CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-575

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/ Sequence Number:	22-575/ 0001, 0012
Drug Name:	VPRIV® (velaglucerase alfa, Gene-Activated® Glucocerebrosidase [GA-GCB]) 60 Units/kg Intravenous Every Other Week
Indication(s):	Type I Gaucher Disease
Applicant:	Shire Human Genetic Therapies
Date(s):	Date Submitted: August 31, 2009 PDUFA Goal Date: February 26, 2010
Submission Type:	Type 1 NDA (NME); 505(b)(1)
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Keywords: clinical studies, NDA review

1.0 Executive Summary

1.1 Conclusions and recommendations

The results from all four studies were positive in that they each showed a clinically significant change from baseline, based on clinical judgement, in the endpoints of interest (hemoglobin concentration, platelet count, and liver and spleen volumes) for patients dosing with VPRIV. This was principally established in study TKT032. The HGT-GCB-039 study showed that these differences were consistent with patients dosing with Cerezyme. HGT-GCB-039 satisfied the requirements for non-inferiority to Cerezyme regarding the primary endpoint of interest which was the increase in hemoglobin concentration from baseline.

1.2 Brief overview

VPRIV has been studied by Shire for the treatment of Type I Gaucher Disease. The clinical efficacy of VPRIV for the treatment of Type I Gaucher Disease was evaluated through a pivotal Phase III, multinational, multicenter, long term (12 month), randomized, double-blind, and parallel dose group study, TKT032. Supportive principal efficacy results from a Phase III, multinational, multicenter, randomized, double-blind, and parallel group (active control with Cerezyme® [imiglucerase]) study, HGT-GCB-039, was also included in the submission. Further supportive efficacy data, albeit marginal, were provided from study TKT034, an open-label switchover (with patients previously using Cerezyme).

1.3 Statistical Issues and Findings

The current prevailing primary endpoint for Type I Gaucher Disease is percentage change from baseline in spleen volume (note that VPRIV did show a significant reduction in spleen volume in pivotal study TKT032). However, due to previous commitments by the Division of Gastroenterology Products (DGP), change from baseline in hemoglobin was accepted as the primary endpoint of interest for the relevant studies in this submission.

The efficacy results from study TKT034are marginally supportive at best due to the utilized open-label switchover design which designated safety as the primary endpoint of interest. Had study TKT034 been designed as a double-blind randomized withdrawal or randomized add-on study, the efficacy conclusions might have been stronger.

The primary issue in this NDA pertained to manufacturing. The non-comparability of the manufacturing process for the initial study supply used in the Phase 1 trials and the processes used for future drug supplies creates a disconnect in that the clinical results of all the conducted trials were reviewed but can not technically be used to directly understand the safety and efficacy of the to-be-marketed drug product.

2.0 Introduction

2.1. Background

Pursuant to Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act, Shire Human Genetic Therapies (Shire) submitted a New Drug Application (NDA 22-575) for VPRIV® (velaglucerase alpha [GA-GCB]) for the proposed indication of long term-term enzyme replacement therapy (ERT) for patients with Type I Gaucher Disease. This application consists of data from a global clinical development program conducted under IND 61,220. This NDA is designated as a Type 1/New Molecular Entity (NME) and filed as a rolling submission. On July 15, 2009, VPRIV was granted *Fast Track Drug Development* status for the above indication as it is intended to treat a serious life-threatening condition and addresses the current unmet medical need of patients with Type I Gaucher disease. Shire was also granted Priority Review status for the review of this NDA. VPRIV received *Orphan Drug Designation* on June 8, 2009 and therefore qualified for Orphan exception from the Prescription Drug User Fee under section 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act.

The NDA was submitted in eCTD format in accordance with all applicable electronic submission and eCTD guidances. The submission was sent via the FDA Electronic Submissions Gateway and its content, along with the electronic data sets and labeling information, has been stored in the electronic document room.

2.2. Brief Overview and Summary of Relevant Trials

VPRIV has been studied by Shire for the treatment of Type I Gaucher Disease. The clinical efficacy of VPRIV for the treatment of Type I Gaucher Disease was evaluated through a pivotal Phase III, multinational, multicenter, long term (12 month), randomized, double-blind, and parallel dose group study, TKT032. Supportive principal efficacy results from a Phase III, multinational, multicenter, randomized, double-blind, and parallel group (active control with Cerezyme® [imiglucerase]) study, HGT-GCB-039, was also included in the submission. Further supportive data, albeit marginal, from an open-label switchover (with patients previously using Cerezyme) study, TKT034, and an open-label dose escalation study, TKT025, were provided. Table 1 below contains further summary information for these relevant clinical trials.

Table 1 – Summary Information for Relevant Trials

Type of Study; Phase	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Dosed Subjects	Patient Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety; Phase III/ **Pivotal**	TKT032	*Primary*: To determine the efficacy of every other week dosing of VPRIV at a dose of 60 U/kg in treatment naïve patients; *Secondary*: Same as above except at a dose of 45 U/kg, and to study overall safety and tolerability	Multinational, multicenter, randomized, double-blind, parallel dose group	VPRIV 60 U/kg and 45 U/kg; Every other week dosing; Intravenous (IV)	60 U/kg: 12 45 U/kg: 13 Total: 25	Patients diagnosed with Type I Gaucher Disease	12 months	Complete; Full
Efficacy and Safety; Phase III/ **Supportive**	HGT-GCB-039	*Primary*: To compare the effects of VPRIV and Cerezyme on hemoglobin concentration in treatment naïve patients; *Secondary*: To compare the effects of the said interventions on platelet counts and liver and spleen volumes while also studying overall safety and tolerability	Multinational, multicenter, randomized, double-blind, parallel group	VPRIV and Cerezyme at 60 U/kg each; Every other week dosing; IV	VPRIV: 17 Cerezyme: 17 Total: 34	Patients diagnosed with Type I Gaucher Disease	9 months	Completed; Principal results only

Table 1 (continued)

Type of Study; Phase	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Dosed Subjects	Patient Diagnosis	Duration of Treatment	Study Status; Type of Report
Safety and Efficacy; Phase II/III	TKT034	*Primary*: To evaluate the safety of every other week dosing of VPRIV in patients previously treated with Cerezyme; *Secondary*: To evaluate changes from baseline in hemoglobin concentration (key), platelet counts, and liver and spleen volumes	Multinational, multicenter, open-label, switchover to monotherapy	VPRIV 15 - 60 U/kg; Every other week dosing; IV	60 U/kg: 7 45 U/kg: 7 30 U/kg: 12 15 U/kg: 14 Total: 40	Patients diagnosed with Type I Gaucher Disease	12 months	Complete; Abbreviated
Safety; Phase I/II	TKT025	*Primary*: To evaluate the safety of every other week dosing of VPRIV in treatment naïve patients; *Secondary*: To evaluate changes from baseline in hemoglobin concentration (key), platelet counts, and liver and spleen volumes	Open-label, 3+3 design	VPRIV 15 - 60 U/kg; Every other week dosing; IV	Initial Dose: 60 U/kg: 9 15 U/kg: 3 Total: 12	Patients diagnosed with Type I Gaucher Disease	9 months	Complete; Full

Section 3.0 Statistical Evaluation

3.1 Study TKT032

A. Background Information

As stated and shown previously in Table 1, study TKT032 enrolled patients diagnosed with Type I Gaucher Disease. As the designated pivotal trial of this clinical development program, its primary objective was to determine the efficacy of every other week intravenous (IV) dosing of VPRIV at a dose of 60 U/kg in treatment naïve patients

(defined herein as patients who were not treated for Gaucher Disease within 12 months of study start). The secondary objective of TKT032 was the same, except at a dose of 45 U/kg, in addition to studying the overall safety and tolerability of VPRIV usage. This was a Phase 3, multinational, multicenter, randomized, double-blind, parallel dose group study with treatment naïve patients being administered every other week IV dosing of 60 U/kg or 45 U/kg VPRIV.

Thirty-nine subjects enrolled in TKT032 with the number of patients ultimately randomized (1:1) between the 60 U/kg and 45 U/kg VPRIV groups, utilizing covariate adaptive randomization (balancing on gender [male vs. female] and age [2-17 vs. ≥18]), being 25; 12 patients to 60 U/kg and 13 to 45 U/kg. Using a two-sided α level of 0.05 and assuming a 1 g/dL increase from baseline in hemoglobin, considered clinically significant, along with a standard deviation (of this change from baseline) of 0.824, 12 patients in the 60 U/kg dose group provides >90% power to detect a significant change from baseline in hemoglobin for patients in the aforementioned dose group. All 25 patients completed the study, i.e. there were no discontinuations, and the duration of treatment was 12 months (with bi-weekly visits).

B. Statistical Analysis Information

The primary and secondary endpoints in the TKT032 study are as follows:

- ***Primary Endpoint***
  - Change from baseline in hemoglobin at Week 53 for the 60 U/kg VPRIV group

- ***Secondary Endpoints***
  - Change from baseline in hemoglobin at week 53 for the 45 U/kg VPRIV group
  - Change from baseline in platelet count at week 53 for both dose groups
  - Change from baseline in normalized (% of body weight) spleen volume at week 53 for both dose groups
  - Change from baseline in normalized (% of body weight) liver volume at week 53 for both dose groups

There were no between group comparisons made for any endpoint, consequently, the statistical methodology for the analysis of each endpoint, specifically utilizing the mean change from baseline at week 53, was a paried t-test with corresponding Confidence Intervals (CI). Unless specified, all analyses were conducted under the Intent-to-Treat (ITT) analysis set (defined as all randomized subjects who received at least one study drug infusion).

The Missing Data handling strategy was to administer Last Observation Carried Forward (LOCF); however, no missing data was encountered from this study (all patients finished the study with no assessments missed). The pre-specified Multiplicity Adjustment strategy for testing the secondary endpoints utilized the stepwise Holm procedure.

C. Primary and Secondary Efficacy Analyses

1. Principal Results

Table 2 - Primary (Bold) and Secondary Efficacy Analyses: 60 U/kg

Parameter	Change from Baseline to Week 53				
	n	Median	Mean	95% CI	p-value
Hemoglobin (g/dL)	**12**	**2.2**	**2.429**	**(1.717, 3.141)**	**<0.0001**
Platelets (x10^9/L)	12	35.00	50.88	(23.97, 77.78)	0.0016 *
Normalized Liver Volume (% of Body Weight)	12	-0.70	-0.84	(-1.58, -0.11)	0.0282
Normalized Spleen Volume (% of Body Weight)	12	-1.40	-1.92	(-3.04, -0.79)	0.0032 *

Figure 1 – Mean Change from Baseline in Hemoglobin throughout Study: 60 U/kg

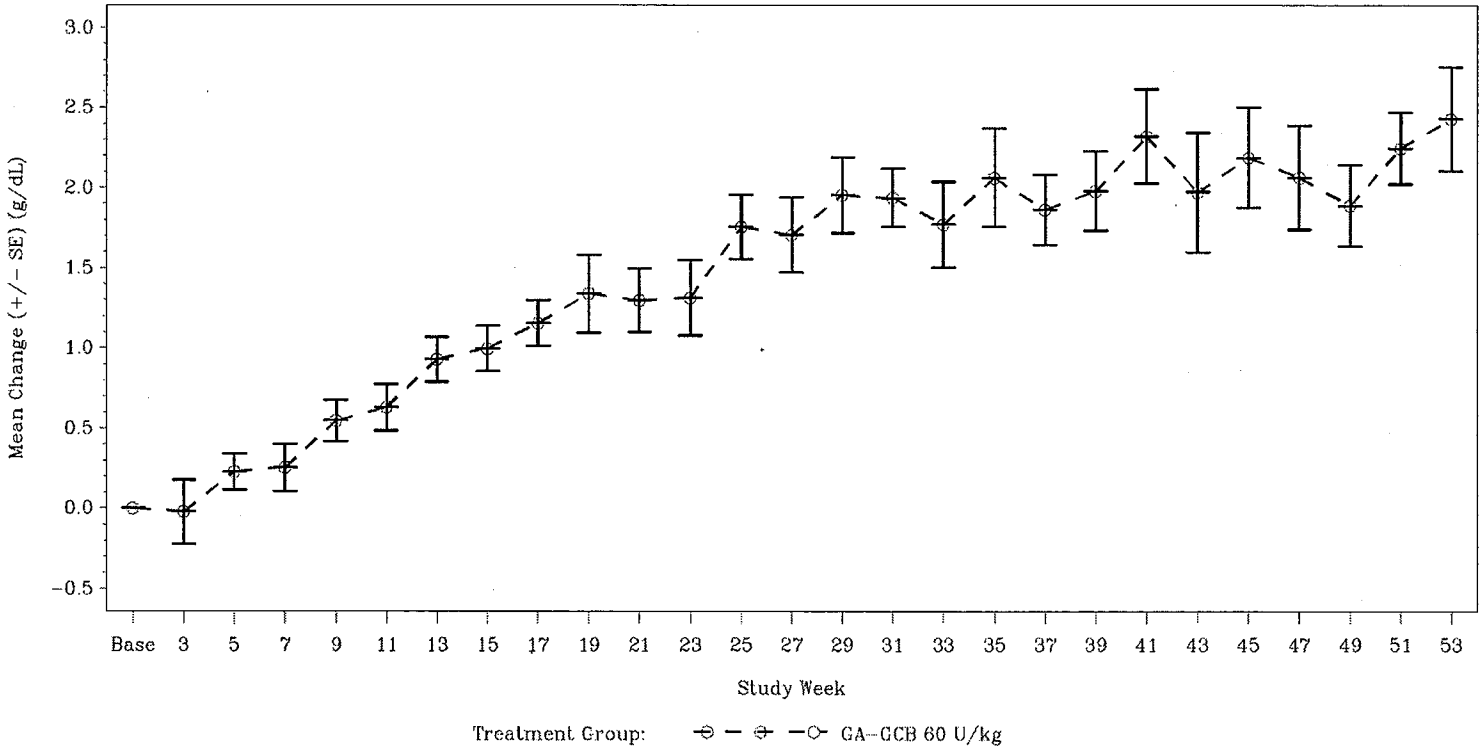
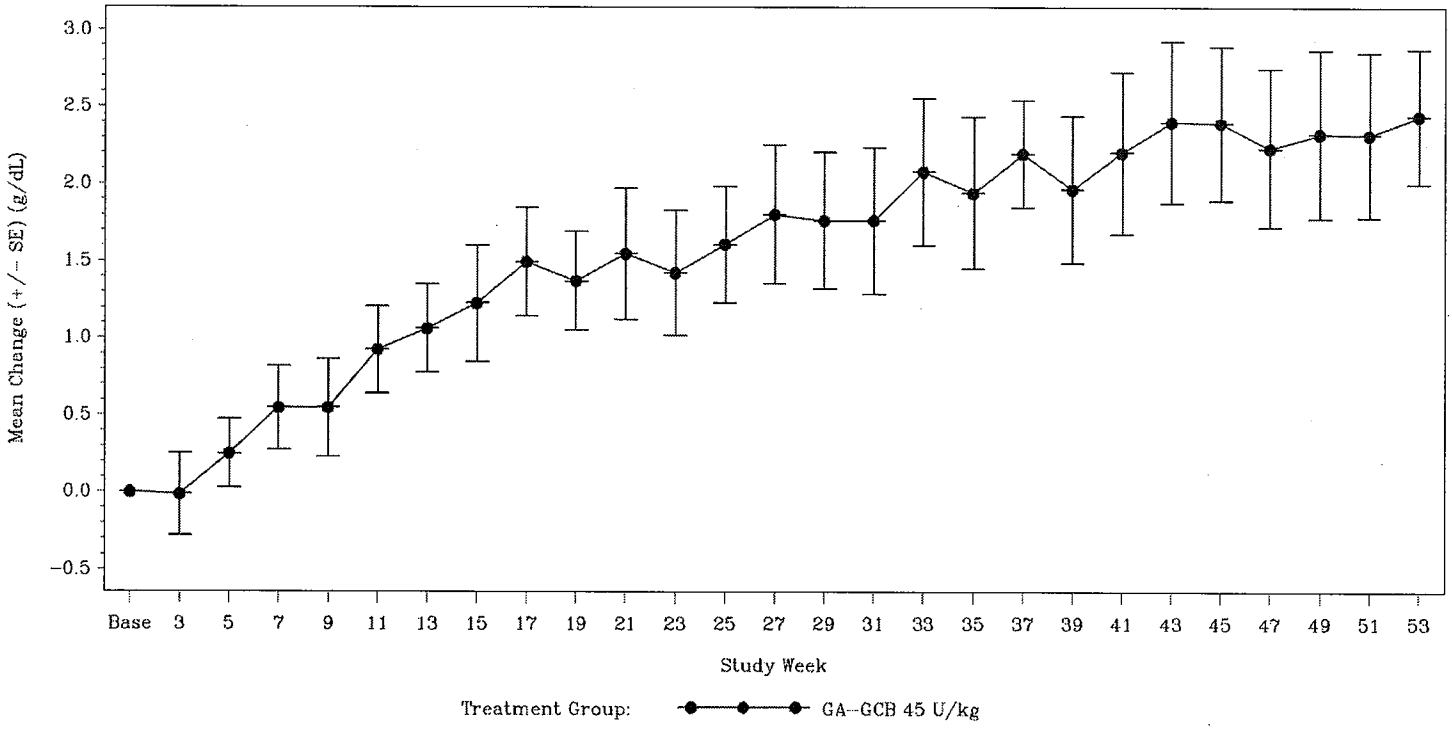


Table 3 - Secondary Efficacy Analyses: 45 U/kg

Parameter	Change from Baseline to Week 53				
	n	Median	Mean	95% CI	p-value
Hemoglobin (g/dL)	13	1.900	2.438	(1.488, 3.389)	0.0001 *
Platelets (x10^9/L)	13	20.50	40.92	(11.20, 70.64)	0.0111 *
Normalized Liver Volume (% of Body Weight)	13	-0.40	-0.30	(-0.92, 0.32)	0.3149
Normalized Spleen Volume (% of Body Weight)	13	-0.90	-1.87	(-3.17, -0.57)	0.0085 *

Figure 2 – Mean Change from Baseline in Hemoglobin throughout Study: 45 U/kg



As can be seen from Table 2, above, the primary efficacy analysis results at week 53 show a significant increase from baseline in hemoglobin. This mean increase from baseline of 2.429 g/dL is substantially greater than the widely considered clinically significant difference of 1 g/dL. These results can be visually confirmed from Figure 1, above, which shows the mean change from baseline in hemoglobin throughout all time points during the study.

The remainder of the analysis results displayed in Table 2 and also those displayed in Table 3, above, correspond to the secondary efficacy endpoints. Note that the p-values associated with these analyses marked by * are those which correspond to statistically significant results after adjusting for multiplicity through the pre-specified stepwise Holm procedure. The change from baseline in normalized (% of body weight) liver volume at week 53 was the only endpoint which was shown to not result in a positive outcome. This result was evident for both the 60 U/kg and 45 U/kg dose groups. It can also be observed from Figure 2, above, that the mean change from baseline in hemoglobin throughout all time points during the study for patients in the 45 U/kg dose group behaved almost in sync with those previously presented in Figure 1 corresponding to patients in the 60 U/kg dose group.

2. Sensitivity Analyses

The following two sensitivity analyses were conducted:

- Analysis utilizing the Wilcoxon Signed-Rank Test
- Per-Protocol Analysis

The analysis for the primary endpoint was re-administered utilizing the Wilcoxon Signed-Rank Test. The primary efficacy analysis was also re-administered on a Per-Protocol (PP) analysis set of patients defined to be the ITT subjects in the 60 U/kg dose group who received ≥80% (≥21 out of 26) of the scheduled infusions, qualified for enrollment, had non-missing hemoglobin assessments at baseline and week 53, and did not commit any protocol violations. There was only one ITT patient in the 60 U/kg dose group who did not qualify for the PP analysis set, thus there was a total of 11 patients in this analysis set. The results from both of these analyses were consistent with the initial primary efficacy analysis; consequently, these results were not reported.

3. Subgroup Analysis

Two subgroup analyses were administered pertaining to age (2-17 and ≥18) and gender (male and female). The principal results (shown to be generally robust) are presented respectively in Table 4 below.

Table 4 – Subgroup Analysis

	Change from Baseline to Week 53 in Hemoglobin (g/dL)							
	VPRIV 60 U/kg				VPRIV 45 U/kg			
Subgroup	**n**	**Median**	**Mean**	**95% CI**	**n**	**Median**	**Mean**	**95% CI**
Age								
2 – 17	4	1.575	1.738	(0.718, 2.757)	3	2.100	2.767	(-0.995, 6.529)
≥ 18	8	2.725	2.775	(1.790, 3.760)	10	1.650	2.340	(1.156, 3.524)
Gender								
Male	7	2.650	2.779	(1.630, 3.927)	8	1.850	2.788	(1.207, 4.368)
Female	5	1.600	1.940	(0.957, 2.923)	5	1.900	1.880	(0.978, 2.782)

3.2 Study HGT-GCB-039

A. Background Information

Study HGT-GCB-039 was designated by the Division of Gastroenterology Products as the key supportive trial in this clinical development program. Its primary objective was to compare the effects of VPRIV and Cerezyme on hemoglobin concentration in treatment naïve patients. The secondary objective of HGT-GCB-039 was to compare the effects of the said interventions on platelet counts and liver and spleen volumes while also studying overall safety and tolerability. This was a Phase 3, multinational, multicenter, randomized, double-blind, parallel group study with treatment naïve patients being administered every other week 60 U/kg IV dosing of VPRIV or Cerezyme. This was a non-inferiority trial designed to demonstrate that VPRIV is non-inferior to Cerezyme in terms of efficacy.

Forty-two subjects enrolled in HGT-GCB-039 with the number of patients ultimately randomized (1:1) between the VPRIV and Cerezyme groups, utilizing covariate adaptive randomization (balancing on age [2-17 vs. ≥18], hemoglobin concentration [<8 g/dL vs. ≥8 g/dL], and splenectomy status [Yes vs. No]), being 35; 17 patients to VPRIV and 18 to Cerezyme. This sample size provides >80% power to detect a difference, between the two treatment groups, in the mean change from baseline in hemoglobin of greater than -1 g/dL (the pre-specified non-inferiority margin; explained in greater detail below), assuming that the expected difference in means is 0, and the common standard deviation is 0.90.

All randomized patients, except one in the Cerezyme group, had at least one study drug infusion during the trial. Thirty-two out of the 35 randomized patients completed the study (one VPRIV patient was lost to follow-up; one Cerezyme patient withdrew consent; one Cerezyme patient had the study terminated by the investigator), and the duration of treatment was 9 months (with bi-weekly visits). Note that only principal results (i.e. top-line) were reported to the FDA by the sponsor.

B. Statistical Analysis Information

The primary and key secondary endpoints in the HGT-GCB-039 study are as follows:

- ***Primary Endpoint***
  - Change from baseline in hemoglobin at week 41/End of Study (EOS)

- ***Key Secondary Endpoints***
  - Change from baseline in platelet count at week 41/EOS
  - Change from baseline in normalized (% of body weight) liver volume at week 41/EOS
  - Change from baseline in normalized (% of body weight) spleen volume at week 41/EOS

Two additional secondary endpoints were designated as lower priority by the sponsor and, consequently, will not be discussed in this review. Statistical analysis methodology for the primary endpoint was required to formally test the difference of the mean change from baseline to week 41 in hemoglobin concentration between the two treatment groups. As stated previously, this was a non-inferiority trial designed to demonstrate that VPRIV is non-inferior to Cerezyme in terms of efficacy (specifically primary efficacy). Non-inferiority was to be demonstrated by a one-sided 97.5% CI (based on the t-distribution resulting from an independent two-sample t-test) for testing the null hypothesis that the treatment difference between VPRIV and Cerezyme is less than or equal to the pre-specified non-inferiority margin of -1 g/dL hemoglobin versus the alternative that the treatment difference is greater than this pre-specified margin. This margin was selected solely on the basis of clinical judgment. The hypothesis can be equivalently stated as:

H_0: $\mu_{VPR} - \mu_{Cer} \leq -1$ vs. H_A: $\mu_{VPR} - \mu_{Cer} > -1$

H_0: VPRIV is inferior to Cerezyme with respect to the mean hemoglobin concentration

H_A: VPRIV is non-inferior to Cerezyme with respect to the mean hemoglobin concentration

Statistical analysis methodology for the secondary endpoints utilized linear mixed effect models while adjusting for age, splenectomy status (this adjustment was not incorporated when analyzing the change from baseline in normalized spleen volume) and demographics. Unless specified, all analyses were conducted under the Intent-to-Treat (ITT) analysis set (defined as all randomized subjects who received at least one study drug infusion).

The Missing Data handling strategy for the primary and secondary endpoints was to administer Last Observation Carried Forward (LOCF). There was no Multiplicity Adjustment strategy adopted for testing the secondary endpoints.

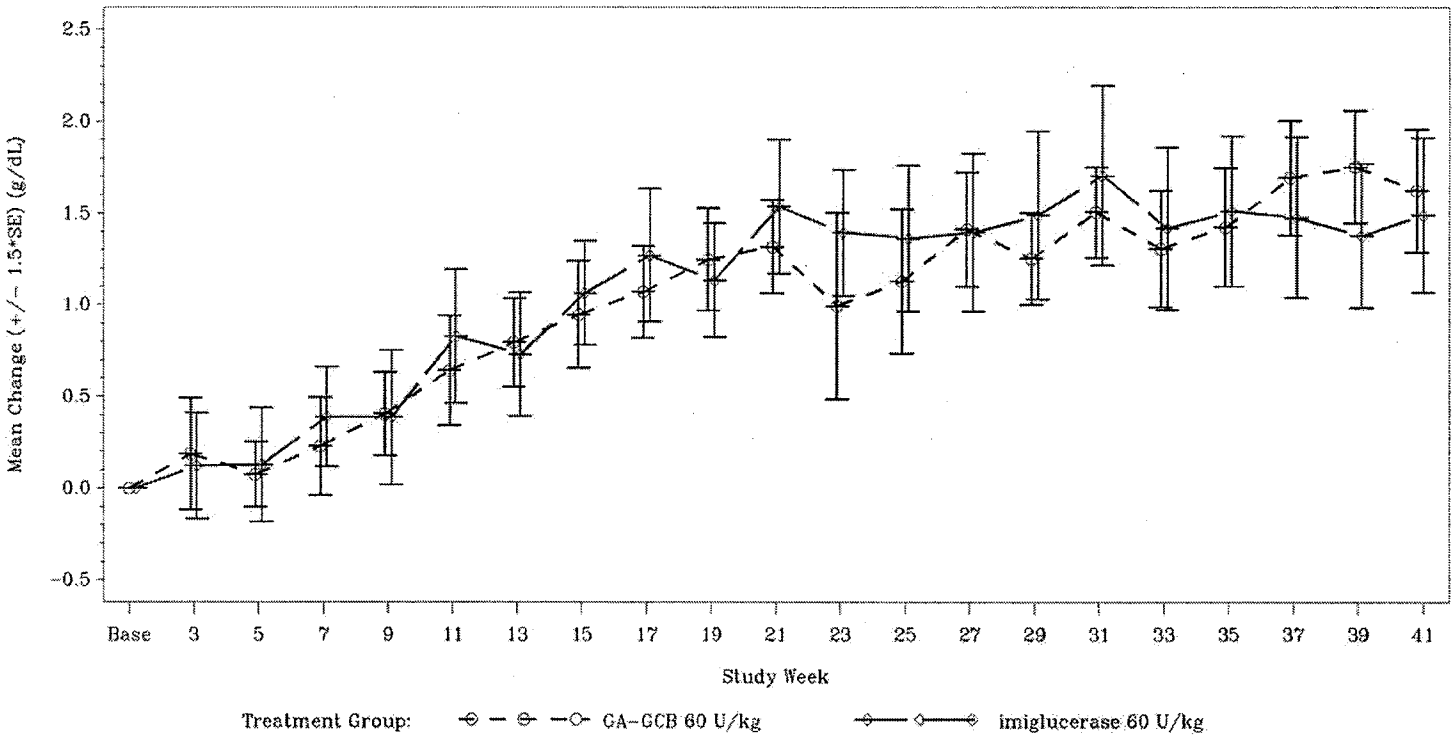
C. Primary Efficacy Analysis

1. Principal Results

Table 5 – Treatment Difference (VPRIV 60 U/kg - Cerezyme 60 U/kg) in Mean Change from Baseline to Week 41

Parameter	n	Mean Treatment Difference	One-Sided 97.5% CI
Hemoglobin (g/dL)	34	0.135	(-0.596, ∞)

Figure 3 – Mean Change from Baseline in Hemoglobin throughout Study by Treatment Group



As you can see from Table 5, above, the lower bound of the one-sided CI, -0.596, is greater than -1 g/dL. This result is supported by Figure 3, above, which shows the mean change from baseline in hemoglobin for both treatment groups throughout all time points during the study. Note that the mean increase of hemoglobin from baseline at week 41 was 1.624 g/dL (± 0.223 SE) for patients in the VPRIV group. Consequently, VPRIV can be claimed to be clinically and statistically non-inferior to Cerezyme.

2. Sensitivity Analyses

The following three sensitivity analyses were conducted:

- Two separate analyses, each corresponding to a different approach to handling missing data
  1. Multiple Imputation
  2. Worst-Case Imputation
- Per-Protocol Analysis

Only four patients had a missing hemoglobin measurement at week 41 (two patients from each treatment group). Results of the analysis utilizing multiple imputation (note that only three imputations were conducted) and worst-case imputation (i.e. no change from baseline) were consistent with the initial primary efficacy analysis; consequently, these results were not reported.

The primary efficacy analysis was also re-administered on a Per-Protocol (PP) analysis set of patients defined to be ITT subjects who completed the study and received ≥80% (≥16 out of 20) of the scheduled infusions, had non-missing hemoglobin assessments at baseline and week 41, and did not commit any protocol violations. There were only two ITT patients in each treatment group who did not qualify for the PP analysis set (15 VPRIV, 15 Cerezyme). The results from this analysis were also consistent with the initial primary efficacy analysis; consequently, these results were also not reported.

3. Subgroup Analysis

Three subgroup analyses were administered pertaining to age (2-17 and ≥18), gender (male and female), and race (white and non-white). The principal results are presented respectively in Table 6, below, with non-significant results consistently throughout.

Table 6 – Treatment Difference (VPRIV 60 U/kg - Cerezyme 60 U/kg) in Mean Change from Baseline to Week 41 in Hemoglobin (g/dL) by Subgroup

Subgroup	n	Mean Treatment Difference	95% (Two-Sided) CI
Age			
2 – 17	9	-0.355	(-1.909, 1.199)
≥ 18	25	0.378	(-0.444, 1.200)
Gender			
Male	16	-0.031	(-1.310, 1.248)
Female	18	0.283	(-0.424, 0.991)
Race			
White	22	0.569	(-0.238, 1.376)
Non-White	12	-0.441	(-1.935, 1.052)

D. Key Secondary Efficacy Analysis

The principal results of the key secondary efficacy analyses are presented in Table 7, below, with non-significant results consistently throughout. Note that 20 splenectomized patients (10 from each treatment group) were excluded from the analysis of normalized spleen volume.

Table 7 – Treatment Difference in Change from Baseline to Week 41

Parameter	n	Mean Treatment Difference	95% (Two-Sided) CI
Platelets (x10^9/L)	34	-38.71	(-88.42, 10.99)
Normalized Liver Volume (% of Body Weight)	34	-0.07	(-0.43, 0.29)
Normalized Spleen Volume (% of Body Weight)	14	0.08	(-0.52, 0.68)

3.3 Study TKT034

A. Background Information

Trial TKT034 was designed as a switchover study whereby patients undergoing treatment with Cerezyme for at least 30 consecutive months would be switched over to receiving monotherapy with VPRIV at an equivalent dose. The primary objective of this study was to evaluate the safety of every other week dosing of VPRIV in these 'switch-over' patients. The key secondary objective of TKT034 was to evaluate changes from baseline in hemoglobin concentration. This efficacy objective was exploratory in nature.

This was a Phase 2/3, multinational, multicenter, and open-label study with 'switch-over' patients being administered every other week IV dosing of VPRIV equivalent to the previously administered Cerezyme dose. The number of patients in this study was 40 with 14 receiving a dose of 15 U/kg, 12 at 30 U/kg, 7 at 45 U/kg, and 7 at 60 U/kg. The duration of treatment was 12 months (with bi-weekly visits).

B. Statistical Analysis Information

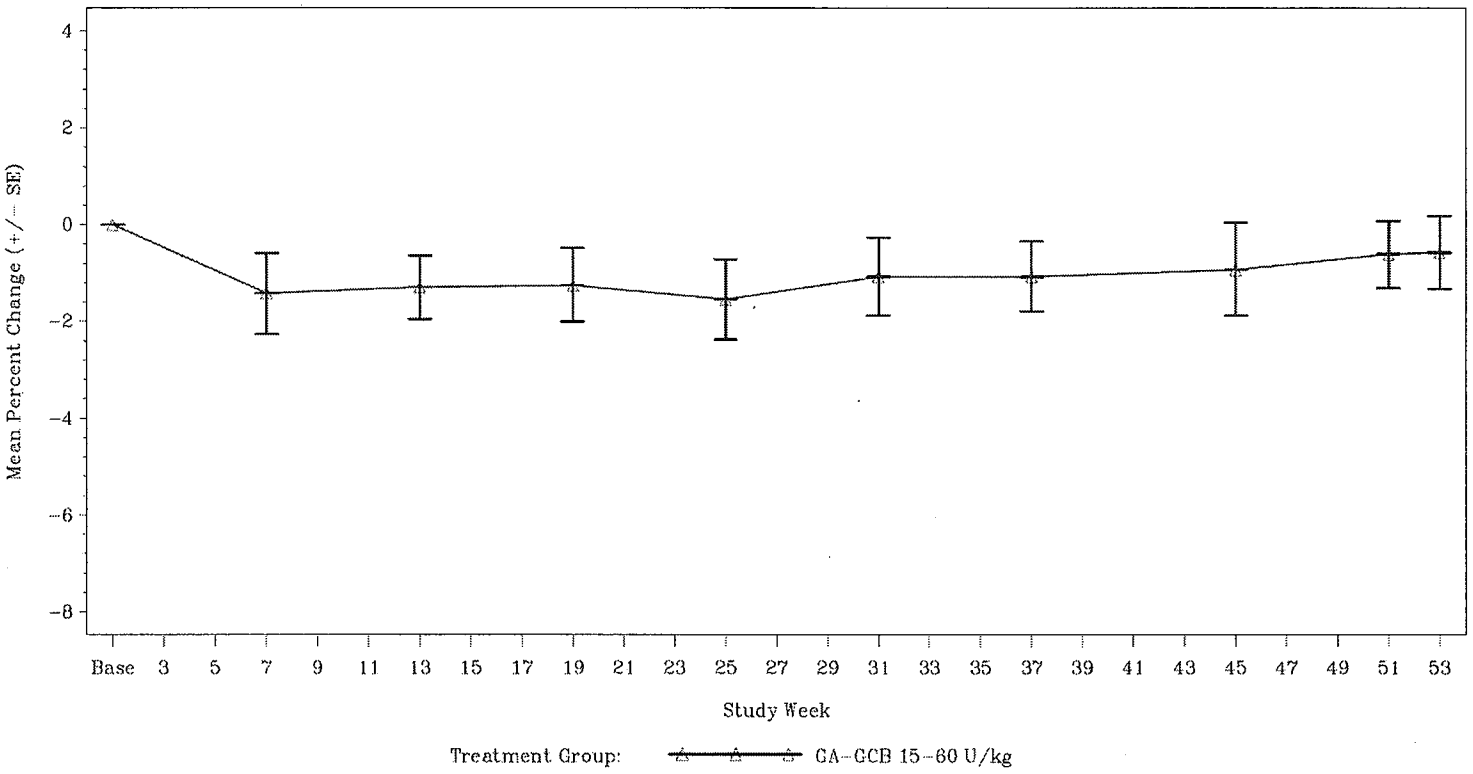
Since this was an open-label switchover study with a primary objective pertaining to safety, all efficacy analyses were considered exploratory in nature, with the sole purpose of marginally informing clinical decision making. Nonetheless, the key endpoint pertaining to efficacy in this study was the change from baseline in hemoglobin at week 53/EOS. The statistical methodology required to analyze this endpoint, specifically to test the if the mean change from baseline to week 53 was significantly greater than zero, utilized a 90% (note, not 95%) CI based on the t-distribution (resulting from a paired t-test). This analysis was conducted under the Intent-to-Treat (ITT) analysis set (defined as all eligible subjects who received at least one study drug infusion). The Missing Data handling strategy for this endpoint was to administer Last Observation Carried Forward (LOCF). There was no Multiplicity Adjustment strategy adopted for this study.

C. Key Efficacy Analysis

Table 8 – Exploratory Efficacy Analysis

	Change from Baseline to Week 53			
Parameter	**n**	**Median**	**Mean**	**90% CI**
Hemoglobin (g/dL)	40	0.025	-0.101	(-0.272, 0.070)

Figure 4 – Mean Percent Change from Baseline in Hemoglobin throughout Study



As you can see from Table 8, above, the efficacy analysis result at week 53 does not show a significant change from baseline in hemoglobin concentration. This result can be visually confirmed from Figure 4, above, which shows the mean percentage change from baseline in hemoglobin, pooling all patients from the overall VPRIV dosing range experienced, throughout all time points during the study. This result is marginally supportive, in a purely clinical context, to the non-inferiority claim established by study HCT-GCB-039.

3.4 Study TKT025

A. Background Information

Trial TKT025 was designed as 3+3 dose escalation study with the primary objective being to evaluate the safety of every other week dosing of VPRIV in treatment naïve patients. The key secondary objective of TKT025 was to evaluate changes from baseline in hemoglobin concentration. This efficacy objective was exploratory in nature.

This was an open-label Phase 1/2 study with patients being administered every other week IV dosing of VPRIV. The number of patients in this study was 12 with 3 initially receiving a dose of 15 U/kg and 9 initially receiving a dose of 60 U/kg. The duration of treatment was 9 months (with bi-weekly visits).

B. Statistical Analysis Information

Since this was an open-label study with a primary objective pertaining to safety, all efficacy analyses were again considered exploratory in nature, with the sole purpose of marginally informing clinical decision making. Nonetheless, the key endpoint pertaining to efficacy in this study was the change from baseline in hemoglobin at week 41. The statistical methodology required to analyze this endpoint, specifically to test if the mean change from baseline to week 41 was significantly greater than zero, utilized a paired t-test. This analysis was conducted under the Intent-to-Treat (ITT) analysis set (defined as all eligible subjects who received at least one study drug infusion). The Missing Data handling strategy for this endpoint was to administer Last Observation Carried Forward (LOCF). There was no Multiplicity Adjustment strategy adopted for this study.

C. Key Efficacy Analysis

The efficacy analysis result at week 41 did show a significant change from baseline in hemoglobin concentration. The mean change from baseline to week 41 was 1.99 g/dL with a nominal p-value <0.001 from the associated paried t-test. This result is marginally supportive, in a purely clinical context, to the results established by study TKT032.

4.0 Findings in Special Populations

Age, gender and race subgroup comparisons are presented in Section 3. No other special subpopulations were identified. Examination of age and gender subgroups did not identify differences in response to VPRIV among these subgroups. The number of non-Caucasian patients in these studies was too small to assess adequately any difference in effects by race.

5.0 Review Issues and Conclusions

There were some review issues pertaining to this NDA. The first (not an issues per se, but a point to be made) regards the primary endpoint utilized to measure the clinical effectiveness of VPRIV. The current prevailing primary endpoint for Type I Gaucher Disease is percentage change from baseline in spleen volume (note that VPRIV did show a significant reduction in spleen volume in pivotal study TKT032). However, due to previous considerations by DGP, change from baseline in hemoglobin was accepted as the primary endpoint of interest for the relevant studies in this submission.

Study TKT034 could have been designed as a double-blind randomized withdrawal or randomized add-on study. This would have resulted in much more useful and supportive efficacy data. As it stands now, the efficacy results from this study are marginally supportive at best due to the utilized open-label switchover design which designated safety as the primary endpoint of interest.

The primary issue in this NDA pertained to manufacturing. Study TKT025 patients were administered a study supply of VPRIV) which was found by the Division of Therapeutic Proteins (DTP) to not be comparable with the study supply used in future studies TKT032 and HGT-GCB-039 known as AF1). Furthermore, the to-be-marketed drug supply is manufactured by yet another process known as AF2, however DTP has determined that the AF1 and AF2 processes appear to be comparable. Nonetheless, the non-comparability of the manufacturing process for the initial study supply used in the Phase 1 trials and the AF1/AF2 processes (along with the fact that no trial drug supply utilized the AF2 process) creates a disconnect in that the clinical results of all the previously presented trials were reviewed but can not technically be used to directly understand the safety and efficacy of the to-be-marketed drug product.

b(4)

Ultimately, due to the orphan nature of Type I Gaucher Disease, the determination of the clinical effectiveness of VPRIV was established more with clinical judgment than by the usual required statistical rigor. The results from all four studies were positive in that they each showed a clinically significant change from baseline, based on the aforementioned clinical judgement, in the endpoints of interest (hemoglobin concentration, platelet count, and liver and spleen volumes) for patients dosing with VPRIV. This was principally established in study TKT032. The HGT-GCB-039 study (also supported by the results from TKT034) showed that these clinically significant differences were consistent with those patients dosing with Cerezyme. HGT-GCB-039 specifically established non-inferiority between VPRIV and Cerezyme regarding the primary endpoint of interest which was the increase in hemoglobin concentration from baseline.

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

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/s/

BEHRANG D VALI
02/25/2010

MICHAEL E WELCH
02/25/2010
Concur with review.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 22-575	Applicant: Shire Human Genetic Therapies	Stamp Date: 31AUG2009
Drug Name: Velaglucerase Alpha (GA-GCB)	NDA/BLA Type: Type 1 NDA (NME); 505(b)(1)	Indication: Type I Gaucher Disease

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

	Content Parameter for RTF	Yes	No	NA	Comments
1A	Paper Submission: Index is sufficient to locate necessary reports, tables, data, etc.			X	This was an electronic submission.
1B	Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.	X			This electronic submission was of good quality and very easy to work with and navigate through.
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			Module 5 provided only an abbreviated ISS and ISE which solely contained tables and figures (no ISS and ISE study reports were included). Module 2 did present the corresponding ISS and ISE summary reports.
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups (if applicable).	X			For the TKT032 study, gender and age (pediatric subgroup: 2-17 vs. ≥18) were investigated in the primary efficacy analysis. Race was not investigated because all participants were Caucasian. No subgroup analyses were presented for the HGT-GCB-039 study as only top-line efficacy results (with no subgroup analyses) were provided.
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			All relevant data sets were CDISC compliant with appropriate data definition files in Define.XML format.

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the statistical perspective, please state below the reasons and provide comments to be sent to the Applicant.

N/A

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

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			The designs utilized were adequate.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			Note that the prevailing primary efficacy endpoint for Type I Gaucher Disease is percentage change from baseline in spleen volume. However, due to previous considerations by DGP, change from baseline in hemoglobin count is the primary efficacy endpoint of interest for the relevant studies in this submission.
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	There were no interim analyses with regard to efficacy or safety in any of the pivotal or supportive studies.
Appropriate references for novel statistical methodology (if present) are included.	X			References for statistical methodology were presented (although the methodology was not novel per se).
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			Safety datasets were submitted for each study individually, however this data can be integrated. Resulting ISS datasets were also submitted.
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.		X		LOCF was the approach used to handle missing data for the primary efficacy analysis in both the TKT032 and HGT-GCB-039 studies. This approach is only valid for data whose missingness mechanism is assumed to be Missing Completely at Random (MCAR). MCAR is an unrealistic assumption for a missingness mechanism, hence other approaches should be considered.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Please communicate below any additional requests to the Applicant for the 74-day letter.

(1) Study TKT032 uses covariate adaptive randomization to balance treatment allocation to patients in the age (2-17 or ≥18) and gender (Male or Female) subgroups. In general, adaptive randomization techniques compromise the independence assumption applied to data captured during the study. Consequently, a permutation/re-randomization test should be conducted where possible, as a sensitivity analysis, for all appropriate efficacy endpoints.

(2) The missing data handling strategy for both the TKT032 and HGT-GCB-039 studies was insufficient. Both studies utilized LOCF to handle missing data for their respective primary efficacy analyses. The LOCF approach is only valid for data whose missingness mechanism is assumed to be Missing Completely at Random (MCAR). However, MCAR is an unrealistic assumption hence other approaches for handling missing data in a primary analysis context should be considered under more realistic assumptions for the missingness mechanism. Multiple Imputation, under a Missing at Random (MAR) assumption, is an acceptable approach and should be conducted to handling missing data in these primary efficacy analyses. The previously specified LOCF approach and also an additional worst-case imputation (no change from baseline) should be used as sensitivity analyses.

(3) No subgroup analyses were conducted for the HGT-GCB-039 study. Primary efficacy results in this study should be further investigated for gender, racial and appropriate age subgroups.

Background

Pursuant to Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act, Shire Human Genetic Therapies (Shire) is submitting a New Drug Application (NDA 22-575) for Velaglucerase Alpha (GA-GCB) for the proposed indication of long term-term enzyme replacement therapy (ERT) for patients with Type I Gaucher Disease. This application consists of data from a global clinical development program conducted under IND 61,220. This NDA is designated as a Type 1/New Molecular Entity (NME) and filed as a rolling submission. On July 15, 2009, Velaglucerase Alpha was granted, and continues to meet the criteria for, *Fast Track Drug Development* status for the above indication as it is intended to treat a serious life-threatening condition and addresses the current unmet medical need of patients with Type I Gaucher disease. Shire also has requested that this NDA be granted Priority Review status.

Velaglucerase Alpha received *Orphan Drug Designation* on June 8, 2009 and therefore qualifies for Orphan exception from the Prescription Drug User Fee under section 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act.

The NDA was submitted in eCTD format in accordance with all applicable electronic submission and eCTD guidances. The submission was sent via the FDA Electronic Submissions Gateway (ESG) and its content along with the electronic data sets and labeling information have been stored in the electronic document room (EDR) at this path location: `\\Cdsesub1\evsprod\NDA022575`. The submission can thus be accessed directly at the previous path specified or by using the FDA Global Submit (GS) Review software.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Brief Overview and Summary of Relevant Trials

Velaglucerase Alpha (GA-GCB) has been studied by Shire for the treatment of Type I Gaucher Disease. The clinical efficacy of Velaglucerase Alpha for the treatment of Type I Gaucher Disease was evaluated through a pivotal Phase III, multinational, multicenter, long term (12 month), randomized, double-blind, and parallel dose group study, TKT032. Supportive top-line (i.e. of highest importance) efficacy results from a Phase III, randomized, double-blind, and parallel group (active controlled by Imiglucerase) study, HGT-GCB-039, was also included in the submission. Further supportive data from an open-label switchover (with patients previously using Imiglucerase) study, TKT034, and an open-label dose escalation study, TKT025, were provided.

The following table contains information on the relevant trials contained in this submission.

Type of Study; Phase	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Dosed Subjects	Patient Diagnosis	Duration of Treatment	Study Status; Type of Report
·acy Safety; ·.·ase III/ **Pivotal**	TKT032	*Primary*: To determine the efficacy of every other week dosing of GA-GCB at a dose of 60 U/kg in treatment naïve patients; *Secondary*: Same as above except at a dose of 45 U/kg, and to study overall safety and tolerability	Multinational, multicenter, randomized, double-blind, parallel dose group	Velaglucerase Alpha (GA-GCB) 60 U/kg and 45 U/kg; Every other week dosing; Intravenous (IV)	60 U/kg: 12 45 U/kg: 13 Total: 25	Patients diagnosed with Type I Gaucher Disease	12 months	Complete; Full
Efficacy and Safety; Phase III/ **Supportive**	HGT-GCB-039	*Primary*: To compare the effects of Velaglucerase Alfa and Imiglucerase on hemoglobin concentration in treatment naïve patients; *Secondary*: To compare the effects of the said interventions on platelet counts and liver and spleen volumes while also studying overall safety and tolerability	Multinational, multicenter, randomized, double-blind, parallel group	Velaglucerase Alpha (GA-GCB) and Imiglucerase at 60 U/kg each; Every other week dosing; IV	GAGCB: 17 Imiglucer.: 17 Total: 34	Patients diagnosed with Type I Gaucher Disease	39 weeks	Completed; Top-line results only

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Type of Study; Phase	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Dosed Subjects	Patient Diagnosis	Duration of Treatment	Study Status; Type of Report
Safety and Efficacy; Phase II/III	TKT034	*Primary*: To evaluate the safety of every other week dosing of GA-GCB in patients previously treated with Imiglucerase; *Secondary*: To evaluate changes from baseline in hemoglobin concentration, platelet counts, and liver and spleen volumes	Multinational, multicenter, open-label, switchover to monotherapy	Velaglucerase Alpha (GA-GCB) 15 - 60 U/kg; Every other week dosing; IV	60 U/kg: 7 45 U/kg: 6 30 U/kg: 12 15 U/kg: 15 Total: 40	Patients diagnosed with Type I Gaucher Disease	12 months	Complete; Abbreviated
Safety; Phase I/II	TKT025	*Primary*: To evaluate the safety of every other week dosing of GA-GCB in treatment naïve patients; *Secondary*: To evaluate changes from baseline in hemoglobin concentration, platelet counts, and liver and spleen volumes	Open-label, 3+3 design	Velaglucerase Alpha (GA-GCB) 15 - 60 U/kg; Every other week dosing; IV	Initial Dose: 60 U/kg: 9 15 U/kg: 3 Total: 12	Patients diagnosed with Type I Gaucher Disease	9 months	Complete; Full

Review Issues

All review issues determined so far have been captured above in the additional requests to the Applicant for the 74-day letter.

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/s/

BEHRANG D VALI
10/27/2009

MICHAEL E WELCH
10/27/2009