RC96-1101: A Study of the Efficacy of Cerezyme® in Treating Skeletal Disease in Patients with Type 1 Gaucher Disease

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INVESTIGATORS AND STUDY CENTER(S)

This was a multicenter study conducted at 7 centers in the United States.

STUDIED PERIOD

08 December 1997 (first patient enrolled) to 01 July 2004 (last patient completed)

PHASE OF DEVELOPMENT

Phase 4

OBJECTIVES

The objectives of the study were to a) evaluate and quantify skeletal responses compared to baseline in patients receiving Cerezyme® therapy over a period of 48 months and b) assess and compare the use of skeletal parameters, such as dual energy X-ray absorptiometry (DEXA) and quantitative computerized tomography (QCT) to measure bone density, quantitative chemical shift imaging (QCSI) to measure fat fraction, X-rays to measure cortical thickness, and serum and urine bone markers, as indicators of treatment response which may be useful in dose management.

METHODOLOGY

This was a multicenter, open-label, prospective study of the efficacy of Cerezyme® in treating patients with skeletal manifestations secondary to Type 1 Gaucher disease.

All patients received 60 U/kg of Cerezyme® by infusion every 2 weeks for the first 24 months of therapy. At both 24 and 36 months of therapy, patients underwent evaluation to determine whether specific therapeutic goals had been achieved or maintained, and whether a patient was consequently eligible for a reduction in their Cerezyme® dose. If therapeutic goals had been met, the patient could maintain the current Cerezyme® dose or the dose could be reduced to 45 U/kg or 30 U/kg every 2 weeks.

If the patient did not meet therapeutic goals, the Cerezyme® dose was to be maintained at 60 U/kg every 2 weeks or, if the patient's dose had been reduced after 24 months and the therapeutic goals had not been maintained at 36 months, the dose was to be increased back to 60 U/kg every 2 weeks.

Standard assessments, including medical history and physical exam, assessments of bone pain and bone crises, complete blood counts with differential, and recording of concomitant medications, procedures, and illnesses were performed every 3 months. Quality of life (QOL) was assessed at Baseline, 6 months, 12 months, and yearly thereafter. Serum chemistries, angiotensin converting enzyme (ACE), and serum and urine biochemical markers of bone metabolism were assessed every 6 months. Liver and spleen volumes and skeletal assessments were performed every 12 months.

NUMBER OF PATIENTS (PLANNED AND ANALYZED)

A total of 25 to 40 patients were planned to be enrolled. Thirty-three patients were enrolled in the study and were analyzed for efficacy and safety. Twenty-three of 33 enrolled patients completed 48 months of Cerezyme® treatment on study.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION
Males and females (non-pregnant, non-lactating, and non-perimenopausal) without major concurrent disorders, more than 1 joint replacement, or taking medications known to affect bone homeostasis were enrolled if they met the following primary inclusion criteria: 1) confirmed diagnosis of Type 1 Gaucher disease (glucocerebrosidase enzyme assay), with no prior enzyme replacement therapy, gene therapy, or bone marrow transplantation, and who were ambulatory; 2) age of 10–65 years (patients between 66 and 70 years of age were considered on a case-by-case basis following careful medical review with Genzyme Corporation’s Medical Affairs Staff); 3) DEXA of the femoral neck with a T score ≤ -1.0; and 4) a documented history or baseline evidence of bone disease secondary to Gaucher disease.

**TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION**

Cerezyme®, 60 U/kg/2 weeks, intravenous.

**DURATION OF TREATMENT**

Duration of treatment per patient was 48 months for the study.

**REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION**

None.

**CRITERIA FOR EVALUATION**

**Criteria for Evaluation – Efficacy**

The primary endpoint of the study was the proportion of patients who succeeded in exhibiting skeletal response to treatment. This analysis focused on established techniques, including severity of bone pain, incidence of bone crises, and evaluation of bone density using DEXA. Other radiological skeletal assessments to quantify improvement in bone manifestations of Gaucher disease were: QCSI to measure fat fraction; X-rays to measure cortical thickness; and single energy quantitative computerized tomography (SEQCT) to measure bone density. Clinical outcomes of improvement included biochemical bone markers and QOL as measured using the SF-36 questionnaire.

**Criteria for Evaluation – Safety**

Safety parameters included the incidence of clinical adverse events (AEs); discontinuations due to AEs; drug-related, serious, and severe AEs; and results of physical examinations and clinical laboratory measurements (chemistry, hematology, and urinalysis).

**STATISTICAL METHODS**

For all variables, analyses were conducted for the Intent-to-Treat population, which included all patients enrolled in the study.

Changes from baseline to later time points were summarized for the following variables: mobility; bone pain; bone crises; proportion of patients who succeed in exhibiting improvement; marrow infiltration; medullary infarction and avascular necrosis (MRI); fat fraction (QCSI); bone density by DEXA and SEQCT; fractures, lytic lesions and Erlenmeyer flask deformity (X-rays); QOL using the SF-36 (eight domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health and 2 summary measures: physical health and mental health). All statistical comparisons were carried out as 2-sided tests. Probability values (p-values) were presented to 3 decimal places.

**SUMMARY / CONCLUSIONS**

**Summary / Conclusions – Efficacy**

Significant improvements in bone pain, bone crises, and bone density measured using DEXA were observed in patients treated with Cerezyme® for up to 48 months. Improvements in bone pain were evident as early as 3 months following treatment, and improvement continued throughout the study. While 13 patients were reported to have a history of bone crises, and 5 patients reported at least one bone crisis within the 2 months prior to baseline, bone crises were reported in only 3 patients in the 48 months of the study. Statistically significant improvements in bone density as measured using DEXA manifested after approximately 24 months of treatment. These measures demonstrate improvement in the skeletal manifestations of Gaucher disease when patients are treated with Cerezyme®. Results obtained from other radiological skeletal assessments indicated that such assessment modalities may have only limited utility in patients with Gaucher disease.
Biochemical markers of bone formation and resorption were suggestive of greater bone formation at 6 to 24 months, supporting the increases in bone density noted with DEXA scanning. New instances of medullary infarction, avascular necrosis, lytic lesions, and fractures were few, occurred generally within the first 12 months of therapy, and were rarely observed after 24 months of therapy, suggesting that the events that did occur reflected processes that were already present at baseline and resolved with therapy. Erlenmeyer flask deformities generally showed improvement through the course of the study.

Statistically significant improvements in QOL as measured using the SF-36 were noted; both physical and mental standardized component scores, as well as most of the SF-36 subscales, showed statistically significant improvement at one or more time points. SF-36 scores in this population were below the US normal at baseline, and most domains appeared to have improved to normal by Month 48. Mobility of patients was also assessed, but results were difficult to interpret due to small numbers of patients with limited mobility at any time point.

As expected, patients showed marked clinical improvement in the other major signs and symptoms of Gaucher disease, as shown by organ volume, hemoglobin levels, and platelet count, consistent with expected outcomes and Genzyme’s previous reports.

When the study protocol was initially written in 1997, the primary analysis was designed to include a composite score of the radiological measures of bone response. However, the methodological problems which were encountered early in the course of the study in regards to the individual radiographic instruments of the planned composite endpoint call into question the appropriateness of this type of analysis for skeletal disease in Type I Gaucher patients. Therefore, although the protocol-specified analyses were performed and are presented in this report as originally planned, evaluation and quantification of skeletal response to Cerezyme® will focus on techniques that are currently considered reliable, including severity of bone pain, incidence of bone crisis and evaluation of bone density using DEXA. In light of current clinical knowledge, these specific evaluation techniques have been determined to be the most sensitive tools to monitor clinical improvement in Gaucher related bone disease.

Radiological composite score: Relatively few patients met the criteria for response using this score. Given the challenges identified over the course of the study in the use of several of the various imaging techniques for this patient population, it was determined that bone pain, bone crises, and DEXA were most indicative of skeletal response. Apparent artifactual declines in fat fraction and SEQCT made interpretation of the composite score impossible.

**Summary / Conclusions - Safety Results**

Long-term Cerezyme® treatment was well-tolerated in the majority of patients. Overall, the most commonly reported events were chills, flushing, and arthralgia. The most common AE considered at least possibly related to study drug was chills, occurring in 4 patients (12%). Of the 11 patients (33%) who experienced SAEs, 4 experienced SAEs related to their underlying bone involvement. Two patients experienced SAEs thought to be probably or definitely related to Cerezyme®; both of these patients had symptoms characteristic of infusion reactions, and one patient discontinued the study due to the reaction.

**CONCLUSION**

The proposed methodology for primary analysis using a composite score of the radiological measures was found to be problematic because of the imaging techniques; however, significant improvements in bone pain, bone crises, and bone density measured using DEXA were observed. Improvements in bone pain were evident as early as 3 months following treatment, while statistically significant improvements in bone density were apparent after approximately 24 months of treatment. These standard measures demonstrate improvement in the skeletal manifestations of Gaucher disease when patients are treated with Cerezyme®. Improvements in other measures of Gaucher disease, as well as QOL as measured using the SF-36 assessment, were also noted. Treatment with Cerezyme® was generally well-tolerated and led to improvement in the skeletal aspects of Gaucher disease, including bone pain, incidence of bone crises, and bone density.

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