Protocol AGAL-1-002-98. A Multicenter, Placebo-Controlled, Double-Blind, Randomized Study of the Safety And Efficacy of Recombinant Human α - Galactosidase (r-h α GAL) Replacement in Patients with Fabry Disease.

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Investigators and Study Center(s)

This was a multicenter study conducted at 8 sites in the United States (US) and European Union (EU).

Studied Period

First Patient Enrolled 14 March 1999
Last Patient Completed 04 February 2000

Phase of Development

Phase 3

Objectives

The primary objective of the study was to evaluate the safety and efficacy of recombinant human α-galactosidase (r-hα GAL) compared to placebo for the treatment of patients with Fabry disease. Primary efficacy was evaluated by measuring the change from Baseline to Visit 11 (Week 20) in globotriaosylceramide (GL-3) accumulation in the capillary endothelium (vasculature) of the kidney. The incidence of adverse events (AEs) and changes in vital signs, electrocardiograms (ECGs), echocardiograms (ECHOs), and clinical laboratory parameters were used to evaluate safety.

Secondary objectives of the study included assessment of the effectiveness of r-hα GAL compared to placebo based on changes from Baseline to Visit 11 (Week 20) in the McGill Pain Questionnaire (short form) and the in the composite score of GL-3 inclusions in the capillary endothelium (vasculature) of the kidney, skin, and heart. The change from Baseline to Visit 11 (Week 20) in composite score of GL-3 levels, as measured by Enzyme Linked Immunosorbant Assay (ELISA) in kidney tissue and urine, was also a secondary objective.

Methodology

This was a multinational, multicenter, placebo-controlled, double-blind, randomized study of patients with a current diagnosis of Fabry disease who had no prior treatment with r-hα GAL. Patients received approximately 1.0 mg/kg (0.9 to 1.1 mg/kg) of r-hα GAL or placebo every 2 weeks for 20 weeks (11 Patient Visits) for a total of 11 infusions of study medication. Twenty-eight additional days were allowed for some of the final safety and efficacy procedures associated with Visit 11 (Week 20). Therefore, the total duration that a patient was involved in the study after the first infusion was up to 168 days.

Number of Patients (Planned and Analyzed)

Approximately 60 patients were planned for enrollment and 58 patients were treated (29 patients with r-hα GAL and 29 with placebo) and these 58 patients were analyzed.

Diagnosis and Main Criteria for Inclusion

Patients who met all of the following inclusion criteria were eligible to participate in the study:

Patients were $\geq$ 16 years old and had a current diagnosis of Fabry disease with no prior treatment with r-hα GAL. Patients had documented plasma α-galactosidase (αGAL) activity of < 1.5 nmol/hr/mL or a documented leukocyte αGAL activity of <

4.0 nmol/hr/mg. Patients had a clinical presentation consistent with Fabry disease. Patients had to be able to comply with the clinical protocol, which required extensive clinical evaluations and completion of questionnaires.

Female patients of childbearing potential had a negative pregnancy test (urine β -hCG) prior to dosing at each study visit. In addition, all female patients of childbearing potential were required to use a medically accepted method of contraception throughout the study.

Test Product, Dose, and Mode of Administration

r-hαGAL was supplied in 20-mL vials (35 mg/vial) as a lyophilized preparation. Each vial of r-hαGAL was reconstituted with 7.2 mL of sterile water for injection. The appropriate amount of reconstituted r-hαGAL was further diluted with a 0.9% sodium chloride solution to a final total volume of 500 mL.

Patients received approximately 1.0 mg/kg (0.9 to 1.1 mg/kg) of r-hαGAL intravenously every 2 weeks, for a total of 11 infusions. The number of vials used was based on each patient's body weight (kg), so as to provide the total dose close to 1.0 mg/kg. Patients were to receive their intravenous infusion at a rate of no more than 0.25 mg/min over approximately 6 hours. Adjustments that allowed for longer infusion rates were made in those patients who experienced suspected hypersensitivity reactions associated with the study medication.

Duration of Treatment

20 Weeks (11 infusions of study medication)

Reference Therapy, Dose and Mode of Administration

Placebo: The placebo was a lyophilized preparation of mannitol with a phosphate buffer in vials identical to those used for r-hαGAL. Placebo vials were reconstituted with 7.2 mL of sterile water for injection and further diluted with a 0.9% sodium chloride solution to a final total volume of 500 mL.

Patients received a placebo formulation intravenously every 2 weeks, for a total of 11 infusions. The number of vials used was based on each patient's body weight (kg). Patients received their intravenous infusion over approximately 6 hours. In those patients who experienced suspected hypersensitive reactions associated with the study medication, adjustments were made that allowed for longer infusion rates.

Criteria for Evaluation
Efficacy

The primary efficacy parameter for this study was the morphological assessment of GL-3 inclusions of the capillary endothelium (vasculature) of the kidney after dosing with randomized study medication for 20 weeks. Three blinded, independent pathologists graded the degree of accumulation of GL-3 inclusions by light microscopy (LM) of kidney tissue samples on a none-mild-moderate-severe scale (0-1-2-3). At least 2 of the 3 pathologists had to independently agree on the same score, with the third pathologist's score differing by no more than 1. If there was a difference in any score greater than 1 or if each pathologist scored the sample differently, a blinded adjudication process involving the 3 pathologists was implemented. After the adjudication process, slides that were scored as either 0 or 1, were reread by each pathologist in order to evaluate the number of vessels per slide. These numbers were recorded by each pathologist and sent to biometrics where an overall score was assigned.

The criteria for an evaluation of "none" was met when more than 50% of the capillary endothelial vessels were completely clear (score = 0) of GL-3 and a maximum of 5% of vessels were scored as mild, moderate, or severe (i.e., 1, 2, or 3). The remaining vessels could be scored either as zero or trace. The primary endpoint analysis was based on the number of patients who had a consensus ($\geq$ 2 of 3 pathologists) score of zero at 20 weeks.

Secondary efficacy measures included the change from Baseline to Visit 11 (Week 20) in the composite score of GL-3 inclusions in the capillary endothelium (vasculature) of the kidney, skin, and heart, as assessed by LM, and in the composite score of kidney tissue and urinary GL-3 levels, as measured by ELISA. LM assessments of heart and skin tissue samples were performed by separate groups of 3 blinded independent pathologists who were specialists in the tissue being evaluated. The reduction in pain, as assessed by the Short Form McGill Pain Questionnaire, was also evaluated as a secondary endpoint.

Pharmacokinetics

Patients who were enrolled at the study centers located in Europe participated in the evaluation of the pharmacokinetic (PK) profile of r-hαGAL. Enzyme uptake in leukocytes was also evaluated in these patients.

Safety

Safety was measured in terms of the incidence of AEs and changes in vital signs, ECGs, ECHOs, physical examinations, and clinical laboratory safety parameters.

Statistical Methods
Efficacy

Hypothesis testing was performed to determine if there were any statistically significant differences in demographics, history of Fabry disease, or medical/surgical history between the 2 treatment groups. Data is provided for the "Intent-To-Treat" and the "As Treated" populations.

Efficacy analyses for the primary endpoint were performed on the "Intent-To-Treat", the "As Treated," and the "Per Protocol" populations. A chi-square test was used as the primary analysis of the primary endpoint. The test was used to compare the proportion, for each treatment group, derived from the number of patients with a LM consensus score of the capillary endothelium of the kidney equal to 0 at Visit 11 (Week 20), divided by the total number of patients with a score greater than 0 at Visit 11 (Week 20). An additional analysis of the primary endpoint was performed using analysis of variance (ANOVA) to test for a significant difference in 20-week mean change scores between treatments and study centers. In addition, subgroup analyses based on age, ethnicity, and study site were evaluated to determine the effect of r-hαGAL on kidney LM score at Visit 11 (Week 20).

The secondary endpoints were analyzed and presented similarly to the primary efficacy endpoint. These endpoints were analyzed for the "Intent-To-Treat" and the "As Treated" populations.

A PK analysis that directly compared the r-hαGAL plasma concentration-time data across 3 visits was performed. A similar analysis was performed across the same time points for the leukocyte uptake data.

Safety

Safety analyses were performed on all patients who were assigned to a treatment group. Physical examination results and reported AEs were tabulated according to treatment group. Vital signs, 12-lead ECG, ECHOs, and laboratory evaluations observed at specified time points were summarized for each treatment arm. Additionally, the change from Baseline to each time period was summarized.

The incidence of treatment emergent AEs incidence was tabulated according to treatment group, treatment group and severity, and treatment group and relationship to treatment. Statistical comparisons of specific individual AEs were made, when indicated.

All analysis of safety parameters was conducted on the "As Treated" populations.

Summary – Conclusions
Efficacy

Analysis of efficacy was performed on 3 study populations, the "Intent-To-Treat", "As Treated", and the "Per-Protocol" populations. The primary efficacy parameter for this study was the between-treatment group comparison of the clearance of GL-3 inclusions in the capillary endothelium (vasculature) of the kidney after 20 weeks of treatment with study medication. As previously described, each patient had a consensus score ranging from 0 to 3, expressed as an integer. A score of 0 represented a successful treatment outcome. In the "Intent-To-Treat" population, there was a statistically significant difference ($p<0.001$) between treatment groups, with the greater proportion of patients having a kidney LM consensus score of 0 in the r-hαGAL group. In the "Intent-To-Treat" population, 18 of 29 r-hαGAL-treated patients (62%) had a score of 0 versus 2 of 29 placebo treated patients (7%). The 2 placebo-treated patients having a score of 0 had been randomized to placebo but actually received r-hαGAL. This is reflected in the "As Treated" population, 20 of 29 r-hαGAL-treated patients (69%) achieved the primary endpoint was versus 0 of 29 placebo-treated patients. There was not a single case in the "As Treated" placebo population where the vascular endothelium of the kidney was cleared of GL-3. The level of efficacy, based on the odds ratio, was 95 % compared to placebo and the results were highly consistent among the 3 blinded pathologists who performed the LM assessment as well as across the 8 investigative sites. An additional sensitivity analysis was performed which conclusively demonstrated the robust nature of the result obtained for the primary endpoint. No significant study site effect was noted and immunoglobulin G (IgG) antibody formation had no effect on efficacy results.

In the “Intent-To-Treat” population, r-hαGAL significantly reduced GL-3 inclusions in the vascular endothelium of kidney, heart, and skin tissue and the composite score of all 3 tissues. A statistically significance difference ($p<0.001$) between treatment groups favoring r-hαGAL-treated patients was attained for all 4 variables. Achieving this critical secondary endpoint demonstrates that r-hαGAL effectively removed GL-3 from all 3 organs studied, which are affected by Fabry disease. The same result was obtained for the “As Treated” patient population.

In the Intent-To-Treat population results of the ELISA evaluation of GL-3 levels in urine demonstrated a difference between the treatment groups that approached statistical significance ($p = 0.053$) when data from study sites that performed inappropriate sample collections were removed. A median of a 41% increase in urinary GL-3 was observed in the placebo treatment group compared to an 18% decrease in the r-hαGAL treatment group. No statistically significant difference was seen, as measured by ELISA, between the treatment groups with regard to the percent change in kidney tissue GL-3 levels.

Baseline values for McGill Short Form Pain Questionnaire tended to be comparable between treatment groups but relatively low (i.e., low to moderate pain). There was a statistically significant difference in the change from Baseline between the treatment groups, however, there was no difference between the 2 treatment groups at Visit 11 (Week 20).

Pharmacokinetic Results

The mean PK parameters of r-hαGAL at Baseline (Infusion 1) show that total clearance (CL) averaged 1.75 ± 0.77 mL/min/kg, volume of distribution (V_z) averaged 0.23 ± 0.14 L/kg and volume of distribution,at steady-state (V_{ss}) averaged 0.12 ± 0.08 L/kg. The mean elimination half-life (t½) was 88.6 ± 20.2 min and mean residence time was 66.4 ± 14.1 min. The PK parameters, area under the curve (AUC_∞) and CL for r-hαGAL following repeat administration were different at Infusion 7 and appeared to be associated with the formation of IgG antibodies to r-hαGAL. The observed changes in PK did not appear to affect the efficacy outcomes. Cellular uptake of the enzyme, as measured in leukocytes was not reduced, but rather appeared to increase with repeat infusions.

Safety Results

There were no deaths, and no patients discontinued from the study because of AEs. The occurrence of SAEs was similar between the 2 treatment groups (5 patients experienced SAEs in each treatment group), and no SAE was considered related to study treatment.

All patients in each treatment group reported at least 1 AE during participation in the study. A statistically significant difference was observed for 3 AEs that were reported more frequently in patients treated with r-hαGAL compared to patients treated with placebo. These AEs included rigors (52% versus 14%; $p=0.004$), fever (48% versus 17%; $p=0.024$), and skeletal pain (21% versus 0%; $p=0.023$).

Postoperative pain, which captures pain related to a biopsy procedure, was the most frequently reported adverse event in both the r-hαGAL (76%) and the placebo (55%) treatment groups. Other frequently occurring adverse events in the r-hαGAL treatment group included headache (45%), rhinitis (38%), haematuria (34%), abdominal pain (28%), anxiety (28%), nausea (28%), pharyngitis (28%), anaemia (24%), and coughing (24%). Adverse events that occurred frequently in the placebo treatment group included headache (38%), anaemia (34%), abdominal pain (31%), renal function abnormal (31%), rhinitis (24%), haematuria (24%), and bradycardia (24%). The incidence of these frequently occurring adverse events in both treatment groups did not differ significantly.

In order to assess infusion associated reactions (IARs) to the drug, all related AEs occurring on the day of infusion were evaluated. Sixteen of the 29 patients (55%) treated with r-hαGAL experienced related AEs associated with an infusion.

Fourteen patients experienced febrile reactions (fever, chills), 3 patients experienced one or more symptoms of hypersensitivity (dyspnoea, throat tightness, chest tightness, flushing, pruritus, urticaria, rhinitis), 3 patients experienced 1 or more cardiovascular symptoms (hypertension, tachycardia, palpitations), 3 patients experienced 1 or more gastrointestinal symptoms (abdominal pain, nausea, vomiting) 5 patients experienced infusion related pain (Fabry pain, myalgia), and 3 patients experienced headache. (Patients experiencing events from more than 1 symptom complex were counted in both groups). All of these AEs have been successfully managed with pre treatment medications and a reduction of the infusion rate.

The majority of IARs were associated with IgG antibody formation to r-hαGAL and/or complement activation during or immediately after the reaction and were not IgE mediated.

Overall, treatment of Fabry disease patients with r-hαGAL was associated with IARs in approximately 55% of patients. These reactions were IgG mediated and readily controllable by adjustments in the infusion rate and the administration of preventive medications. Currently, no other safety concerns related to treatment of Fabry patients with r-hαGAL have been identified.

There were no clinically significant changes in physical examinations, laboratory parameters, ECGs, or ECHOs.

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