

Protocol AGAL-007-99: A Multicenter, Open-Label Study of the Safety and Efficacy of Recombinant Human α -Galactosidase A (r-h α GAL) Replacement in Patients with Fabry Disease

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NAME OF SPONSOR/COMPANY

Genzyme LLC, 500 Kendall Street, Cambridge, Massachusetts, 02142

Investigators and Study Center(s)

Five study centers in Japan participated in this clinical trial and patients at 3 study centers were eligible to be enrolled.

Studied Period

05 August 2000 (first patient enrolled) to
07 May 2001 (last patient completed)

Phase of Development

Phase 2

Objectives

The objective of this study was to evaluate the safety and efficacy of r-h α GAL in Japanese patients diagnosed with Fabry disease.

Methodology

This was a multicenter, open-label study of patients diagnosed with Fabry disease with no prior treatment with r-h α GAL. Patients received approximately 1 mg/kg (0.9 to 1.1 mg/kg) of r-h α GAL every 2 weeks for 20 weeks (11 infusions total).

Number of Patients (Planned and Analyzed)

Thirteen patients were enrolled.

Diagnosis and Main Criteria for Inclusion

To be enrolled in the trial, the patient was to provide written informed consent prior to any study-related procedures being performed; was to be a \geq 16 year old male; was to have a current diagnosis of Fabry disease with no prior treatment with r-h α GAL; was to have a documented history of plasma α GAL activity of $<$ 1.5 nmol/hr/mL or a documented leukocyte α GAL activity of $<$ 4 nmol/hr/mg; was to have a clinical presentation consistent with Fabry disease; was to have the ability to comply with the clinical protocol which required extensive clinical evaluations and the completion of pain and quality of life questionnaires.

A patient was not eligible for the study if the patient had current evidence of kidney failure or significant renal insufficiency, as defined by serum creatinine $>$ 2.2 mg/dL (194.7 μ mol/L); had undergone kidney transplantation or was currently on dialysis; had end-stage cardiac disease, defined as not likely to stabilize including any significant evidence of wall damage (large myocardial infarction), ejection fraction $<$ 20%, or any other significant findings; had a clinically significant organic disease (with the exception of symptoms relating to Fabry disease), including clinically significant cardiovascular, hepatic, pulmonary, neurologic, or renal disease that in the opinion of the Investigator would preclude participation in the trial; had taken an investigational drug or had participated in a study employing an investigational drug within 30 days of the start of this trial; or was unwilling to comply with the requirements of the protocol.

Test Product, Dose, and Mode of Administration

Test Product: Fabrazyme® (agalsidase beta)

Dose: approximately 1 mg/kg (0.9 to 1.1 mg/kg) every 2 weeks

Mode of Administration: intravenous (IV) infusion

The infusions were to be administered at a rate of no more than 0.25 mg/min. In addition, all patients were to be pretreated with acetaminophen (not to exceed 500 mg) or ibuprofen (not to exceed 200 mg), and hydroxyzine (not to exceed 30 mg orally). Pretreatment medications were to be administered approximately 1 hour prior to infusion.

Duration of Treatment

Patients were treated for a total of up to 20 weeks (11 infusions).

Reference Therapy, Dose and Mode of Administration

None.

Criteria for Evaluation

EFFICACY: The efficacy parameters for this study were: Reduction of GL-3 accumulation from the capillary endothelium (vasculature) of the kidney, heart and skin tissues as measured by Light Microscopy (LM) assessments of GL-3 in tissue samples; improvement in McGill Pain Questionnaire (short form) scores from Baseline to Visit 11 (Week 20); improvement in GL-3 levels from Baseline to Visit 11 (Week 20) as measured by kidney tissue and urine levels both assayed by ELISA; improvement in SF-36 Health Survey scores from Baseline to Visit 11 (Week 20); improvement in Physician Assessment of Fabry symptoms from Baseline to Visit 11 (Week 20); improvement from Baseline to Visit 11 (Week 20) in plasma GL-3 levels as measured by ELISA; improvement from Baseline to Visit 11 (Week 20) in creatinine clearance test results; change from Baseline to Visit 11 (Week 20) in skin and kidney additional cell reads as measured by LM.

PHARMACOKINETICS: Pharmacokinetic parameters included area under the activity-time curve from 0 to last time point (AUC_{0-LT}) and from 0 to infinity ($AUC_{0-\infty}$); peak concentration (C_{max}); time to peak concentration (T_{max}); elimination and half-life ($t_{1/2}$). These were measured at the time of first infusion and at last infusion.

SAFETY: Safety was evaluated by adverse experiences/events (AEs), clinical laboratory parameters (including assessment of antibody development to r-hαGAL), physical exams, vital signs, ECGs, head MRIs, ophthalmic examinations and echocardiograms..

Statistical Methods

EFFICACY: A one-sample, two-tailed Wilcoxon signed-rank test was used for analyses conducted on continuous variables. A p-value of .05 or less ($\alpha=.05$) denotes statistical significance. All p-values were rounded to three decimal places and presented as "<0.001" if they were less than 0.001.

Efficacy analyses were performed on the Intent-to-Treat population. For GL-3 accumulation in the kidney as measured by light microscopy (LM), hypothesis testing for the Intent-to-Treat population was based on missing values at Baseline or Visit 11 (Week 20) assigned worst outcome (non-zero). An Exact Binomial Matched Pair Procedure was used as the analysis for GL-3 accumulation in the kidney. It analyzed the proportion of patients with a score of 0 at Baseline compared to the proportion of patients with a score of 0 at Visit 11 (Week 20) from the LM assessment of the capillary endothelium (vasculature) of the kidney. An additional analysis of the efficacy endpoints was tested by way of a one sample Wilcoxon signed-rank test. This test was used to determine if there was a significant difference from zero in the median change score from Baseline to Visit 11 (Week 20). For the Intent-To-Treat population, descriptive statistics (N, mean, standard deviation, median) were presented for changes from Baseline to Visit 11 (Week 20).

Endpoints created, analyzed, and presented similarly to the efficacy endpoints on GL-3 accumulation and analyzed for the Intent-to-Treat population included GL-3 accumulation from the skin and heart as measured by light microscopy (LM); the change in pain as measured by the Short Form McGill pain questionnaire was calculated from Baseline to Visit 11 (Week 20); the change from Baseline to Visit 11 (Week 20) for urinary GL-3 and kidney GL-3; the change in the SF-36 Health Survey scores from Baseline to Visit 11 (Week 20); the change in the Physician Assessment of Fabry Symptoms from Baseline to Visit 11 (Week 20); the change in plasma GL-3 from Baseline to Visit 11 (Week 20); and the change in creatinine clearance from Baseline to Visit 11 (Week 20).

PHARMACOKINETICS: Descriptive statistics (N, mean, median, standard deviation, and range) were used to display the pharmacokinetic parameters generated from the series of blood samples at Visit 1 and Visit 11 (Week 20).

SAFETY: All analyses on safety parameters were conducted on the Intent-To-Treat population. All adverse experiences were summarized by body system and by preferred term based on the WHOART coding dictionary. Frequencies of emergent adverse events were tabulated.

For laboratory tests, descriptive statistics (N, mean, median, standard deviation, range) were presented for continuous laboratory values for each time the measurement was collected and for change scores from Baseline to each consecutive visit. Frequencies and percentages were presented for discrete laboratory values. For echocardiograms and electrocardiograms, descriptive statistics (N, mean, median, standard deviation, range) were presented.

Summary – Conclusions

Efficacy Results

There was a statistically significant difference ($p < 0.001$, Exact Binomial Matched Pairs Procedure) in the proportion of zero-scores at Baseline and at Visit 11 (Week 20). Of patients with kidney capillary endothelial cell GL-3 accumulation (non-zero score) at Baseline, 12/13 (92%) patients achieved complete clearance (zero score) at Visit 11 (Week 20). One patient (8%) achieved clinically significant GL-3 clearance to a non-zero score with a reduction in accumulation from moderate (score = 2) to mild (score = 1). The difference observed from zero in the mean change score from Baseline to Visit 11 (Week 20) was statistically significant ($p < 0.001$, Wilcoxon Signed Rank Test). Thirteen patients with a mean Baseline GL-3 accumulation score of 1.2 (median = 1.0, SD = 0.44) had a mean Visit 11 (Week 20) GL-3 accumulation score of 0.1 (median = 0.0, SD = 0.28). Therefore, from Baseline to Visit 11 (Week 20) the mean change score decreased by approximately 1.2 (median decrease = 1.0, SD = 0.38).

For kidney tissue GL-3, the difference observed in the mean change score from Baseline to Visit 11 (Week 20) was statistically significant ($p = 0.003$, Wilcoxon Signed Rank Test). Thirteen patients with mean kidney Baseline GL-3 accumulation of 2972.3 ng/mg (median = 3148.8, SD = 1528.9) had mean Visit 11 (Week 20) GL-3 accumulation of 1667.5 ng/mg (median = 1182.4, SD = 1760.1). Therefore, from Baseline to Visit 11 (Week 20) the mean change in GL-3 accumulation decreased by approximately 46.2% (median decrease = 51.9, SD = 38.6). For urine GL-3, the difference observed in the mean change score from Baseline to Visit 11 (Week 20) was not statistically significant ($p = 0.244$, Wilcoxon Signed Rank Test).

For the capillary endothelial cells of the skin, there was a statistically significant difference ($p < 0.001$, Exact Binomial Matched Pairs Procedure) in the proportion of zero-scores at Baseline and at Visit 11 (Week 20). Of patients with skin capillary endothelial cell GL-3 accumulation (non-zero score) at Baseline, 12/13 (92%) patients achieved complete clearance (zero score) at Visit 11 (Week 20). The majority of patients who achieved complete clearance had severe (score = 3) or moderate (score = 2) GL-3 accumulation at Baseline. One patient achieved a reduction in GL-3 accumulation from a Baseline score of moderate (score = 2) accumulation to mild (score = 1) accumulation.

For the capillary endothelial cells of the heart, the biopsy was only performed on those patients with cardiac abnormalities demonstrated at Baseline assessments. One patient met this criteria. The patient had mild (score = 1) GL-3 accumulation in cardiac capillary endothelial cells at Baseline and achieved complete clearance at Visit 11 (Week 20).

Among the 13 patients in the Intent-to-Treat population, mean levels of plasma GL-3 showed clearance between Baseline and Visit 11, decreasing by a mean of 89.4%. The median improvement from Baseline to Visit 11 (Week 20) in plasma GL-3 levels was statistically significant ($p < 0.001$, Wilcoxon signed rank test). The median decrease from Baseline to Visit 11 (Week 20) in creatinine clearance measures was not statistically significant ($p = 0.216$, Wilcoxon signed rank test).

Improvement in other efficacy measurements was also observed for kidney tissue GL-3, Short Form McGill Pain Questionnaire, SF-36 Health Survey, and plasma GL-3 levels.

Short Form McGill Pain Questionnaire results demonstrated that mean pain scores were at the low end at Baseline and showed slight improvement at Visit 11 (Week 20) in all parameters. The median change score for Present Pain Intensity (PPI) approached statistical significance ($p = 0.063$, Wilcoxon signed rank test). Mean improvement in all categories was observed with the SF-36 Health Survey.

PHARMACOKINETICS

At Baseline (Infusion 1), total clearance (CL) averaged 3.0 ± 0.92 mL/min/kg, volume of distribution (V_z) 0.42 ± 0.15 L/kg and volume of distribution, steady-state (V_{ss}) 0.19 ± 0.06 L/kg. The mean elimination half-life ($t_{1/2}$) was 96.7 ± 24.7 min and mean residence time averaged 61.3 ± 5.10 min.

The mean AUC_∞ of r-hαGAL appeared to increase, the mean CL decreased, and $t_{1/2}$ increased after intravenous infusion of approximately 1 mg/kg (0.9 to 1.1 mg/kg) once every 2 weeks for 20 weeks to patients with Fabry disease. Neither V_z nor V_{ss} appeared to be affected by the duration of treatment.

Safety Results

No deaths were reported in the trial. All patients experienced at least one adverse event but no patient was discontinued from the study as a result. Two patients experienced serious adverse events (SAEs). One patient had drug-related SAEs of fever, limb pain, malaise and rhinitis during an infusion. The second patient had drug-unrelated SAEs of gastroenteritis, pain and a positive C-reactive protein. Both patients recovered.

The most commonly reported adverse events without regard to causality were albuminuria (11 patients, 85%), bradycardia (9 patients, 69%), fever (8 patients, 62%), rhinitis (8 patients, 62%), pain (7 patients, 54%), post-operative pain (7 patients, 54%), abdominal pain (5 patients, 38%), diarrhea (5 patients, 38%), hypertension (5 patients, 38%), hypoproteinemia (5 patients, 38%), pharyngitis (5 patients, 38%) and rigors (5 patients, 38%). The most commonly-reported infusion-related symptoms were chills (rigors) and fever. Fever and rigors were managed with administration of antihistamines (e.g., chlorpheniramine maleate) and antipyretics (e.g., ibuprofen) accompanied by a reduction in the infusion rate by 1/4 to 1/2 of the original rate, until the episode abated.

Albuminuria was reported for 11 patients. Of these 11 patients, 7 patients had a current medical history of proteinuria.

Bradycardia (< 60 bpm) was reported for nine patients. Of these patients, three had bradycardia recorded as part of their medical histories. All episodes were considered mild in intensity. A likely explanation for the collection of bradycardia as an adverse event was the use of pulse rates assessed manually as bradycardic rather than an ECG reading.

Results of laboratory studies that included clinical chemistry, hematology, and urinalysis did not suggest that treatment with r-hαGAL had any toxic effects. This was further supported by electrocardiogram, echocardiogram, and MRI findings.

The development of IgG antibody in 11/13 (85%) patients was anticipated.

No patient that received r-hαGAL demonstrated IgE seroconversion in this trial. Ten of the 13 patients who received r-hαGAL experienced related adverse events on the day of infusion. Seven patients also underwent IgE and complement testing. None of the patients was IgE positive.

The observed spectrum of symptoms described above are not the result of IgE mediated-hypersensitivity-type reactions either by major symptoms or immunologic testing. The influence of IgG-mediated immune responses and complement activation during or immediately after the reaction are considered to be the likely cause of a number of the observed symptoms including fevers and chills.

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