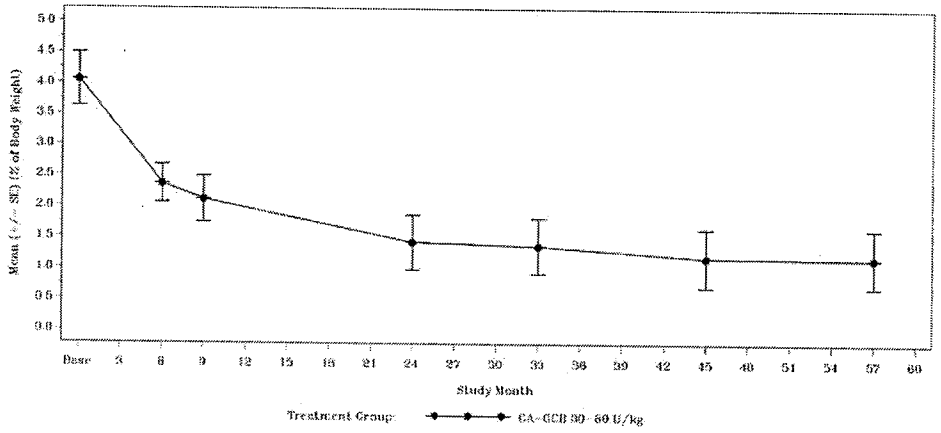


Figure 16: Mean Normalized Spleen Volume (±SE) in 025 and Extension



Plasma chitotriosidase and CCL18 levels decreased steadily from baseline during the trial. Marked mean decreases from baseline were seen in chitotriosidase 32,892 nmol/mL/h (normal range 150 nmol/mL/h) and CCL18 1,510 ng/mL (normal range 10 - 72 ng/mL) were observed at Week 13 (Month 3) for chitotriosidase (-17728 nmol/mL/h) and CCL18 (-412 ng/mL). By Week 37 (Month 9), the mean percent changes from baseline in plasma chitotriosidase had decreased by 74% and CCL18 levels had decreased by 57%.

No clinically significant changes or trends were observed in pulmonary function, bone density, bone marrow (as evaluated by MRI), or cardiac function (as evaluated by echocardiogram).

5.3.43 Safety Evaluation

There were no apparent trends in AE incidence rates, and generally the AEs were those expected among a Gaucher disease population. No deaths or serious adverse events were reported and no patient discontinued from the trial due to the occurrence of an adverse event. All 12 patients experienced one or more treatment-emergent AEs; in total, 103 AEs were reported. The most frequently reported AEs were dizziness, bone pain, and headache (each 5 patients; 42%). Arthralgia, back pain, pain in the extremities, influenza, upper abdominal pain, and asthenia (each 3 patients; 25%) were reported. All AEs were mild (Grade 1) except one event of bone pain, which was of moderate (Grade 2) severity and unrelated to study drug, per the investigator. None of the 103 AEs was considered severe or life threatening (Grade 3 or 4).

Ten patients experienced 22 AEs that were considered possibly or probably related to study drug: dizziness (3/12; 25%); back pain, bone pain, headache, increased body temperature, and nausea (each 2/12; 17%); and abdominal pain, asthenia, burning sensation, migraine, pain in extremity and tremor (each 1/12; 8%). Two of these AEs (dizziness and migraine) occurred more than once in a patient.

Nine (9/12, 75%) patients experienced a total of 17 infusion-related AEs: dizziness, headache, back pain, bone pain, fever (each 2; 17%), migraine, tremor, abdominal pain, nausea, pain in extremity and asthenia (each 1; 8%). No patient developed antibodies to velaglucerase. Additionally, no patient required pre-infusion medication during this study and no one had an infusion-related adverse event requiring interruption of administration of velaglucerase.

Table 30: TEAEs in >1 Patient Likely Related to Treatment in 025 (from Shire)

System Organ Class Preferred Term	GA-GCB 60 U/kg n = 12 patients	
	Patients n (%)	Events n (%)
Any Adverse Event	**10 (83.3)**	**22 (21.8)**
Nervous System Disorders	**6 (50.0)**	**11 (10.9)**
Dizziness	3 (25.0)	4 (4.0)
Headache	2 (16.7)	2 (2.0)
Burning sensation	1 (8.3)	1 (1.0)
Migraine	1 (8.3)	3 (3.0)
Tremor	1 (8.3)	1 (1.0)
Gastrointestinal Disorders	**3 (25.0)**	**3 (3.0)**
Nausea	2 (16.7)	2 (2.0)
Upper abdominal pain	1 (8.3)	1 (1.0)
Musculoskeletal and Connective Tissue Disorders	**4 (33.3)**	**5 (5.0)**
Back pain	2 (16.7)	2 (2.0)
Bone pain	2 (16.7)	2 (2.0)
Pain in extremity	1 (8.3)	1 (1.0)
General Disorders and Administration Site Conditions	**1 (8.3)**	**1 (1.0)**
Asthenia	1 (8.3)	1 (1.0)
Investigations	**2 (16.7)**	**2 (2.0)**
Body temperature increased	2 (16.7)	2 (2.0)

Clinical Laboratory Evaluations

For the majority of patients who received velaglucerase, there were no significant changes in nonclinical activity-related laboratory values. Additionally, only one patient experienced a laboratory abnormality that was reported as an AE (mild elevated serum glucose determined to be unrelated to study drug, as the patient has diabetes). Although many patients had values reported as clinically significant, most were transient and determined to be unrelated to study drug by the Investigator.

There were no clinically significant changes observed in vital signs analysis other than in two patients who had mild fevers. ECGs were performed and no abnormalities due to treatment were reported. No clinically significant changes were observed in the exploratory parameters of pulmonary function, bone density, bone marrow (as evaluated by MRI), or cardiac function (as evaluated by echocardiogram).

None of the patients developed antibodies to velaglucerase during the trial.

5.3.44 Conclusion

In this study of 12 patients with type 1 Gaucher disease, 60 U/kg velaglucerase administered IV EOW for nine months was well tolerated. Infusion-related adverse events were mild and transient; none of the patients had to interrupt velaglucerase infusion due to an infusion reaction and none required premedication. No patient developed antibodies to velaglucerase. Reported adverse events were generally mild in

severity and unrelated to treatment. Treatment appears to be clinically active in organ systems affected by Gaucher disease. Statistically significant improvements from baseline were seen in hemoglobin concentrations, platelet counts, and liver and spleen volumes and a reduction in biomarker values were observed three to six months after initial dosing.

As mentioned in Section 4.1, patients in 025 were treated with a drug supply that is not considered comparable to the to-be-marketed drug supply. However, the active moiety appears to have activity in type 1 Gaucher disease according to the data submitted.

Trial 025 EXT (Phase 1/2)

An Open-Label Extension of Study 025 Evaluating Long Term Safety in Patients with Type 1 Gaucher Disease Receiving Velaglucerase Alpha Enzyme Replacement Therapy

5.3.45 General Design and Objective

This trial is currently ongoing. The safety data included in this report encompass the time period of Feb 3, 2005, to June 1, 2009 (date of data cut-off). Only an abbreviated safety report was submitted to the NDA, efficacy data are not available at this time.

Objectives
The primary objective of this trial is to:

- Evaluate the long term safety of velaglucerase, when administered at doses of 60 and 30 U/kg every other week (EOW) by intravenous (IV) infusion to patients.

The secondary objectives of this study are to:

- Assess the effects of velaglucerase ERT on hemoglobin and platelet counts, liver and spleen size, and disease biomarkers in patients.
- Analyze pulmonary function tests, MRI of the femor and lumbar spine, skeletal survey and bone densitometry to evaluate clinical activity.

Trial 025EXT is an open-label extension study of 025. Ten patients, who were previously enrolled in 025, continued in 025EXT. All patients were to receive 60 U/kg velaglucerase IV EOW for a minimum of one year including treatment in Trial 025. Patients were then evaluated to determine whether they could receive velaglucerase at a transitional reduced dose of 45 U/kg administered every other week for 13 weeks, followed by 30 U/kg thereafter, for the remainder of the treatment period. To receive the reduced dose, patients had to meet at least two of four, year-one therapeutic criteria for ERT treatment of type 1 Gaucher disease.

5.3.46 Safety Evaluation

Safety was evaluated by assessments of adverse events (including infusion-related adverse events), concomitant medications, and vital signs. Additional safety assessments include ECG, echocardiograms, physical examinations, and collection of samples for clinical laboratory tests (hematology, serum chemistry, and urinalysis). Determination of the presence of anti-velaglucerase alfa antibodies and enzyme neutralizing antibodies were conducted approximately every 12 weeks and will continue to be collected until a patient's participation in the trial ends. Patients who were found to be positive for anti-velaglucerase alfa antibodies were to have pharmacokinetics assessed within six weeks of positive antibody status.

Ten patients have been treated for a median of 59 months, including treatment in 025 and 025EXT, and for a median of 50 months in 025EXT alone. The median actual average dose was 38 U/kg, and in 025EXT alone, the median actual average dose was 35 U/kg.

Deaths or Serious Adverse Events
No deaths have been reported. Four patients experienced a total of seven treatment-emergent SAEs. All SAEs were considered by the Investigator as not related to study drug. No patient experienced an adverse event that led to discontinuation of treatment. See Section 7.3.2 for the narratives of the SAEs reported for this extension trial.

Treatment Emergent Adverse Events
As of June 1, 2009, TEAEs were reported in all patients. The most frequently reported TEAEs were arthralgia (8 patients, 80%); back pain, pyrexia (6 patients each, 60%); headache, pharyngolaryngeal pain, upper abdominal pain (5 patients each, 50%); influenza, pain in extremity, abdominal pain, gingival bleeding, nausea, and fatigue (4 patients each, 40%). Most TEAEs were considered not related to study drug by the investigator. Two patients experienced a total of three TEAEs that were considered to be possibly or probably related to study drug. The events were tremor, pain in extremity, and fatigue. The events of tremor and pain in extremity by two patients are thought to be infusion related adverse reactions.

Most TEAEs were mild or moderate (Grade 1 or Grade 2) in severity. Two patients experienced a total of three severe (Grade 3) TEAEs. One patient experienced a severe headache and one patient experienced severe arthralgia and osteonecrosis. These events are described under serious adverse events which were deemed as unrelated to the treatment by the investigators. No patient experienced life-threatening (Grade 4) AEs.

Vital signs, ECG, nor echocardiogram reports were included in this submission. There are no clinically significant changes seen in the basic clinical chemistry and hematology parameters as determined by the investigators. No patients developed anti-velaglucerase alfa antibodies as of the cut-off date.

5.3.47 Conclusion

From this abbreviated study report, long-term treatment with velaglucerase appears to be well-tolerated. Thus far, no patients have discontinued treatment due to an infusion related reaction, required interruption of the infusion, or premedication for treatment. There have been no deaths and the SAEs are not thought to be related to study treatment by the Investigator. The majority of TEAEs were mild to moderate in intensity.

6 Review of Efficacy

Efficacy Summary

See Section 5 for detailed discussion of efficacy for the single pivotal Phase 3 trial (032). In this section, I combine the information obtained from 032 and the two other phase 3 trials 034 and 039. The full clinical reports for the later two trials were not required for filing, however, given the small size of the development program and the fact that each of the trials addresses distinct and important aspects of understanding use of velaglucerase in the treatment of Type 1 Gaucher disease, the most relevant efficacy information is pooled for analysis in this section.

Statistical review of the submission by Behrang Vali, MS, confirmed that the 032 results from analysis using the MITT and PP populations are robust. Analysis of 039 had only a total of four patients with missing hemoglobin data at end of study (two from each treatment group). Results from analysis of the 039 data using multiple imputation and worst-case imputation are robust. Lastly, efficacy results from the switch study, 034, were felt to be marginally supportive by the statistical reviewer due to the open-label switch design and with primary endpoint pertaining to safety.

6.1 Indication

Treatment of Type 1 Gaucher disease.

6.1.1 Methods

Note: Due to data availability limitations, only data for the primary endpoint of change in hemoglobin concentration and the secondary endpoint of change in platelet count data from study are presented for all three Phase 3 trials. The patient population in 034 was different (transitioned from ERT) and these data were made available recently. The 039 study has only recently been completed. Because the analyses for both these studies are ongoing, only abbreviated efficacy data sets are provided.

There were six efficacy measures common to all studies in the velaglucerase alfa clinical program, namely changes in the following parameters: hemoglobin concentration, platelet count, normalized liver volume measured by MRI, normalized spleen volume measured by MRI, plasma chitotriosidase level, and plasma CCL18 level. Many patients had undetectable levels of plasma chitotriosidase and the number of missing values of plasma CCL18 levels, thus these parameters are reported with descriptive statistics only in the individual trial reviews. Other secondary or tertiary efficacy measures used in one or more of the four studies were: pulmonary function, bone abnormalities, bone density, bone marrow, growth velocity, skeletal growth, Tanner staging, bone disease, and overall quality of life (QoL), as measured by the

Short Form-36 (SF-36) for patients ≥18 years and the Childhood Health Questionnaire (CHQ, PF50) for patients 5 to 17 years. Due to the limited availability of these data for purposes of pooling, the data are described for individual trials in Section 5.3.

The long-term benefit of velaglucerase alfa on bone parameters is being monitored in the ongoing 025EXT and 044 studies. Data will be collected and submitted for review when they become available.

The choice of patient population differed slightly between studies but all the trials evaluated the efficacy of velaglucerase alfa in patients with type 1 Gaucher disease. In Trial 034 patients who were positive anti-imiglucerase antibodies were allowed to enroll to assess efficacy in this patient population. Although testing positive for anti-imiglucerase antibodies was an exclusion criterion for Trial 039, no patient tested positive at baseline.

Trial 039 was a nine-month trial, whereas 032 and 034 were both of one-year duration. For Trials 032 and 039, the efficacy endpoints are all changes from baseline values that were outside the range of normal values (i.e., low hemoglobin concentration and platelet counts, and enlarged liver and spleen) as the patient populations were treatment-naive. However, for Trial 034, the patient population was already stabilized on ERT with imiglucerase and had hemoglobin concentrations close to or within the normal range. Here, the endpoint of a change in hemoglobin concentration would represent a departure from stable values.

Brief Description of the Three Phase 3 Trials

Trial 032 was a randomized, double-blinded, parallel group, multi-center, 12-month trial designed to evaluate the efficacy and safety of velaglucerase in patients ≥2 years of age with type 1 Gaucher disease. To be eligible, patients were to be treatment-naïve within the 30 months prior to study entry. Patients were randomized 1:1 to receive either 60 or 45 U/kg velaglucerase IV EOW for 51 weeks (12 months). Splenectomized patients were excluded. Twenty-five patients were randomized, 13 to 45 U/kg and 12 to 60 U/kg. All 25 patients completed the trial.

Trial 039 was a multi-center, non-inferiority, randomized, double-blind, parallel-group, nine month trial designed to compare the safety and efficacy of ERT with velaglucerase and imiglucerase. To be eligible for this study, patients were to be treatment-naïve. Eligible patients were randomly allocated to a 1:1 ratio to receive velaglucerase or imiglucerase 60 U/kg every other week. The primary objective of this trial was to compare the effects of velaglucerase and imiglucerase on hemoglobin concentration. The secondary objectives included effect comparison of platelet count, liver and spleen volume, and plasma chitotriosidase and CCL18 levels between velaglucerase and imiglucerase treatment. There were 35 patients were randomized; 34 patients received at least one dose (full or partial) of study drug and 1 patient was removed from the study by the investigator following randomization but prior to receiving study drug.

Trial 034 was a multi-center, open-label, 12-month trial evaluating the safety of velaglucerase EOW for patients ≥ 2 years of age who had received imiglucerase therapy for type I Gaucher disease for at least 30 consecutive months. Splenectomized patients and patients who were positive for imiglucerase antibodies were not excluded. Patients were to receive the same dose of imiglucerase during the six months prior to study enrollment. Eligible patients were to receive the same dose (U/kg) of velaglucerase EOW as their imiglucerase dose, which ranged between 15 U/kg and 60 U/kg. Administration of velaglucerase at home was available to patients who met the necessary requirements. Patients were monitored throughout the treatment period for changes in clinical parameters (i.e., hemoglobin, platelets, and liver and spleen volumes). There were 41 patients enrolled; 40 patients received at least 1 dose (full or partial) of velaglucerase alfa. One patient withdrew consent prior to receiving study drug.

6.1.2 Demographics

See Individual Trial Reports in Section 5.3, as efficacy was not pooled. Table 35 is the basic demographics for the safety population and serves as a reference as the efficacy and safety populations, which are very similar.

6.1.3 Subject Disposition

For the three Phase 3 trials, the following is the summary of patient disposition:

Trial 032: All patients completed the trial (25/25).
Trial 034: Of a total of 41 patients, 38 completed and 3 discontinued.
Trial 039: Of a total of 17 patients on velaglucerase, 16 completed and 1 discontinued.

6.1.4 Analysis of Primary Endpoint(s)

The following figures, copied from Shire, depict the mean change in hemoglobin for all Phase 3 trials.

Figure 17: Mean Change in Hemoglobin Across Visits (60 U/kg) for Trial032 (Dose Ranging)

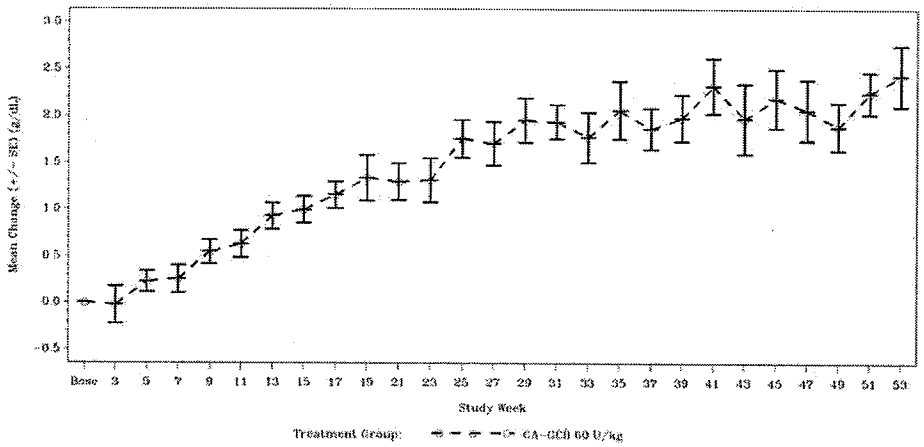


Figure 18: Mean Change in Hemoglobin Concentration from Baseline for Trial034 (Cross-Over)

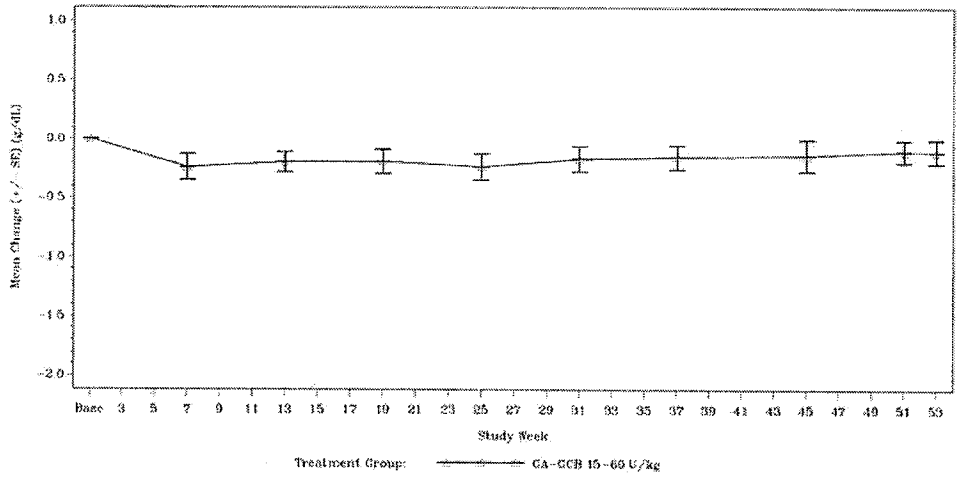
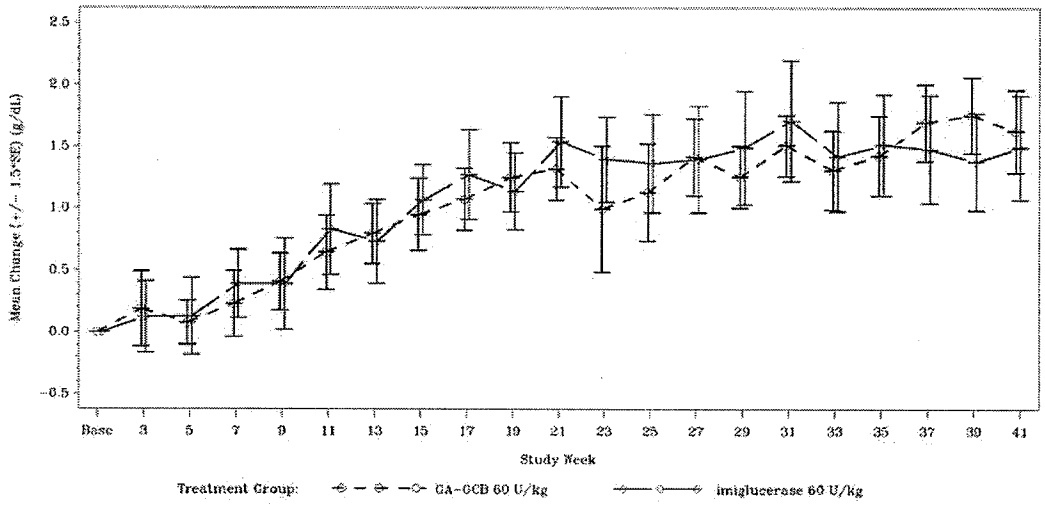


Figure 19: Mean Change in Hemoglobin Across Visits for Trial039 (Active Control)



For the Phase 3 trials, this reviewer asked Shire to provide a scatter plot of the hemoglobin values at baseline versus at completion of the trial (Figure 20 and Figure 21). This was to evaluate if baseline hemoglobin values had an influence on treatment results, i.e., if the severity of anemia correlated with treatment effect. Given the plots, it does not appear that patients with more anemia had increased treatment effect compared to those with less anemia. Modified baseline values (average of screening and baseline results) were plotted against the imputed end of study visit values to be consistent with how the primary endpoints in the trials were analyzed.

Figure 20: Scatter Plot of Hemoglobin at Baseline vs End of Study for 032 (from Shire)

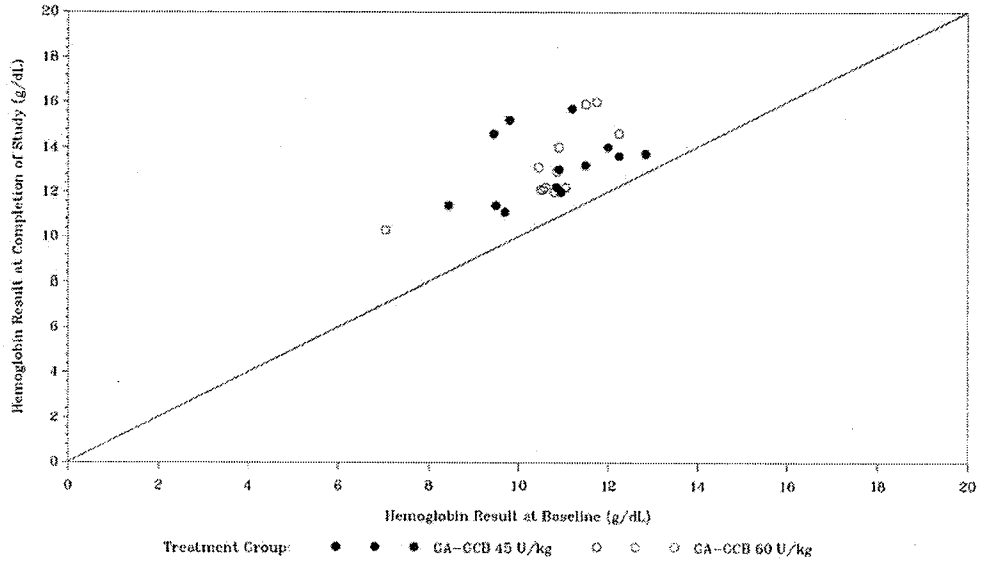
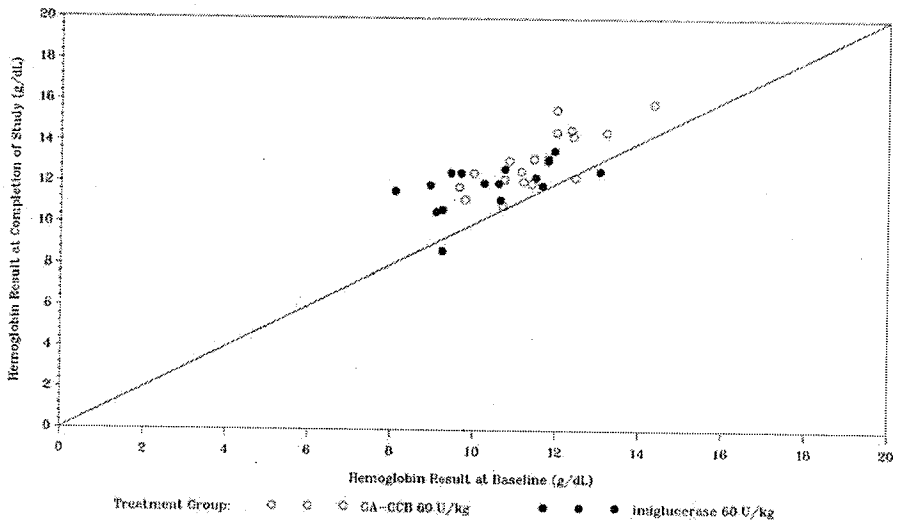
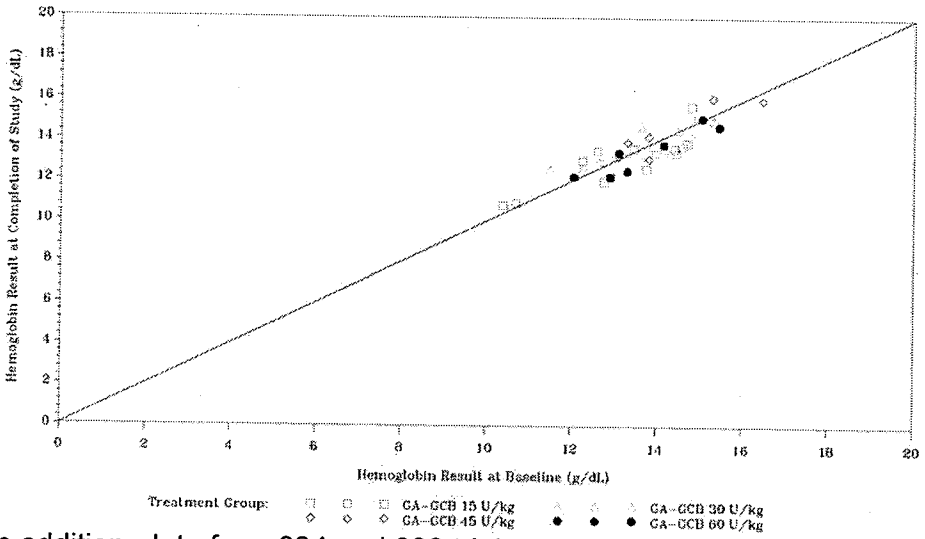


Figure 21: Scatter Plot of Hemoglobin at Baseline vs End of Study for 039 (from Shire)



In conclusion, the collection of data from 032 and 039 trials provide reasonable evidence that velaglucerase treatment leads to clinically significant increase in hemoglobin levels after approximately one year of treatment.

Table 31: Scatter Plot of Hemoglobin at Baseline vs End of Study for 034 (from Shire)



In addition, data from 034 and 039 trials provide evidence that velaglucerase and imiglucerase generally perform similarly with respect to hemoglobin after approximately one year of treatment and that transitioning from imiglucerase treatment does not lead to loss of therapeutic effect.

6.1.5 Analysis of Secondary Endpoints(s)

Data on platelet counts from the Phase 3 trials support efficacy of velaglucerase in Type 1 Gaucher patients. The following figures from 032 and 039 show steady improvements which are clinically meaningful in platelet counts for the patients who were treatment naïve or that platelet counts are relatively maintained even when transitioned from previous alternative ERT therapy from 034.

Figure 22: Mean Change in Platelets from Baseline by Study Week in 032 (from Shire)

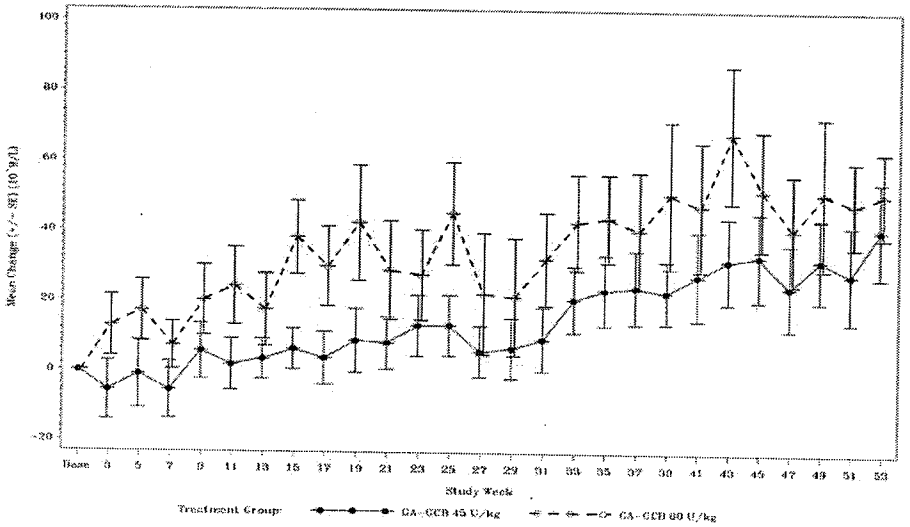


Figure 23: Mean Change in Platelets from Baseline by Study Week in 034 (from Shire)

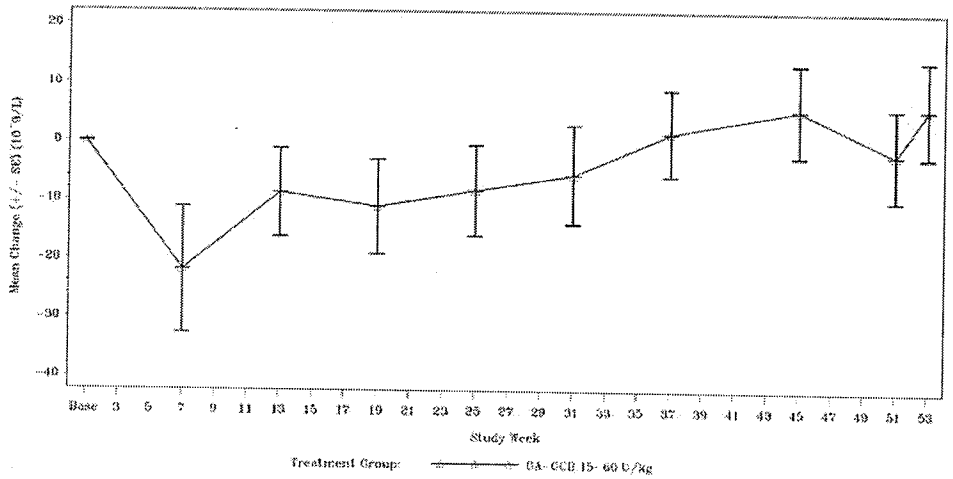
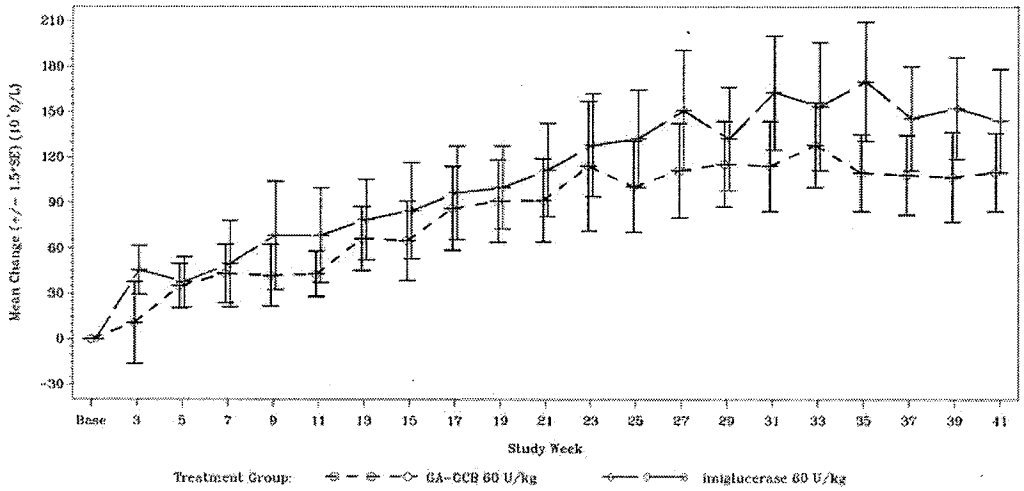


Figure 24: Mean Platelet Change from Baseline in 039 (From Shire)



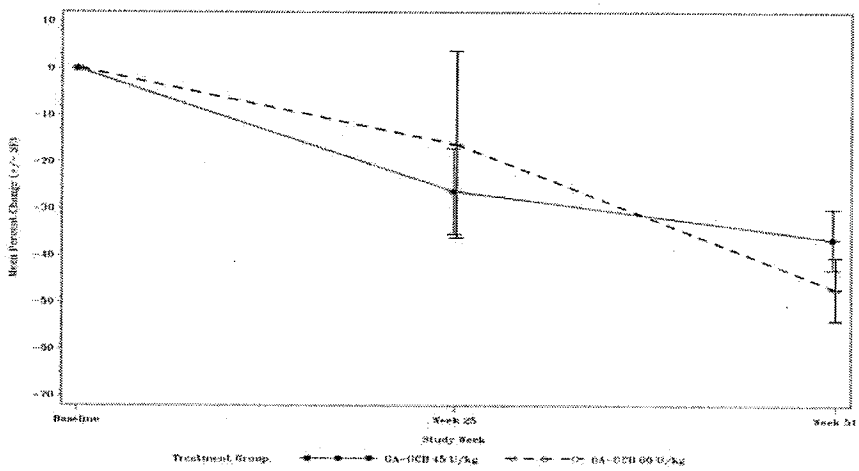
Comparison of liver volume data from the 032 and 039 support efficacy of velaglucerase in Type 1 Gaucher patients. The following table summarizes the velaglucerase treatment effect on liver volume.

Table 32: Comparison of Liver Volumes in 032 and 039

Liver Volume (% of body weight)	032	039
Baseline mean	60 U/kg= 3.9 45 U/kg= 4.0	Velaglucerase=3.9 Imiglucerase=4.0
End of Study mean (mean change from baseline)	Week 53 60 U/kg= 3.1 (-0.8) 45 U/kg=3.7 (-0.3)	Week 41 Velaglucerase=2.6 (-1.3) Imiglucerase=3.0 (-1.1)

Spleen volume data is only available for 032 among the phase 3 trials. Figure 25 shows clearly decreasing spleen size over time with velaglucerase treatment.

Figure 25: Mean Normalized (%of Body Weight) Spleen Volume (±SE) by Treatment Group – Mean Percent Change from Baseline in 032



In addition to the data available supporting the primary efficacy endpoint, combining the data from the various secondary endpoints, I feel there is substantial evidence supporting the efficacy of velaglucerase in improving pertinent clinical manifestations of type 1 Gaucher disease.

6.1.6 Other Endpoints

Integrated information on other exploratory is not available at this time for all three Phase 3 trials.

6.1.7 Subpopulations

No differences in efficacy among age and gender groups were noted.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Trial 032 was the only dose ranging trial. Please refer to Section 5.3.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

None.

6.1.10 Additional Efficacy Issues/Analyses

Previous experiences with alglucerase and imiglucerase have shown that enzyme replacement therapy results in significant improvement in hematological and organ volume parameters that are clinically beneficial for patients (see Table 33). Patients

who have discontinued therapy lose clinical benefit and there is noticeable decrease in hemoglobin and platelet counts, which result in anemia/fatigue and bleeding. Skeletal disease involvement is important in Gaucher patients; however, skeletal lesions are more difficult to measure and respond very slowly to treatment. Therefore, in designing a clinical development program for type 1 Gaucher therapy the parameters of hemoglobin level, platelet count, as well as spleen and liver volume have been used to evaluate treatment effect. These parameters are objective and easily measurable and we have developed an understanding of improvement in laboratory values that are clinically meaningful (e.g., increase in hemoglobin >1.5 g/dL is a good response, and severity of anemia is known to correlate with degree of fatigue). Furthermore, observational studies have shown that in this disease, spontaneous improvement or resolution is not expected (see Section 9.1).

Table 33: Ceredase and Cerezyme Changes in Disease Markers from Baseline

b(4)

*for mean % decrease from Baseline
The above table is from Grabowski et al. Enzyme Therapy in Type1 Gaucher Disease: Comparative Efficacy of Mannose Terminated Glucocereborsidase from Natural and Recombinant Sources. Ann Intern Med 1995;122:33-29.

The basis for approval of velaglucerase for the treatment of Gaucher disease is two-fold:

1. The pivotal trial 032 did not show a clear dose-response effect, both 45 and 60 U/kg of velaglucerase treatment resulted in similar improvements in all four measured parameters of hemoglobin, platelet, spleen and liver volumes. Treatment effect would have been easier to demonstrate had there been a clear linear relationship between dose and response. However, we have observational data on the natural history of type 1 Gaucher disease that show that these hematological parameters and organ volumes are not expected to improve over time. Therefore, using historical controls, the data from the velaglucerase trials demonstrate convincingly that there is a positive and meaningful treatment effect.

2. We have experience from alglucerase and imiglucerase enzyme therapies that were approved for type 1 Gaucher in 1991 and 1994, respectively. Table 33

Thus, it is my opinion that the data submitted in the three Phase 3 trials provide sufficient evidence of efficacy using both historical and active controls as basis for comparison.

7 Review of Safety

Safety Summary

Velaglucerase is generally well tolerated in treatment-naïve and transitioned (from imiglucerase) pediatric and adult patients with Type 1 Gaucher disease at doses ranging from 15 to 60 U/kg. Most TEAEs are mild or moderate in severity. There were no deaths, and of 12 SAEs, few appear to be directly related to velaglucerase treatment. Common AEs are infusion reactions, headache, URI-type symptoms, bone pain, pyrexia, arthralgia, dizziness, myalgia, and back pain. Adverse reactions considered related to the use of velaglucerase as stated by Shire include headache, dizziness, abdominal pain, nausea, bone pain, arthralgia, back pain, aPTT prolonged, infusion related reactions, fatigue, pyrexia, hypertension, hypotension, flushing, tachycardia, rash, urticaria, allergic dermatitis, and anaphylactoid reaction. Only one patient in the development program thus far has developed antibodies to velaglucerase. My independent safety analysis did not find major discrepancies compared with the Applicant analysis.

7.1 Methods

Important safety parameters in individual trials were reviewed by assessing for outliers from the standard range. Abnormal results were subsequently assessed for relationship to treatment and for clinical significance.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The four completed trials 025, 032, 034, and 039, as well as one extension study (025EXT) were reviewed for safety signals. As the drug substance used in 025 is not comparable to those used for the other trials, the safety data from this trial was not pooled with the others mentioned above in my analysis. Furthermore complete safety data and analysis were unavailable from the Applicant for 034 and 039 due to recent completion of these trials (laboratory, vital signs, and ECG data are pending).

7.1.2 Categorization of Adverse Events

MedDRA Version 9.0 was used to categorize adverse events. I reviewed each of the adverse event patient verbatim terms and Applicant coded preferred terms from all trials. Preferred terms were revised to maintain consistency across trials and to minimize splitting or clumping of events (for example: nasopharyngitis, common cold, and upper respiratory infection were all recoded as upper respiratory infection; whereas, the preferred term arthralgia was recategorized as joint pain or bone pain and by location).

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

In my analysis, individual events were recoded as needed as mentioned in 7.1.2 and data were pooled from the three Phase 3 Trials (032, 034, and 039 velaglucerase treated patients only). Trials 032 and 034 were both 12 months and 039 was 9 months in study duration, which are all relatively comparable. Naïve patients AE rate from 032 and 039 were also compared to rates in 034, and each of these subgroups were compared to the pooled safety analysis. My analysis was compared to the Applicant analysis. Data from 025 and the extension trial were also reviewed and compared for major differences to the Phase 3 safety data. The 025 data were not pooled, as the study drug used is not comparable.

7.2 Adequacy of Safety Assessments

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

There is an adequate safety database that includes 94 patients with type 1 Gaucher disease (treatment-naïve or transitioning from imiglucerase) treated with velaglucerase alfa EOW with doses from 15 to 60 U/kg.

A total of 52 of 54 treatment-naïve patients have completed treatment with velaglucerase for 9 months; 35 patients have completed treatment with velaglucerase of 12 months. Of the treatment-naïve patients, 41 patients have been treated at a dose of 60 U/kg. There were 10 of 11 patients who completed nine months of treatment in 025 who elected to continue treatment in the open-label extension study 025EXT. In 025EXT, 8/10 patients have received 51 months of treatment in this study, for a cumulative (025 + 025EXT) exposure to velaglucerase alfa of 60 months.

Velaglucerase has also been administered to 40 patients transitioning from ERT with imiglucerase, at doses of 15 to 60 U/kg (same dose as the patient's imiglucerase ERT); 38 patients completed one year of velaglucerase treatment.

Table 34: Number of Patients by Completed Treatment with Velaglucerase - Safety Population

	9 months	12 months	51 months
Treatment-naïve (n=54)	52 (96%)	35 (65%)	8 (15%)
Transitioned (n=40)	38 (95%)	38 (95%)	-

Table 35: Basic Demographics for Safety Population

Baseline Characteristics		Treatment Naive			Non-Naive
		45 U/Kg N=13	60 U/Kg N=41	Total N=54	Total N=40
Age (years)	2-4	0	1 (2%)	1 (2%)	0
	5-10	1 (8%)	5 (12%)	6 (11%)	2 (5%)
	11-17	2 (15%)	2 (5%)	4 (7%)	7 (17%)
	≥ 18	10 (77%)	33 (81%)	43 (80%)	31 (78%)
	Mean±SD Min-Max	31±17 6-62	31±17 4-69	31±17 4-69	36±18 9-71
Sex	Male	8 (62%)	20 (49%)	28 (52%)	18 (45%)
	Female	5 (39%)	21 (51%)	26 (48%)	22 (55%)
Race	Caucasian	13 (100%)	36 (88%)	49 (91%)	37 (93%)
	Other		5 (12%)	5 (9%)	3 (7%)

7.2.2 Explorations for Dose Response

Relationship between dose and response was evaluated in 032. There was no clear dose response relationship in terms of safety signals seen in the pivotal 032 trial. See Section 7.5.1 for evaluation of AEs and various dosages of velaglucerase treatment.

7.2.3 Special Animal and/or In Vitro Testing

None.

7.2.4 Routine Clinical Testing

There was appropriate routine clinical testing of patients to collect safety data.

7.2.5 Metabolic, Clearance, and Interaction Workup

Velaglucerase alfa is not metabolized by CYP enzymes, therefore, drug-drug interaction via CYP is not expected. The clearance pathway for this product is distributive process, that is, uptake into target tissues by mannose receptors.

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 and an AERS database search by the Office of Surveillance and Epidemiology (see Section 7.7).

7.3 Major Safety Results

7.3.1 Deaths

There have been no deaths reported in this development program to date.

7.3.2 Nonfatal Serious Adverse Events

Twelve SAEs were included in the safety database for patients given velaglucerase treatment. Table 36 describes the specific serious adverse events reported in the various trials for velaglucerase treated patients only.

Table 36: Patients with Serious Adverse Events in Various Trials

025	032	034	039
0/12 025EXT 4/10 • Fever/abd pain • Hernia repair • Hip surgery • Cosmetic surgery	1/25 (4%) • Seizure (previous history of seizures)	4/40 (10%) • Anaphylaxis • Facial swelling/urticaria • Arthralgia • Drug hypersensitivity (to alteplase)	3/17 (18%) • Convulsions • Allergic Dermatitis • Thrombocytopenia

Narratives for the reported SAEs:

Probably or Possibly Related to Velaglucerase Treatment
Patient 034-048-0001 (Anaphylactic infusion reaction – 15 U/kg dose)
This 52-year-old female discontinued treatment with imiglucerase and one month later received her first dose of velaglucerase. The patient had no known food or drug allergies and no reported previous allergic reactions. The patient presented for her first dose of study medication and after receiving half of the infusion, the patient reported itching. She was noted to have red hives and swelling on the left side of the neck and cheek area. At 30 minutes after the initiation of the infusion, the patient's heart rate was 75 bpm and blood pressure was 107/85 mmHg. The infusion was stopped as per the protocol. Normal saline was infused and vital signs and pulse oximetry were monitored.

The patient then complained of a swelling or closing sensation in her throat, chills, stomach discomfort, and feeling anxious. Diphenhydramine and hydrocortisone were administered. The patient's vital signs remained stable throughout the episode. Itching, redness and throat discomfort resolved after approximately one hour. Blood samples were obtained for C3/C4, tryptase and CH 50 measurements. The patient was instructed by the physician to take diphenhydramine and to return to the center the next

day for follow-up blood work. The patient did not continue with the diphenhydramine at home. She was discharged the same day in stable condition and the event was considered resolved without sequelae.

One week later, screening for anti-velaglucerase and anti-imiglucerase IgG and IgE antibodies was completed on samples collected prior to the first velaglucerase infusion and 24 hours post infusion. A third sample was collected two weeks later. All test results were considered negative. Velaglucerase was permanently discontinued at the patient's request after this event. The investigator considered the anaphylactic infusion reaction moderate in intensity and probably related to study therapy.
Comment: I agree with the analysis of the Investigator that this hypersensitivity reaction is likely due to velaglucerase treatment.

Patient 039-165-0001 (Allergic dermatitis – 60 U/kg dose)
A 50-year old female without a previous history of allergies had episodes of allergic skin reaction 214 days after initial velaglucerase treatment and 7 days after the most recent dose. She was hospitalized for treatment with oxygen and steroids, adrenaline, and antihistamines. The patient continued to receive after two doses of treatment were withheld due to the SAE. Study treatment did resume and continue until completion with premedications.
Comment: The events were considered likely related to treatment by the Investigator and I agree with this analysis.

Patient 039-185-0001 (Convulsions – 60 U/kg dose))
This 9-year old female had a SAE of convulsions 117 days after her first treatment dose. The convulsions occurred immediately after completion of a treatment infusion. The patient did not have a prior history of seizures. Neurology evaluation and hospitalization for observation ensued. Treatment was discontinued and patient was lost to follow-up.
Comment: The investigator reported the event as unrelated to the infusion, however, it is my opinion that from the brief narrative provided, there is a possibility that the SAE was an infusion reaction.

Likely Unrelated to Velaglucerase Treatment
Patient 034-154-0002 (Allergic reaction – 45 U/kg dose)
This 20-year-old female discontinued treatment with imiglucerase on and received her first dose of velaglucerase a few weeks later. The patient's medical history included Bertolotti's syndrome and clinical depression. Sixteen days after the initial dose, the patient presented for her second dose of velaglucerase. It was noted that her mediport (which was ten years old) was not functioning properly so a peripheral intravenous catheter was inserted. The patient received velaglucerase through the peripheral catheter without event. Alteplase was injected into the port in an attempt to regain patency. Tenderness, swelling and erythema were noted at the port site. Soon after the second infusion the patient complained of flushing, throat tightness, throat swelling,

difficulty swallowing and a feeling of hotness. The patient had no rash or difficulty breathing. Diphenhydramine was administered, with little improvement in symptoms. By the following morning she asymptomatic and was discharged on diphenhydramine for two days. The event was considered resolved without sequelae. Study drug administration was unchanged due to this event. The investigator considered the event severe in intensity and unrelated to study therapy (attributed to alteplase). It was noted that the patient had a large component of anxiety and it was difficult to differentiate whether this reaction may be attributed to anxiety as well as alteplase.
Comment: I agree with the analysis of the Investigator that it is more likely that this reaction was secondary to the alteplase, however, it can not be completely ruled-out that the patient did not have a reaction to velaglucerase infusion.

Patient 034-154-0003 (Allergic reaction – 30 U/kg dose)
This 23-year-old male discontinued imiglucerase on and received his first dose of velaglucerase alfa one month later. Medical history included a recent back ache. About six months after his initial dose of study medication and 1 day after his most recent dose) he experienced a backache while at work. He applied an Absorbine Jr. (menthol) back patch to his lower back. When the patch was removed some of the contents of the patch had leaked out. Later that day he noticed a rash on his back, shoulders and stomach. He went to an urgent care center and was treated with a methylprednisolone and hydroxyzine HCl. Two days after taking the hydroxyzine he noted facial swelling and hives on both shoulders, neck and back. The patient went to the emergency department and was admitted the same day. He was treated with methylprednisolone, famotidine, and diphenhydramine. The urticaria was considered resolved without sequalae the next day and the patient was discharged with a short course of methylprednisolone. Study drug administration remained unchanged due to these events. The investigator considered the face edema and urticaria as severe in intensity and unrelated to velaglucerase (attributed to Absorbine patch or hydroxyzine).
Comment: I agree with that the allergic reaction does not appear related to treatment given the timing of events.

Patient 032-152-0006 (Seizure – 60 U/kg dose)
This patient was a 26-year old female with a history of temporal lobe epilepsy with tonic clonic convulsions randomized to the 60 U/kg treatment. On the 203rd day after the first dose of study drug, and two days after most recent dose, the patient experienced a tonic clonic convulsion, this episode repeated four days after. Both episodes self resolved, and although the serum valproic acid level was normal, the medication was increased by a neurologist. The study medication was not interrupted. This was a grand mal seizure of moderate intensity considered not drug-related by the Investigator.
Comment: I agree that the seizures are not due to treatment but from underlying disorder.

Patient 034-009-0003 (Ankle pain – 45 U/kg dose)
This 45-year-old male (with a history of ankle pain) discontinued treatment with imiglucerase sometime and received his first dose of velaglucerase a few weeks later. Approximately six months after his initial dose of study drug, and 1 day after his most recent dose, the patient was hospitalized for right ankle pain. Treatment medications included methylprednisolone, dextrose infusion, Hartman's solution, and ondansetron. This event was considered resolved without sequelae. Study drug administration remained unchanged due to this event.
Comment: I agree with the ankle pain is unlikely due to treatment as the pain resolved while velaglucerase therapy continued.

Patient 039-180-0003 (Epistaxis, thrombocytopenia – 60 U/kg dose))
This 7-year old male had SAE events of epistaxis and thrombocytopenia seven weeks after treatment started. The patient was hospitalized for platelet transfusion twice and observed for the third episode with spontaneous improvement in platelet count. The events were considered resolved. Treatment was continued unchanged. The events were considered not related per Investigator.
Comment: From the information provided, I agree that the episode is likely due to underlying disease.

Patient 025-071-0001 (Lower abdominal pain, headache, fever – 30 to 60 U/kg dose)
This 29-year-old female was hospitalized with an acute illness described as fever, headache, and abdominal pain approximately five years after her first dose of study medication and nine days after her most recent dose. Treatment medication included antibiotics. She was discharged from the hospital a few days later, and the events were considered resolved without sequelae. The investigator considered the fever as moderate, and the headache and abdominal pain as mild. All events were considered unrelated to treatment with study medication.
Comment: I agree that the SAE is unlikely related to study treatment given the event occurred five years into treatment.

Patient 025-071-0002 (Repair of left inguinal hernia– 30 to 60 U/kg dose)
This 66-year-old male was hospitalized for elective repair of a left inguinal hernia approximately four years after the initiation of study medication and four days after his most recent dose. Study medication was not interrupted during this event. The investigator considered the repair of left inguinal hernia as moderate and unrelated to treatment with study medication.
Comment: I agree that the SAE is unlikely related to treatment, this was an elective surgery for pre-existing hernia.

Patient 025-071-0003 (Avascular necrosis of left femoral head– 30 to 60 U/kg dose)
This 37-year-old male was hospitalized with pain in the left hip one year after starting treatment. Relevant medical history included osteopenia, osteonecrosis, and bone pain. An MRI showed avascular necrosis of the entire left femoral head and the patient

underwent bone marrow instillation of the left femoral head. The patient was discharged the following day with the event considered resolved without sequelae. Approximately 20 months after his first dose of study medication and five days after his most recent dose, he was hospitalized for a total hip replacement following worsening avascular necrosis of the left hip. The surgery was complicated by a fever. The patient was discharged from hospital soon thereafter, and the event was considered resolved without sequelae. Study medication was not interrupted during these events. Neither event was considered related to treatment with study medication by the Investigator.
Comment: The avascular necrosis is likely related to the underlying disease process and not related to study treatment.

Patient 025-071-0011 (Scar removal– 30 to 60 U/kg dose)
This 19-year old female was hospitalized for elective cosmetic surgery for a depressed McBurney scar on the abdomen. She was discharged the following day with the event considered resolved without sequelae. Study medication was not interrupted during this event. The investigator considered the scar as mild and not related to treatment with study medication.
Comment: This was an elective surgery unlikely to be related to study treatment.

Overall, from the review of narratives, 3 of the 12 reported SAEs are likely due to velaglucerase treatment, all of which appear to be hypersensitivity reactions. Given the number of patients followed and length of treatment evaluated, the safety profile of velaglucerase is reassuring.

7.3.3 Dropouts and/or Discontinuations

Table 37 describes the frequency and specific reasons for discontinuations reported in the various trials on velaglucerase treatment. Overall, the vast majority of patients completed the trials with good compliance. There were five discontinuations, of which two were due to an SAE.

Table 37: Discontinuations Reported in Various Trials

025	032	034	039
1/12 (8%) • Consent (personal reasons)	0/25	3/40 (8%) • Anaphylaxis SAE • Consent (2 –lack of improvement, other)	1/17 (6%) • Convulsions SAE

7.3.4 Significant Adverse Events

Among the treatment-naïve patients with up to 12 months velaglucerase treatment, most AEs were mild or moderate in severity. There were 5 of 54 patients reporting six severe AEs. From these patients, 2 of 6 events were considered related to treatment by

the investigator (aPTT prolonged and allergic dermatitis); the rest were considered unrelated to treatment by the investigator (thrombocytopenia, syncope, back pain, and convulsions).

Among the patients transitioned from imiglucerase, five patients had seven severe AEs. All the severe AEs were considered unrelated to treatment by the investigator. One patient had three severe AEs at the same time (toothache, facial swelling, and urticaria). The other severe AEs reported were: drug hypersensitivity (to alteplase per investigator), headache, arthritis, and joint dislocation. See narratives in Section 7.3.2 for SAEs urticaria/facial swelling and drug hypersensitivity.

7.3.5 Submission Specific Primary Safety Concerns

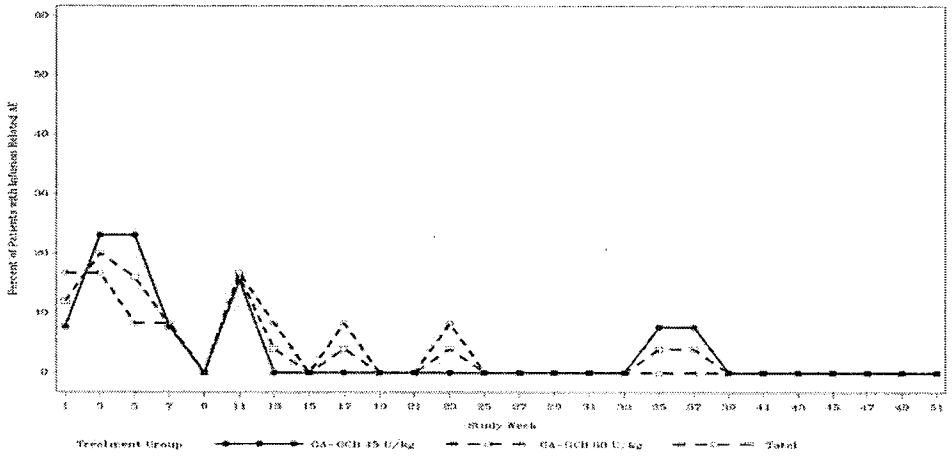
Infusion reactions are a known concern for biologic products. Table 38 describes the occurrence of adverse events likely to be infusion reactions. An infusion-related AE is defined as any AE occurring within 12 hours of the start of infusion and possibly or probably related to study drug (such as dizziness, headache, body pain, fatigue, hypotension, etc.). For 025, the reporting time was up to 24 hours post-infusion.

Table 38: Infusions Reactions Reported in Various Trials

025	032	034	039
9/12 (75%)	14/25 (56%)	9/40 (23%)	5/17 (29%) Velaglucerase 4/17 (24%) Imiglucerase

Overall, infusion-related AEs were mild in severity and did not impact the patient's ability to receive their scheduled infusions. Compliance was high through the trials. From 032, it appears that most infusion-related AEs were reported in the first six months of the trial.

Figure 26: Percentage of Patients Reporting Infusion-Related Adverse Event by Treatment Group in 032 (from Shire)



DGP requested the Applicant to perform standardized MedDRA queries on the safety data to identify and evaluate adverse reactions of specific interest for therapeutic proteins, such as: anaphylactic reactions, anaphylactic shock conditions, immunogenicity, pulmonary hypertension, pneumonia, infusion reaction, and injection site reactions.

There were no cases found under immunogenicity or pneumonia, and no serious cases of pulmonary hypertension or injection site reactions were identified. There was one SAE classified in the anaphylactic shock condition topic. This is the only reported event of this type, to date, and the patient responded to discontinuation of the drug infusion and to supportive care (see Section 7.3.2). No changes to the benefit/risk conclusions are made from this evaluation.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In my analysis, the following are the most common adverse events reported for the pooled Phase 3 trials 032, 034, and 039. The adverse events seem consistent with expected general illnesses to be reported over the course of one year as well as with typical Type 1 Gaucher symptoms. Overall, the patient numbers are small, thus although trends can be captured, no definitive absence of a safety signal can be established.

Table 39: Common Adverse Events Reported ≥10% (Pooled 032, 034, and 039)

AE	15 U/kg N (%) N=14	30 U/kg N (%) N=12	45 U/kg N (%) N=20	60 U/kg N (%) N=19	All Groups N (%) N=82
Headache	2 (14%)	5 (42%)	9 (45%)	12 (63%)	28 (34%)
URI	3 (21%)	4 (33%)	6 (30%)	14 (74%)	27 (33%)
Joint pain	3 (21%)	3 (25 %)	7 (35%)	7 (37%)	20 (24%)
Cough	0	2 (17%)	8 (40%)	7 (37%)	17 (21%)
Fever	2 (14%)	1 (8%)	4 (20%)	10 (53%)	17 (21%)
Infl. & flu-like	5 (36%)	2 (%)	3 (15%)	6 (32%)	16 (20%)
Abd pain	5 (36%)	1 (8%)	2 (10%)	7 (37%)	15 (18%)
Myalgia	1 (7%)	1 (8%)	7 (35%)	6 (32%)	15 (18%)
Bone pain	2 (14%)	1 (8%)	1 (5%)	11 (58%)	15 (18%)
Back pain	4 (29%)	3 (25%)	3 (15%)	4 (21%)	14 (17%)
Diarrhea	1 (7%)	2 (17%)	2 (10%)	6 (32%)	11 (13%)
Throat pain	0	2 (17%)	4 (20%)	5 (26%)	11 (13%)
Dizziness	3 (21%)	0	4 (20%)	3 (16%)	10 (12%)
Injury	0	0	7 (35%)	3 (16%)	10 (12%)
Rash	0	1 (8%)	3 (15%)	6 (32%)	10 (12%)

AE	15 U/kg N (%) N=14	30 U/kg N (%) N=12	45 U/kg N (%) N=20	60 U/kg N (%) N=19	All Groups N (%) N=82
PTT inc.	0	0	3 (15%)	5 (26%)	9 (11%)
Bronchitis	0	1 (8%)	3 (15%)	4 (21%)	8 (10%)
Hypertension	2 (14%)	1 (8%)	2 (10%)	3 (16%)	8 (10%)
Nasal cong.	0	1 (8%)	4 (20%)	3 (16%)	8 (10%)
Vomiting	1 (7%)	1 (8%)	3 (15%)	3 (16%)	8 (10%)

For 025, the most common adverse events are the same as those listed above. In the extension trial, asthenia and gingival bleeding are also reported as common AEs to date.

My common AE analysis was compared to Shire's analysis looking at treatment naïve patients with 0-9 months exposure and 0-12 months exposure, as well as patients previously exposed to imiglucerase (see Table 39). The conclusions are similar.

7.4.2 Laboratory Findings

Abnormal laboratory values that were considered clinically significant by the Investigator were reported as AEs. The only AE in this category that was noteworthy was prolonged activated partial thromboplastin time (aPTT). In the pooled population (032, 034, and 039), there were eight patients (10%) reporting elevated aPTT. In the 039 trial, no patients in the imiglucerase arm had elevated aPTT. In the literature[2], it has been reported that Type 1 Gaucher patients can have abnormal aPTT due to disease. However, given that 10% of patients had this AE and there were patients for whom aPTT became prolonged after starting treatment, I recommend that prolongation of aPTT be a labeled adverse reaction.

7.4.3 Vital Signs

Clinically significant abnormalities, as determined by the Investigator, in vital signs were to be reported as an AE. Overall there were few AEs reported in this category. Within the first nine months of velaglucerase treatment among patients who were treatment-naïve the following were reported: fever, 12 (22%); hypertension or hypotension, 4 each (7% each); tachycardia, 2 (4%); and sinus tachycardia or sinus bradycardia, 1 each (2%). For patients switched to ERT with velaglucerase from imiglucerase the following were reported: cardiac conduction disorder unrelated to study drug per Investigator, 1 (3%); hypertension, 3 (8%); and fever, 5 (13%). Of patients with hyper- or hypotension reported as an AE, the datasets were reviewed. Approximately half of these appear to

2 Hllak C, Levi M, Berends F, et al. Coagulation abnormalities in type1 Gaucher disease are due to low-grade activation and can be partly restored by enzyme supplementation therapy. *British J of Haematology* 1997:96(3)470-77.

be related to treatment (range of systolic BP 60 to 160). Of note, most patients did not require premedication for management of infusion-related adverse events.

7.4.4 Electrocardiograms (ECGs)

Clinically significant abnormalities in ECG were to be reported as AEs. There were no ECG abnormalities reported in the ISS datasets under the "Investigations" category (see Section 5.3). Any patient who had a normal ECG at baseline whose repeat ECG changed was reviewed. None had persistently abnormal ECGs or ECG abnormalities that were considered clinically significant.

7.4.5 Special Safety Studies/Clinical Trials

None.

7.4.6 Immunogenicity

Preliminary review of the immunogenicity assay by Dr. Fred Mills reports that the Applicant's assay was very specific but not sensitive. Given this context, there was only one patient who was treatment naive (032) who developed antibodies to velaglucerase among the 94 patients (treatment naïve and transitioned). These antibodies were neutralizing IgG. No adverse events were reported by this patient and the patient appeared to have a meaningful increase in the primary efficacy endpoint. Of 17 treatment naïve patients treated with imiglucerase, 4 (24%) tested positive for anti-imiglucerase antibodies.

There are ten patients who have been treated in 025EXT for up to five years with 30 to 60 U/kg velaglucerase EOW. As of June 1, 2009, these patients have been negative for anti-velaglucerase antibodies. Of the 40 patients who transitioned from imiglucerase, no patients have tested positive for anti-velaglucerase antibodies over the one year course of the trial, including the three patients who tested positive for anti-imiglucerase antibodies at screening.

Given Dr. Mills's review, I am unable to make an assessment whether velaglucerase treatment confers an advantage over other available ERT for type 1 Gaucher disease in terms of decreased immunogenicity.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Trial 032 is the only trial that has directly relevant information regarding this safety analysis in treatment naïve patients. Trial 025 was a first-in-human dose ranging study;

however, the drug supply is not chemically comparable to the to-be-marketed AF2 supply. Evaluation of AEs in 032 by dose showed that of the top 30 AEs reported, one third was reported more frequently in the 60 U/kg dose compared to two thirds of these being reported more frequently in the 45 U/kg group. The AEs in which there was > two patients reported in 60 U/kg compared to 45 U/kg were: rash, URI, and cheilitis. Conversely, the following were reported more frequently in the lower dose group compared to the higher dose: cough and injury. There were 25 patients in 032. The patient numbers are too small to make any definitive conclusions, but there does not appear to be an obvious dose dependency for adverse events at this time.

Table 40: Adverse Events Reported by Dose Group in 032 (≥10%)

Recoded PT	% AE (45U/kg)	% AE (60U/kg)	Difference (60 U- 45U)	% AE Total
Headache	54	42	-12	48
URI	23	50	27	36
Cough	46	25	-21	36
Injury	46	17	-29	32
Myalgia	31	25	-6	28
Pyrexia	31	25	-6	28
Rash	8	42	34	24
Dizziness	31	17	-14	24
Knee pain	31	17	-14	24
Abdominal pain	15	25	10	20
aPTT increased	15	25	10	20
Influenza	23	17	-6	20
Nasal congestion	23	17	-6	20
Vomiting	23	17	-6	20
Diarrhoea	15	17	1	16
Rhinitis	15	17	1	16
Back pain	23	8	-15	16
Petechiae	23	8	-15	16
Cheilitis	0	25	25	12
Bone pain (Hip)	8	17	9	12
Erythema	8	17	9	12
Hypotension	8	17	9	12
Toothache	8	17	9	12
Asthenia	15	8	-7	12
Bronchitis	15	8	-7	12
Ecchymosis	15	8	-7	12
Giardiasis	15	8	-7	12
Hypertension	15	8	-7	12
Throat pain	15	8	-7	12
Rhinorrhoea	15	8	-7	12
Thrombocytopenia	15	8	-7	12

In Trial 034, there were a total of 40 patients receiving doses ranging from 15 U/kg to 60 U/kg. These were patients switched from imiglucerase to velaglucerase. In this trial, among the AEs reported in ≥10% of patients, there appears to be an increase incidence of reporting of the following AEs with increasing dose: URI, throat pain, and cough.

Table 41: Adverse Events Reported by Dose Group for 034 (≥10%)

Recoded-PT	%AE 15U/kg	%AE 30U/kg	%AE 45U/kg	%AE 60U/kg	%Total
URI	21	33	43	43	33
Headache	14	42	29	43	30
Back pain	29	25	0	14	20
Influenza	36	17	0	14	20
Throat pain	0	17	29	43	18
Abd pain	36	8	0	0	15
Cough	0	17	29	29	15
Myalgia	7	8	43	14	15
Fatigue	14	0	14	29	13
Pyrexia	14	8	0	29	13
Diarrhoea	7	17	0	14	10
Pain in extremity	0	17	14	14	10
Hypertension	14	8	0	14	10
Nausea	7	17	14	0	10

Combining the information from the two trials, it appears that patients may be susceptible to URIs, rash, and an increase in aPTT with increased dosing of velaglucerase.

7.5.2 Time Dependency for Adverse Events

I evaluated AE reporting frequency compared to event date for the pooled trials (032, 034, and 039). Particular attention was made to terms that may be associated with an infusion reaction such as: dizziness, rash, malaise, nausea, edema etc. Of the 263 AE terms reviewed, only one term (hypotension) had all events occurring on or before 90 days of treatment initiation. There also appears to be a slight decrease in reporting for dizziness and vomiting over time. Whereas, for hypertension there appears to be a slight increase in reporting over time. For the other terms, the occurrence seems to be more variably spread through the entire trial period (see Section 7.3.5 for Infusion Reactions).

7.5.3 Drug-Demographic Interactions

Age and gender do not appear to be significant factors in safety of treatment. Adverse events in children were compared to those in adults. For the most part, those AEs occurring more frequently (≥10%) in children compared to adults and adults compared to children are reasonable. For example, children commonly have more rashes and

colds compared to adults. Conversely, more musculoskeletal complaints are reported in the adult population compared to children, which also appears reasonable. The AE of aPTT prolonged was further reviewed as this did not seem to make sense that children should have more problems with this than adults.

Table 42: Adverse Events Occurring More Commonly in Children than Adults (≥10%) – Pooled from Trials 032, 034, and 039

AE Term	Children (n=20) (< 18 yrs)	Adults (n=62) (≥ 18 yrs)	% Difference (Children – Adults)
Rash	7 (35%)	3 (5%)	30%
Throat pain	7 (35%)	4 (6%)	29%
URI	10 (50%)	17 (27%)	23%
Nasal congestion	5 (25%)	3 (5%)	20%
Cough	7 (35%)	10 (16%)	19%
PTT prolonged	4 (20%)	4 (6%)	14%
Vomiting	4 (20%)	4 (6%)	14%
Fever	6 (30%)	11 (18%)	12%
Injury	4 (20%)	6 (10%)	10%
Bronchial obstruction	2 (10%)	0	10%
Eosinophil increased	2 (10%)	0	10%
Tachycardia	2 (10%)	0	10%
Tooth loss	2 (10%)	0	10%

Table 43: Adverse Events Occurring More Commonly in Adults than Children (≥10%) – Pooled from Trials 032, 034, and 039

AE Term	Children (< 18 yrs)	Adults (≥ 18 yrs)	% Difference (Adults – Children)
Joint pain	1 (5%)	19 (31%)	26%
Bone Pain	0	15 (24%)	24%
Back pain	0	14 (23%)	14%
Dizziness	1 (5%)	9 (15%)	10%
UTI	0	6 (10%)	10%
Toothache	0	6 (10%)	10%

The vast majority of patients were Caucasian, therefore, no safety subgroup analyses were performed for race.

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

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 completed reproductive studies in animals and is proposing inclusion in category B. There is no human experience with the use of velaglucerase in pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

There were few pediatric patients in the development program. There were the following numbers of patients in specific age ranges: ages 2 to 4 years (1), ages 5 to 10 years (8), ages 11 to 17 years (11). See Section 5.3.11 for discussion of growth parameters from 032.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No data are available. Velaglucerase 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

Three-month Safety Update
The original NDA submission was dated Aug 31, 2009. A three-month safety update was submitted that included safety information up through Dec 1, 2009. In this recent update, two reporting time periods were added, namely "greater than 12 months to 30 months" and "greater than 30 months." These reporting periods include data from the 044 extension trial that was not included in the original submission.

Overall, there is no change in the safety profile of velaglucerase. There have been no deaths reported to date. Three additional SAEs were reported in Trial 044, all of which appear to be related to the underlying disease and not to treatment [hip replacement (2) and femoral head osteonecrosis (1)]. In each of the three patients, velaglucerase treatment remained unchanged.

Cerezyme Literature Review
Imiglucerase (Cerezyme) has been marketed since 1994. The Applicant conducted a literature search and concluded that treatment with imiglucerase has a long track record

of safety and acceptability for most patients with symptomatic Gaucher disease. Rare instances of immune reactions or hypersensitivity to imiglucerase have occurred. Many patients receive treatment at home, and some will even administer the medication themselves. Doses as high as 240 U/kg administered EOW have been reported without any obvious toxicity. Schmitz et al. reported in 2007 that imiglucerase is well tolerated and side effects are usually both rare and mild and that long-term safety experience with imiglucerase therapy demonstrated a stable and low rate of adverse events and seroconversion from 1994 through 2005. The majority of frequently reported adverse events related to imiglucerase were infusion-associated reactions, which were predominantly self limiting and did not require discontinuation of treatment. Between 1994 and 2005, IgG antibodies to imiglucerase were detected in approximately 15% of treatment-naive patients.

The Applicant further states that the following adverse event profile emerges for imiglucerase from the US Prescribing Information, European SPC, and the published literature. Approximately 15% of patients treated and tested to date have developed IgG antibody to Cerezyme during the first year of therapy. Patients who developed IgG antibody did so largely within the first 6 months of treatment and rarely developed antibodies to Cerezyme after 12 months of therapy. Approximately 46% of patients with detectable IgG antibodies experienced symptoms of hypersensitivity. Patients with antibody to Cerezyme have a higher risk of hypersensitivity reaction. Conversely, not all patients with symptoms of hypersensitivity have detectable IgG antibody. The Cerezyme prescribing information suggests that patients be monitored periodically for IgG antibody formation during the first year of treatment. Treatment with Cerezyme should be approached with caution in patients who have exhibited symptoms of hypersensitivity to the product.

Anaphylactoid reaction has been reported in less than 1% of the patient population. In the event of an anaphylactoid reaction further treatment with imiglucerase should be conducted with caution. Most patients have successfully continued therapy after a reduction in the rate of infusion and pretreatment with antihistamines and/or corticosteroids. In addition, Charrow et al. commented that adverse events related to the administration site represent some of the adverse events related to imiglucerase and have been experienced by 14% of patients. Hypersensitivity type reactions have occurred in 7% of patients. These hypersensitivity reactions include pruritus, flushing, urticaria, angioedema, chest discomfort, dyspnea, coughing, cyanosis, and hypotension. These typically begin during or shortly after the infusion. Other adverse events, including pyrexia, chills, nausea, headache, abdominal pain, vomiting, diarrhea, fatigue, dizziness, rash and tachycardia, have occurred in 7% of patients.

Each of these events has occurred in less than 1% of the patient population. Anaphylaxis and other IgE mediated reactions have been extremely rare. Production of neutralizing antibodies (inhibiting the activity of the infused enzyme) has been documented in only a few patients, most of whom successfully continued therapy after

induced tolerance or with increased doses of imiglucerase. Furthermore, 90% of patients with IgG antibodies tolerize over time, with a mean time to tolerization of 28 months. Patients suspected of a decreased response to the treatment are recommended to be monitored periodically for IgG antibody formation to imiglucerase. Patients with antibody to imiglucerase have a higher risk of hypersensitivity reactions. If a patient experiences a reaction suggestive of hypersensitivity, subsequent testing for imiglucerase antibodies is advised.

AERS Database Search

A search on Cerezyme and other ERTs was performed in the AERS database by Ann Corken Mackey of OSE. The majority of adverse events reported for Cerezyme appear to be related to the underlying disease. From the available information, there does not appear to be new safety signals that require additional surveillance when velaglucerase is marketed to the public.

8 Postmarket Experience

None.

9 Appendices

9.1 Literature Review/References

Patients with type 1 Gaucher disease may have bone pain, skeletal anomalies, spleen or liver enlargement, anemia, fatigue, bruising, and epistaxis. As discussed in the introduction, the primary clinical manifestations of this disease are: hepatomegaly, anemia, and thrombocytopenia which are related to spleen status at baseline. Patients who have had a splenectomy tend not to have thrombocytopenia. Systematic follow-up of patients over years by Beutler et al. (1995) show that Gaucher disease related changes in untreated patients, if they occur at all, are slowly progressive and noted over decades. Hematologic measures of anemia and decreased platelet counts as well as spleen and liver sizes do not typically show spontaneous improvement.

Dr. Beutler states young pediatric patients with unfavorable genotypes (such as 1448C/1448C), marked hepatosplenomegaly, thrombocytopenia (below 50,000/µl), bone lesions, and frequent skeletal crises are factors that should lead to institution of therapy. For adults, marked hepatosplenomegaly, thrombocytopenia (below 40,000/ µl), extensive bone disease, or pulmonary disease are indications for institution of enzyme replacement therapy. Previous experience with enzyme replacement therapy has shown definitive improvement in anemia, thrombocytopenia, and organ volumes which are clinically beneficial for these patients with this chronic disease which typically does not improve or resolve spontaneously.

1. Barton N, Brady R, Dambrosia J, et al. Replacement therapy for inherited enzyme deficiency – macrophage targeted glucocerebrosidease for Gaucher disease. *The New England J of Med* 1991:324(21)1464-70.
2. Beutler E, Demina K, Laubscher, et al. The clinical course of treated and untreated Gaucher disease. A study of 45 patients. *Blood Cells, Molecules, and Diseases* 1995:21(10)86-108.
3. Charrow J. Enzyme replacement therapy for Gaucher Disease. *Expert Opinion Biol Ther* 2009:9(1)121-31.
4. Grabowski G, Barton N, Pastores G, et al. Enzyme replacement therapy in type 1 Gaucher disease: comparative efficacy of mannose terminated glucocerebrosidase from natural and recombinant sources. *Annals of Int Med* 1995:122(1)33-39.
5. Mehta A. Gaucher disease: unmet treatment needs. *Acta Paediatr Suppl* 2008:97(457)88-93.
6. Rohrback M, Clarke J. Treatment of lysosomal storage disorders: progress with enzyme replacement therapy *Drugs* 2007:67(18)2697-716.

9.2 Labeling Recommendations

This is labeling for a new molecular entity and will be in PLR format. Content and formatting is carefully reviewed to meet the latest best-practices. Labeling for other enzyme replacement therapies are reviewed to ensure consistency across these drug products.

I recommend that VPRIV be indicated for the treatment of type 1 Gaucher disease, with a notice that children under age 2 have not been evaluated. The recommended dosage is 60 U/kg every other week as a 60-minute intravenous infusion. Dosage adjustments can be made on an individual basis based on achievement and maintenance of therapeutic goals. Clinical studies have evaluated doses ranging from 15 U/kg to 60 U/kg.

Although all adult adverse reactions to VPRIV are considered relevant to pediatric patients, those AEs most frequently reported in pediatric patients should be described separately in Section 6, Adverse Reactions. A statement should be added in Section 8.4, Pediatric Use, that VPRIV was not studied in children less than two years of age. When describing the trials in Section 14, Clinical Studies, the labeling should focus on describing the three phase 3 trials as the drug supply used in the phase 1/2 study is different than the to-be-marketed drug supply. Lastly, as this drug product is administered under the care of a health care provider, a separate "FDA-Approved Patient Labeling" should not be required.

9.3 Advisory Committee Meeting

None.

9.4 Attachment

List of Investigators and Study Sites.

Study TKT025 Investigator List				
Site number	**Principle Investigator**	**Site Address**	**Site Telephone/Fax/Email**	**Number of patients enrolled**
071	Dr. Ari Zimran	Gaucher Clinic The Hebrew University Haddassah Medical School Shaare Zedek Medical Center 12 Hans Bayt Jerusalem 91031, Israel	T: 972 2-6555143 Cell: 972 55 728284 F: 972 2 6517979 azimran@gmail.com gaucher@szmc.org.il	12

Study TKT025EXT Investigator List				
Site number	**Principle Investigator**	**Site Address**	**Site Telephone/Fax/Email**	**Number of patients enrolled**
071	Dr. Ari Zimran	Director Gaucher Clinic Associate Professor of Medicine The Hebrew University Haddassah Medical School Shaare Zedek Medical Center 12 Hans Bayt Jerusalem 91031, Israel	T: 972 2-6555143 Cell: 972 55 728284 F: 972 2 6517979 azimran@gmail.com gaucher@szmc.org.il	8
096	Dr. Florea Iordachescu	Maria Sklodowska Curie Children's Hospital 20, Constantin Brancoveanu St. Bucharest, sector 4, cod 75544 Romania	T: 004.012.777.2649 F: 004.021.460.1260 iordachescuflorea@mscurie.ro	1*
150	Dr. Maja Djordjevic	Mother and Child Health Care Institute of Serbia Radoja Dakica 6, 11 070 Belgrade Serbia	T: 381 (11) 3108276 F: 381 (11) 3108276 mayamark@eunet.yu mayamark@sbb.co.yu	1*

*Ten patients enrolled in study TKT025EXT. Patients enrolled in Serbia and Romania received only infusions at these sites; the remaining study assessments occurred at the main study site in Israel.

Study TKT032 Investigator List				
Site number	**Principle Investigator**	**Site Address**	**Telephone/Fax/Email**	**Number of patients enrolled**
071	Dr. Ari Zimran	Gaucher Clinic The Hebrew University Haddassah Medical School Shaare Zedek Medical Center 12 Hans Bayt Jerusalem 91031, Israel	T: 972 2-6555143 Cell: 972 55 728284 F: 972 2 6517979 azimran@gmail.com gaucher@szmc.org.il	7
094	Dr. Marie- Françoise Ben Dridi	Pediatric Department - La Rabta Hospital Jabbari 1007 BS, Tunis, Tunisia	T: 00.216.71.572.470 T: 00.216.71.57.8923 F: 00.216.71.572.470 francoise.bendridi@rns.tn	3
152	Dr. Derlis Emilio Gonzalez Rodríguez	Sociedad Española de Socorros Mutuos (Sanatorio Español) Gobernador Irala y Coronel Lopez Barrio Sajonia Asunción Paraguay	T: (595)21-420.888 Direct: (595)21-423-603 Cell: (595)971-223286 F: (595)21-420.888 degonzal@conexion.com.py gderlis@conexion.com.py	11
165	Dr. Isaac Kisinovsky	Your Health S.A. Hipólito Yrigoyen 5136 Ezpeleta – B1882AQY Buenos Aires Argentina	T: 54 11 42261623 F: 54 11 4139-4799 kisi@ociopro.com	1
191	Prof. Elena A. Lukina	Institution of Russian Academy of Medical Science National Research Center for Haematology Novyi Zykovskii pr., 4a 125167, Moscow, Russia	Tel/fax: 7 (495) 612-0923 Cell: 8 (903)689-5521 lukina@blood.ru kira-l@mail.ru	3

Study TKT034 Investigator List				
Site number	**Principle Investigator**	**Site Address**	**Telephone/Fax/Email**	**Number of patients enrolled**
009	Dr. Atul Mehta	The Royal Free Hospital Pond Street Department of Haematology United Kingdom	T : +44-207-794-0500 Ext. 4608 T: +44-207-830-2814 F: +44-20-7830-2808 Atul.Mehta@royalfree.nhs.uk	3
015	Dr. William J. Rhead	Children's Hospital of Wisconsin CHW Genetics Center MS716 9000 W. Wisconsin Avenue Milwaukee, WI 53226	T: +1 414 266-2979 F: +1 414 266-1616 wrhead@mcw.edu	1
027	Dr. Gregory Pastores	NYU School of Medicine Neurogenetics Department 2nd Floor 403 E 34th Street New York, New York 10016	T: +1 212-263-8344 F: +1 212-263-8310 gregory.pastores@med.nyu.edu	3
046	Dr. Paul Harmatz	Pediatric GI and Nutrition Children's Hospital & Research Center Oakland 747 52nd Street Oakland, CA 94609	T: +1 510-428-3058 pharmatz@mail.cho.org	2
048	Dr. Christine Eng	Baylor College of Medicine Texas Children's Hospital One Baylor Plaza NAB 2015 Houston, TX 77030	T: +1 713-798-8997 T: +1 713-798-4951 F: +1 713-796-9718 ceng@bcm.tmc.edu	2
071	Dr. Ari Zimran	Gaucher Clinic The Hebrew University Haddassah Medical School Shaare Zedek Medical Center 12 Hans Bayt Jerusalem 91031, Israel	T: 972 2-6555143 F: 972 2 6517979 Cell: 972 55 728284 azimran@gmail.com gaucher@szmc.org.il	9
154	Dr. Greg Grabowski	Cincinnati Children's Hospital Division of Human Genetics 3333 Burnet Avenue, ML 4006 Cincinnati, Ohio 45229	T: +1 513-636-7290 T: +1 513 636-4507 F: +1 513-636-0124 greg.grabowski@cchmc.org	3
162	Dr. Anna Tylki-Szymanska	Department of Metabolic Diseases Children's Memorial Health Institute 04-730 Warszawa, Al. Dzieci Polskich 20 Poland	T: +4822 (815) 75 84 Cell : +48 695 192 922 F: +4822 (815) 74 90 atylki@op.pl a.tylki@czd.pl	5

Study HGT-GCB-039 Investigator List				
Site number	**Investigator**	**Address**	**Telephone/Fax/Email**	**Number of patients**
009	Dr. Atul Mehta	The Royal Free Hospital Pond Street Department of Haematology United Kingdom	T: +44-207-794-0500 Ext. 4608 T : +44-207-830-2814 F: +44-20-7830-2808 Atul.Mehta@royalfree.nhs.uk	1
071	Dr. Ari Zimran	Gaucher Clinic The Hebrew University-Haddassah Medical School Shaare Zedek Medical Center 12 Hans Bayt Jerusalem 91031, Israel	T: 972 2-6555143 Cell: 972 55 728284 F: 972 2 6517979 azimran@gmail.com gaucher@szmc.org.il	3
094	Dr. Marie-Françoise Ben Dridi	Pediatric Department - La Rabta Hospital Jabbari 1007 BS, Tunis, Tunisia	T: 00.216.71.572.470 T: 00.216.71.57.8923 F: 00.216.71.572.470 francoise.bendridi@rns.tn	6
152	Dr. Derlis Emilio Gonzalez Rodríguez	Sociedad Española de Socorros Mutuos (Sanatorio Español) Gobernador Irala y Coronel Lopez Barrio Sajonia Asunción Paraguay	T: (595)21-420.888 Direct: (595)21-423-603 Cell: (595)971-223286 F: (595)21-420.888 degonzal@conexion.com.py gderlis@conexion.com.py	5
164	Dr. Pilar Girlado	S° de Hematologia. Hospital de Día Pta 1ª Impar Hospital General Hospital Universitario Miguel Servet P° Isabel La Catolica 1-3 50009 Zaragoza. Spain	T: +34 0 976562565 Cell : +34 670285339 F: +34 0 976 468041 pgiraldo@salud.aragon.es giraldo.p@gmail.com	1
165	Dr. Isaac Kisinovsky	Your Health S.A. Hipólito Yrigoyen 5136 Ezpeleta – B1882AQY Buenos Aires Argentina	T: 54 11 42261623 F: 54 11 4139-4799 kisi@ociopro.com	3
167	Dr. Priya Kishnani	Duke University Medical Center Department of Pediatrics Division of Medical Genetics Box 103856 DUMC 2th Floor GSRBI 595 LaSalle Street Durham, North Carolina 27710	T: 919.684.2036 F: 919.684.8944 kishn001@mc.duke.edu	1
180	Dr. Madhulika Kabra	Genetics Unit, Department of Pediatrics Old O.T. Block All India Institute of Medical Sciences	T: 91 2658 8500 F: 91 2658 8480 mkabra_aiims@yahoo.co.in or madhulikakabra@hotmail.com	5

Study HGT-GCB-039 Investigator List				
Site number	**Investigator**	**Address**	**Telephone/Fax/Email**	**Number of patients**
		New Delhi – 110 029 India		
184	Dr. I. C. Verma	Department of Genetic Medicine Sir Ganga Ram Hospital Rajinder Nagar New Delhi 110060 India	Tel : +91-11-25861767 Cell:+91- 9810109629 F: 91 11 42257034 dr_icverma@yahoo.com	0
185	Dr. Sureshkumar E. K.	Malabar Institute of Medical Sciences Ltd., Mini By-pass Road, Govindapuram P.O., Calicut-- 673 016 Karala India	Cell: 9895078820 F: 91495 3091169 drskumarek@gmail.com	1
191	Prof. Elena A. Lukina	Institution of Russian Academy of Medical Science National Research Center for Haematology Novyi Zykovskii pr., 4a 125167, Moscow, Russia	Tel/fax: 7 (495) 612-0923 Cell: 8 (903)689-5521 lukina@blood.ru kira-l@mail.ru	4
194	Dr. Ashish Bavdekar	KEM Hospital Research Centre Department of Pediatrics Rasta Peth, 411 011 Pune, India	Tel : 91 020 66037342 Cell: +919822056174 F: 91 20 2612560 bavdekar@vsnl.com	2

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

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

/s/

II-LUN CHEN
02/05/2010

JOHN E HYDE
02/05/2010
Concur.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22-575 **Applicant: Shire** **Stamp Date: 8/31/09**

Drug Name: velaglucerase alpha **NDA/BLA Type: NDA**

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

	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.				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?				NME, new NDA 505(b)1
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: Study Title:TKT032 Sample Size: 25 Arms: 2 Location in submission: Module 5	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1= TKT032 Indication:Type 1Gaucer	X			Single pivotal trial and several supportive trials.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	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			This treatment is for an orphan population.
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	This treatment is for an orphan population. The patient numbers studied are small, however, there are data on longterm use of the study drug.
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 new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested	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
	by the Division)?				
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			Patients ages 2 years and older were studied.
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			

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.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

Ii-Lun Chen, MD	9/14//2009
Reviewing Medical Officer	Date
John Hyde, PhD, MD	
Clinical Team Leader	Date

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

/s/

Il-LUN CHEN
10/05/2009

JOHN E HYDE
10/05/2009