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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

Individual Study Table
Referring to Part
of the Dossier

(For National Authority
Use only)

Name of Finished Product: velaglucerase alfa

Volume:

Name of Active Ingredient: velaglucerase alfa

Page:

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

Investigators and Study Centers: Multicenter

Publication (reference): Not applicable

Studied Period:
29 January 2008 (first patient enrolled) to
05 May 2009 (last patient completed)

Study Phase: III

Objectives: The primary objective of this study was to compare the effects of velaglucerase alfa and imiglucerase on hemoglobin concentration in patients with type 1 Gaucher disease.

The secondary objectives of this study were:

• To compare the effects of velaglucerase alfa and imiglucerase on platelet count.
• To compare the effects of velaglucerase alfa and imiglucerase on liver and spleen volumes (by magnetic resonance imaging [MRI]).
• To compare the effects of velaglucerase alfa and imiglucerase on Gaucher-disease-specific biomarkers (plasma chitotriosidase and CCL18 levels).
• To evaluate the safety of velaglucerase alfa and imiglucerase in patients with type 1 Gaucher disease, as measured by standard clinical laboratory assessments (including rates of antibody formation and enzyme neutralizing antibody activity) and safety evaluations (including rates of infusion-related adverse events [AEs] and the proportion of patients requiring premedication use to manage infusion-related adverse events) for each treatment group.
• To compare the effects of velaglucerase alfa and imiglucerase on the earliest time to response for hemoglobin (defined as a ≥1 g/dL improvement in hemoglobin levels relative to baseline).
Methodology:

**Number of Patients (Planned and Analyzed):** Up to 32 (16 per group) patients were planned; 34 patients were analyzed for safety; 34 patients were analyzed for efficacy.

**Diagnosis and Main Criteria for Inclusion:**
Each patient had to meet the following criteria to be eligible for the study:

1. The patient had a documented diagnosis of type 1 Gaucher disease, as determined by deficient glucocerebrosidase (GCB) activity relative to normal, as measured in leukocytes or by genotype analysis.
2. The patient was at least 2 years of age.
3a. The patient had Gaucher-disease-related anemia, defined as a hemoglobin concentration below the lower limit of normal for age and gender (based on the results obtained during Screening and at Baseline).

AND 1 OR MORE OF THE FOLLOWING 3 CRITERIA:

3b. The patient had at least moderate splenomegaly (2 to 3 cm below the left costal margin) by palpation. (Patients who have undergone splenectomy must have satisfied either Inclusion Criterion 3c or Inclusion Criterion 3d to be eligible for this study.)

OR

3c. The patient had Gaucher-disease-related thrombocytopenia (defined as a platelet count \(\leq 120 \times 10^3/mm^3\)).

OR

3d. The patient had a Gaucher-disease-related readily palpable enlarged liver.

4. The patient had not received treatment for Gaucher disease (investigational products, miglustat, or imiglucerase) within 12 months prior to study entry, as documented in the patient’s medical history.

5. Female patients of child-bearing potential must have agreed to use a medically acceptable method of contraception at all times during the study and must have had negative results to a pregnancy test performed at the time of enrollment and as required throughout their participation in the study. Male patients must have used a medically acceptable method of birth control throughout their participation in the study and were required to report pregnancy of a partner.

6. The patient, the patient’s parent(s), or the patient’s legal guardian(s) had provided written informed consent that had been approved by the Institutional Review Board/Independent Ethics Committee (IRB/IEC).

7. The patient must have been sufficiently cooperative to participate in this clinical study as judged by the Investigator.

1.1.1 **Exclusion Criteria**

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

1. The patient had type 2 or 3 Gaucher disease or was suspected of having type 3 Gaucher disease.
2. The patient was antibody-positive to imiglucerase or velaglucerase alfa at Screening, or the patient had experienced an anaphylactic or anaphylactoid reaction to imiglucerase or velaglucerase alfa, or the patient required routine premedication use to manage infusion reactions to imiglucerase or velaglucerase alfa.

3. The patient had received treatment with any non-Gaucher disease-related investigational drug or device within the 30 days prior to study entry; such use during the study was not permitted.

4. The patient was receiving red blood cell growth factor (eg, erythropoietin) or had received chronic systemic corticosteroids within the last 6 months. (NOTE: Inhaled corticosteroid therapy [eg, treatment for asthma] was acceptable. Use of intermittent corticosteroids as premedication to prevent infusion reactions was allowed.)

5. The patient was known to be positive for human immunodeficiency virus (HIV) (ie, had a documented positive result). Patients who did not have a documented positive result were to be tested for HIV at Screening.

6. The patient was known to be positive for hepatitis B and/or C and had active disease. Patients who did not have a documented positive result were to be tested for hepatitis at Screening.

7. The patient presented with exacerbated anemia at Screening (eg, due to folic acid and/or vitamin B₁₂ deficiency).

8. The patient presented with serum transferrin saturation <20 and serum ferritin <50 ng/mL.

9. The patient, patient’s parent(s), or patient’s legal guardian(s) was/were unable to understand the nature, scope, and possible consequences of the study.

10. The patient had a significant comorbidity(ies) that might have affected study data or confounded the study results (eg, malignancies, primary biliary cirrhosis, autoimmune liver disease).

11. The patient was unable to comply with the protocol (eg, had a clinically relevant medical condition making implementation of the protocol difficult, had an uncooperative attitude, was unable to return for safety evaluations, or was otherwise unlikely to complete the study, as determined by the Investigator).

12. The patient was pregnant or lactating.

**Test Product, Dose and Mode of Administration, Lot Number:**
velaglucerase alfa, 60 U/kg as a 1-hour IV infusion every other week
Lot numbers: 

**Duration of Treatment:** 39 weeks (20 total infusions per patient)

**Reference Therapy, Dose and Mode of Administration, Lot Number:** imiglucerase, 60 U/kg as a 1-hour IV infusion every other week
Lot numbers: 

Criteria for Evaluation:

Efficacy:
Primary endpoint:
The primary efficacy endpoint was the difference of the mean change from Baseline to Week 41 in hemoglobin concentration between the 2 treatment groups.

Secondary endpoints:
- The difference in the mean and percent changes from Baseline in platelet count between treatment groups.
- The difference in the mean and percent changes from Baseline in liver and spleen volumes by MRI between treatment groups.
- The mean and percent changes from Baseline in plasma chitotriosidase activity and plasma CCL18 levels between treatment groups.
- Difference in time to response for hemoglobin concentration (defined as a ≥1 g/dL improvement in hemoglobin concentrations relative to baseline) between treatment groups.
- Time to first response (+≥1g/dL) in hemoglobin concentration

Safety:
- Adverse events
- Vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiration rate, temperature)
- Physical examination
- Concomitant medications
- Electrocardiogram (ECG)
- Clinical laboratory tests (serum chemistry, hematology, urinalysis)
- Measurement of serum anti-velaglucerase alfa antibodies

Statistical Methods:
This is a non-inferiority, randomized controlled trial designed to demonstrate that velaglucerase alfa is non-inferior to imiglucerase in terms of efficacy in treating patients with type 1 Gaucher disease. Non-inferiority was to be demonstrated by testing the null hypothesis that the treatment difference is less than or equal to the lower equivalence margin in hemoglobin concentration (-1 g/dL) versus the alternative that imiglucerase treatment difference is greater than the lower equivalence margin

For variables following a continuous distribution, tabular summaries were to consist of number of patients (n), mean, standard deviation, minimum, maximum, and median. Graphs of the key efficacy variables will be presented by treatment groups. For categorical variables, tabular summaries will present the frequency and the percentage in each category by treatment group.
Efficacy:
For the primary endpoint (change in hemoglobin from baseline to Week 41) a 1-sided 97.5% confidence interval was used to test the null hypothesis that the treatment difference between velaglucerase alfa and imiglucerase was less than or equal to the lower equivalence margin (-1 g/dL) versus the alternative that the treatment difference with imiglucerase was greater than the lower equivalence margin. The primary analysis population was the ITT population and the analysis was repeated using a per protocol population.

For the secondary efficacy parameters (platelet counts, liver, and spleen volumes, chitotriosidase, and CCL18) comparing changes from Baseline between treatment groups, statistical tests were used to evaluate if the difference in mean changes from Baseline to Week 41 in the 2 treatment groups is statistically significant (defined as a $P$ value < 0.05). A 95% confidence interval was presented for the difference in mean changes from Baseline between the 2 treatment arms using a linear mixed model.

For time to first hemoglobin response, Kaplan-Meier survival curves were presented for each treatment group and a log-rank test was used to compare treatments.

Safety:
No formal statistical tests were performed on the safety parameters. Vital signs, 12-lead ECG, clinical chemistry, hematology, and urinalysis safety parameters were summarized. For categorical variables, such as AEs, the number and percentage of patients experiencing each AE were tabulated. AEs were summarized by severity of event. The number and percentage of patients experiencing drug-related AEs and infusion-related AEs, as well as AEs that are not considered related to study drug were displayed. Results of physical examinations were summarized. Clinical laboratory evaluations (hematology, serum chemistry, urinalysis, and determination of anti-velaglucerase alfa and anti-imiglucerase antibodies including enzyme neutralizing antibodies) were used to assess the safety of velaglucerase alfa.
Summary of Results

The primary endpoint was met.

Secondary endpoints were met, including increase in platelet counts, reduction in spleen and liver volumes and reduction in the plasma biomarkers if chitotriosidase and CCL18 following 9 months of treatment and the time to first hemoglobin response. Mean treatment differences between velaglucerase alfa and imiglucerase for these parameters affected by type 1 Gaucher disease were not statistically significant.

Demographics and Baseline Disease Characteristics

Patients in this global study were treatment-naïve and 73.5% were adult. An algorithm was used to balance age at randomization (2 to 17 years vs ≥18 years), hemoglobin concentration (<8 g/dL vs ≥8 g/dL), and splenectomy status (Yes vs No) between the 2 treatment groups. As a result the 2 treatment groups were similar in the number of pediatric patients (4 patients in the velaglucerase alfa group and 5 patients in the imiglucerase group). No patient had a screening hemoglobin concentration of <8 g/dL. The proportion of patients with splenectomy was balanced between the 2 treatment groups and relatively high (58.8% each group). The median modified platelet count at Baseline was 172.0 x 10^9 in the velaglucerase alfa group and 188 x 10^9 in the imiglucerase group, which is within the normal range. The 2 treatment groups were balanced with respect to gender.

Efficacy Results

Hemoglobin Change

In the ITT population, mean absolute change of hemoglobin concentration from Baseline to Week 41 was 1.624 and 1.488 g/dL in the velaglucerase alfa and imiglucerase groups, respectively. The change was similar between the 2 treatment groups and the estimated mean treatment difference (n=34) was 0.135 g/dL. These results were consistent with a PP population (n=30) analysis. The primary endpoint was met.

Time to the first hemoglobin response (change of +1 g/dL) was similar between the 2 treatment groups.

Platelets

At Week 41, the end of the study, the unadjusted mean change from Baseline in platelet count was 110.4 x10^9/L in the velaglucerase alfa group and 144.4 x10^9/L in the imiglucerase group. Part of the difference in mean change in platelet counts could be explained by the fact that all 4 children under the age of 5 years were randomized to the imiglucerase group and these patients responded quite robustly. The fact that these children required ERT at such a young age is indicative of the severity of their disease. Children with severe disease are expected to have a better response to treatment than less severely affected type 1 Gaucher patients. Nevertheless, the difference in mean change of platelet counts between velaglucerase alfa and imiglucerase was not statistically significant.
Liver and Spleen Volume

Baseline median normalized liver volume was 3.9% and 4.0% of body weight in the velaglucerase alfa and imiglucerase groups, respectively. These volumes had decreased to 2.6% and 3.0% of body weight at Week 41. The mean change was similar between the 2 treatment groups (no statistically significant difference detected) and this secondary endpoint was met.

Baseline median normalized spleen volumes were 1.90% and 1.40% of body weight in the velaglucerase alfa and imiglucerase groups, respectively. These volumes had decreased to 1.00% and 0.90% body weight at Week 41. These results were based on 7 patients per treatment group as 10 patients per treatment group had been splenectomized. The mean change was similar between the 2 treatment groups (no statistically significant difference detected) and this secondary endpoint was met.

Subgroup Results

Hemoglobin response was similar between velaglucerase alfa and imiglucerase treatment for the following subgroups: pediatric patients (age 2 to 17 years), adult patients (age ≥18 years), male patients, female patients, splenectomized patients, and patients not splenectomized. No statistically significant treatment differences in mean change in hemoglobin at Week 41 were detected.

Safety Results

Both velaglucerase alfa and imiglucerase were safe and generally well tolerated in both adult and pediatric patients. Adverse events reflecting the appearance or exacerbation of the signs and symptoms of type 1 Gaucher disease. Also expected were mild or moderate infusion reactions that might result from the intravenous administration of a protein. It was expected that a large proportion of patients would have AEs and 16 of 17 patients (94.1%) in each treatment group had at least 1 AE. Eight of 17 patients (47.1%) of patients in the velaglucerase alfa group and 6 of 17 (35.3%) patients in the imiglucerase group had AEs considered by the Investigator to be related to study drug. Most patients reported only AEs of mild or moderate severity; 14 of 17 patients (82.4%) in the velaglucerase alfa group and 15 of 17 patients (88.2%) in the imiglucerase group reported AEs of only mild or moderate severity. Of the 17 patients who received velaglucerase alfa 3 patients (17.6%) had a severe AE (back pain or allergic dermatitis, aPTT prolonged) while 1 patient (5.9%) had a life-threatening AE (convulsions). Of 17 patients who received imiglucerase, 2 (11.8%) had severe AEs (arthralgia, chills). No patients discontinued prematurely in this study due to adverse events, although 1 patient who received imiglucerase withdrew consent and reported infusion-related reactions as the reason. No patients died during this study.

Three patients in the velaglucerase group had a total of 4 SAEs (allergic dermatitis, 2 events of thrombocytopenia in 1 patient, and convulsion). The event of allergic dermatitis was considered by the Investigator to be probably related to study drug, the other 3 events were considered not related.

A majority of patients who had AEs considered related to study drug also had infusion-related
reactions. Infusion-related adverse events were reported by 5 of 8 (62.5%) patients in the velaglucerase alfa group and 4 of 6 (66.7%) patients in the imiglucerase group reported infusion-related AE. Two of 17 patients in the velaglucerase group at the same site were premedicated to prevent infusion-related reactions. Overall, infusion-related reactions were most likely to be reported in the first 6 months of the study. No patient in the velaglucerase alfa group developed antibodies to velaglucerase alfa, while 4 patients (23.5%) in the imiglucerase group developed anti-imiglucerase antibodies.

The safety of treatment with velaglucerase alfa appeared to be comparable to the safety with imiglucerase in adult and pediatric patients.

CONCLUSIONS

This section contained Summary and Conclusion information which could be considered promotional in nature. This section has been removed to allow the reader to draw their own conclusions.
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Final Date: 01 October 2009