CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-575

CHEMISTRY REVIEW(S)

Memo

To: file
From: Fred Mills, Staff Scientist, DTP, OBP, CDER
Through: Susan Kirshner, Ph.D., Deputy Chief, Laboratory of Immunology, DTP, OBP, CDER, Amy Rosenberg, M.D., DTP, OBP,CDER

Subject: NDA 22575
original licensing application
Immunogenicity of Velaglucerase alfa for treatment of Gaucher's disease
Sponsor: Shire
Date: January 27, 2010
Revised February 17, 2010 and February 24, 2010

Introduction
Velaglucerase alfa is an Enzyme Replacement Therapy developed by Shire for treatment of Gaucher's disease , a hereditary deficiency in the lysosomal enzyme acid β glucosidase (glucocerebrosidase), which mediates the breakdown and recycling of the ganglioside glucocerebroside. Cells of the macrophage lineage are particularly affected and cause enlargement of the liver and spleen, anemia, skeletal disorders, and, in some instances, lung and kidney impairment..Patients usually bruise easily and experience fatigue due to anemia and low blood platelets. Gaucher's disease is the most prevalent Lysosomal Storage Disease (LSD), with an overall frequency of 1 in 20,000 live births.

Velaglucerase alfa is produced in a human cell line (HT-1080), in which the endogenous acid β glucosidase gene has been activated by targeting of a strong enhancer/ promoter to the gene locus. The enzyme has a 497 amino acid sequence, with 4 occupied N glycosylation sites. During [redacted] culture, the mannosidase I inhibitor kifunensine is is added to prevent maturation of complex glycosyl groups, resulting in side chains with mannose termini. This allows targeting of the replacement enzyme to receptors on macrophages. Kifunensine is not expected to pose a safety concern as the sponsor has spiked [redacted] cultures with [redacted] times the normal kifunensine concentration, and demonstrated clearance in the drug substance below the level of detection. b(4)

Shire has completed a study comparing velaglucerase and imiglucerae (Cerezyme) treatment of naïve patients (TKT024), two additional studies of naïve patients with velaglucerase only (TKT032 and HGT-GCB-039) and a study in which patients were transitioned from imiglucerase (TKT034) to velaglucerase treatment.. Immunogenicity data for these studies are provided in the BLA, and include non isotype-specific screening for anti-velaglucerae and anti-imiglucerase antibodies, confirmatory evaluation for IgG antibodies, evaluation for antibodies capable of neutralizing velaglucerase and immiglucerase enzyme activity, and evaluation of IgE antibodies. I have reviewed these data, the immunogenicity assay methods, and their validation. I recommend that Shire provide PMCs to develop more sensitve cutpoints for the screening, confirmatory, and IgE assays. I also recommend a PMC for development of an assay to assess potential for antibody neutralization of velaglucerase by inhibition of product uptake into target cells.

Table of Contents

b(4)

__2__ Page(s) Withheld

__X__ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

*Withheld Track Number: Chemistry Review Section(Immunogenicity Review)-*_____

Immunogenicity PMCs

1. Please develop 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

Rationale
You have established a high cutpoint (5 ng/ ml) for defining patient serum samples as positive for anti-velaglucerase and anti-imiglucerase antibodies, resulting in an expected 1/2000 false positive rate for normal serum samples. You have found that using a mean assay output (ECL) + 1.645 SD (as per Mire-Sluis, et. al., 2004) derived from healthy volunteer serum samples results in an unacceptably high (20%) level of positive values for sera from treatment-naïve Gaucher patients. Therefore, it is reasonable to attempt to establish a cutpoint based on mean+ 1.645 SD for assay values from treatment-naïve Gaucher patients. It may also be reasonable to link this cutpoint to the calibration curve and positive control values on individual assay plates used for analysis of patient sera.

Update incorporating information provided by Shire current to February 23, 2010.

Shire evaluated 65 Gaucher patient baseline samples, and found that the mean + 1.645 SD of this data set was 241 ECL counts. Shire is concerned that this ECL value is within the manufacturer's specified background noise range for the instrument used for the ECL analysis. This concern is merited is being discussed with by Fred Mills and Susan Kirshner (See below). b(4)

Shire investigated an alternative approach in which they determined 153 ECL units to be the mean value at 0 ng/ ml control antibody for 42 assay runs, and multiplied this empirical background noise level by a factor of two to arrive at a cutpoint of 306 ECL units. Using this cutpoint, Shire found all the patients continued to be negative except for a total of 15 samples from the following 4 subjects.

Patient 032-191-002 – a treatment-naïve patient previously identified as the single positive patient was still positive, as expected.

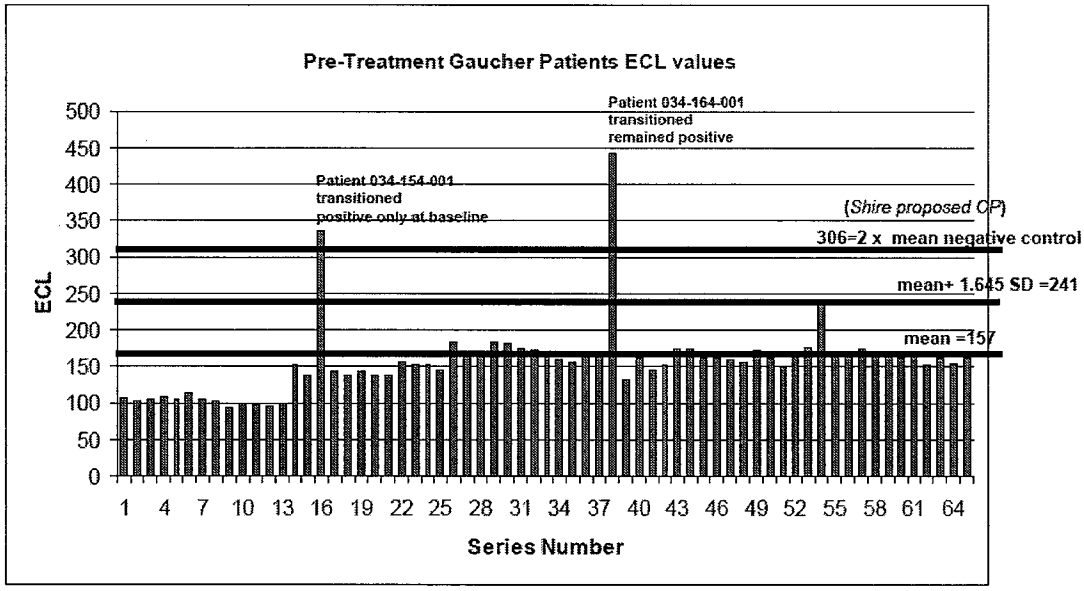
Patient 032-191-003- a second treatment-naïve patient was above the cutpoint for a 3 week sample, and negative otherwise

Patient 034-154-001 –a patient transitioned from imiglucerase who was only positive for cross-reactive antibodies at baseline screening.
n.b.Shire stated that the apparent waning antibody responses observed in Patients 032-191-003 and 034-154-001 could not result from on-board product, since the serum half-life of velaglucerase is 24 hours, and antibody samples are taken 14 days after the previous infusion, and before the next infusion. I agree with this interpretation

Patient 034-164-001-a second transitioned patient who was positive for cross-reactive antibodies at baseline screening and, remained positive throughout the study.

Shire found that 14 out of these 15 positive samples were also positive for the confirmatory assay, indicating that the revised cutpoint detects true reactivity. The single sample that was not positive in the confirmatory assay was from Patient 032-191-003, who showed a single positive screening assay result at 3 weeks. Shire believes this sample is an outlier.

ECL values were provided to this reviewer for the 65 pre-treatment Gaucher samples, as well as the ECL values for all the samples (15) identified as positive using the revised screening cutpoint. Analysis of the pre-treatment Gaucher data demonstrates a relatively uniform response in the range 95-176 ECL units, with two outliers from patients confirmed to be positive (transitioned patients 034-154-001 and 034-164-001, discussed above), and a 3rd apparent false positive. A graph of these data is shown below



On February 24, 2010 Susan Kirshner and I discussed the ECL machine background with [redacted] *technical support for the ECL machines. The machine background (dark noise) should actually be very low in the range -16 to 16 ECL units, whereas the ECL signal seen in the assay for naive Gaucher patients is in the 95-176 ECL range. Shire can confirm the machine background in a 15 mintue test with a PQ kit* [redacted]*. This will be suggested* b(4)

Thus, a cutpoint of 241 ECL units based on a mean +1.645 SD of pre-treatment Gaucher values is appropriate.

2. Please revise the cutpoint for the confirmatory anti-velaglucerase and anti-imiglucerase screening assay so that it is consistent with a revised cutpoint in the antibody screening assay.

Rationale
For the RIP assay, the positive cut point is currently set at the Limit of Detection LOD value, that is, [redacted] You have been asked in PMC # 1 to re-evaluate the cutpoint of the screening assay [redacted] to yield a higher false positive rate. This re-evaluation will in all likelihood result in a lower cutpoint for the screening assay. Therefore, the cutpoint of the confirmatory assay will need to be revised to be less than or equal to the cuptoint for the revised screening assay. b(4)
In discussion with the FDA on 2-23-2010, Shire agreed to this PMC.

3. Please develop an assay for detection of anti-velaglucerase and anti-imiglucerase IgE that has a sensitivity commensurate with the expected range of IgE responses.

Rationale
A high degree of linearity was demonstrated for the response of this assay over the range 0.156 -10 µg / ml using the [redacted] antibody crosslinked to human IgE. However, the calibration range is much greater than the expected [redacted] range for an IgE response. In order to establish a new, lower cutpoint, you will need to re-validate your IgE assay over a lower range appropriate to that expected for IgE responses. If adequate sensitivity cannot be demonstrated in a lower range, your will need to develop a new, more sensitive IgE assay. b(4)
In discussion with the FDA on 2-23-2010, Shire agreed to this PMC.

4. Please develop an assay that will measure the ability of patient antibodies to block the uptake of velaglucerase and imiglucerase into target cells.
In discussion with the FDA on 2-23-2010, Shire agreed to this PMC.

Enzyme Replacement Therapies (ERT) require that ERT products are active within target cells for which the deficiency of a given enzyme is deleterious. Thus uptake of enzyme replacement products into appropriate target cells is a critical aspect of their mechanism of action. For this reason an assay for antibody neutralization of cell uptake of enzyme is an important part of profiling patient immune responses, and will need to be developed.

Immunogenicity Section from Package Insert,
(as per agreement with Shire 2-22-2010)

b(4)

Executive Summary

Shire has submitted NDA 22575, which is a marketing application for treatment of Gaucher's Type I disease with velaglucerase. Velaglucerase is produced in human HT1080 cells, and is an alternative to Ceredase and Cerezyme, the two marketed products for Gaucher's disease from Genzyme

Patient Immunogenicity Results
Shire has completed a study comparing velaglucerase versus imiglucerae (Cerezyme) treatment of naïve patients (TKT024), two additional studies of naïve patients with velaglucerase only (TKT032 and HGT-GCB-039) and velaglucerase treatment of patients transitioned from imiglucerase (TKT034). Immunogenicity data from these studies was provided in the NDA. Samples positive in the antibody screening assay were analyzed with confirmatory assays, which were RIP (RadioImmunoprecipitation) for IgG and ECL (ElectroChemiLuminescence) for IgE. Shire's protocol specified that samples negative for IgG in RIP would be tested for IgM and IgA, but no samples met this criterion. The immunogenicity data are summarized in the following table.

Treatment	**N**	**Naïve or Transitioned?**	**anti-Velaglucerase**	**neutralizing**	**anti-Imiglucerase**	**neutralizing**
Velaglucerase	94	Total	1(1.1%)	1(1.1%)	Not tested	Not tested
Velaglucerase	54	Treatment naive	1(1.9%)	1(1.9%)	Not tested	Not tested
Velaglucerase	40	transitioned	1 Cross reactive	0	1 Cross reactive	Not Tested
Imiglucerase	17	Imiglucerase only – treatment naive	1(5.9%) Cross-reactive	1(5.9%)	4(23.5%) 3 positive at screening	Patients positive not tested

Out of 54 treatment-naïve velaglucerase-treated patients, one patient was positive for antibodies. This patient was a treatment-naïve adult male who completed 12 months of treatment with 45 U/kg velaglucerase alfa. These antibodies were characterized as IgG and neutralizing and were detected after 1 year of treatment.

One out of 40 transitioned patients had anti-imiglucerase antibodies at screening that were cross-reactive with velaglucerase. These antibodies persisted thoughout the course of velaglucerase treatment.

There was an additional patient in the imiglucerase comparator arm of Study TKT024, who developed antibodies to immiglucerase, cross-reactivity with velaglucerase, and neutralizing antibodies. This patient discontinued at week 23 of the study due to infusion-related adverse events

There were two other patients who experienced episodes of hypersensitivity.

One patient developed a mild allergic skin reaction at 214 days (7 days after her last velaglucerase infusion), which became severe 10 days later and required hospitalization. The reaction was resolved in the hospital and the patient continued on velaglucerase treatment with premedication. A second patient who was being transitioned from imiglucerase to velaglucerase experienced a moderate anaphylactod reaction upon receiving a first dose of velaglucerase. This reaction was reported as an SAE.

Screening for anti-velaglucerase and anti-imiglucerase IgG and IgE antibodies was completed on samples collected prior to the first velaglucerase infusion, 24 hours post infusion, and at a three week time point. All test results were below the provisional positive cut points for these assays and were therefore considered negative for these antibodies.

Reviewer comment
The apparent low immunogenicity of velaglucerase is not unexpected , since Type I Gaucher's patients generally have some glucocerebrosidase expression, ie are CRIM positive,, and are therefore presumed to be immunologically tolerant to the enzyme. However, the exact levels of positive patients should be viewed with some caution, since review of the assay validations indicates that the assay cutpoints should be revised in the direction of higher sensitivity.

b(4)

Reviewer comment

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X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

*Withheld Track Number: Chemistry Review Section (Immunogenicity Review)-*_____

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/

FREDERICK C MILLS
02/24/2010

SUSAN L KIRSHNER
02/25/2010

AMY S ROSENBERG
02/25/2010

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

BLA/NDA Number: **Applicant:** **Stamp Date:**

Established/Proper Name: **BLA/NDA Type:**

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

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y	
Form 356h completed ❑ including list of all establishment sites and their registration numbers	Y Y	
Comprehensive Table of Contents	N	Use eCTD tabs, it is equivalent to table of contents
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling: ❑ PI –non-annotated ❑ PI –annotated ❑ PI (electronic) ❑ Medication Guide ❑ Patient Insert ❑ package and container ❑ diluent ❑ other components ❑ established name (e.g. USAN) ❑ proprietary name (for review)	Y Y Y N N N Y N N Y Y	Medication Guide and Patient Insert not necessary for this product, administered in clinic. No diluent is provided, the product is reconstituted in the clinic with WFI. There are no other components. Fileable.

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y	
❑ legible	Y	
❑ English (or translated into English)	Y	
❑ compatible file formats	Y	
❑ navigable hyper-links	Y	
❑ interpretable data tabulations (line listings) & graphical displays	Y	
❑ summary reports reference the location of individual data and records	Y	
❑ all electronic submission components usable (e.g. conforms to published guidance)	Y	
Companion application received if a shared or divided manufacturing	Y N	NOT APPLICABLE

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

Examples of Filing Issues	Yes?	If not, justification, action & status
arrangement		

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	There are no novel excipients and comparability protocols were not submitted at this time. Fileable.
❑ Drug Substance	Y	
❑ Drug Product	Y	
❑ Facilities and Equipment	Y	
❑ Adventitious Agents Safety Evaluation	Y	
❑ Novel Excipients	N	
❑ Executed Batch Records	Y	
❑ Method Validation Package	Y	
❑ Comparability Protocols	N	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y	
Drug Substance [3.2.S]		
❑ general info o nomenclature o structure (e.g. sequence, glycosylation sites) o properties	Y	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ description of manufacturing process and process control o batch numbering and pooling scheme o cell culture and harvest o purification o filling, storage and shipping	Y	
❑ control of materials o raw materials and reagents o biological source and starting materials o cell substrate: source, history, and generation o cell banking system, characterization, and testing	Y	
❑ control of critical steps and intermediates	Y	

CTD Module 3 Contents	Present?	If not, justification, action & status
○ justification of specifications ○ stability ❑ process validation (prospective plan, results, analysis, and conclusions) ❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes) ❑ characterization of drug substance ❑ control of drug substance ○ specifications ○ justification of specs. ○ analytical procedures ○ analytical method validation ○ batch analyses ❑ reference standards ❑ container closure system ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results ○ method validation	Y Y Y Y Y Y Y Y Y Y Y	
Drug Product [3.2.P] [Dosage Form] ❑ description and composition ❑ pharmaceutical development ○ preservative effectiveness ○ container-closure integrity ❑ manufacturers (names, locations, and responsibilities of all sites involved) ❑ batch formula ❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) ❑ controls of critical steps and intermediates ❑ process validation including aseptic processing & sterility assurance:	Y Y Y Y Y Y Y Y Y	

CTD Module 3 Contents	Present?	If not, justification, action & status
○ Filter validation ○ Component, container, closure depyrogenation and sterilization validation ○ Validation of aseptic processing (media simulations) ○ Environmental Monitoring Program ○ Lyophilizer validation ○ Other needed validation data (hold times)		
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y	
❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y	
❑ reference standards or materials	Y	
❑ container closure system [3.2.P.7] ○ specifications (vial, elastomer, drawings) ○ availability of DMF & LOAs ○ administration device(s)	Y	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results ○ method validation	Y	
Diluent (vials or filled syringes) [3.2P'] ❑ description and composition of diluent ❑ pharmaceutical development ○ preservative effectiveness ○ container-closure integrity ❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N Y N Y N Y N Y N Y N	There is no diluent for this product and this section is NOT APPLICABLE.

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ batch formula		
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N Y N Y N	
❑ controls of critical steps and intermediates		
❑ process validation including aseptic processing & sterility assurance: o Filter validation o Component, container, closure depyrogenation and sterilization validation o Validation of aseptic processing (media simulations) o Environmental Monitoring Program o Lyophilizer sterilization validation o Other needed validation data (hold times)	Y N Y N Y N Y N Y N	
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y N	
❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N	
❑ reference standards	Y N	
❑ container closure system o specifications (vial, elastomer, drawings) o availability of DMF & LOAs	 Y N	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results		
Other components to be marketed (full description and supporting data, as		This section is NOT APPLICABLE

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 3 Contents	Present?	If not, justification, action & status
listed above): ❑ other devices ❑ other marketed chemicals (e.g. part of kit)	 Y N Y N	
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	 Y Y N	No Novel Excipients are present in the product. Fileable.
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	 Y Y N	Comparability protocols were not submitted at this time. Fileable.
Literature references and copies [3.3]	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y	
Includes data demonstrating consistency of manufacture	Y	
Includes complete description of product lots and manufacturing process utilized	Y	

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

Examples of Filing Issues	Yes?	If not, justification, action & status
for clinical studies		
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y	
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y	
Certification that all facilities are ready for inspection	Y	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y	
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: ❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility	N N Y N	This is an NDA and these regulations do not apply.
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y	
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? **Yes**

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

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

Product Quality Reviewer(s) Date

Branch Chief/Team Leader/Supervisor Date

Division Director Date

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

/s/

EMANUELA LACANA
09/25/2009

GIBBES R JOHNSON
09/25/2009

BARRY W CHERNEY
09/25/2009

Review Cover Sheet

NDA 22575

VPRIV™ (Velaglucerase alfa)

Shire Human Genetic Therapies

Division of Therapeutic Proteins

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QUALITY EXECUTIVE SUMMARY

I. RECOMMENDATIONS

A. Recommendation and Conclusion on Approvability

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of NDA 022575 for velaglucerase alfa, manufactured by Shire Human Genetic Therapies, Inc. The data submitted in this application support the conclusion that the manufacture of velaglucerase is well controlled, and leads to a product that is pure and potent. The processes used in manufacturing have been validated, and a consistent product is produced from different production runs. It is recommended that this product be approved for human use (under conditions specified in the package insert).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable:

We propose the following post-marketing commitments:

1. Shire commits to develop and implement a kinetic assay with physiologically relevant substrate for drug substance and drug product release and stability testing. Results and specifications will be included in the final report.

   Final Report Submission: December 31, 2011

2. Shire commits to develop and implement a quantitative method that measures total carbohydrate content. Results and specifications will be included in the final report.

   Final Report Submission: February 28, 2011

3. Shire commits to replace the non-quantitative SDS-PAGE Silver stain method with a quantitative SDS-PAGE Coomassie test. Results and specifications will be included in the final report.

   Final Report Submission: February 28, 2011

4. Shire commits to demonstrating that ——— is well controlled, to ensure no impact on product quality. The results will be included in the final report. b(4)

   Final Report Submission: February 28, 2011

5. Shire commits to demonstrate the clearance capability of the process to remove ——— through ——— spike studies. The results will be included in the final report.

Final Report Submission: November 30, 2010

6. Shire commits to re-evaluating drug substance and drug product release and stability specifications. Shire will submit the revised specifications and supporting data in the final report.

   Final Report Submission: December 31, 2011

7. Shire commits to update the specifications for SEC, RP-HPLC, and glycan map, to include acceptance criteria for the leading shoulder in SEC-HPLC, for peak — in RP-HPLC, and for peak — in the glycan map. b(4)

   Final Report Submission: July 1, 2010

8. Shire commits to update the peptide map specification using new acceptance criteria to reflect control of impurities. Shire commits to adding the peptide map as a drug substance and drug product release and stability test with the new acceptance criteria.

   Final Report Submission: July 1, 2010

9. Shire commits to include the cellular uptake bioassay for drug product release testing.

   Final Report Submission: April 1, 2010

10. Shire commits to provide a report containing the sub-visible particulates — analyses, risk assessment and risk mitigation strategies. b(4)

    Final Report Submission: September 30, 2010

11. Shire commits to include drug substance and drug product stress condition in the annual stability program. The revised stability protocols will be included.

    Final Protocol Submission: April 1, 2010

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

    Final Protocol Submission: December 31, 2010

II. SUMMARY OF CHEMISTRY ASSESSMENTS

Description of the Drug Product and Drug Substance

General: Velaglucerase (VPRIV) is the United States Approved Name (USAN) name for the active pharmaceutical ingredient in VPRIV. Velaglucerase is a recombinant glucocerebrosidase produced by gene-activation technology in the human fibrosarcoma cell line HT1080.

b(4)

- Drug Product Presentation: VPRIV is supplied in single-use glass vials, stoppered with a fluororesin-coated butyl rubber stopper and sealed with a aluminum seal with a plastic flip-off cap. VPRIV is a sterile, lyophilized to be reconstituted in Water For Injection (WFI), followed by dilution in saline for intravenous infusion. VPRIV is available in two presentations, 200 units (5 mg) or 400 units (10 mg) of velaglucerase/vial. Velaglucerase is formulated in sucrose, sodium citrate dehydrate, citric acid monohydrate and polysorbate 20. The sponsor requested a drug product shelf life of 24 months when stored at 2-8°C and the request is supported by data provided in the NDA. The drug product is designated as "**protect from light**", based on results of photodegradation studies. b(4)

- Excipients: All excipients are compendial, tested and specified according to compendial standard. There are no novel excipients or excipients of animal origin. Sucrose sodium citrate and citric acid are and polysorbate 20 b(4)

- Complexity: Velaglucerase is a single chain polypeptide, consisting of 523 amino acid residues. A signal sequence for secretion is located at the N-terminus of the protein and is removed following translocation in the endoplasmic reticulum of the cells, resulting in a mature polypeptide of 497 amino acids. Velaglucerase contains five potential N-linked glycosylation sites and studies have shown that Asn19, Asn59, Asn146 and Asn270 are

b(4)

- Biological activity and mechanism of action: Velaglucerase is intended to replace glucocerebrosidase, the defective enzyme in Gaucher's patients.

Glucocerebrosidase catalyzes the cleavage of the sphingolipid glucocerebroside into glucose and ceramide. The defect leads to accumulation of glucocerebroside in the cells' lysosome. As a consequence, macrophages become enlarged, with a prominent cytoplasm (Gaucher's cells). Gaucher's cell accumulate in liver, spleen, bone marrow and lungs, causing organomegaly, anemia and bone problems. In order to reach the substrate accumulated inside the cells, velaglucerase alfa has to be internalized by the target cells and directed to the lysosomal compartment. The mannose receptor on the surface of macrophages belongs to a family of lectin-type receptors and its function involves the recognition of carbohydrate patterns on pathogens and the uptake of pathogens by phagocytosis for clearance by the lysosome. The mannose receptor also binds serum-circulating lysosomal enzymes and other glycosylated proteins and delivers them to the lysosomal compartment. Velaglucerase binds to the cell surface mannose receptor via the exposed mannoses present in the glycan chains of the protein, is internalized and directed to the lysosomal compartment. In the lysosome, velaglucerase reduces the glucocerebroside substrate accumulated by converting it into glucose and ceramide. The reduction in substrate levels in the lysosome correlates with a reduction in size of macrophages and consequently leads to spleen and liver reduction and restoration of hemoglobin levels.

- Potency Assays to Measure Activity: The sponsor has developed four assays that have been used in drug substance characterization studies.

    1) Enzyme activity assay: this assay is based on cleavage of the surrogate substrate p-nitrophenyl glucopyranoside to yield yellow p-nitrophenol that can be detected with a spectrophotometer.
    2) Enzyme activity assay: this assay is based on the cleavage of the physiologically relevant substrate C18-glucocerebroside. The glucose released in the reaction is measured by HPLC. The kinetic parameters K_m and k_{cat} have been measured for both assay types and it was demonstrated that the assay conducted using the physiologically relevant substrate is a more sensitive indicator of product quality, compared to the assay conducted using the surrogate substrate.
    3) Receptor binding assay: recombinant mannose receptor is bound on a biosensor surface and incubated with biotinylated velaglucerase. The association, dissociation and affinity constants are measured using a [redacted] instrument.
    4) Cellular uptake assay: A mouse macrophage cell line is incubated with velaglucerase. At the end of incubation, cells are lysed and internalized velaglucerase is measured with an enzyme-linked immunosorbant assay (ELISA)-based assay. The sponsor is using the surrogate substrate-based enzyme assay for drug substance and drug product release and stability, and the cellular uptake assay for drug substance release and drug product stability. The cellular uptake assay is adequate to evaluate the potency of velaglucerase at release and during storage. We

recommended that Shire uses the cellular uptake assay for both drug product release and stability. The enzyme activity assay is insufficient to monitor product quality and stability and we recommend that Shire develops an enzyme activity assay that measure K_m and k_{cat} using a physiologically relevant substrate (addressed by PMC).

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b(4)

- Drug Product Manufacture: The drug substance is ——— formulated with sucrose, sodium citrate, citric acid and polysorbate 20, filled into ——— ——— glass vials, and lyophilized. The drug product is available in 2 presentations, a 200U/vial and a 400U/vial. The vials are labeled and packaged in single vial ——— containers. b(4)

- Release Tests for Drug Substance and Product: The control strategy for drug substance and drug product is very similar. The assays included in the release protocols measure potency (cellular uptake and enzyme activity), purity (SEC-HPLC, RP-HPLC, SDS-PAGE and ELISA for Host Cell Proteins) and microbiological quality (endotoxin, bioburden and sterility). Process-related impurities that are not measured in the drug substance include ——— ———). The sponsor validated removal of these impurities by the manufacturing process. Additional process-related impurities , ——— Since the sponsor has not validated removal of these impurities, we recommend that assays that measure amounts ——— — be included in the release protocol for drug substance. This issue will be addressed with a post-marketing commitment (PMC). Furthermore, the sponsor uses SDS-PAGE with silver staining detection. This assay is very sensitive but is not quantitative and we recommend that SDS-PAGE with Coomassie staining detection, a more quantitative method, be included in the release protocols (addressed by PMC). Critical quality attributes include: b(4)

    - Glycosylation: Glycan chains are critical for the mechanism of action of velaglucerase and clinical efficacy. Glycosylation is monitored by

glycan mapping. However, additional assays need to be included in the control strategy to ensure that the total glycans/mole of protein is constant (addressed by PMC).

- Enzyme activity: Enzyme activity is critical for clinical efficacy. Enzyme activity is monitored by conversion of a surrogate substrate under optimal assay conditions. However, these conditions are not optimal to monitor product quality. We recommend including in the release protocol, a more sensitive enzyme assay that measures the kinetic parameters K_m and k_{cat} using a physiologically relevant substrate (addressed by PMC).
- Cellular uptake: Cellular uptake is crucial for the function of velaglucerase. In order to reduce the levels of glucocerebroside accumulated in lysosome, velaglucerase must be internalized, via the cell surface mannose receptor.
- Oxidation: The sponsor has shown that oxidation of Cys126 reduces velaglucerase enzyme activity. Oxidation of Cys126 can be [redacted]

b(4)

[redacted]

- Development and Comparison of Drug Substances: Modifications to the process throughout product development included:

[redacted]

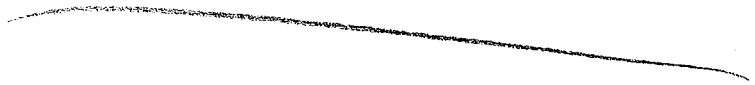
b(4)

[redacted]

The sponsor provided an extensive comparability study to address the comparability of drug substances AF1 and AF2. The results of the study indicated that the two drug substances were comparable for the quality attributes examined. Small differences were noted in the glycan mapping and IEX-HPLC profiles .These differences are caused by decrease in neutral glycan species. The decrease is relatively small (6-8%) and we concluded that it was unlikely that the differences would have clinical consequences, based on the following:

1) No differences were noted in cellular uptake when AF1 and AF2 drug substances were used. The sponsor chose the lots of drug substance

b(4)



Drug Substance: The sponsor is requesting a drug substance shelf life of 36 months at -65°C. The data and information submitted by the sponsor, in the NDA support the requested dating period from the date of manufacture.

Drug Product: The sponsor is requesting a drug product shelf life of 24 months stored at 2-8°C from the date of manufacturing, which begins with final sterile filtration of the formulated bulk drug product. The data and information submitted by the sponsor, in the NDA support the requested dating period. Drug product is designated as "protect from light."

- **DESCRIPTION OF HOW THE DRUG PRODUCT IS INTENDED TO BE USED** VPRIV™ is indicated for the treatment of Type I Gaucher's disease in children and adults. VPRIV™ should be administered as a 60 minute intravenous (IV) infusion at 60 units/kg. The recommended dose of VPRIV™ is 60 units/kg IV infusion every two weeks. VPRIV™ is supplied in two presentations: 200 and 400 units/vial. VPRIV™ is a sterile lyophilized —— free of preservatives. b(4)
  - VPRIV™ vials should be refrigerated at 2-8°C and protected from light. The recommended expiration dating period for VPRIV™ Drug Product is 24 months under these storage conditions.
  - VPRIV™ is prepared for IV infusion by reconstituting each vial with sterile water for injection (WFI) to obtain 100 units/ml. The reconstituted product is added to 100 ml of 0.9% sodium chloride for injection (USP)

for intravenous infusion. Both the reconstituted drug product and the product diluted in the infusion bag can be stored at 2-8°C for up to 24 hrs. Adequate data are provided in the submission to ensure that the product is stable over the period of time of infusion.

III. CHEMISTRY, MANUFACTURING AND CONTROLS INSPECTIONAL ACTIVITIES INVOLVING PRODUCT REVIEWERS

200 Alewife in Cambridge, MA; 300 Patriot Way, Lexington, MA and Belmont, Cambridge, MA (November 16 –20, 2009): These facilities are owned by Shire Human Genetic Therapies. Alewife is the site of drug substance manufacture. The laboratories (Analytical Biochemistry for in-process testing, Microbiology for bioburden and sterility testing, Biologics Quality Control for drug substance and drug product release and annual good manufacturing practices (GMP) stability testing, Quality Control Chemistry for raw materials qualification) are located at 300 Patriot Way. The Belmont site is a warehouse and a storage and shipping facility. Product reviewer Emanuela Lacana along with Office Of Regulatory Affairs (ORA) inspectors Rory Geyer and Robert Horan (lead investigator) participated in this inspection. A 5 item FDA Form 483 was issued to the firm. Three of the items were derived from the product reviewer. The facility was found to be in compliance with current GMPs and capable of manufacturing velaglucerase drug substance in a controlled and consistent manner.

173 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

*Withheld Track Number: Chemistry Review Section(Division of Therapeutic Proteins) -*_____

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/

EMANUELA LACANA
02/25/2010

GIBBES R JOHNSON
02/25/2010

BARRY W CHERNEY
02/25/2010

AMY S ROSENBERG
02/25/2010

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22575/000	**Sponsor:**	SHIRE HUMAN GENETIC
Org. Code:	180		700 MAIN ST
Priority:	1		CAMBRIDGE, MA 02139
Stamp Date:		**Brand Name:**	VPRIV
PDUFA Date:		**Estab. Name:**	VELAGLUCERASE ALFA
Action Goal:		**Generic Name:**	
District Goal:	30-DEC-2009	**Product Number; Dosage Form; Ingredient; Strengths**	001; POWDER, FOR INJECTION SOLUTION; VELAGLUCERASE ALFA; 400UNT 002; POWDER, FOR INJECTION SOLUTION; VELAGLUCERASE ALFA; 200UNT

Application:	NDA 22575/000	**Sponsor:**	SHIRE HUMAN GENETIC
Org. Code:	180		700 MAIN ST
Priority:	1		CAMBRIDGE, MA 02139
Stamp Date:	31-AUG-2009	**Brand Name:**	VPRIV
PDUFA Date:	28-FEB-2010	**Estab. Name:**	VELAGLUCERASE ALFA
Action Goal:		**Generic Name:**	
District Goal:	30-DEC-2009	**Product Number; Dosage Form; Ingredient; Strengths**	001; POWDER, FOR INJECTION SOLUTION; VELAGLUCERASE ALFA; 400UNT 002; POWDER, FOR INJECTION SOLUTION; VELAGLUCERASE ALFA; 200UNT

FDA Contacts:	E. LACANA	Review Chemist	(HFD-122)	301-827-1965
	G. JOHNSON	Team Leader	(HFD-122)	301-827-1770

Overall Recommendation: ACCEPTABLE on 22-FEB-2010 by M. STOCK (HFD-320) 301-796-4753

Establishment:

b(4)

DMF No: **AADA:**

Responsibilities:

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 05-FEB-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: [redacted]

b(4)

DMF No:	[redacted]	**AADA:**	
Responsibilities:			
Profile:	CONTROL TESTING LABORATORIES "ALSO" (DRUGS)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	25-NOV-2009		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment: [redacted]

b(4)

DMF No:	[redacted]	**AADA:**	
Responsibilities:	[redacted]		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	20-NOV-2009		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment: [redacted]

b(4)

DMF No:	[redacted]	**AADA:**	
Responsibilities:			
Profile:	[redacted]	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	09-NOV-2009		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Es nent: [redacted]

b(4)

DMF No:

AADA:

Responsibilities:

Profile:

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 21-JAN-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: [redacted]

b(4)

DMF No:

AADA:

Responsibilities:

Profile: CONTROL TESTING LABORATORY

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Mil e Date: 23-NOV-2009

De ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** **FEI:**

SHIRE HUMAN GENETIC THERAPIES
33 BRIGHTON STREET

BELMONT, MA 02478

DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: BIOTECHNOLOGY CRUDE DRUG

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-FEB-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:**	**FEI:**	
	SHIRE HUMAN GENETIC THERAPIES INC 300 PATRIOT WAY LEXINGTON, MA 02421		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	07-JAN-2010		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:**	**FEI:**	
	SHIRE HUMAN GENETIC THERAPIES INC 205 ALEWIFE BROOK PARKWAY CAMBRIDGE, MA 02138		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	BIOTECHNOLOGY CRUDE DRUG	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Mil[illegible]e Date:	07-JAN-2010		
D[illegible]	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:**	**FEI:**	
	SHIRE HUMAN GENETIC THERAPIES INC 700 MAIN STREET CAMBRIDGE, MA 02139		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	BIOTECHNOLOGY CRUDE DRUG	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	07-JAN-2010		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		