

# Protocol AGAL-019-01. A Cautious Graded Rechallenge With Intravenous r-hαGAL: A Multicenter, Open-Label Safety Study Of Fabry Patients Who Have Previously Tested Serum Immunoglobulin E Positive To r-hαGAL Or Who Had Positive Skin Tests To r-hαGAL

*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 3 sites in the US and 1 site in the EU.

## STUDIED PERIOD

04 September 2002 (first patient enrolled) to  
01 October 2004 (last patient completed)

## PHASE OF DEVELOPMENT

Phase 2

## OBJECTIVES

The primary objective of this study was to evaluate the safety of re-challenging Fabry patients who had previously tested serum IgE positive to Fabrazyme® or who had positive skin tests to Fabrazyme. The positive predictive value of skin testing and of assays that detect serum IgE antibody to Fabrazyme was not known, hence the exploratory nature of this study.

## METHODOLOGY

This was a multicenter, open-label, safety study of patients with Fabry disease who had received Fabrazyme in previous clinical trials, but were excluded from continued treatment due to the detection of IgE antibodies to Fabrazyme in serum or as a result of positive skin testing. Re-administration of Fabrazyme under the current study was performed with caution under the close supervision of the Principal Investigator, infusion nurse, and qualified allergist as immediate hypersensitivity reactions could occur. Pre-treatment was not permitted for at least the first 4 infusions in order to permit early recognition of acute systemic reactions. Plasma samples for GL-3 were obtained at Screening and Weeks 26 and 52. Serum samples for tryptase and plasma samples for complement activation testing were obtained prior to and 2 hours into the first 3 infusions and in the event of any moderate or severe infusion-associated reactions (IARs).

## NUMBER OF PATIENTS (PLANNED AND ANALYZED)

A minimum of 4 patients and no more than 8 patients were planned to be enrolled in this study. A total of 6 male patients were screened for entry into the study. All 6 patients were enrolled into the study.

## DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

To be eligible for participation in the Rechallenge Study, patients provided written informed consent prior to any study-related procedures being performed and had previously received Fabrazyme but had been excluded from continued treatment due to detection of IgE antibodies to Fabrazyme in the serum or as a result of positive skin testing. In addition, female patients of childbearing potential must have had a negative pregnancy test (urine  $\beta$ -hCG) prior to dosing at each study visit and, if of childbearing potential, must have used a medically accepted method of contraception throughout the study. Patients were not eligible for participation if they had clinically significant organic disease, severe congestive heart failure or severe ischemic heart disease requiring  $\beta$ -adrenergic blocking agents, were pregnant or lactating, or were unwilling to comply with the study requirements.

## TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION

Patients were cautiously rechallenged with Fabrazyme under the following regimen:

For the first 2 graded infusions (0.5 mg/kg), patients received two weekly graded intravenous infusions at a dose of 0.5 mg/kg Fabrazyme. The initial infusion rate was no more than 0.01 mg/min (0.60 mg/hr) for the first 30 minutes (1/25 the initial standard recommended rate). If the infusion proceeded without any significant or intolerable infusion-associated symptoms (cardiac or respiratory symptoms such as shortness of breath, wheezing, bronchospasm, angioedema, hypotension, etc.), the infusion rate could be doubled every 30 minutes for the remainder of the infusion up to a maximum rate of 0.25 mg/min.

Any mild or moderate infusion-associated reactions experienced by the patient during the first 4 infusions (the first 2 infusions at 0.5 mg/kg and the next 2 infusions at approximately 1 mg/kg), was managed by 10-fold infusion rate reductions and, as necessary, antihistamines or  $\beta$ -agonists. The administration of epinephrine was recommended for severe or life-threatening reactions (significant hypotension and/or severe bronchospasm).

Following the successful completion of the first 2 graded infusions with no moderate, severe, or life-threatening infusion-associated reactions, the Principal Investigator and qualified allergist could consider a dose increase to 1 mg/kg Fabrazyme intravenously every 2 weeks for the duration of the study. An Allergy Board was consulted prior to such dose adjustments if any moderate or severe infusion-associated reactions occurred during the first 2 infusions. The occurrence of severe or life-threatening infusion-associated reactions could preclude patients from further treatment.

The infusions were administered at a rate of no more than 0.25 mg/min (15 mg/hr) for a minimum of 8 infusions. If well tolerated, the infusion rate was increased by up to 0.08 mg/min/infusion (5 mg/hr/infusion), at the discretion of the Investigator and qualified allergist. The total infusion period could not be less than 2 hours.

## **DURATION OF TREATMENT**

The study duration for a patient to be considered as having completed the study was a minimum of 6 months and a maximum of 52 weeks (27 infusions). The duration of study participation for each enrolled patient ranged from 1 infusion to approximately 27 infusions.

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

None.

## **CRITERIA FOR EVALUATION**

### **Criteria for Evaluation – Safety**

Safety was measured in terms of adverse events (AE), vital sign parameters, electrocardiogram (ECG) parameters, echocardiograms (ECHO), physical examinations, and laboratory safety parameters including antibody monitoring.

### **Criteria for Evaluation – Efficacy**

Efficacy was measured in terms of plasma GL-3 obtained at Screening, Week 26, and Week 52 or study discontinuation.

## **STATISTICAL METHODS**

Physical Exam, Vital signs, 12-lead electrocardiogram, echocardiogram, and laboratory evaluations were summarized at each time point. Additionally, the change from baseline was summarized. Adverse events were coded using an internationally recognized medical terminology dictionary; all adverse events were summarized by Body System and by Preferred Term.

## **SUMMARY / CONCLUSIONS**

### **Summary / Conclusions – Efficacy**

Among the 5 patients with Screening and post-Screening plasma GL-3 measurements for comparison, 4 patients' plasma GL-3 levels were normal ( $\leq 7.03 \mu\text{g/mL}$ ) during the study. One patient with abnormal plasma GL-3 levels had received only 4 infusions in 8 weeks, with 2 of those infusions at a dose of 0.5 mg/kg. This patient's plasma GL-3 had normalized in a previous study after a longer duration of treatment with Fabrazyme (1 mg/kg). Plasma GL-3 levels that were normal under treatment with Fabrazyme in three patients tended to return to abnormal levels among patients with extended periods of time (at least 187 days) between their last infusions in prior studies and first infusion in this Rechallenge Study.

### **Summary / Conclusions - Safety Results**

The safety data reported herein all occurred during the rechallenge study. All patients enrolled in this study experienced at least 1 AE during this study. A total of 83 AEs were experienced by the 6 patients enrolled. The most frequently occurring AEs were Urticaria (4 patients); Nausea (3 patients), Coughing and Vomiting (3 patients); and Rigors (2 patients), Diarrhoea

(2 patients), Arthralgia (2 patients), Influenza-like Symptoms, Hypertension, Dyspnoea, Sinusitis, Pruritus, and Rash (2 patients). The majority of the AEs were considered by the Investigators to be mild in intensity; no severe AEs were noted by the Investigators. Most AEs were considered by the Investigators to be related to treatment with Fabrazyme.

During this study, a total of 4 serious adverse events (SAEs) were experienced by 3 patients. These SAEs were bronchospasm, urticaria, hypotension, and a repeat positive skin test. Three of the events were considered by the Investigators to be moderate in severity, while the bronchospasm was considered to be mild. All SAEs were considered by the Investigators to be related to treatment with Fabrazyme. The SAEs were successfully managed with Fabrazyme infusion rate decreases or interruption and, when needed, additional medication. All patients recovered without sequelae.

The most frequently reported IARs during this study were Urticaria (4 patients); Vomiting (3 patients); Hypertension (2 patients); Nausea (2 patients); Pruritus (2 patients); and Rigors (2 patients). Complement activation in association with an IAR was noted for 2 patients who both had events of urticaria considered by the Investigator to be moderate in severity. All patients recovered from these IARs.

Throughout this study, there were no reports of anaphylaxis.

Four of the 6 patients were IgG seropositive at screening prior to their enrollment in the rechallenge study. Ultimately, all 6 patients were IgG seropositive at their final rechallenge study visit or at their last visit prior to withdrawal. Titer values for all patients had trended downwards or had plateaued.

Skin testing in this study was conducted at the discretion of the Investigator for 2 patients who experienced moderate IARs. One patient experienced urticaria and nausea, while the second patient experienced urticaria, nausea, and vomiting. Scarification skin testing post-IAR was negative for both patients at all dilutions of Fabrazyme. Intradermal skin testing of both patients post-IAR was positive for wheals and erythema which was also documented at Screening prior to enrollment in the rechallenge study. However, only one of these repeat positive skin test results was reported as an SAE by the Investigator, as noted above.

No direct toxic effects were demonstrated by laboratory findings, vital signs, ECGs, or ECHOs.

Fabrazyme® Fabrazyme® Fabrazyme® Fabrazyme® **Based on Report Prepared On:** 11 April 2005  
**Synopsis Prepared on:** 11 October 2006