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Personally identifiable information (PII) within this document is either removed or redacted (i.e., specific content is masked irreversibly from view with a black bar) to protect personal privacy. Personally identifiable information includes:

- All named persons associated with the study
- Patient identifiers within text, tables, or figures
- By-patient data listings

Anonymized patient data may be made available subject to an approved research proposal submitted. Information which is considered intellectual property or company confidential was also redacted.
SYNOPSIS

Sponsor: Shire HGT, Inc.

<table>
<thead>
<tr>
<th>Name of Finished Product:</th>
<th>velaglucerase alfa (GA-GCB)</th>
<th>Volume:</th>
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</thead>
<tbody>
<tr>
<td>Name of Active Ingredient:</td>
<td>velaglucerase alfa (GA-GCB)</td>
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Study Title:
A Multicenter, Open-Label Study of Gene-Activated Human Glucocerebrosidase (GA-GCB) Enzyme Replacement Therapy in Patients with Type 1 Gaucher Disease Previously Treated with Imiglucerase

Investigators and Study Centers: Multicenter

Publication (reference): No publications to date

Studied Period:
25 July 2007 (first subject enrolled) to 26 June 2009 (last subject completed)

Phase of Development: Phase II/III

Objectives:
The primary objective of this study was to evaluate the safety of every other week (EOW) dosing of velaglucerase alfa in patients with type 1 Gaucher disease who were previously treated with imiglucerase.

The secondary objectives were:

- To evaluate changes from Baseline in hemoglobin concentration after EOW dosing of velaglucerase alfa
- To evaluate changes from Baseline in platelet count after EOW dosing of velaglucerase alfa
- To evaluate changes from Baseline in liver and spleen volumes by abdominal magnetic resonance imaging (MRI) after EOW dosing of velaglucerase alfa

Methodology: This was a global, 12-month, multicenter, Phase II/III, open-label study designed to evaluate the safety of intravenous (IV) velaglucerase alfa therapy for patients currently receiving imiglucerase therapy for type 1 Gaucher disease.

Patients with type 1 Gaucher disease previously treated with imiglucerase were to be enrolled, including those patients who tested positive for anti-imiglucerase antibodies at Screening. The previous imiglucerase dose was to range between 15 and 60 U/kg with an EOW dosing regimen. For each patient, the same imiglucerase dose was to have been administered by 1-hour IV infusion for at least 6 months prior to enrollment. A patient’s velaglucerase alfa dose was to be the same dose as the previous imiglucerase dose received.
Patients were to receive up to 26 IV infusions of velaglucerase alfa. After the first 3 infusions of velaglucerase alfa therapy, patients who had not experienced a treatment-related serious adverse event (SAE) or an infusion-related adverse event (AE) were eligible to receive subsequent infusions at home, administered by qualified and trained medical personnel, per the discretion and under the direction of the Investigator.

Patients were monitored throughout the treatment period for changes in clinical parameters (ie, hemoglobin concentration, platelet count, and liver and spleen volumes). If a patient demonstrated a clinically significant change in these parameters, the Investigator could increase the patient’s dose by 15 U/kg. If the clinical parameters did not return to Baseline within 3 months, the Investigator would have the option of increasing the dose by increments of 15 U/kg. No dose increase would be offered to patients already receiving 60 U/kg; no dose above 60 U/kg was allowed. If the patient failed to respond at a maximum dose of 60 U/kg, the patient could have been withdrawn based on the Investigator’s clinical judgment.

Stopping rules were created to ensure patient safety. If any patient experienced a life-threatening (Grade 4) serious adverse event (SAE) or a death occurred that was considered possibly or probably related to the study drug, the study would have been stopped and the safety data reviewed.

The study completion visit was defined as Week 53. Patients were considered to have completed this study once they had 1) completed the 51-week treatment period, and 2) completed the study visits at Week 51 and Week 53.

Patients who completed Study TKT034 were provided the opportunity to enroll in a subsequent long-term, open-label clinical study (HGT-GCB-044). For patients who elected to enroll in HGT-GCB-044, it was intended that patients would receive continuous velaglucerase alfa treatment across the 2 studies. Patients who completed TKT034 and did not elect to enroll in HGT-GCB-044 were to have a safety assessment (for collection of adverse events and concomitant medications) by site visit or telephone 30 days after their last infusion of study drug.

### Number of Subjects (Planned and Analyzed):
A maximum of 40 subjects were planned to be enrolled in this study; 40 subjects were included in the intent-to-treat (ITT) and safety populations.

### Diagnosis and Main Criteria for Inclusion:
Patients, 2 years of age and older, with type 1 Gaucher disease who had received consistent treatment with imiglucerase for a minimum of 30 consecutive months, were eligible for the study.
**Sponsor:**
Shire HGT, Inc.  

<table>
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<th>Individual Study Table</th>
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**Test Product, Dose and Mode of Administration, Lot Number:**
Velaglucerase alfa, 15-60 U/kg IV EOW. Lot numbers used in this study were: , , and .

**Duration of Treatment:** Patients were to be treated for 12 months (51 weeks).

**Reference Therapy, Dose and Mode of Administration, Lot Number:**
Not applicable

**Criteria for Evaluation:**

**Safety:**
Safety was assessed throughout the study by assessments of AEs (including infusion-related AEs) concomitant medication use, and vital signs. Additional safety assessments, including, 12-lead electrocardiograms (ECGs,) physical examinations (PEs), clinical laboratory tests (hematology, serum chemistry, and urinalysis), were made at Weeks 13, 25, 37, 51, and 53. Determination of the presence of anti-velaglucerase alfa antibodies and enzyme neutralizing antibodies was conducted approximately every 6 weeks until Week 53.

**Efficacy:**
Hemoglobin concentration and platelet counts assayed by the central laboratory were used for efficacy analyses. Quantitative abdominal MRI of the liver and spleen was performed at the trial sites and read by a central reader for the determination of changes in liver and spleen volume. Other efficacy assessments included plasma levels of the biomarkers, chitotriosidase and CCL18, assessment of bone biomarkers, and, for patients 2 to 17 years old only, assessments of growth velocity, skeletal growth, and Tanner stages of puberty.

**Statistical Methods:**
Safety analyses were performed on the safety population and efficacy analyses were performed on the intent-to-treat population (ITT). Both the safety and ITT analysis populations were defined as all enrolled patients who received at least 1 study drug infusion (full or partial).

No formal statistical tests were performed on the safety parameters. An overall summary of treatment-emergent adverse events, a summary of treatment-emergent adverse events and infusion-related adverse events, and a summary of serious adverse events will be presented by velaglucerase alfa dose groups (15 U/kg, 30 U/kg, 45 U/kg, and 60 U/kg). To determine the velaglucerase alfa dose groups, doses were averaged across all infusions for a particular patient.

Mean within patient changes from baseline and mean within patient percent changes from baseline were calculated and presented for hemoglobin concentration and platelet count. For the change from Baseline to Week 53 in hemoglobin concentration and the percent change from Baseline to Week 53 in platelet count, a 2-sided 90% confidence interval around the means were computed.
If the 2-sided 90% confidence interval fell within the corresponding pre-specified clinically meaningful range (±1 g/dL for hemoglobin concentration, ±20% for platelet count, and ±15% for normalized liver and spleen volume) then it was to be concluded that the clinical efficacy parameter is no different from the start of the study (e.g., at the end of imiglucerase therapy) to the end of 12 months of velaglucerase alfa exposure.

Summary of Results

Safety:
Thirty-four (34) of 40 patients (85.0%) experienced at least 1 treatment-emergent adverse event; treatment-emergent AEs were experienced by 12 of 15 patients (80.0%) in the 15 U/kg group, 11 of 12 patients (91.7%) in the 30 U/kg group, 5 of 6 patients (83.3%) in the 45 U/kg group, and 6 of 7 patients (85.7%) in the 60 U/kg group. The most common treatment-emergent AEs were headache, arthralgia, nasopharyngitis, back pain, myalgia, cough, pharyngolaryngeal pain, upper abdominal pain, pain in extremity, fatigue, pyrexia, diarrhea, nausea, upper respiratory tract infection, influenza, and influenza-like illness.

Overall, 11 of 40 patients (27.5%) experienced adverse events that were considered possibly or probably related to study drug by the investigator; drug-related AEs were reported by 6 of 15 patients (40.0%) in the 15 U/kg group, 3 of 12 patients (25.0%) in the 30 U/kg group, 1 of 6 patients (16.7%) in the 45 U/kg group, and 1 of 7 patients (14.3%) in the 60 U/kg group. The majority of these events were considered to be infusion related.

Overall 5 of 40 patients (12.5%) experienced adverse events that were severe, and no patient experienced an AE that was life threatening; severe AEs were experienced by 2 of 12 patients (16.7%) in the 30 U/kg group, 1 of 6 patients (16.7%) in the 45 U/kg group, and 2 of 7 patients (28.6%) in the 60 U/kg group. No patient in the 15 U/kg group experienced a severe AE.

Overall, 4 of 40 patients (10.0%) experienced a total of 5 treatment-emergent SAEs; SAEs were reported by 1 of 15 patients (6.7%) in the 15 U/kg group, 1 of 12 patients (8.3%) in the 30 U/kg group, and 2 of 6 patients (33.3%) in the 45 U/kg group. No patient in the 60 U/kg group experienced a SAE.

One patient (in the 15 U/kg group) experienced a SAE of anaphylactoid reaction upon receiving their first dose of velaglucerase alfa that led to discontinuation. This remains the first and only reaction of this kind across the entire development program to date. The patient responded rapidly to discontinuation of the study drug and to supportive care, recovered without sequelae, and did not develop anti-velaglucerase alfa antibodies.
No deaths were reported during the study. No patient developed anti-velaglucerase antibodies during the study, including 3 patients who had tested positive for anti-imiglucerase antibodies at Screening.

The safety profile of velaglucerase alfa in the pediatric population (2 to 17 years of age) was similar to that seen in patients overall.

**Efficacy:**

The mean baseline hemoglobin concentration was sustained from Baseline over the course of 12 months in patients who transitioned from imiglucerase to velaglucerase alfa. At Baseline, the median hemoglobin concentration was 13.775 g/dL. After 53 weeks of treatment with velaglucerase alfa, the mean change from Baseline was -0.101 g/dL. The 90% confidence interval for mean change in hemoglobin concentration was -0.272 to 0.070, within the efficacy criterion of ±1 g/dL.

The mean baseline platelet count was sustained from Baseline over the course of 12 months in patients who transitioned from imiglucerase to velaglucerase alfa. At Baseline, the median platelet count was 162,000 ×10⁹/L. After 53 weeks of treatment with velaglucerase alfa, the percent change from Baseline in platelet count was 7.04%. The 90% confidence interval for percent change in platelet count was 0.54 to 13.53, within the efficacy criterion of ±20%.

The mean baseline normalized liver volume was sustained from Baseline over the course of 12 months in patients who transitioned from imiglucerase to velaglucerase alfa. At Baseline the mean normalized liver volume was 2.1%. After 51 weeks of treatment with velaglucerase alfa the mean percent change from Baseline in normalized liver volume was -0.03%. The 90% confidence interval for percent change in normalized liver volume was -2.62% to 2.56%, within the predefined efficacy criterion of 15%.

The mean baseline normalized spleen volume was sustained from Baseline over the course of 12 months in patients who transitioned from imiglucerase to velaglucerase alfa. At Baseline, the mean normalized spleen volume was 0.84%. After 51 weeks of treatment with velaglucerase alfa, the mean percent change from Baseline in normalized spleen volume was -5.56%. The 90% confidence interval for percent change in normalized spleen volume was -10.77% to -0.35%, within the predefined efficacy criterion of 15%.
CONCLUSIONS

The following conclusions can be made from the results presented in this abbreviated clinical study report:

- Velaglucerase alfa was generally well tolerated in adult and pediatric patients with type 1 Gaucher disease who transitioned from imiglucerase to velaglucerase alfa over the course of 12 months of treatment.
- Patients who transitioned from imiglucerase to velaglucerase alfa treatment have demonstrated sustained clinical stability in hemoglobin concentration and platelet counts, liver volume and spleen volume through 12 months of velaglucerase alfa treatment.

Final Report Date: 29 January 2010