# Protocol RC 92-0501: An Extended Evaluation of the Safety and Effectiveness of Recombinant, Human-derived, Macrophage-Targeted β Glucocerebrosidase in Patients with Gaucher disease.

*These results are supplied for informational purposes only.*
*Prescribing decisions should be made based on the approved package insert in the country of prescription.*

**Investigators and Study Center(s)**

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

**Studied Period**

First Patient Enrolled July 1992
Last Patient Completed May 1994

**Phase of Development**

Phase 3

**Objectives**

To evaluate the safety and effectiveness of Cerezyme® in the treatment of patients with Gaucher disease with respect to the following:

- The maintenance of safety and effectiveness in patients who crossed over from the Ceredase® treatment group in the Pivotal Study to Cerezyme® treatment in the Extended Study;
- Dose reduction in 50% increments (initial dose: 60 U/kg) at 3-month intervals; and
- Long-term evaluation of antibody formation to Cerezyme®.

**Methodology**

This study (referred to as the Extended Study) was designed to continue treatment of patients who completed the pivotal Cerezyme® study (RC 91-0110). The Pivotal Study evaluated the safety and effectiveness of Cerezyme® in comparison to the commercially available enzyme replacement therapy, Ceredase®, in a randomized, double-blind, parallel-group manner. This study provided for extended treatment for all study subjects until Cerezyme® market approval by the FDA in 1994. Patients were treated in this Extended Study for an additional 18-20 months, for a total of 26 months of treatment (including the Pivotal Study).

Patients participating in the Pivotal Study were randomized to receive either Ceredase® or Cerezyme® in a blinded manner; enzyme replacement therapy was administered at a dose of 60 U/kg once every 2 weeks. For the first 3 months of the Extended Study, patients continued to receive, under blinded conditions, the same study drug (either Cerezyme® or Ceredase®) that they were randomized to receive in the Pivotal Study. Following 3 months of treatment in the Extended Study (a total of 9 months of treatment), the blind

was broken to allow patients to cross-over from Ceredase® to Cerezyme®.

At the 3-month visit and every 3 months thereafter, an evaluation of the patient's current therapy was made. Hemoglobin levels were assessed as the primary efficacy criteria. Patients who had a sustained hemoglobin level of ≥1.0 g/dL above baseline during the preceding evaluation period were eligible for a 50% dosage reduction.

**Number of Patients (Planned and Analyzed)**

30 patients were planned, enrolled, and treated. 29 patients completed the study and were analyzed for efficacy, and 30 patients were analyzed for safety.

**Diagnosis and Main Criteria for Inclusion**

Patients who successfully completed Protocol RC 91-0110 (Pivotal Study) were eligible for participation in this Extended Study. Patients treated in protocol RC 91-0110 had a confirmed diagnosis of Gaucher disease, had not been previously treated with Ceredase®, had not undergone a splenectomy, were between 2 and 75 years of age, and had a hemoglobin value of at least 1.0 g/dL less than the 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, 30, or 15 U/kg body weight once every 2 weeks via I.V. infusion

**Duration of Treatment**

18 to 20 months beyond the initial 6-month Pivotal Study.

**Reference Therapy, Dose and Mode of Administration**

Ceredase® 60, 30, or 15 U/kg body weight once every 2 weeks via I.V. infusion

**Criteria for Evaluation**
**Efficacy**

Primary efficacy variables were: an increase in hemoglobin concentration of at least 1.0 g/dL; an increase in platelet count of ≥30%; and a decrease of ≥10% in liver and spleen volume. The secondary effectiveness variables included a greater increase (≥1.5 g/dL) in hemoglobin concentration; improvement in liver function based on SGOT and SGPT levels; a decrease in acid phosphatase and angiotensin-converting enzyme (ACE); and a change in bone density.

**Safety**

Formation of a specific immune response (antibody formation) to Cerezyme® was considered to be the primary safety variable. This variable was measured at baseline (Pivotal Study), every 3 months and at the end of the Extended Study. Other safety evaluations included: comparison of laboratory values to baseline values within each patient; and monitoring and analysis of adverse events and concomitant medications, illnesses, and therapeutic

procedures.

**Statistical Methods**

Fisher's Exact test was applied to compare treatment groups for all categorical measures, including hemoglobin level, platelet count, and liver and spleen volume. Student's t test was applied to analyze the continuous measures. Two-sided hypotheses were used at the 5% level of significance. Also, baseline for measures indicating improvement was defined as the initial Protocol RC91-0110 baseline value. For measures indicating maintenance, baseline was defined as the mean of the last 3 measured values in protocol RC91-0110.

The incidence of "improvement from baseline" and of "maintenance of benefit" were reported for 3 months following crossover, 3, 6, and 9 months following first reduction in dose for each of Ceredase® and Cerezyme® and 3 months following the second reduction in dose for Ceredase® and Cerezyme®. For example, mean hemoglobin levels and their associated Confidence Intervals were also presented for each. A patient was considered to have an "improvement from baseline" at a timepoint if the value was 1.0 g/dL or greater than the patient's hemoglobin at baseline in study Protocol RC91-0110. Similar methods were applied to the other primary efficacy parameters.

**Summary – Conclusions**
**Efficacy**

Twenty-nine patients were evaluable for efficacy; 1 patient who withdrew from the Extended Study after four infusions of Ceredase® was not evaluable. At the end of the Extended Study, 25 of 29 (86%) patients achieved a primary response to treatment as demonstrated by a $\geq$1.0 g/dL change in hemoglobin from baseline. Thirteen of 29 (45%) patients with an abnormally low baseline hemoglobin level achieved a normal hemoglobin level at the end of the Extended study. Nineteen of 29 (66%) patients achieved an increase in platelet count of $\geq$30% at the end of this study. In addition, 15 of 29 (52%) patients had a $\geq$50% increase in platelet count at the end of the study. Twenty-five of 29 (86%) patients demonstrated a $\geq$10% reduction from baseline in liver volume and 28 of 29 (97%) patients demonstrated a $\geq$10% reduction in the splenic volume at the end of the study. Fifteen (52%) patients achieved a $\geq$20% reduction in liver volume and 26 (90%) patients achieved a $\geq$20% reduction in splenic volume. No significant changes were observed in the following blood chemistries: SGOT, SGPT, ACE, or acid phosphatase; however, decreases in ACE and acid phosphatase were observed. Following 2 years of treatment, bone radiographs were evaluated for 11 patients (6 Ceredase®/Cross-Over and 5 Cerezyme®). Bone radiographs showed improvement following 2 years of treatment in 7 of the 11 (64%) evaluable patients. No significant statistical difference was noted between the two treatment groups in any of the efficacy parameters.

Subjects who crossed over to Cerezyme® from Ceredase® and were evaluated for approximately 10 treatment months demonstrated no significant change in response to treatment. Additionally, treatment response was maintained in subjects who received dosage reduction. The immunologic data demonstrated that there were no significant differences in antibody formation between Cerezyme® and Ceredase®.

**Safety Results**

During the course of the Pivotal and Extended Studies, 9 of 30 (30%) patients treated were noted to develop antibodies to either Cerezyme® or Ceredase® during a 2-year course of treatment. Three of 15 (20%) patients in the Cerezyme® group developed antibodies and 6 of 15 (40%) patients in the

Ceredase® group developed antibodies prior to being rolled over to Cerezyme®. The initial detection of antibodies to Ceredase® or Cerezyme® occurred between baseline and 12 months of study treatment. Following 12 months of therapy, no patient was found to have developed newly detectable antibodies. Two of the 9 patients (22%) with detectable antibodies during the study no longer tested positive for antibodies after 24 months of enzyme replacement therapy. All patients who developed antibody to either Ceredase® or Cerezyme® responded to treatment as evidenced by improvements in the primary efficacy variables.

All patients were monitored for AEs during this clinical study. A total of 385 AEs were reported, 215 AEs in the Ceredase®/Cross-Over arm and 170 AEs in the Cerezyme® arm. None of the reported AEs were considered serious. The majority of AEs in each treatment group were considered unrelated to study treatment (90% of Ceredase®/Cross-Over AEs and 91% of Cerezyme® AEs). Overall, the most frequently reported AEs regardless of relationship to study drug were epistaxis (37 events), pain (31 events), ecchymosis (29 events), pharyngitis (20 events), headache (15 events), diarrhea (14 events), rhinitis (13 events), asthenia (10 events), infection (10 events) dizziness (9 events), fever (9 events), rash (9 events), back pain (8 events) and chest pain (7 events). The most frequently reported AEs considered related to study drug were headache (4 Cerezyme® patients), pruritus (1 Cerezyme®, 3 Ceredase®/Cross-Over patients), fever (3 Ceredase®/Cross-Over patients), dizziness (1 Cerezyme®, 2 Ceredase®/Crossover patients) and rash (1 Cerezyme®, 1 Ceredase®/Cross-Over patient). No other AEs were reported for more than 1 patient. The majority of AEs were of mild or moderate intensity and a total of 8 AEs in 6 patients were considered severe. The AE profile of the 9 patients who developed antibodies was specifically reviewed for the presence of any significant clinical events. One antibody-positive patient was discontinued from the study due to infusion-associated AEs, which developed following 6 months of treatment with Ceredase and prior to actual cross-over to Cerezyme®. The AEs for this patient included the development of moderate pruritus and urticaria, in the absence of respiratory or cardiovascular symptoms, during the administration of treatment. The AEs were considered definitely related to the study drug and resolved without sequelae. No other patients discontinued the study due to AEs. Overall, there was no apparent difference between the 2 treatment groups in the safety parameters evaluated. Cross-over of patients from Ceredase® to Cerezyme® demonstrated no effect on the safety profile.

Based on Report Prepared on: October 1996
Synopsis Prepared on: 22 June 2005