Protocol RC 91-0110: An Evaluation of the Safety and Effectiveness of Recombinant, Human, Macrophage-Targeted β-Glucocerebrosidase.

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Investigators and Study Center(s)

This was a multi-center study conducted at two sites in the United States (US).

Studied Period

First Patient Enrolled January 1992
Last Patient Completed October 1992

Phase of Development

Phase 3

Objectives

To evaluate and demonstrate that Cerezyme® (imiglucerase for injection) exhibits a comparable safety and effectiveness profile when compared to Ceredase® in the treatment of patients with Gaucher disease.

Methodology

This double-blind, randomized, parallel group study evaluated 30 subjects naïve to enzyme replacement therapy (Ceredase®). The subjects were randomized to receive either Ceredase® or Cerezyme® by I.V. infusion once every two weeks for 6 months (13 treatments) at 2 investigational sites.

Number of Patients (Planned and Analyzed)

30 patients were planned; 31 patients enrolled; 30 patients treated and analyzed.

Diagnosis and Main Criteria for Inclusion

Male and female patients with a confirmed diagnosis of Gaucher disease, who were between 2 and 75 years of age, had not been previously treated with Ceredase®, had not undergone a splenectomy, and had a hemoglobin value of at least 1.0 g/dL less than normal lower limit for their age and sex, defined as: male adults 13.9-16.3 g/dL; female adults 12.0-15.0 g/dL; children (≤18 years) 11.1-14.4 g,/dL.

Test Product, Dose, and Mode of Administration

Cerezyme®, 60 U/kg body weight once every 2 weeks via I.V. infusion

Duration of Treatment

6 months

Reference Therapy, Dose and Mode of Administration

Ceredase® 60 U/kg once every 2 weeks via I.V. infusion

Criteria for Evaluation
Efficacy

An increase in hemoglobin concentration and platelet count, a decrease in spleen and/or liver volume, decreases in serum transaminases (SGOT and SGPT), decrease in acid phosphatase and angiotensin converting enzyme (ACE), and change in bone density (X-rays).

Safety

Routine monitoring for antibody formation and laboratory (hematology and chemistry) values; monitoring and analysis of adverse events and concomitant medications, illnesses, and therapeutic procedures.

Statistical Methods
Efficacy

Baseline demographic characteristics were compared for both treatment groups and for both sites. Continuous variables were compared using the Student's t-test and Wilcoxon Rank-Sum test. Categorical variables were compared using Fisher's Exact test. The proportions of patients achieving an increase in hemoglobin of 1.0 g/dL or greater, or an increase in hemoglobin of 1.5 g/dL or greater, were compared using Fisher's Exact test. All tests of significance were two-sided, using a 5% level of significance. Time to response in hemoglobin was compared in the two treatment groups using Kaplan-Meier estimates. Log-rank and Wilcoxon statistics were used to assess any differences in the two treatment groups.

Safety

Mean changes in laboratory values for the two treatment groups were compared using the Student's t-test and the Wilcoxon Rank-Sum test.

Summary – Conclusions
Efficacy

The results of this study demonstrated that following repeated administration of Cerezyme®, no significant differences were found in any of the primary or secondary efficacy endpoints when compared to Ceredase®. Significant reductions in hepatomegaly and splenomegaly were demonstrated as well as significant improvements in hematologic parameters and disease markers. Additionally, bone status improved in many of the subjects.

Eleven of 15 subjects (73%) treated with Cerezyme® and 12 of 15 subjects (80%) treated with Ceredase® achieved an absolute increase in hemoglobin concentration of at least 1.0 g/dL from baseline. This difference was not statistically significant. Subjects treated with Cerezyme® showed a mean increase in hemoglobin of 1.92 g/dL from baseline to final value while subjects receiving Ceredase® demonstrated a mean increase of 1.58 g/dL. Increases in hemoglobin from baseline to study completion were statistically significant in both groups ($p \leq 0.001$).

Changes in platelet counts from baseline to study completion were also assessed. Changes of $\geq$30% from baseline were considered clinically significant. Subjects treated with Cerezyme® showed a mean increase of 33% ($23x10^3$/mL) in platelet count from baseline to study completion, while those treated with Ceredase® showed an increase of 26% ($16x10^3$/mL). Change from baseline to study completion was statistically significant in both groups ($p < 0.001$); no significant difference was seen between the two treatment groups in this measure.

Patients in the Cerezyme® treatment arm showed a mean decrease in liver volume of 310 cc (11% mean reduction from the baseline value) while patients in the Ceredase® group demonstrated a mean decrease of 307 cc (10% mean reduction from the baseline value). In addition, all patients in the Cerezyme® group showed a reduction in the volume of their spleen of greater than 10% within the first 6 months of treatment. The mean decrease in spleen volume for the Cerezyme® treatment arm was 902 cc (35%) and 873 cc (30%) for the Ceredase® treatment arm. Decreases in organ volume from baseline to study completion were significant in both arms; no significant differences were seen between the two treatment groups.

The secondary measures of efficacy in this clinical trial were mean changes from baseline in acid phosphatase and angiotensin converting enzyme (ACE). The Cerezyme® group showed a significant decrease (mean % ± S.D, -54% ±19%) in acid phosphatase levels from baseline. The decrease in acid phosphatase levels in the Ceredase® group was not significantly different from the Cerezyme® treatment group (-43%±19%). Acid phosphatase levels decreased by 30% or more in 14 of 15 patients in the Cerezyme® treatment group and 11 of 15 patients in the Ceredase® treatment group. In addition, 14 of 15 patients in the Cerezyme® treatment group and 11 of 15 patients in the Ceredase® treatment group showed a $\geq$30% decrease in angiotensin converting enzyme (ACE) level. Thirteen patients in the Cerezyme® group had an elevated baseline ACE value; 3 of these returned to normal range with Cerezyme® treatment. The mean decrease in ACE value from baseline was 57% in the Cerezyme® group and 43% in the Ceredase® group. Treatment with Cerezyme® resulted in possibly significant amelioration of cachexia demonstrated by a mean increase in body weight of 1.65 kg (p=0.04,

paired t-test; p=0.07, Wilcoxon signed rank). As a relative change, the mean was 2.9%. The Ceredase® group showed an average weight gain of 0.56 kg (1.1%). The difference in weight gain between the Cerezyme® and Ceredase® treatment groups was not significant. Of the 15 patients in the Cerezyme® group, 7 demonstrated changes in skeletal radiographs between the baseline and 6 month examinations which suggested improvement. The changes in these patients included decreases in lytic bone lesions, improvement in growth and maturation of bone, decrease in trabecular sclerosis, increased density and cortical thickness, and a decrease in endosteal buttressing or “chevrons”.

Safety Results

During the study there was a similar rate of IgG antibody formation among the patients receiving Cerezyme® as compared to those receiving Ceredase®. During the initial six months of the study, 20% of all patients (6 patients, 3 in each treatment group) developed antibodies to the enzyme. There was no evidence of a diminution of treatment efficacy in the 6 patients treated with Cerezyme® or Ceredase® who demonstrated development of antibodies to the enzyme.

No serious adverse events were reported in this study. There were a total of 185 non-serious adverse events (AEs) reported among the 30 patients. Thirteen of 15 patients in the Cerezyme® group experienced 82 AEs and 12 of 15 patients in the Ceredase® group reported 103 AEs. Nine of the 82 AEs (11%) in the Cerezyme® group and 10 the 103 AEs (10%) in the Ceredase® group were considered possibly related to study drug. Overall, the most frequently reported AEs regardless of relationship to study drug were pain (21 events), ecchymosis (19 events), epistaxis (17 events), pharyngitis (11 events), diarrhea (8 events), asthenia (7 events), rash (7 events), fever (6 events), headache (6 events), back pain (6 events), rhinitis (6 events), dizziness (5 events) menorrhagia (5 events), bone pain (4 events) and pruritus (5 events). The most frequently reported AEs considered related to study drug were fever (3 Ceredase® patients), dizziness (2 Ceredase® patients, 1 Cerezyme® patient), pruritus (2 Ceredase® patients, 1 Cerezyme® patient) and headache (2 Cerezyme® patients). No other related AEs were reported in more than 1 patient across treatment groups. The majority of AEs were reported as mild. Three (3) AEs, all in the Ceredase® group, were reported as severe. Overall, the AE profile for patients treated with Cerezyme® did not differ in nature from the observed profile associated with Ceredase®.

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