Protocol AGAL-006-99: An Open-Label Extension Study of the Safety and Efficacy of Recombinant Human α-Galactosidase A (r-hα GAL) Replacement Therapy in Patients with Fabry Disease who Participated in Protocol No. FB9702-01.

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 multicenter study conducted at 10 sites in the United States (US) and the United Kingdom (UK).

Studied Period

First Patient Enrolled: 23 May 2000
Last Patient Completed: 29 July 2003

Phase of Development

Open-label extension of the Phase 1/2 Study (Protocol No. FB9702-01).

Objectives

The objective of this study was to obtain additional information regarding the safety and efficacy of Fabrazyme® when used as enzyme replacement therapy in patients with Fabry disease, after an interruption in therapy.

Methodology

This was a multicenter, non-randomized, open-label extension study of 14 patients with Fabry disease who were previously treated under the original Phase 1/2 study.

Number of Patients (Planned and Analyzed)

All 15 patients from the Phase 1/2 study (Protocol No. FB9702-01) were eligible for enrollment into the extension study. Fourteen of 15 patients enrolled into the extension study, and 1 patient was treated as part of a Compassionate Use Program in Australia.

Diagnosis and Main Criteria for Inclusion

Patients were to be included in this study if they participated in the Phase 1/2 Study (Protocol No. FB9702-01) and signed written informed consent.

Test Product, Dose, and Mode of Administration

Patients were to receive 1.0 mg/kg (0.9 to 1.1 mg/kg) Fabrazyme® intravenously (IV) every 2 weeks. If a patient experienced renal disease progression (> 50% increase in serum creatinine from Study Entry), a dose increase to 3.0 mg/kg every 2 weeks was permitted.

Duration of Treatment

The first infusion was administered on 25 May 2000. Patients were to be treated until marketing approval of Fabrazyme® in the US, which occurred on 24 April 2003. The final infusion was administered on 30 June 2003.

Reference Therapy, Dose and Mode of Administration

No reference treatment was used in this study.

Criteria for Evaluation
Efficacy

Efficacy evaluations consisted of the Fabry Symptom Assessments (for the first 12-months of the study), plasma globotriaosylceramide (GL-3) levels, skin tissue GL-3 levels, and renal function testing.

Safety

Safety evaluations consisted of physical examinations, vital signs (heart rate, blood pressure, respiratory rate, and body temperature), electrocardiograms (ECGs), clinical laboratory evaluations (chemistry, hematology, electrolytes, and urinalysis), adverse event (AE) monitoring, monitoring for antibody development, complement activation, and use of concomitant medications.

Statistical Methods
Efficacy

Summary tables show the n, mean, standard deviation, median, and range for each continuous variable and its change score. The n and percentage were shown for discrete variables. Graphs may have been used to show how endpoints change over time

Safety

Physical examinations, vital signs, and laboratory evaluations were summarized. Descriptive statistics (n, mean, median, standard deviation, minimum and maximum) were presented for the investigator reads of ECG results. AEs were coded using the WHO ART dictionary. All AEs were summarized by body system and preferred term. A detailed listing of patients who experienced AEs and serious adverse events (SAEs) was presented. Frequency and percentage of seroconverted (developed Immunoglobulin G [IgG] antibody) patients and time to seroconversion in days from the first infusion were presented. In addition, antibody titers for the IgG positive patients who seroconverted were provided. Complement activation test results were displayed in a listing. Concomitant medications were summarized.

Summary – Conclusions
Efficacy

The median duration of time patients were off-treatment, between the Phase 1/2 study (last infusion) and the extension study (first infusion), was 986 days (2.7 years), with a range 685 to 1414 days (1.9 to 3.9 years).

Due to the small sample size in this extension study and the heterogeneity of the patient population in terms of kidney function at Study Entry, an evaluation of the effectiveness of Fabrazyme® in maintaining or improving renal function was limited. While 2 patients experienced a > 50% increase in their serum creatinine from Study Entry, neither patient received a dose increase to 3.0 mg/kg because their serum creatinine elevations were not sustained, or serum creatinine elevations did not occur until the Final Visit. Notably, the serum creatinine levels for these 2 patients were 2.0 and 2.9 mg/dL, respectively, at Entry into the Phase 1/2 Extension Study. There was a significant time interval between the original Phase 1/2 Study and the Extension Study when these patients were off therapy. Given the progressive nature of Fabry disease, it is likely that irreversible renal damage occurred during this time interval.

Fabrazyme® was effective in clearing GL-3 from the skin and plasma of all patients with available data. After 12 months of treatment, GL-3 was cleared from the capillary endothelial cells of the skin, and with the exception of 1 patient, all patients with available data also experienced clearing of GL-3 from the deep vessel endothelial cells in all patients with available data. This treatment effect was maintained through the final study visit.

The median plasma GL-3 level decreased from 9.7 µg/mL at Study Entry (n=13) to 4.8 µg/mL (n=14) and 5.2 µg/mL (n=9) at 6 and 12 months respectively. The median plasma GL-3 level remained well below normal (normal: < 7.03 µg/mL) through Month 30, as well as the Final Visit. All patients had a sustained reduction in plasma GL-3 following infusion of Fabrazyme® including 2 patients who had normal plasma GL-3 levels at study Entry.

Safety Results

Two patients voluntarily withdrew from the study, however, 1 of the 2 patients continued to be treated with Fabrazyme® as part of a Compassionate Use Program. A total of 12 patients (86%) completed the study.

Ten of 14 patients received infusions of Fabrazyme® through Visit 43 (approximately 21 months of treatment in the extension study). Doses of Fabrazyme® ranged from approximately 0.9 mg/kg to 1.1 mg/kg. Patients successfully tolerated decreasing infusion times throughout the duration of treatment. The median infusion time decreased significantly from approximately 4.5 hours at Study Entry, to 2 hours by Visit 54 (24 months of treatment), and all but 1 patient (93%) was able to receive at least 1 full infusion in $\leq$ 2 hours.

The safety conclusions from this study are as follows:

- There were no deaths in the study and no new safety concerns were identified during this study.
- Six patients experienced a total of 50 SAEs. All but 2 SAEs were considered unrelated to Fabrazyme®. One patient experienced severe fatigue and shortness of breath, which were considered possibly related to treatment. Concurrently, the patient developed chest pain which resulted in hospitalization but was considered unlikely related to treatment. The patient was withdrawn from the study but was re-enrolled approximately 19 months later and went on to complete the study. After this patient was reenrolled into the study, the patient developed a hernia that was reported as unrelated to therapy and was subsequently hospitalized.
- The most frequently occurring AEs in the study patient population without regard to causality were: headache (20 events), nausea (18), rhinitis (17), abdominal pain (17), upper respiratory tract infection (12), vomiting (11), rigors (10), dizziness (10), fever (9), hypoesthesia (9), fatigue (8), Fabry pain (8), diarrhea (8), pharyngitis (7), myalgia (6), pain (6), anemia (6), renal function abnormal (5), gout (5), coughing (5), oedema dependent (5), dyspnea (4), insomnia (4), albuminuria (4), rash (4), oedema legs (3), infection (3), tremor (3), sepsis (3), and hypotension (3). All other events did not occur more than twice.
- The majority of all reported AEs were mild to moderate in intensity.
- Nine of 14 patients experienced IARs. The most frequently reported IARs were rigors (3 patients), headache (3), nausea (3), fatigue (2), and hypoaesthesia (2). All other IARs occurred only in one patient. The majority of IARs were mild to moderate in intensity. In addition, one patient who experienced a severe IAR was successfully managed with an interruption in treatment, medication, and adjustments in the infusion rate. The patient went on to receive subsequent infusions without incident.
- No direct toxic effects were demonstrated, as evidenced by laboratory findings and ECGs.
- Three of the 7 patients who had seroconverted during the original Phase 1/2 Study (Protocol No. FB9702-01) remained seropositive after being off therapy for over 2 years. Most patients seroconverted soon after their first infusion in the Phase 1/2 Extension Study. Fifty percent of patients who seroconverted showed a downward trend in titer levels over the duration of treatment.
- Infusion times decreased over time during the study. The median infusion time was 275 minutes (4 hours 35 minutes, n=14 patients) at Visit 1, and 120 minutes (2 hours, n=7) at Visit 54 (Month 24).
- Two patients were on dialysis at the start of the study and tolerated infusions of Fabrazyme®. While one patient was hospitalized on multiple occasions during the study, the SAEs were judged by the Investigator as not related to treatment. Fabrazyme® can be safely administered to patients on dialysis.
- Fabrazyme® was safely administered at home in 7 of the 14 patients.

Based on Report Prepared on: 08 April 2004
Synopsis Prepared on: 20 July 2005