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APPLICATION NUMBER:

22-575

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	February 26, 2010
From	John E. Hyde, Ph.D., M.D., Clinical Team Leader, DGP
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement #**	NDA 22-575 N000
Applicant	Shire HGT
Date of Submission	Dated August 31, 2009; Received August 31, 2009
PDUFA Goal Date	February 26, 2010
Proprietary Name / **Established (USAN) names**	VPRIV Velaglucerase alfa
Dosage forms / Strength	Lyophilized powder for solution for injection 200 Units/vial and 400 Units/vial
Proposed Indication	Long-term enzyme replacement therapy for pediatric and adult patients with type 1 Gaucher disease
Recommended Action	Approval

1. Introduction

This application was received August 31, 2009, as an electronic submission. This application is for Vpriv, a formulation of velaglucerase alfa, which is being proposed "for the long-term enzyme replacement therapy for adult and pediatric patients with type 1 Gaucher disease."

Velaglucerase alfa is an enzyme manufactured using recombinant technology and containing the same amino acid sequence as human glucocerebrosidase. It is a new molecular entity. Velaglucerase alfa is not approved in any foreign country, although it is currently being made available to patients in a treatment protocol under IND 61,220.

All the review disciplines recommend in favor of approval, but several Phase 4 commitments were recommended in order to address deficiencies in manufacturing, immunogenicity assays, and pharmacokinetic assessments.

2. Background

General Background

Gaucher disease
Gaucher disease is a lysosomal storage disease caused by an inherited deficiency of glucocerebrosidase. The deficiency results in accumulation of glucocerebroside in macrophages. In type 1 disease, the principally affected organs are liver, spleen, bone marrow, skeleton, and lungs. Clinical manifestations are anemia, thrombocytopenia, organomegaly (liver and spleen), bone deformities, bone pain, growth retardation, and lung

disease. Only a minority have CNS involvement. Types 2 and 3 are marked by significant neurologic involvement, with type 2 being the more acute. Type 1 Gaucher disease is estimated to affect 30,000 people worldwide.

Disease-specific therapies for type 1 Gaucher disease include enzyme replacement, substrate reduction therapy, bone marrow transplantation, and experimental gene therapy. The three currently approved drug therapies for type 1 Gaucher disease are Cerezyme (imiglucerase, NDA 20-367), Zavesca (miglustat, NDA 21-348), and Ceredase (alglucerase, NDA 20-057). Cerezyme is an infusional enzyme replacement therapy that employs a glycosylated protein differing by only one amino acid from the human enzyme. It was approved in 1994 for long-term treatment of Gaucher disease. (It replaced the placenta-derived enzyme Ceredase, which was approved in 1991 but has negligible use at present.) Due to manufacturing problems, there is currently a drug shortage of Cerezyme. Zavesca is an oral therapy that is an inhibitor of glucosylceramide synthase. It acts by reducing the synthesis of glucocerebroside. Because of its toxicities, Zavesca is only indicated in adults for whom enzyme replacement therapy is not an option.

Proposed Labeling
The proposed dosing is 60 mg/kg IV every other week. The Applicant has proposed labeling with warnings regarding hypersensitivity reactions and infusion-related. The proposed pregnancy category is B.

Product
The drug substance is a produced by recombinant technology. Velaglucerase alfa is based on a single chain polypeptide with 523 amino acids, with a sequence that is identical to that of the human enzyme. This is the same as the amino acid sequence in the approved product Ceredase, but velaglucerase alfa is a new molecular entity because of its different glycan chains. The glycosylation of the protein facilitates its uptake by macrophages. The drug product is a lyophilized powder for reconstitution with sterile water followed by dilution with sterile normal saline for IV administration.

Presubmission Activity

Vpriv was developed under IND 61,220, which was received on 12/31/03. The original IND was sponsored by Transkaryotic Therapies, Inc., but was taken over by the Applicant in 2006.

The following events during the development of Vpriv are of note:

- January 11, 2006: The IND sponsor met with the FDA to discuss pivotal clinical protocols, nonclinical studies required for an NDA, and CMC issues, including formulation change and comparability. The FDA advised that a long-term therapy indication would require 12-month studies.
- November 20, 2006: The IND was placed on hold because comparability was not demonstrated after a change in manufacturing process. It was changed to partial hold on 12/7/06 to allow several patients already being treated to continue treatment. The IND came off hold on 12/21/06.

- June 8, 2009: Orphan designation was granted based on the expectation of clinical superiority to Cerezyme (imiglucerase). The reasons stated were evidence of faster uptake providing an expectation of faster onset of action, and reduced antibody formation.
- June 2009: Contamination of the Genzyme manufacturing facility at Allston Landing, Massachusetts led to suspension of production of Cerezyme and caused a drug shortage for enzyme replacement therapies for Gaucher disease. The shortage is ongoing and currently expected to last through March or April 2010.
- July 15, 2009: Fast track designation was granted to Vpriv in consideration of the unmet need due to the shortage of Cerezyme.
- July 30, 2009: A treatment IND was approved to make Vpriv available to help address the shortage of Cerezyme.
- July 30, 2009: Rolling submission Modules 3 and 4 (CMC, Nonclinical) were received.
- August 10, 2009: CMC pre-NDA meeting was held.
- August 11, 2009: Clinical pre-NDA meeting was held. The Division agreed it would be acceptable to submit an NDA with complete study reports and data only for Study 32 (a dose-response study), but that preliminary reports and major efficacy and safety findings should be provided for the recently completed Study 39 (Vpriv vs. Cerezyme) and Study 34 (switch study).

Submission and Review

The original NDA was dated August 31, 2009, and was received on that date. In view of the ongoing shortage problems with Cerezyme, the application was given Priority review status, with an action date of February 26, 2010.

Because the application is for an orphan indication, PREA requirements for pediatric studies do not apply, and the submission was not presented to the Pediatric Review Committee (PeRC). No Advisory Committee meeting was convened to discuss this application.

The relevant review disciplines have all written review documents. The primary review documents relied upon are the following:

Clinical Review, by I. Chen, dated 2/5/10.
Clinical Review Addendum, by I. Chen, dated 2/23/10.
Statistical Review and Evaluation, by B. Vali, dated 2/25/10.
Pharmacology/Toxicology Review and Evaluation, by T. Chakraborti, dated 1/28/10.
Addendum to Pharmacologist's Review, by T. Chakraborti, dated 2/19/10.
Pharmacology/Toxicology Comments on NDA 22-575, by A. Jacobs, dated 2/22/10.
Office of Clinical Pharmacology Review, by L. Fang, dated 2/1/10.
Immunogenicity Review Memo, by F. Mills, dated 2/25/10.
Division of Therapeutic Proteins Review, by E. Lacana, H. Anderson, Y. Fan, A. Nagaich, and L. Tang, dated 2/25/10.
Product Quality Microbiology Review, by D. Miller, dated 2/3/10.
Clinical Inspection Summary, by L. Iacono-Conners, 1/29/10.

Regulatory Project Manager Labeling Review (PLR Review), by R. Ishihara, dated 10/30/09.
Project Manager' Review (OBP Label Review), by K. Rains, dated 11/24/09.
DMEPA Proprietary Name Review, by D. Hamilton-Stokes, 12/10/09.
DMEPA Label and Labeling Review, by D. Hamilton-Stokes, 1/27/10.
DDMAC Labeling Comments Memo, by S. Doshi and K. Klemm, dated 1/28/10.

The reviews should be consulted for more specific details of the application and review conclusions. This memorandum summarizes selected information from the primary review documents.

3. CMC

Velaglucerase alfa is a recombinant cerebrosidase produced by gene-activation technology in a human fibroblast cell line by insertion of the CMV promoter and other sequences upstream of the glucocerebrosidase gene. Velaglucerase alfa contains a polypeptide with 523 amino acids identical to the sequence in the natural human enzyme. Four of the five potential glycosylation sites contain glycans with 7 to 9 mannoses. The mannosidase I inhibitor, kifunensine, is added to the culture media to preserve the high mannose content, which is important for uptake by macrophages.

b(4)

The drug product is formulated with sucrose, sodium citrate, citric acid, and polysorbate 20. It is filled into glass vials and lyophilized. It is available in 200 U/vial and 400 U/vial presentations. Because exposure to light has been shown to cause aggregation and fragmentation, the product is designated as "protect from light." The Applicant requested a 24 months expiry.

The product is manufactured and warehoused at Applicant's facilities in Cambridge, MA. The Applicant's testing facility is in Lexington, MA.

Quality Review
The CMC Reviewer concluded that the information in the application supports the conclusion that the manufacture is well controlled and leads to a pure and potent product. She determined that the processes had been validated and that consistent product is produced. However, she identified several issues that the Applicant needed to address, and she recommended Phase 4 commitments from the Applicant to do the following:

1. Develop and implement a kinetic assay with a physiologically relevant substrate for drug substance and drug product release and stability testing.

2. Develop and implement a quantitative method that measures total carbohydrate content.

3. Replace the non-quantitative SDS-PAGE Silver stain method with a quantitative Coomassie test.

4. Demonstrate that [redacted] is well controlled to ensure no impact on product quality. b(4)

5. Demonstrate the clearance capability of the process to remove [redacted] through [redacted] spike studies.

6. Re-evaluate drug substance and drug product release and stability specifications.

7. Update the specifications for SEC, RP-HPLC, and glycan map, and include acceptance criteria for the leading shoulder in SEC-HPLC, for peak [redacted] in RP-HPLC, and for peak [redacted] in the glycan map.

8. Update the peptide map specification using new acceptance criteria to reflect control of impurities, and add the peptide map as a drug substance and drug product release and stability test with the new acceptance criteria.

9. Include the cellular uptake bioassay for drug product release testing. b(4)

10. Provide a report containing the sub-visible particulates [redacted] analyses, risk assessment and risk mitigation strategies.

11. Include drug substance and drug product stress conditions in the annual stability program.

12. Evaluate the impact of pH on the in-use stability of the drug product and provide assurance that procedures are in place to control this risk to product quality.

Microbiology Review

The manufacturing process includes sterilization [redacted] and lyophilization. The Microbiology Reviewer found the procedures acceptable and identified no microbiological deficiencies. She recommended the product for approval. No Phase 4 commitments or requirements were recommended regarding microbiology. b(4)

Immunogenicity Review

The Applicant developed assays for IgG and IgE anti-velaglucerase alfa antibodies and an evaluation for neutralizing antibodies. Of the 94 patients treated with velaglucerase alfa formulations in the development program, only one patient (who was treatment-naïve) developed anti-velaglucerase alfa antibodies after one year of therapy; it was a neutralizing IgG antibody. Also, one patient who received only imiglucerase was found to have anti-imiglucerase antibodies, cross-reactive antibodies to velaglucerase alfa, and neutralizing antibodies. One patient who switched from imiglucerase to Vpriv had a moderate anaphylactic reaction, but antibody testing was negative. The Immunogenicity Reviewer felt the low incidence of antibody development could be expected given the homology of velaglucerase alfa with the natural enzyme and the fact that Gaucher patients generally have some residual enzyme expression and would be expected to be tolerized. However, the

Reviewer was concerned that the cutpoints use for the assays were high and not adequately justified, leading to assays that may be lacking in sensitivity.

The Immunogenicity Reviewer recommended some modifications to labeling under the Immunogenicity heading in Section 6. He negotiated removal of a statement that accurate comparisons of incidence of antibodies to Vpriv and other products can be made in a well controlled comparator study. He also recommended Phase 4 commitments from the Applicant to do the following:

1. Use a cut point based on a mean + 1.645 standard deviation for assay values from treatment naïve Gaucher patients, and use the same method to calculate the anti-imiglucerase ECL cut point.

2. Revise the cut point for the confirmatory anti-velaglucerase and anti-imiglucerase screening assay to a level that is less than or equal to the cut point of the screening assay.

3. Re-assess the IgE cut point for the current ECL method using a chemically synthesized hybrid control and support assay validation using patient baseline values.

4. Develop an assay to measure the ability of patient antibodies to block the uptake of velaglucerase and imiglucerase into target cells.

Formulations Used in Development

During the development program, formulations were made from difference drug substance manufacturing processes. The substance used in nonclinical studies was made [redacted]. For Phase 1/2 (Study 25), the process used [redacted] Process AF1, used in the formulation for the Phase 3 studies, used [redacted]. In the scale-up to process AF2, for the to-be-marketed formulation, the main changes were [redacted]. The CMC Reviewer concluded that material from the AF1 ad AF2 processes could be considered comparable. However, she determined that the information in the application did not establish the comparability of the [redacted] process material with that of the to-be-marketed formulation.

b(4)

Conclusions and Recommendations

The Quality and Microbiology Reviewers recommended Vpriv for approval. None of the reviewers recommended Phase 4 requirements. However, the Quality Reviewer recommended several Phase 4 commitments, as listed above, regarding testing procedures for drug substance and drug product release and stability testing as noted above. The Immunogenicity Reviewer recommended Phase 4 commitments, as listed above, to revise and re-assess the antibody assays and to develop a neutralizing assay.

4. Nonclinical Pharmacology/Toxicology

The application provided results of the following toxicology studies using IV velaglucerase alfa:

- Acute single-dose, and three- and six-month repeated-dose studies in SD rats.
- A six-month repeated-dose study in Rhesus monkeys

In the acute rat study, the maximum nonlethal dose was 20 mg/kg. In the three-month rat study, which used doses up to 17 mg/kg IV biweekly, there were no toxicologically significant treatment-related effects, but there were treatment-related effects at all doses. Possible target organs were the lungs, liver, and testes. In the 25-week rat study, using doses up to 17 mg/kg IV biweekly, no target organ was identified, but there were treatment-related effects at all doses. Antibody formation was seen at all doses in both repeated-dose studies.

In the monkey study, which used up to 17 mg/kg IV biweekly, no target organ was identified. Significant antibody production was seen at the high dose.

No genotoxicity or carcinogenicity studies were conducted.

Reproductive and developmental toxicology studies consisted of Segments I, II, and III studies in rats and a Segment II study is rabbits. No effects on fertility were seen with dosing up to 17 mg/kg biweekly in the Segment I study. Velaglucerase alfa was not teratogenic in the Segment II studies at up to 17 mg/kg biweekly in rats and up to 20 mg/kg biweekly in rabbits. Velaglucerase alfa did not cause any significant adverse effects on pre- and post-natal development in the Segment III study up to 17 mg/kg biweekly. The Reviewer noted that two male mice in the Segment I study had small testes, high incidence of abnormal sperm, low epididymal sperm concentrations, and too few sperm to assess motility; but he felt the relationship of the findings to treatment was not clear.

A mouse mode of type 1 Gaucher disease exits (D409V/null) that exhibits pathology in lung, liver, and spleen, but not in the brain. In a study using this model to compare velaglucerase alfa and imiglucerase given as weekly IV injections, similar effects of the two drugs were seen in reducing glucocerebroside in the liver and spleen, but neither affected the lung.

The Nonclinical Reviewer recommended changes to the labeling in Section 8.1 (Pregnancy) to supplement the dose information and (in the 2/19/10 Addendum) to include information about the Segment III study. He also recommended changes to Section 13.1 (Carcinogenesis, etc.) to bring it into compliance with the labeling regulations for that section. See the nonclinical review and addendum for details of the recommendations.

Conclusions and Recommendations

The Nonclinical Pharmacology Reviewer concluded that velaglucerase alfa had been tested adequately in general and reproductive toxicology studies. He concluded that velaglucerase alfa was well tolerated in rats and monkeys at up to 17 mg/kg IV biweekly.

The Reviewer recommended the NDA for approval from the nonclinical standpoint, with recommendations for changes to the labeling as noted above. The Reviewer did not recommend any nonclinical Phase 4 commitments or requirements.

5. Clinical Pharmacology/Biopharmaceutics

General clinical pharmacology/biopharmaceutics.
PK evaluations were conducted at Weeks 1 and 37 in Study 32 (a parallel comparison of the 45 and 60 U/kg doses). Vpriv is administered by IV infusion over two hours. During infusion, velaglucerase alfa concentrations rose rapidly for the first 20 minutes. The C_{max} concentrations were as shown below:

Mean Velaglucerase Alfa C_{max} (mg/mL) ± SD During Infusion

	Biweekly IV Dose	
	45 U/kg	60 U/kg
Week 1	3.4 ± 1.3	5.3 ± 2.3
Week 37	4.0 ± 2.9	5.7 ± 2.8

At the end of infusion, concentrations fell with a mean half life of 11 to 12 minutes for both doses. The mean volume of distribution at steady state ranged from 82 to 108 mL/kg. No significant accumulation was observed with repeated dosing, and the PK parameters did not appear to change over time.

The mean C_{max} and AUC were approximately 40% to 50% higher for the 60 U/kg dose compared to the 45 U/kg dose, suggesting a slight superlinearity (expected 33% increase if dose proportional).

Two doses of Vpriv were used in Study 32, and the efficacy responses were similar. An exposure-response analysis found no relationship for hemoglobin response.

The PK of velaglucerase alfa was not evaluated in Study 34, in which patients were switched from imiglucerase to Vpriv at doses ranging from 15 to 60 U/kg.

No PK or PD comparability studies were conducted comparing the formulations made from the AF1 process drug substance (used in most clinical studies) and AF2 process drug substance (to-be-marketed) two drug substances. Because the CMC reviewer determined that biochemical comparability was demonstrated between the two processes, such studies were not needed.

Drug-drug interactions
No drug-drug interaction studies were conducted.

Pathway of elimination
Velaglucerase alfa is though to be cleared by absorption by macrophages. No metabolism, excretion, or mass balance studies were conducted.

Demographic interactions/intrinsic factors/special populations
No apparent trend for AUC or clearance (CL) with age was seen for the 45 U/kg dose, but a trend for lower AUC and higher CL in subjects younger than 18 years was seen for the 60 U/kg dose. However, due to the small sample size, the Reviewer considered the findings overall inconclusive. There were no apparent differences in PK parameters by gender.

Studies of PK in patients with hepatic impairment or renal impairment were not conducted. The Reviewer felt that such studies did not appear to be necessary for this large molecular protein product.

None of the subjects was positive for anti-velaglucerase alfa antibodies on the days of PK assessment, so no relationship between PK and antibody can be determined.

QT assessment
No thorough QT or other specific QT assessments were conducted. Given the protein nature of this product, the Reviewer did not consider a thorough QT study to be required.

Other issues – assay validation
The evaluation of the in-process velaglucerase alfa assay was insufficient because duplicates rather than 5 replicates of quality control samples were used in the assays. The Reviewer concluded that the PK parameters cannot be considered accurate and reliable for labeling purposes. In light of the drug shortage with Cerezyme, the Clinical Pharmacology Division decided that PK parameters could be provided in labeling along with a qualifying statement regarding the inadequacy of the validation. The Reviewer recommended Phase 4 commitments requesting the Applicant to do the following:

1. Re-analyze all archived pharmacokinetic (PK) samples for Study 32 (using adequate in-process quality controls and standard curves) and recalculate velaglucerase alfa PK parameters.

2. Conduct a prospective PK study in patients with Type 1 Gaucher disease in the case that the Applicant is unable to characterize velaglucerase alfa PK adequately using the archived PK samples.

The Reviewer also recommended labeling changes for Section 6 (Adverse Reactions) concerning immunogenicity, for Section 7 (Drug Interactions), and Section 12 (Clinical Pharmacology). See Section 3 of the Clinical Pharmacology Review for details.

Conclusions and Recommendations
The Clinical Pharmacology Reviewer found that the PK parameters provided in the application could not be considered reliable because of inadequate process validation of the assays. In light of the supply shortage, she recommended approval, with Phase 4 commitments to repeat the PK measurements using proper assay validation or to conduct a new PK study using proper validations methods if the measurements cannot be repeated. She also recommended changes to several sections of the labeling.

6. Clinical Microbiology

Clinical Microbiology considerations do not apply to this application, because it is not intended as an antimicrobial product.

7. Clinical/Statistical-Efficacy

The efficacy of Vpriv was assessed in three clinical studies in a total of 99 patients with type 1 Gaucher disease. Vpriv was administered to 82 patients age 4 years and older, and 17 patients 3 years and older received imiglucerase. Studies 32 and 39 were conducted in patients who were not currently receiving Gaucher disease-specific therapy. Study 34 was conducted in patients who were receiving imiglucerase treatment immediately before starting Vpriv. In all these studies, Vpriv was administered intravenously over 60 minutes at doses ranging from 15 Units/kg to 60 Units/kg every other week. Hemoglobin concentration was taken as the primary measure of clinical effect, but platelet count, liver volume, and spleen volume were all major clinical parameters. These correspond to the major evaluative criteria used in the approval of Cerezyme.

Study 32

This was 12-month, randomized, double-blind, multinational, dose-ranging study of two doses of Vpriv as initial therapy in 25 patients age 4 years and older with type 1 Gaucher disease.

Eligibility, treatment, and assessments

To be eligible, patients needed to have Gaucher disease-related anemia and either thrombocytopenia or organomegaly. Patients were not allowed to have had disease-specific therapy for at least the previous 30 months. Patients were randomized to receive Vpriv at a dose of either 45 Units/kg (n=13) or 60 Units/kg (n=12) IV every other week. Therapy with red cell growth factors was not allowed. Blood counts were measured biweekly. Liver and spleen volumes were measured by MRI at Baseline, Week 25, and Week 51.

Endpoints

The primary endpoint was change in hemoglobin concentration from baseline to Month 12. The primary analysis was a paired t-test of Month 12 vs. Baseline hemoglobin in the group receiving 60 Units/kg.

Protocol-specified secondary endpoints were hemoglobin concentration in the 45 Units/kg groups, as well as the platelet count change, liver volume change, and spleen volume change for both dose groups. Adjustment for multiplicity of comparisons was made using a stepwise Holm procedure.

Results

The mean age was 26 years and 60% were male. At baseline, mean hemoglobin concentration was 10.6 g/dL, mean platelet count was 97 x 10^9/L, mean liver volume was 3.6% of body weight (% BW), and mean spleen volume was 2.9 % BW.

At the end of 12 months, hemoglobin concentrations were statistically significantly higher than baseline in both treatment groups. The change was considered to be clinically significant in light of the natural history of untreated Gaucher disease.

Vpriv 45 & 60 U/kg: Mean Hemoglobin Change from Baseline (g/dL) ±SE in Study 32 – ITT Population

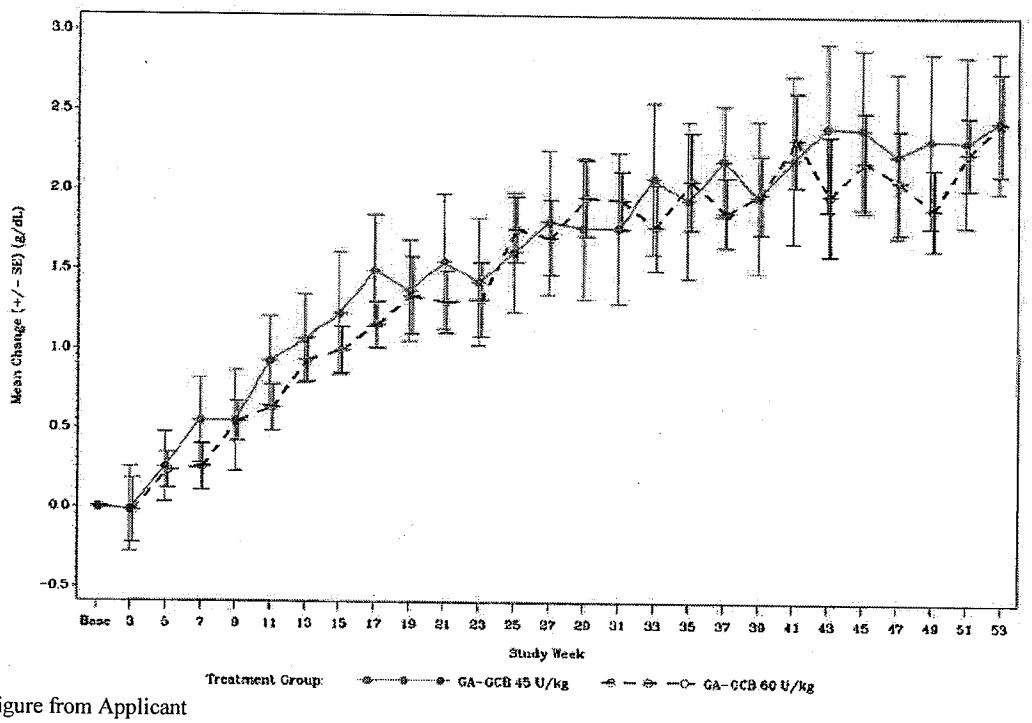

Figure from Applicant

Platelet counts also rose, and spleen volumes fell. No statistically significant changes were seen in liver volumes. The changes in clinical parameters after 12 months of treatment are shown in the Table below:

Mean Change from Baseline to Month 12 for Clinical Parameters in Patients with Type 1 Gaucher Disease Initiating Therapy with VPRIV in Study I

Clinical Parameter	Mean Changes from Baseline ± Std. Err. of the Mean	
	VPRIV Dose (given every other week)	
	45 Units/kg n = 13	60 Units/kg n = 12
Hemoglobin change (g/dL)	2.5 ± 0.5*	2.4 ± 0.3**
Platelet count change (x 10^9/L)	41 ± 14*	51 ± 12*
Liver volume change (% BW)	-0.30 ± 0.29	-0.84 ± 0.33
Spleen volume change (% BW)	-1.9 ± 0.6*	-1.9 ± 0.5*

** Primary study endpoint, $p < 0.001$

* Statistically significant changes from baseline after adjusting for performing multiple tests

The Statistical Reviewer noted that subgroup analyses by age and gender showed the principal results were generally robust. The study population was 100% Caucasian, so no analysis by race could be done.

Conclusions and Recommendations

The Statistical Reviewer concluded that that the primary efficacy analysis showed a statistically significant change from baseline in hemoglobin at Week 53 in the 60 U/kg group. Changes from baseline in each group for hemoglobin, platelet count, and spleen volume showed statistically significant increases, but liver volume did not.

The Clinical Reviewer concluded that Vpriv 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. She noted that an analysis by response categories showed greater improvement with 60 U/kg than 45 U/kg, but the difference was not statistically significant.

Study 39

This was as 9-month randomized, double-blind, active-controlled (imiglucerase), multinational study comparing Vpriv and Cerezyme as initial therapy in 34 patients age 3 years and older with type 1 Gaucher disease. Only a preliminary report was submitted for the NDA.

Eligibility, treatment, and assessments

To be eligible, patients needed to have Gaucher disease-related anemia and either thrombocytopenia or organomegaly. Patients were not allowed to have had disease-specific therapy for at least the previous 12 months. Patients were randomized to received either 60 Units/kg of VPRIV (n=17) or 60 Units/kg of imiglucerase (n=17) every other week. Therapy with red cell growth factors was not allowed. Blood counts were measured biweekly; more extensive testing was done quarterly.

Endpoints

The primary endpoint was change from baseline to Month 9 in hemoglobin concentration. The primary analysis was a non-inferiority test with a margin of -1.0 g/dL.

Secondary analyses were comparisons of the changes from Baseline in platelet count, liver volume, and spleen volume.

Results

The mean age was 30 years and 53% were female; the youngest patient who received VPRIV was age 4 years. At baseline, the mean hemoglobin concentration was 11.0 g/dL, mean platelet count was 171 x 10^9/L, and mean liver volume was 4.3 % BW. For the patients who had not had splenectomy (7 in each group) the mean spleen volume was 3.4 % BW.

After 9 months of treatment, the mean absolute increase from baseline in hemoglobin concentration was 1.6 g/dL ± 0.2 (sem) for patients treated with VPRIV. The mean treatment difference of change from baseline to 9 months [VPRIV – imiglucerase] was 0.1 g/dL.

Mean Hemoglobin Change from Baseline ±SE by Study Week for Study 39

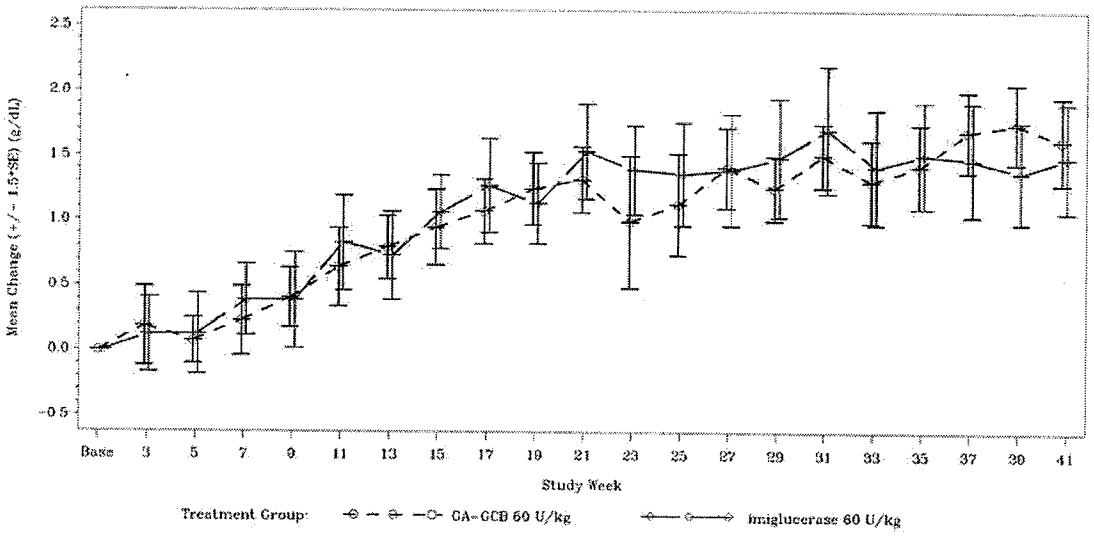

Figure from Applicant

There were no statistically significant differences between VPRIV and imiglucerase for changes in platelet counts and liver and spleen volumes.

The Statistical Reviewer noted that sensitivity analyses confirmed the primary efficacy analysis showing non-inferiority. He showed that subgroup analysis by age and sex had generally similar outcomes. The non-Caucasians in the study were mostly Asians; the treatment difference in hemoglobin change was almost 1 g higher in Caucasians, but the confidence intervals were wide.

Conclusions and Recommendations
The Statistical Reviewer concluded that the criteria for non-inferiority to Cerezyme had been met for change in hemoglobin.

The Clinical Reviewer also concluded that, from the preliminary report, the efficacy of Vpriv appeared similar to that of imiglucerase for hemoglobin, platelet count, liver volume and spleen volume (see Clinical Review Addendum regarding spleen volumes).

Study 34

This study was a 12-month, open-label, single-arm, multinational study of 40 patients with type 1 Gaucher disease age 9 years and older to evaluate the effects of switching from Cerezyme to Vpriv. Only a preliminary report was submitted for the NDA, and the only efficacy data included were hemoglobin and platelet counts.

Eligibility, treatment, and assessments
To be eligible, patients must have been receiving treatment with imiglucerase at doses ranging between 15 Units/kg to 60 Units/kg for a minimum of 30 consecutive months. Patients also were required to have a stable biweekly dose of imiglucerase for at least six months prior to enrollment.

This was a single-arm study, so patients were not blinded or randomized. Imiglucerase therapy was stopped, and treatment with VPRIV was administered every other week IV as the same number of units as the patient's previous imiglucerase dose. Adjustment of dosage was allowed by study criteria if needed in order to maintain clinical parameters. Therapy with red cell growth factors was not allowed. Laboratory testing was done every six weeks. Liver and spleen volumes were measured by MRI at Baseline, Week 25, and Week 51.

Endpoints
The primary efficacy variables were hemoglobin, platelet count, liver volume, and spleen volume. The efficacy analyses were considered exploratory. Secondary endpoints included biomarkers for all patients and growth parameters for pediatric patients.

Results
The mean age was 36 years and 55% were female. At baseline (defined as the end of treatment with imiglucerase), median hemoglobin concentration was 13.8 g/dL (range: 10.4, 16.5), and median platelet count was 162 x 10^9/L (range: 29, 399).

Hemoglobin concentrations and platelet counts remained stable on average through 12 months of VPRIV treatment: After 12 months of treatment with VPRIV the median hemoglobin concentration was 13.5 g/dL (range: 10.8, 16.1) vs. the baseline value of 13.8 g/dL, and the median platelet count after12 months was 174 x 10^9/L (range: 24, 408) vs. the baseline value of 162 x 10^9/L. No patient required dosage adjustment during the 12-month treatment period.

Hemoglobin Concentrations (±SE) Across Visits for Study 34

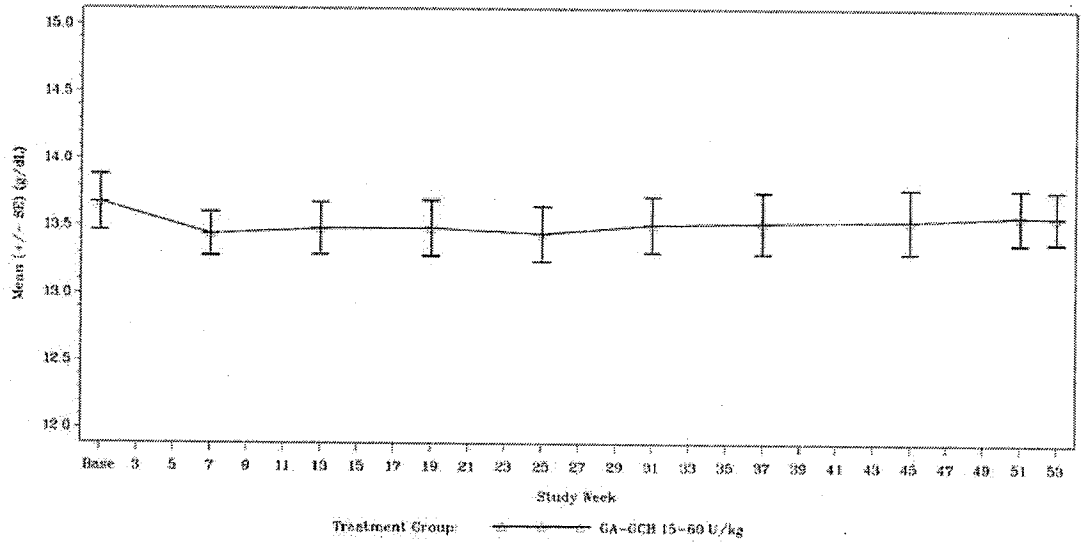

Figure from Applicant

The preliminary report did not include information regarding subgroups of age, gender, or race.

Conclusions and Recommendations

The Statistical Reviewer concluded that the result were marginally supportive, in a purely clinical context, of the non-inferiority result established in Study 39.

The Clinical Reviewer concluded that patients transitioned from imiglucerase to Vpriv in the dose ranges studied appear to have sustained clinical stability in hemoglobin concentration and platelet counts through 12 months without dosage adjustment of Vpriv.

Study 25

This Phase 1/2 study use the 30L drug substance, which has not been demonstrated comparable to the to-be-marketed material, and the results were considered supportive at best.

This was an open label study in which 12 patients were treated with 60 U/kg for 41 weeks (an initial cohort of 3 patients was escalated from a starting dose of 15 U/kg). The patients showed an increase in hemoglobin from 11.6 to 13.9 g/dL, increase in platelets from 57 to 95 x 10^9, a decrease in liver volume from 4.2 % BW to 3.3 % BW, and a decrease in spleen volume from 3.8% BW to 2.0 % BW. Each change had a nominal p-value ≤ 0.001.

Conclusions and Recommendations

The Statistical Reviewer considered the study marginally supportive, in a clinical context, of the findings of changes from baseline in Study 32. The Clinical Reviewer noted that the study was not done with the to-be-marketed drug, but felt the study showed the active moiety appears to have activity in type 1 Gaucher disease.

Inspections

The Division of Scientific Investigations inspected clinical sites in Israel and Paraguay, an imaging center in St. Louis, MO, and the Applicant's site in Lexington, MA. Although some deficiencies were identified, The DSI Reviewer recommended, based on preliminary EIRs, that all the data could be used in support of the NDA.

Overall Efficacy Conclusions

Overall Conclusions and Recommendations
The Statistical Reviewer concluded that all four studies showed changes from baseline but that the significance was based on clinical judgment, and that the change was principally established in Study 32. He stated that Study 39 satisfied the requirement for non-inferiority to Cerezyme regarding increase in hemoglobin concentration. He felt that Study 34 provided marginally supportive efficacy data.

The Clinical Reviewer concluded that Study 32 did not show a dose-response effect and that 45 U/kg and 60 U/kg resulted in similar improvements in all four measured parameters. She felt that, using observational data from the natural history of type 1 Gaucher disease as a historical control, Study 32 convincingly demonstrated that there was a positive and meaningful treatment effect. She also noted the results of Study 32 showed similar effects as seen in the trials used for the approval of Ceredase and Cerezyme. She concluded that the data in the three Phase 3 trials provide sufficient evidence of efficacy using both historical and active controls.

8. Safety

The safety data for Vpriv come from the experience in Studies 32, 34, and 39, as well as the extension study for Study 25. Study 25 (not the extension) used a non-comparable formulation of velaglucerase alfa, so the safety data were reviewed but not integrated. The safety data provided for Studies 34 and 39 were not complete, as those studies were recently completed and the Division had agreed at the pre-NDA meeting that preliminary data for those studies would be acceptable.

The principal safety database consisted of 94 patients with type 1 Gaucher disease, of who 54 received Vpriv as initial therapy, and 40 were switched from imiglucerase. Of these 94, 90 competed treatment for 9 months, 73 received treatment for 12 months, and 8 received treatment for 51 months (the latter in Study 25 Extension). There were also 17 patients treated with imiglucerase in Study 39 available for comparison.

No deaths were reported. The Applicant reported 12 serious adverse events (SAEs). The Reviewer considered two of these likely to be related to Vpriv: anaphylaxis, and allergic dermatitis requiring hospitalization. A case of convulsions occurring immediately after infusion in a 9 year old with no seizure history was reported as unrelated by the investigator, but the Reviewer felt there was a possibility it was an infusion reaction. The Reviewer felt the other nine cases were likely due to underlying disease or were otherwise unrelated.

The Clinical Reviewer reviewed the adverse event database and recoded some events as she felt appropriate to help identify possible patterns of events. The following is the revised tabulation of common adverse events from the Clinical Review, Section 7.4.1. The table shows adverse reactions reported at a rate of ≥ 10% in the three Phase 3 studies.

Common Adverse Events Reported ≥10% (Pooled Studies 32, 34, and 39)

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%)
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%)

Table from Clinical Review, Section 7.4.1

A search of the AERS database was conducted for the pharmacologically related drug, Cerezyme. The adverse events appeared to be mainly related to underlying Gaucher disease, and the search did not identify any new safety signal.

The Safety update received 12/2/09 included data from Study 44, which was an extension study for patients who participated in the Phase 3 trials. There were no deaths, and there were three new SAEs, which the Reviewer considered to be attributable to underlying disease. She determined that the safety update data did not change the conclusions about the safety profile of Vpriv.

Conclusions and Recommendations

The Clinical Reviewer felt the safety database was adequate and that there had been appropriate routine clinical testing. There did not appear to be any dose-dependence of the adverse reactions, but the patient numbers were small.

The Clinical Reviewer concluded that Vpriv was generally well tolerated in treatment-naïve and transitioned pediatric and adults patients with type 1 Gaucher disease at doses ranging from 15 to 60 U/kg. The common adverse reactions were infusion reactions, headache, URI-type symptoms, bone pain, pyrexia, arthralgia, dizziness, myalgia, and back pain. Only one

patient of the 94 receiving velaglucerase alfa in the development program has developed antibodies.

9. Advisory Committee Meeting

No Advisory Committee meeting was convened to discuss this application, because of its close similarity to the previously approved products Ceredase and Cerezyme, and because it did not pose unique concerns beyond those applicable to those other drugs is this class of enzyme replacement therapy.

10. Pediatrics

PeRC & PREA
Because the application is for an orphan indication, PREA requirements for pediatric studies do not apply. The submission was not presented to the Pediatric Review Committee (PeRC).

11. Other Relevant Regulatory Issues

Standard of Evidence for Efficacy
Study 32 provides evidence of a meaningful benefit when compared to observational data on the natural history of type 1 Gaucher disease as a historical control. The conclusion is also corroborated by comparing the results of Study 32 to those of the trials of Ceredase and Cerezyme as historical active controls. Study 39 provided evidence of efficacy through a non-inferiority comparison to Cerezyme. Study 34 provided some support through the ability of Vpriv to maintain the effect of Cerezyme at the same dose. While Study 25 did not use the to-be-marketed formulation, it did provide some confirmatory evidence (comparing to natural history) of the pharmacodynamic effect of the active moiety.

Claims of Similarity to Imiglucerase
The labeling does not make an explicit claim of comparability to Cerezyme, but the statements in Section 14 comparing the effects on hemoglobin of Vpriv and imiglucerase in Study II (Study 39) could be viewed as an implicit claim of comparability, at least for the hemoglobin effect. Given that Study 39 was a successful non-inferiority study, that the hemoglobin results in Study 32 were nearly identical to the results in the approval study for Cerezyme, and the ability of Vpriv to maintain hemoglobin levels for a year after switching from Cerezyme to the same dose of Vpriv, such an implied claim for comparability of hemoglobin response can be considered adequately supported.

Adequacy of Safety Evaluation
The size of the safety database is reasonable, given rarity of the disease. The lack of a thorough QT study for this product is acceptable in consideration of its nature as a large molecule protein and of the marketing experience of the closely related drugs Ceredase and Cerezyme.

Orphan Designation and Exclusivity Issues
Orphan-drug designation was granted "based on a hypothesis for clinical superiority for the use of valaglucerase-alfa [sic] over imiglucerase for the treatment of Gaucher disease." The designation stated that the product would only be granted 7 years of exclusivity if clinical superiority over imiglucerase were demonstrated in clinical trials. The Applicant's contention for superiority was based on the reasons that

- In vitro studies have reportedly shown that cellular uptake of velaglucerase alfa is two to three times that of imiglucerase; this is postulated to have a potential effect on time to clinical response.

- Velaglucerase alfa does not appear, based upon the 42 months of clinical data available, to induce antibodies; imiglucerase is known to induce antibody formation in 15% of treated patients.

The information submitted in this application did not provide substantial evidence leading to a claim of superiority Vpriv over Cerezyme. In the parallel study of Cerezyme and Vpriv (Study 39) the two treatments provided very similar results on the major clinical parameters (cf. Section 5.3.21 of the Clinical Review). In particular, there was no evidence of a faster effect with Vpriv.

Comparison of the totality of Vpriv immunogenicity experience with the generally quoted rates of immunogenicity for imiglucerase does suggest a lower rate of antibody formation with Vpriv. However, there are some questions remaining to be resolved regarding the immunogenicity assay used by the Applicant. Also, in the one head-to-head study (Study 39), only 4 of 17 patients on imiglucerase developed antibody. Even if the frequency of antibody production for Vpriv were accepted as being 0 of 17, the results are not statistically significant; further, the result is not replicated. If the clinical Division were to be presented with a claim of superiority based on reduced antibody production, it is unlikely a superiority claim would be granted without data providing substantial evidence (in the regulatory sense) of a significant clinically meaningful benefit as a result of that reduced immunogenicity, such as lower rates of anaphylaxis, hypersensitivity reactions, infusion-related reactions, loss of efficacy, or some other phenomena that might be related to antibody formation. Evidence of that nature was not presented in this application.

12. Labeling

Proprietary Name
In the name review dated 12/10/09, DMEPA had no objections to the proposed proprietary name of Vpriv. Of the 13 names identified that had some potential for confusion with Vpriv, the Failure Mode and Effect Analysis determined that the similarities were unlikely to result in medication errors. DDMAC did not find the name objectionable on promotional grounds.

Labeling Consults and Reviews
In the first half of the review cycle the RPM identified deficiencies in proposed labeling regarding compliance with PLR format requirements. The OBP Label Reviewer also

identified several points on which the proposed carton and container labels did not conform to regulations, but she recommend that labels could be approved provided the required changes were made.

The Division of Drug Marketing, Advertising, and Communications (DDMAC) provided several comments suggesting improvements to sections that were vague, and calling attention to statements that could be misused promotionally or that misleadingly minimized risk.

DMEPA provided recommendations for improvements to the carton and container labels to minimize the potential for medication errors.

Specific Labeling Issues

a) Dosing and Administration: The recommended initial dosing for Cerezyme is 60 Units/kg every other week, but the labeling for Cerezyme also recommends that dosage should be individualized and adjusted based on therapeutic goals and routine evaluations. From the results of Study 39 (head to head vs. Cerezyme) and Study 34 (switch from Cerezyme), it appears that similar doses of Vpriv and Cerezyme produce similar results, at least for hemoglobin response, suggesting that dosing recommendations can be similar. Given also that initial therapy using 60 U/kg of Cerezyme is well established, that 60 U/kg is the most extensively evaluated dose of Vpriv, that there is a weak suggestion that 60 U/kg Vpriv may have some benefit over 45 as initial therapy, and that there is no concerning dose-related toxicity, the Applicant's proposed dosing of 60 U/kg is acceptable. However, the dosing section should also recommend individualization of dosing and that dose reduction is possible. For patients being switched from imiglucerase, the results of Study 34 suggest the dosing recommendation should be to use the same dose as was being used for imiglucerase.

b) Pediatrics: Because the youngest patient who received Vpriv was 4 years old, Section 8.4 should state that safety for children younger than 4 years has not been established.

c) Clinical Pharmacology: The Clinical Pharmacology review concluded that the PK findings were unreliable due to problems with assay validation. Rather than omitting PK data, the Clinical Pharmacology reviewer recommended they be included in Section 12 but with qualifying language regarding the reliability of the information.

d) Clinical Studies: Because Study 25 was not conducted with the to-be-marketed formulation, and because data from the extension studies did not contribute meaningfully to the determination of efficacy, the clinical review team limited the discussion in Section 14 to the data from Studies 32, 39, and 34.

e) Patient Information: [redacted] Because there was no REMS and because the product is labeled to be used under the supervision of a health care provider, the review team questioned the need and appropriateness of having [redacted]. The Applicant revised the labeling by [redacted] and instead proposed patient counseling information to include in Section 17. b(4)

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
Approval, with postmarketing commitments to address CMC, Immunogenicity, and Clinical Pharmacology issues as noted in the respective sections above.

Risk Benefit Assessment
The benefit of Vpriv for type 1 Gaucher disease has been established in clinical trials. Based on what was found in those trials and what is known about pharmacologically related products, the risks of Vpriv appear to be acceptable in view of the established benefits.

Recommendation for Postmarketing Risk Management Activities
No special postmarketing risk management activities are recommended for this Application.

Recommendation for other Postmarketing Study Commitments or Requirements
The CMC, Immunogenicity, and Clinical Pharmacology reviewers recommended that the Applicant be required agree to Phase 4 commitments, as detailed the corresponding sections above.

Recommended Comments to Applicant
None.

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/

JOHN E HYDE
02/26/2010