DEPARTMENT OF HEALTH & HUMAN SERVICES PUBLIC HEALTH SERVICE
Food and Drug Administration

# Memorandum

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Division of Clinical Trial Design and Analysis
HFM-576

**DATE:** April 22, 2003

**FROM:** James Kaiser, M.D.

**SUBJECT:** Medical Officer's Review
Responses to CBER's requests for information and additional clinical data submitted to BLA STN 103979\0
Applicant: Genzyme
Product: recombinant human α-galactosidase A
Proposed indication: "long-term replacement" in patients with Fabry's disease

**TO:** BLA BL103979 / 0 file

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# BACKGROUND

On June 23, 2000, CBER received Genzyme's BLA for recombinant human α-galactosidase (r-hαGal) for the "long-term replacement" of enzyme in patients with Fabry's disease, with a request for accelerated approval. The BLA included a presentation of three trials, FB9702-01, AGAL-1-002-98, and AGAL-005-99. FB9702-01 was an open-label trial studying several different dosing regimens. AGAL-1-002-98, a controlled trial meant to be the basis for market approval, used an agreed-upon pathological surrogate endpoint, reduction to normal or near normal of substrate deposits in renal interstitial capillaries. AGAL-005-99 is an ongoing open-label extension to AGAL-1-002-98; the initial BLA submission contained 6-month results, including renal interstitial capillary endothelial cell substrate levels.

After review of the initial BLA submission, issues remained that were addressed by submission of additional data. This document reviews these data.

Genzyme initiated a clinical trial (AGAL-008-00) to ascertain whether Genzyme's r-hαGal would confer a clinical benefit. The design of AGAL-008-00 has been the subject of ongoing interactions between CBER and Genzyme. As currently conducted, AGAL-008-00 is a randomized, double-blind, placebo-controlled trial, design features that render a trial potentially able to discern treatment effects reliably. It enrolls subjects who have some decrement in renal function, and its endpoints are measures of renal, cardiac, and neurological deterioration. The trial was projected at inception to last until about January 2004, so that subjects could be in the trial for up to 3 years, considerably longer than the duration of AGAL-1-002-98. This greater duration and the fact that the subjects have evidence of renal dysfunction, unlike the subjects in AGAL-1-002-98, suggests that the trial may be more capable of determining a potential treatment benefit in renal function.

Proposals to redesign AGAL-008-00 and Genzyme's submissions of data to support a redesigning of the trial are reviewed by Dr. Marc Walton in another document.

# DATA SUBMITTED AND SCOPE OF REVIEW

Additional data received from Genzyme include longer-term bioactivity and safety data from AGAL-005-99, a report of an additional clinical trial conducted in Japan (AGAL-007-99), and additional safety data collected from various sources, including clinical trials conducted by Genzyme and post-marketing data.

This document will review clinical issues in the following order:

- The breadth of diversity of cell types that show a treatment effect, and the extent and duration of this effect
- Data on renal function, plasma GL-3, and other outcomes over time
- The nature and severity of adverse events, especially including deaths, serious adverse events, and infusion reactions
- Analyses of antibody levels over time and their effect on histological effects and safety outcomes

This document will first review the results of the non-IND trial, AGAL-007-99, as these results are referred to in the rest of the document.

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## AGAL-007-99

### Design, conduct, and subject characteristics of Japanese trial AGAL-007-99

AGAL-007-99 was an open-label 13-subject trial of r-hαGal at the same dose and frequency as studied in AGAL-1-002-98 and AGAL-005-99. Subject qualifications were the same as in AGAL-1-002-98. While the trial was open-label, evaluation of the primary endpoint, renal

histology, was done on fully blinded slides by the same pathologists and using the same quantitative scoring method as used for the primary endpoint analysis of AGAL-1-002-98 and AGAL-005-99. Nonquantitative methods were used for skin and heart, consistent with AGAL-1-002-98 (heart biopsies were to be performed only on those patients with cardiac abnormalities demonstrated at baseline). Many of the same clinical outcome measures were also assessed. A comparison of the methods used to analyze histology is contained in Table 15.

The first subject was enrolled on August 5, 2000 and the last patient completed the trial on May 7, 2001. Fourteen subjects were screened; 13 met eligibility criteria and enrolled; all completed all 11 infusions.

There were no protocol deviations that would be expected to have a major impact on determinations of safety and efficacy. One subject's physician was not part of a site when a baseline biopsy was performed. One subject's infusion rate was too high at some infusions; another subject's infusion rate was too high at visit 1. One subject had serum chemistries and hematologies taken at an incorrect time.

Demographics

The age and weight of the subjects in AGAL-007-99 was a little lower than that of the treated group in AGAL-1-002-98 (means of 26 vs. 32 years and 59 vs. 67 kg, respectively). In contrast to AGAL-1-002-98, in which there were 2 females, there were no females in AGAL-007-99.

Characteristics

Blood type (B-containing or noncontaining), years since initial diagnosis and onset of symptoms, endogenous plasma and leukocyte α-Gal activity were similar to those in the treated group of AGAL-1-002-98.

## Bioactivity

**Renal interstitial capillary histology**

Potential scores were from 0-3: none, mild, moderate, and severe. Baseline scores tended to be less severe than those in AGAL-1-002-98. At baseline, 10 subjects had a score of 1 and 3 subjects had a score of 2. At the end of the trial, all subjects except one had a score of 0. This was a subject whose score dropped from 2 to 1. The p-value of the result, using the Exact Binomial Matched Pairs procedure, was less than 0.001.

Sensitivity analyses performed by Genzyme

*Consistency of scoring among pathologists*

All the pathologists gave a non-0 score to all baseline slides. At the final evaluation, Dr. Colvin scored all slides 0; Dr. Dikman scored 12/13 as 0, and Dr. Rennke scored 11/13 as 0. As in AGAL-1-002-98, Dr. Rennke evaluated considerably more capillaries per slide (on average about 100 more per slide).

*Effect of proportion of capillaries discounted from evaluation*

The number of subjects with a 0 score at the end of the trial was 12 when the capillary scoring criterion was 1% and 13 when the criterion was 10%. All baseline scores were non-zero irrespective of the criterion.

*Age*

There was only 1 nonzero score; this analysis is not fruitful.

Seroconversion and effect on histology

Eleven subjects became seropositive during the trial. The one nonzero score at the end of the trial was in a seropositive subject.

**Histology of other cell types**

Kidney

Due to some biopsy samples not containing the cell type of interest, sample numbers may not be 13 in all cases for all time points.

- Glomerular endothelial cells. Paired results are presented for 11 subjects. Seven subjects started with severe scores, and 4 with moderate scores; all ended with 0 scores.
- Kidney non-capillary interstitial endothelial cells. Paired results are presented for 12 subjects. Ten subjects started with severe scores, and 2 with moderate scores; all ended with 0 scores.
- Kidney non-capillary interstitial smooth muscle cells. Paired results are presented for 12 subjects. Eight subjects changed from severe to moderate, and 4 changed from severe to mild.
- Kidney podocytes. Paired results are presented for 11 subjects. Nine subjects stayed severe, and 2 changed from severe to moderate.
- Kidney distal convoluted tubules and collecting ducts. Paired results are presented for all subjects. Three started with a moderate score; 1 stayed the same, 1 worsened by 1 point, and 1 improved by one point. Ten subjects started with severe scores: 1 stayed the same, and the rest improved (3 to a moderate score, 5 to a mild score, and 1 to a "none" score).
- Mesangial cell matrix of the kidney. There were 11 samples at baseline and 12 at the end of the trial. Mean and median values were unchanged (0.6 for all).
- Mesangial cells of the kidney. Paired results are presented for 11 subjects. All subjects started with a score of numerous lipid: 2 subjects changed to minimal, and 9 changed no lipid.
- Interstitial cells of the kidney. Paired results are presented for all subjects. All subjects started with a score of numerous lipid: 1 subject was unchanged, 2 subjects changed from numerous lipid to minimal, and 10 changed from numerous lipid to no lipid.

Skin

- Capillary endothelium. Results are presented for all subjects, and all showed reductions. One subject started with a mild score, 7 with a moderate score, and 5 with a severe score. All ended with a score of "none" except for a subject who started in the moderate category.
- Deep vessel endothelial cells. Results are presented for 12 subjects, all with reductions. One subject started with a mild score, 7 with a moderate score, and 4 with a severe score. All ended with a score of "none" except for 2 subjects who started in the moderate category, both of whom ended the trial with a mild score.
- Smooth muscle cells. No paired samples were available.
- Skin perineurium. Paired results are presented for 12 subjects. The majority of subjects experienced no change. Ten subjects started with a moderate score, of whom 4 had a score of mild at the end of the trial. Two started with a mild score, which didn't change with treatment.

Heart

Only 1 subject had heart biopsies at baseline and end of trial. Cardiac capillary endothelial cell accumulation changed from mild to none.

**Other results**

- McGill short form pain questionnaire. Minor differences were noted, but the overall results are difficult to interpret due to the open-label nature of the trial.
- GL-3 levels in kidney tissue and urine as measured by ELISA (Table 1). The range of values for both measurements was very large. Although the mean value for urinary GL-3 did not decrease at the end of the trial, median values for both measurements decreased, as they did in AGAL-1-002-98.

**Table 1. AGAL-007-99: Kidney tissue and urinary GL-3**

| | Statistic | Baseline | Visit 11 | % change from baseline to end | p-value* |
|---|---|---|---|---|---|
| Kidney (ng/mg) | *n* | *13* | *13* | *13* | 0.003 |
| | mean | 2972 | 1668 | -46.2 | |
| | median | 3149 | 1182 | -51.9 | |
| | Std. Dev. | 1529 | 1760 | 38.6 | |
| | min, max | 341, 5098 | 171, 6122 | -90, 52 | |
| Urine (nmol/filter) | *n* | *13* | *13* | *13* | 0.244 |
| | mean | 4085 | 2687 | 65.1 | |
| | median | 3680 | 1278 | -55.4 | |
| | Std. Dev. | 2077 | 2515 | 355 | |
| | min, max | 62, 7340 | 313, 8080 | -94, 1227 | |

*Wilcoxon signed rank test on change from baseline to end of trial

- SF-36. Very small changes were seen in mean values, the clinical significance of which is not described in the submission. The overall results are difficult to interpret due to the open-label nature of the trial.
- Symptoms and signs.
  - Angiokeratoma: Subjects were rated as to whether they had angiokeratoma. Thirteen paired samples are presented, of which the majority (10) were "yes" at baseline. None of these subjects changed to "no" at the end of the trial. Of those who were "no" at baseline (3), 1 was a "yes" at the end of the trial.
  - Abnormal sweating: Thirteen paired samples are presented, of which the majority (11) were "yes" at baseline. None of these changed to "no" at the end of the trial. Of those who did not have abnormal sweating, none were "yes" at the end of the trial.
  - Abdominal pain. Thirteen paired samples are presented. The majority (9) of subjects answered "no" at baseline; 8/9 remained "no." Of the 4 who answered "yes" at baseline, none answered "no" at the end of the trial.
  - Plasma GL-3 (nmol/hr/ml). Based on 13 samples at baseline, 6 weeks, and 11 weeks, the mean value fell from 3.9 ± 2.7 to 0.7 ± 0.9 to 0.2 ± 0.8, respectively.
  - Creatinine clearance (ml/min). Based on 13 samples at baseline and the end of the trial, there was an insignificant decline in mean creatinine clearance (126.6 ± 42 to115 ± 30).

*Comments on bioactivity results of trial AGAL-007-99*

*Histology results were consistent with results seen in AGAL-1-002-98. There was no clinical efficacy, and no notable effect on renal function. Plasma GL-3 fell with treatment.*

## Safety

### Deaths

There were no deaths in the trial.

### Serious adverse events

There were 2 subjects with serious adverse events: 1) fever, limb pain, malaise, and congestion of the nose in association with an infusion 112 days after the start of treatment, and 2) infectious enterogastritis, severe limb pain, and a positive reaction for C-reactive protein 69-70 days after the start of treatment.

### Adverse events

Table 2 shows adverse events stratified by severity, as occurring in 2 or more subjects.

**Table 2. AGAL-007-99: Subjects with adverse events occurring in 2 or more subjects, stratified by severity**

| | Severity of Adverse Experience | | |
|---|---|---|---|
| WHOART Preferred Term | Mild | Moderate | Severe |
| Albuminuria | 10 | 1 | 0 |
| Bradycardia | 9 | 0 | 0 |
| Rhinitis | 8 | 0 | 0 |
| Fever | 6 | 2 | 0 |
| Pain | 5 | 1 | 1 |
| Abdominal Pain | 5 | 0 | 0 |
| Diarrhea | 5 | 0 | 0 |
| Hypoproteinemia | 5 | 0 | 0 |
| Pharyngitis | 5 | 0 | 0 |
| Hypertension | 4 | 1 | 0 |
| Post-Operative Pain | 4 | 3 | 0 |
| Coughing | 4 | 0 | 0 |
| Headache | 4 | 0 | 0 |
| Malaise | 4 | 0 | 0 |
| Rigors | 3 | 2 | 0 |
| Hematuria | 3 | 1 | 0 |
| Flushing | 3 | 0 | 0 |
| Hypercalcemia | 3 | 0 | 0 |
| NPN Increased [creatinine] | 3 | 0 | 0 |
| Hypotension | 2 | 1 | 0 |
| Back pain | 2 | 1 | 0 |
| BUN Increased | 2 | 0 | 0 |
| Dermatitis Contact | 2 | 0 | 0 |
| Dyspnea | 2 | 0 | 0 |
| Hyperglycemia | 2 | 0 | 0 |
| Leukopenia | 2 | 0 | 0 |
| Skeletal Pain | 2 | 0 | 0 |
| Sweating Decreased | 2 | 0 | 0 |
| Vomiting | 2 | 0 | 0 |

Seven subjects had a current history of proteinuria, and 2 had a past medical history of hematuria. All subjects had baseline total protein values less than normal. Genzyme notes that fever and rigors were often captured as part of infusion reactions. Cardiac events were not a notable feature of this trial; mild bradycardia was an isolated event (3 of the subjects had a history of bradycardia). Alternatively, it may have been an artifact of manual pulse recording, as Genzyme hypothesizes.

*Comment*

*Moderate and severe toxicities were rare in this trial. Overall, the adverse events were consistent with those seen in the U.S-European trials.*

Events related to r-hαGal

Table 3 shows events related to r-hαGal. In it, a subject experiencing more than one adverse event within a body system or preferred term is counted once within that body system or preferred term, and if a subject experienced more than one occurrence of an adverse event, only the most severe reported occurrence is counted.

**Table 3. Summary of Related* Adverse Experiences Occurring in Greater Than 10% of Patients Stratified by Severity (Intent-to-Treat)**

| | Severity of Adverse Experience | | |
|---|---|---|---|
| | Mild | Moderate | Severe |
| WHOART Preferred Term | n = 13 | n = 13 | n = 13 |
| Rigors | 3 | 2 | 0 |
| Fever | 2 | 2 | 0 |
| Malaise | 2 | 0 | 0 |
| Dyspnea | 2 | 0 | 0 |
| Rhinitis | 2 | 0 | 0 |
| Hypertension | 1 | 1 | 0 |

* Related includes possible, probable, definite, or unknown relation (uncoded AEs are classified as unknown).

*Comment*

*These toxicities are similar to the infusion reactions seen in the U.S.-European trials.*

*The Japanese definition of "related" includes events with remote/unlikely relationship to a product. For this trial these events included abdominal pain, bradycardia, flushing, albuminuria, and pain (3 subjects each), rhinitis (1 subject added), and headache (2 subjects).*

Adverse events related to infusion on the day of infusion

Other than the serious infusion-related adverse event described briefly in the section on serious adverse events, the following occurred, each representing separate subjects:

- Fever, nasal congestion, and limb pain
- Cough
- Mild rigors and fever despite medication
- Mild chilliness
- Rigors, rhinitis, dyspnea, chest pain
- Rigors and fever
- Dyspnea

Ten of the 13 subjects experienced reactions on the day of infusion. These reactions occurred in some instances despite premedication and medication at the time of the reaction. They are consistent with the reactions that have been described in the U.S.-European trials.

**Table 4. AGAL-007-99: Number of subjects with reaction related to r-hα Gal on the day of infusion**

| Adverse Event Category | Number of Patients (10 unique patients) |
|---|---|
| Febrile Reactions | 6 |
| Cardiovascular symptoms | 5 |
| Hypersensitivity-like symptoms | 5 |
| Gastrointestinal | 2 |
| Pain | 1 |

• Febrile reactions: e.g., fever, chills
• Cardiovascular symptoms: e.g., tachycardia, palpitations, hypertension, hypotension, bradycardia
• Hypersensitivity-like symptoms: e.g., respiratory symptoms (dyspnea, wheezing, cough, rhinitis), throat tightness, flushing, chest tightness/chest discomfort, pruritus, urticaria, increased lacrimation
• Gastrointestinal symptoms: e.g., abdominal pain, nausea, vomiting
• Pain: e.g., limb pain, myalgia

As in prior trials, infusion reactions with a possible IgE relation were reported to Genzyme Pharmacovigilance for IgE and complement testing. Table 5 shows that the characteristics of the 7 subjects with suspicious infusion reactions were similar to those in prior trials, that is, serum IgG to

r-hαGal was present nearly universally and complement activation of serum was common. Tin no case was IgE found; skin testing was not performed in any subject.

**Table 5. AGAL-007-99: IgE and IgG status and complement activation among subjects with reactions reported to Genzyme Pharmacovigilance**

| Patient Number | Infusion Number | IgE Test Result +/– | IgG Test Result +/– | Complement Activation** +/– |
|---|---|---|---|---|
| 101 | 4 | - | + | + |
| | 5 | - | + | + |
| | 6 | - | + | + |
| | 7 | - | + | + |
| | 8 | - | + | + |
| | 9 | - | + | + |
| 102 | 7 | - | - * | - |
| 103 | 6 | - | + | + |
| 105 | 10 | - | + | - |
| 107 | 5 | - | + | + |
| | 6 | - | + | - |
| | 7 | - | + | + |
| 110 | 8 | - | + | - |
| | 9 | - | + | + |
| 201 | 8 | - | + | + |

*Patient 102 was IgG antibody-positive by Infusion 8.
**during or after the reaction

*Comment*

*A substantial number, about ½ of the subjects, in AGAL-007-99 had infusion reactions that merited testing for IgE. As in the U.S. and European trials, these data do not provide a means to predict who will get infusion reactions.*

Seroconversion

Eleven of 13 subjects seroconverted, at a mean time of 63 days (range, 26, 126). All subjects had baseline plasma α-galactosidase activity below the detection limit (< 0.78 nmol/hr/ml), and all but one had leukocyte α-galactosidase activity below the detection limit (< 0.78 nmol/hr/mg).

*Comments*

*The safety results and the report of seroconversion are consistent with those reported in AGAL-1-002-98 and AGAL-005-99.*

### Overall comments regarding trial AGAL-007-99

AGAL-007-99 provides support for the histological, clinical, and laboratory conclusions of AGAL-1-002-98 and its extension, AGAL-005-99.

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## EXTENT AND DURATION OF REDUCTIONS IN ENZYME SUBSTRATE GL-3

FB9702-01 had shown sporadic results of the effect of short-term (up to about 8 weeks) treatment with r-hαGal on various cell types, but the primary evidence of activity came from the controlled trial AGAL-1-002-98, in which substrate reductions from renal interstitial capillary endothelial cell types were shown, but there were no data from other renal cell types.

To address the durability of histological response, Genzyme has submitted results from additional cell types to 6 months of AGAL-005-99, and longer-term data on cells of the skin. Subjects were not required to undergo renal or cardiac biopsies beyond 6 months of AGAL-005-99.

**6-month results on additional cell types (AGAL-005-99)**

The blinding and scoring systems were not reviewed at CBER before their implementation. The key points of the blinding procedure are as follows:

- Treatment assignment was blinded.
- The baseline slide was identified, but the other two time points were not.

Slide scores were based on an overall judgment (Table 6). This method differs somewhat from the final slide scoring procedure for AGAL-1-002-98, in which slides initially scored 0 and 1 by an overall judgment were rescored with a detailed quantitation procedure.

The same three pathologists for each organ were employed as for previously presented analyses of histology in AGAL-008-00 and AGAL-005-99. For each cell type, but not for mesangial cell matrix, a majority score was derived from individual scores. For mesangial cell matrix, up to 8 glomeruli were scored and the average recorded.

**Table 6. AGAL-005-99: 6-month biopsy scoring system**

| Cell/Tissue | Score |
|---|---|
| Kidney:<br>Glomerular Endothelial Cells<br>Non-Capillary Smooth Muscle Cells<br>Non-Capillary Endothelial cells<br>Skin:<br>Deep vessel endothelial cells<br>Deep vessel smooth muscle cells<br>Perineurium | 0 = None or Trace Accumulation<br>1 = Mild Accumulation<br>2 = Moderate Accumulation<br>3 = Severe Accumulation |
| Kidney:<br>Podocytes<br>DCT/Collecting Ducts | No change<br>Decrease<br>Increase |
| Kidney:<br>Mesangial Cells: GL-3 Accumulation<br>Interstitial Cells | 0 = No lipid granules<br>1 = Minimal lipid granules<br>2 = Numerous lipid granules |
| Kidney:<br>Mesangial Matrix | 0 = Normal Mesangium<br>1 = Mild Expansion<br>2 = Moderate Expansion |

*Comments*

*Although the scoring procedure was not a quantitative one, the data were examined for large trends.*

*Genzyme has not submitted additional heart biopsy data.*

Data completeness

- As can be seen in the summaries below, varying numbers of subjects, in some cases only about one half of the subjects in either group, provided data for the 3 time points examined here (baseline for AGAL-1-002-98, week 20 of AGAL-1-002-98, which was the "entry" value for AGAL-005-99, and month 6 of AGAL-005-99) for the various cell types. Details of the baseline characteristics and demographics were not provided for the subject populations for each cell type.
- Data tabulations from the 6-month time point of AGAL-005-99 present 1-year data from subjects 704 and 706, whose biopsies were postponed by 6 months.

Results

Genzyme reports scores from the baseline and end of AGAL-1-002-98, and at 6 months of AGAL-005-99. AGAL-005-99 scores are presented here only for subjects who had scores from the last visit of AGAL-1-002-98 (entry to AGAL-005-99). Results expressed as proportions of those with baseline scores from AGAL-1-002-98 are consistent with these results.

This data review concentrates on results expressed as scores of 0, for simplicity of presentation. The results submitted by Genzyme are more detailed in some cases (for example, subjects with improvements to non-0 scores); the results outlined here are consistent with the more detailed results. In cases where there appeared to be little change in the proportions of subjects with 0 scores, tables summarize changes in scores. For each treatment group for each trial, the nominal group number is 29.

The results are expressed for the as-treated group, which CBER considers equivalent to the intent-to-treat group (as explained in the review of the original BLA submission, a subject in each group had an alternate treatment for the majority of infusions, and 2 subjects in each group had completely alternate infusions given in AGAL-1-002-98).

## Kidney

*Glomerular structures*

- *Glomerular capillary endothelial cells and mesangial cells*

R-hαGal treatment was associated with a large proportion of scores of 0, even after treatment for about a year.

**Table 7. AGAL-1-002-98 and AGAL-005-99: Glomerular capillary endothelial cells and mesangial cells: proportions of subjects with 0 score at time point among subjects with non-0 baseline score**

| | AGAL-1-002-98 End of trial | | 6 months of AGAL-005-99 | |
|---|---|---|---|---|
| | Placebo | r-hαGal | Placebo/ r-hαGal | r-hαGal/ r-hαGal |
| Glomerular capillary endothelial cells | 0/16 | 19/19 | 21/21 | 17/17 |
| Mesangial cells | 0/16 | 19/19 | 19/21 | 17/17 |

- *Podocytes*

Scores of "severe" were common, and there was little effect of treatment. About the same number of subjects had a decrease from baseline at the 6 month time point of AGAL-005-99 (5 in placebo/r-hαGal and 3 in r-hαGal/r-hαGal).

**Table 8. AGAL-1-002-98 and AGAL-005-99: Podocytes, proportions of subjects with no change from baseline***

| AGAL-1-002-98 | | | | 6 months of AGAL-005-99 | |
|---|---|---|---|---|---|
| Baseline | | End of trial | | | |
| Placebo | r-hαGal | Placebo | r-hαGal | Placebo/ r-hαGal | r-hαGal/ r-hαGal |
| Proportion of subjects with "severe" score | | Proportions of subjects with no change from baseline of AGAL-1-002-98 | | | |
| 16/16 | 19/19 | 16/16 | 18/19 | 17/22 | 14/17 |

* all subjects had non-0 score at baseline

- *Mesangial cell matrix*

  There was no notable effect of treatment on the mesangial cell matrix.

**Table 9. AGAL-1-002-98 and AGAL-005-99: Mesangial cell matrix score (mean ± std. deviation)**

| | AGAL-1-002-98 | | | | 6 months of AGAL-005-99 | |
|---|---|---|---|---|---|---|
| | Baseline | | End of trial | | | |
| | Placebo | r-hαGal | Placebo | r-hαGal | Placebo/ r-hαGal | r-hαGal/ r-hαGal |
| Subjects with data available | 21 | 21 | 17 | 21 | 23 | 20 |
| Score (mean ± std. deviation) | 0.9 ± 0.2 | 0.8 ± 0.2 | 0.9 ± 0.2 | 0.7 ± 0.2 | 0.9 ± 0.3 | 0.7 ± 0.2 |

*Other kidney structures*

- *Interstitial cells and noncapillary endothelial cells*

R-hαGal treatment was associated with a large proportion of scores of 0, even after treatment for about a year.

**Table 10. AGAL-1-002-98 and AGAL-005-99: Interstitial and noncapillary endothelial cells, proportions of subjects with 0 score at time point among subjects with non-0 baseline score**

| | AGAL-1-002-98 End of trial | | 6 months of AGAL-005-99 | |
|---|---|---|---|---|
| | Placebo | r-hαGal | Placebo/ r-hαGal | r-hαGal/ r-hαGal |
| Interstitial cells | 0/24 | 16/23 | 19/24 | 23/23 |
| noncapillary endothelial cells | 0/22 | 16/19 | 19/22 | 19/20 |

- *Noncapillary smooth muscle cells*

R-hαGal treatment was associated with a large proportion of decreases from baseline, even after treatment for about a year. The amounts of reductions in score were maintained, and possibly increased, with continued treatment with r-hαGal in AGAL-005-99 (not shown).

**Table 11. AGAL-1-002-98 and AGAL-005-99: Noncapillary smooth muscle cells, proportions of subjects with 0 score at time point among subjects with non-0 baseline score**

| | AGAL-1-002-98 End of trial | | 6 months of AGAL-005-99 | |
|---|---|---|---|---|
| | Placebo | r-hαGal | Placebo/ R-hαGal | r-hαGal/ r-hαGal |
| Proportion of subjects with 0 score | 0/22 | 2/21 | 0/22 | 0/21 |
| Proportion of subjects with any decrease in score from baseline | 2/22 | 18/21 | 19/22 | 17/21 |

- *Distal convoluted tubules and collecting ducts*

During AGAL-1-002-98 most subjects in both groups experienced no change in score; during AGAL-005-99, decreases outnumbered stable scores and increases in score. With continued treatment, more subjects had decreases in score than remained stable or had increases.

**Table 12. AGAL-1-002-98 and AGAL-005-99: Distal convoluted tubules and collecting ducts, proportions of subjects with any decrease from baseline***

| | AGAL-1-002-98 End of trial | | 6 months of AGAL-005-99 | |
|---|---|---|---|---|
| | Placebo | r-hαGal | Placebo/ R-hαGal | r-hαGal/ r-hαGal |
| Proportions of subjects with any decrease from baseline | 1/24 | 6/24 | 18/24 | 12/24 |

* (all subjects had non-0 score at baseline)

Skin

- *Deep vessel endothelial cells*

R-hαGal treatment was associated with a large proportion of decreases from baseline for deep vessel endothelial cells, even after treatment for about a year.

**Table 13. AGAL-1-002-98 and AGAL-005-99: Skin deep vessel endothelial cells, proportions of subjects with 0 score at time point among subjects with non-0 baseline score**

| AGAL-1-002-98 End of trial | | 6 months of AGAL-005-99 | |
|---|---|---|---|
| Placebo | r-hαGal | Placebo/ r-hαGal | r-hαGal/ r-hαGal |
| 1/24 | 19/23 | 19/22 | 23/24 |

- *Deep vessel smooth muscle cells*

Far too little data (1 placebo subject and 6 r-hαGal subjects) are presented from these analysis to make any conclusions.

- *Perineurium*

There was no notable effect of r-hαGal treatment in skin perineurium. In AGAL-1-002-98, about half of the subjects in both groups remained stable and a small number showed an increase; in AGAL-005-99, about 1/3 of subjects were stable, with 2 increases in score in the placebo group and none in the r-hαGal group.

**Table 14. AGAL-1-002-98 and AGAL-005-99: Skin perineurium, proportions of subjects with 0 score at time point among subjects with non-0 baseline score**

| | AGAL-1-002-98 End of trial | | 6 months of AGAL-005-99 | |
|---|---|---|---|---|
| | Placebo | r-hαGal | Placebo/ r-hαGal | r-hαGal/ r-hαGal |
| Proportion of subjects with 0 score | 0/22 | 1/22 | 1/18 | 2/20 |
| Proportion of subjects with any decrease in score from baseline | 7/22 | 10/22 | 11/20 | 13/21 |

*Comments*

*The histological data would not be substantially changed by omitting data from subjects 704 and 706, whose biopsies were included in the 6-month time point, but were actually performed at 12 months. Despite the fact that the data involve subgroups that were not randomly selected, the trends in the data are clear.*

*The scoring procedures for histology were not based on the quantitative methodology that was the cornerstone of the kidney biopsy analysis in AGAL-008-00 and AGAL-005-99.*

*Nevertheless, the trends in the data show that substrate loads in endothelial, mesangial, and interstitial cells are reduced by r-hαGal, and that there is no evidence of reversion after 11 months of treatment. Review of summary tables of results shows that reductions to nonzero scores supported the results shown and expressed as reductions to scores of 0. Some cell types showed minimal to no effects. Responses of capillary smooth muscle cell, podocyte, and distal convoluted tubule and collecting duct were minimal. Mesangial cell matrix showed no effect. Data on deep vessel smooth muscle cell levels were insufficient to draw any conclusions. Overall, the results extend the findings of FB9702-01 that the reduction of substrate may be seen in some cell types other than interstitial capillary endothelial cells.*

*No evidence is shown to support a stabilization or reversal of kidney damage. In fact, the mesangial cell matrix, which Genzyme states is reflective of ongoing glomerular pathology, did not change in either the placebo or r-hαGal groups.*

*No additional data are presented on cardiac tissue, one of the tissues presented in the original BLA submission. However, the primary endpoint of AGAL-1-002-98 was meant to be related to clinical benefit in renal function, so this lack of additional data is not a critical issue.*

**Supportive data on additional cell types**

To provide support for the results of the partially blinded reading of the additional cell types, Genzyme submits results from two other sources:

1) A second reading of the additional kidney cell types, conducted by one of the pathologists from AGAL-1-002-98 on a sample of slides from 25% of the subjects from AGAL-1-002-98. According to Genzyme the slides were completely blinded.
2) A clinical trial of r-hαGal conducted at 5 centers in Japan. This was a 5-site, 13-subject open-label trial using the same dose regimen and duration as used in AGAL-1-002-98 (1 mg/kg every 2 weeks for 20 weeks) in a very similar population of subjects with Fabry's disease as studied in AGAL-1-002-98. Subjects received baseline and end-of-treatment kidney biopsies. The same kidney pathologists as in AGAL-1-002-98 analyzed interstitial capillary endothelial and additional cell GL-3 inclusions histologically in slides blinded for time point. A more detailed review of this trial is included in this review.

Table 15 shows the scoring methods used for the various readings in comparison to those used in AGAL-1-002-98.

**Table 15. Summary of scoring methods used for readings of histology shown in Tables 1 and 2.**

| | **AGAL-1-002-98 2nd reading of additional cell types** | **AGAL-1-002-98 25% re-read** | **Japanese trial AGAL-007-99** |
|---|---|---|---|
| Score | Cell/Tissue | Cell/Tissue | Cell/Tissue |
| 0 = None or Trace Accumulation<br>1 = Mild Accumulation<br>2 = Moderate Accumulation<br>3 = Severe Accumulation | • Glomerular Endothelial Cells<br>• Non-Capillary Smooth Muscle Cells<br>• Non-Capillary Endothelial cells | • Non-Capillary Smooth Muscle Cells<br>• Non-Capillary Endothelial cells<br>• Mesangial Matrix<br>• Podocytes<br>• DCT/Collecting Ducts | • Glomerular Endothelial Cells<br>• Non-Capillary Smooth Muscle Cells<br>• Non-Capillary Endothelial cells<br>• Mesangial Matrix<br>• Podocytes<br>• DCT/Collecting Ducts |
| 0 = No lipid granules<br>1 = Minimal lipid granules<br>2 = Numerous lipid granules | • Mesangial Cells: GL-3 Accumulation<br>• Interstitial Cells | • Mesangial Cells: GL-3 Accumulation<br>• Interstitial Cells | • Mesangial Cells: GL-3 Accumulation<br>• Interstitial Cells |
| 0 = Normal Mesangium<br>1 = Mild Expansion<br>2 = Moderate Expansion | • Mesangial Matrix pre glomeruli (total glomeruli=8) | • Mesangial Matrix pre glomeruli (total glomeruli=8) | • Mesangial Matrix pre glomeruli (total glomeruli=8) |
| Increase<br>No Change<br>Decrease | • Podocytes<br>• DCT/Collecting Ducts | | |

**(**Table 16 **and** Table 17**)** shows the summary results.

**Table 16. Summary of subjects with scores of 0 in renal histology partially blinded full reading and fully blinded partial reading of additional cell types in AGAL-1-002-98, and Japanese open-label trial, blinded for time point**

| Efficacy Endpoint | AGAL-1-002-98 | | AGAL-1-002-98 25% of Additional Cell Reads | | Japanese trial AGAL-007-99 (open-label) |
|---|---|---|---|---|---|
| | Numbers (%s) of subjects with scores of 0 at week 20 (as-treated population) | | Numbers (%s) of subjects with scores of 0 at week 20 (as-treated population) | | Numbers (%s) of subjects with scores of 0 at visit 11 (intent-to-treat population) |
| | R-hαGal | Placebo | R-hαGal | Placebo | R-hαGal |
| Glomerular endothelial cells | 21/21 | 0/18 | 5/5 | 0/5 | 11/11 |
| Interstitial Non-Capillary Endothelial cells | 20/23 (87) | 0/23 | 5/6 (83) | 0/6 | 12/12 |
| Interstitial cells | 17/24 (71) | 0/24 | 6/6 | 0/6 | 10/13 (77) |

**Table 17. Summary of subjects with reductions in scores in partially blinded full reading and fully blinded partial reading of additional cell types in AGAL-1-002-98, and Japanese open-label trial, blinded for time point**

| Efficacy measure | AGAL-1-002-98 | | AGAL-1-002-98 25% of Additional Cell Reads | | Japanese trial AGAL-007-99 (open-label) |
|---|---|---|---|---|---|
| | Numbers (%s) of subjects (week 20, (as-treated population) | | Numbers (%s) of subjects (week 20, (as-treated population) | | Numbers (%s) of subjects (visit 11, intent-to-treat population) |
| | R-hαGal | Placebo | R-hαGal | Placebo | R-hαGal |
| Podocytes, any reduction | 1/19 (5) | 0/16 | 0/5 | 0/4 | 2/11 (18) |
| Distal Convoluted Tubules/Collecting Ducts, any reduction | 6/24 (25) | 1/24 (4) | 2/6 (33) | 2/6 (33) | 10/13 (77%) |
| Mesangial cells, reduction to 0 | 21/21 | 0/18 | 4/5 (80) | 0/3 | 9/11 (82) |
| Non-Capillary Interstitial Smooth Muscle Cells, reduction to 0 | 2/23 (10) | 0/23 | 0/6 | 0/6 | 0/12 |

- In addition, Genzyme summarized the mean change in mesangial cell matrix for the 3 analyses. In AGAL-1-002-98, there was a mean change score of "0" for both groups for each analysis. For AGAL-007-99, the study group also experienced a"0" change score in mesangial cell matrix at the end of the trial.

*Comment*

*The initial additional histological analysis was not fully blinded, as Genzyme acknowledges.*

*The results of the 25% second re-reading and the reading of AGAL-007-99 are consistent with those of AGAL-1-002-98, and provide support to the initial analyses.*

**Histology beyond 6 months in skin (AGAL-005-99)**

Superficial capillary endothelium

The protocol for AGAL-005-99 calls for biopsies of skin at month 6, 12, 30, 42, and 54 (with an optional 18-month biopsy). Genzyme has provided results for skin histology beyond 6 months. Table 18 shows 12-month results for skin superficial capillary endothelium.

**Table 18. 12-month skin superficial capillary endothelium scores (subjects)**

| Treatment Group | Entry Score | 12-Month Post Entry Score | | Total |
|---|---|---|---|---|
| | | Zero | Nonzero | |
| Placebo/ r-hαGal | Zero | 1 | 0 | 1 |
| | Nonzero | 26 | 0 | 26 |
| R-hαGal / r-hαGal | Zero | 27 | 1 | 28 |
| | Nonzero | 0 | 0 | 0 |

Table 19 shows 18-month results for skin superficial capillary endothelium.

**Table 19. AGAL-005-99: 18-month skin superficial capillary endothelium scores (subjects)**

| Treatment Group | Entry Score | 18-Month Post Entry Score | | Total |
|---|---|---|---|---|
| | | Zero | Nonzero | |
| Placebo/ r-hαGal | Zero | 1 | 0 | 1 |
| | Nonzero | 19 | 2 | 21 |
| R-hαGal / r-hαGal | Zero | 21 | 3 | 24 |
| | Nonzero | 0 | 0 | 0 |

Five subjects had an increase in score at 18 months. However, as Table 20 shows, the 30-month scores for these subjects suggests that the increases may have been due to chance.

**Table 20. AGAL-1-002-98 and AGAL-005-99: Skin superficial capillary endothelial cell substrate scores**

| Subject | Treatment | AGAL-1-002-98 | | AGAL-005-99 | | | |
|---|---|---|---|---|---|---|---|
| | | Baseline | End | 6 mo | 12 mo | 18 mo | 30 mo |
| 102 | placebo/r-hαGal | 2 | 2 | 0 | 0 | 1 | 0 |
| 107 | r-hαGal /r-hαGal | 2 | 0 | 0 | 0 | 1 | 0 |
| 201 | placebo/r-hαGal | 3 | 2 | 0 | 0 | 1 | 0 |
| 705 | r-hαGal /r-hαGal | 2 | 0 | 0 | 1 | 2 | 0[1] |
| 806 | r-hαGal /r-hαGal | 2 | 0 | 0 | 0 | 1[2] | Not done |

[1] ~2 year result; subject removed due to serum IgE at 4½ months after 18 month time point

[2] obtained 10 weeks after last treatment with R-hαGal

At 30 months, 20/21 subjects in the placebo/r-hαGal group had scores of 0, while 19/19 in the r-hαGal group had scores of 0. The one subject in the placebo/r-hαGal group with a non-0 score had a score of 1.

Other cell types

Table 19 shows slide score status (0 or non-0) at entry to AGAL-005-99 and at 18 months in several additional cell types presented. Review of individual scores at entry and 18 months showed that for deep vessel endothelial cells, the majority of the placebo crossovers had a decrease in score, while the majority of the r-hαGal continuers stayed at zero. However, in r-hαGal continuers (treatment with r-hαGal for about 24 months) 6 subjects increased their deep vessel endothelial score from a 0 score: none to mild (4) and none to moderate (2).

**Table 21. AGAL-005-99 entry and 18 month additional skin results (subjects)**

| Skin Cell Type | Treatment Group | Score at entry of AGAL-005-00 | Score at 18 Months post-entry | |
|---|---|---|---|---|
| | | | Zero | Non-Zero |
| Deep Vessels Endothelial Cells | Placebo/ r-hαGal | Zero | 1 | 0 |
| | | Non-Zero | 16 | 4 |
| | R-hαGal / r-hαGal | Zero | 14 | 6 |
| | | Non-Zero | 2 | 0 |
| Smooth Muscle Cells | Placebo/ r-hαGal | Zero | 1 | 0 |
| | | Non-Zero | 0 | 2 |
| | R-hαGal / r-hαGal | Zero | 0 | 0 |
| | | Non-Zero | 0 | 1 |
| Perineurium | Placebo/a GAL | Zero | 1 | 0 |
| | | Non-Zero | 0 | 17 |
| | R-hαGal / r-hαGal | Zero | 0 | 1 |
| | | Non-Zero | 3 | 15 |

Review of individual scores at entry and 18 months showed that for deep vessel endothelial cells, the majority of the placebo crossovers had a decrease in score, while the majority of the r-hαGal continuers stayed at zero. However, in r-hαGal continuers (treatment with r-hαGal for about 24 months) 6 subjects increased their deep vessel endothelial score from a 0 score: none to mild (4) and none to moderate (2). However, at 30 months, 18/21 subjects in the placebo/r-hαGal group had scores of 0, while 17/19 in the r-hαGal group had scores of 0. Table 22 shows the details of the subjects with available biopsies who did not have a score of 0 at 30 months. The overall results do not constitute a pattern of regressions. Subject 112's superficial capillary endothelial scores started at 3 and continued at 0 for all remaining time points.

**Table 22. Deep vessel endothelial scores in subjects with non-0 scores at 30 months of AGAL-005-99**

| Subject | AGAL-1-002-98 | | Time point after entry to AGAL-005-99 | | |
|---|---|---|---|---|---|
| | Baseline | Visit 11 | 6 Month Post | 18 Month Post | 30 Month Post |
| 102 (placebo/r-hαGal) | 2 | 2 | 1 | 1 | 2 |
| 116 (placebo/r-hαGal) | 2 | 3 | 1 | 2 | 2 |
| 709 (placebo/r-hαGal) | 3 | 3 | 0 | 1 | 1 |
| 112 (r-hαGal/r-hαGal) | 3 | 0 | 0 | 1 | 2 |
| 307 (r-hαGal/r-hαGal) | 2 | 0 | 0 | 1 | 1 |

*Comments on longer term skin data*

*Interpretation of the longer term skin data is somewhat limited due to the dwindling sample sizes at the later time points. However, given this limitation, the data do not show a pattern of regression out to 30 months of AGAL-005-99.*

## Summary comments on additional histological data

Histological analyses of additional kidney and skin cell types shows that the effects in the kidney as presented in the original BLA submission were not isolated. However, treatment with Genzyme's r-hαGal was not associated with notable reductions in GL-3 levels as histologically

determined in podocytes and mesangial cell matrix. Reductions were small in noncapillary smooth muscle cells and variable in distal convoluted tubules and collecting ducts. The histological reduction in skin capillary GL-3 associated with treatment with r-hαGal does not wane over the treatment period examined.

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## NON-HISTOLOGY OUTCOMES WITH EXTENDED DURATION OF TREATMENT

**Renal function**

The subjects enrolled in AGAL-1-002-98 had normal serum creatinines at baseline. Genzyme submitted analyses of GFR at various time points at up to 18 months of AGAL-005-99.

Table 23 shows the summary of inulin-derived GFR at various time points. Baseline values differ between the treatment arms and numbers of subjects drop dramatically at the end of AGAL-1-002-98. There is no consistent pattern of effect of r-hαGal, either during the controlled period (AGAL-1-002-98) or subsequently.

**Table 23. Inulin-based GFR, expressed as ml/min/1.73 $m^2$, at various time points**

| Trial | Visit | | Treatment arm | |
|---|---|---|---|---|
| | | | Placebo/r-hαGal | R-hαGal /r-hαGal |
| AGAL-1-002-98 | Baseline | *N* | *28* | *29* |
| | | Mean ± s.d. | 97±35 | 82±22 |
| | | Median | 99 | 82 |
| | End | *N* | *19* | *17* |
| | | Mean ± s.d. | 101±35 | 94±36 |
| | | Median | 108 | 78 |
| AGAL-005-99 | Month 6 | *N* | *26* | *24* |
| | | Mean ± s.d. | 117±41 | 82±29 |
| | | Median | 113 | 75 |
| | Month 12 | N | 22 | 28 |
| | | Mean ± s.d. | 101±33 | 80±26 |
| | | Median | 104 | 72 |
| | Month 18 | *N* | *15* | *16* |
| | | Mean ± s.d. | 122±44 | 76±31 |
| | | Median | 131 | 74 |

Genzyme calculates GFR from serum creatinine using an equation derived from one used in the Modification of Diet in Renal Disease Study (reference cited). This equation uses serum creatinine, age, sex, and whether a patient is "black" to calculate GFR. Numbers of subjects at each time point are much more complete. However, it should be noted that this equation is predictive but does not provide actual data on creatinine clearance.

**Table 24. GFR estimated from serum creatinine and MDRD equation**

| Trial | Visit | Statistic | Treatment arm | |
|---|---|---|---|---|
| | | | Placebo/r-hαGal | R-hαGal/r-hαGal |
| AGAL-1-002-98 | Baseline | *N* | *29* | *29* |
| | | Mean ± s.d. | 136±42 | 121±44 |
| | | Median | 133 | 115 |
| | End | *N* | *29* | *29* |
| | | Mean ± s.d. | 136±52 | 118±46 |
| | | Median | 123 | 105 |
| AGAL-005-99 | Entry | *N* | *27* | *27* |
| | | Mean ± s.d. | 138±39 | 110±31 |
| | | Median | 132 | 111 |
| | Month 6 | *N* | *26* | *28* |
| | | Mean ± s.d. | 136±52 | 112±38 |
| | | Median | 129 | 110 |
| | Year 1 | *N* | *28* | *28* |
| | | Mean ± s.d. | 133±50 | 123±46 |
| | | Median | 125 | 112 |
| | Month 18 | *N* | *27* | *28* |
| | | Mean ± s.d. | 124±45 | 111±45 |
| | | Median | 122 | 103 |

*Comment*

*The dwindling numbers of subjects at the later time points in the inulin-based method preclude definitive statements regarding the effect of long-term treatment with Genzyme's r-hαGal; however, there is no evidence of worsening renal function. It is remarkable that the estimate of GFR is radically different from the estimate derived from inulin in many cases; however, the lack of a reliable trend showing an effect of r-hαGal on renal function in the data is the same.*

Review of serum creatinines over time has shown no consistent trends indicating worsening with extended treatment (as stated before, subjects started with normal creatinines). However, Genzyme has identified 3 subjects whose creatinines have risen with extended treatment. These are addressed in the sections of this review concerning safety.

**Plasma GL-3 over time**

Table 25 shows data out to 12 months.

**Table 25. Plasma GL-3 levels in AGAL-005-99 (mean (ng/ml) ± std. dev.*)**

| Period of AGAL-005-99 | Placebo/r-hαGal | R-hαGal/r-hαGal |
|---|---|---|
| Entry | 15 ± 12<br>*n=28* | 2.3 ± 4.3<br>*n=28* |
| 12 months | 0.6 ± 1.8<br>*n=26* | 1.4 ± 5.1<br>*n=26* |

* Values that were below the limit of detection (<1.2 ng/μl) were set to 0

*Comment*

*The calculations in Table 25 may be inaccurate, due to the setting of levels below the limit of detection to 0. However, these data show that even in r-hαGal continuers, plasma levels have dropped and remain low.*

**Other outcomes**

Genzyme submitted 18-month results of the following outcomes:

- McGill short form data

There were no differences between treatment groups. Scores were low with minimal changes from entry.

- Quantitative Sudomotor Axon Reflex (U.S. subjects only)

Sweat volume was imbalanced by treatment group at baseline of AGAL-1-002-98; mean sweat volume decreased for both groups from baseline of AGAL-1-002-98 to 18 months of AGAL-005-99.

- Temperature detection threshold and venous occlusion plethysmography (U.S. subjects only)

Temperature detection threshold and venous occlusion plethysmography "did not show an abnormal status" at any time point. Genzyme points out that the difference from entry to 18 months of the extension in temperature detection threshold was statistically significantly better in the r-hαGal/r-hαGal group; however, due to the multiplicity of statistical tests this conclusion is hard to interpret.

- Vibration detection threshold (U.S. subjects only)

There was a small shift toward normal compared to baseline in both groups at the 18-month time point, after a small increase in scores for both groups during AGAL-1-002-98.

- Total symptom score

Baseline component scores were very low at baseline and differences from baseline or entry at the 18-month time point were slight for both treatment groups.

- SF-36 QoL questionnaire

Very small differences, mostly increases (better scores) occurred in both groups. In scales of 0-100, the range of differences was -7.4 to 12.0, with most of the changes less than about 6.

- Physician assessment of Fabry symptoms

Changes in yes/no score for angiokeratoma, presence of abnormal sweating, and abdominal pain were not common. However Table 26 shows that the numbers of subjects with deteriorations in abnormal sweating and abdominal pain at 18 months of AGAL-005-99 was slightly greater than the numbers with improvements.

**Table 26. Physician assessment of Fabry symptoms**

| | | entry | 18-month | | |
|---|---|---|---|---|---|
| | | | Yes | No | total |
| Angiokeratoma | Placebo/r-hαGal | Yes | 22 | 2 | 24 |
| | | No | 0 | 1 | 1 |
| | R-hαGal /r-hαGal | Yes | 23 | 0 | 23 |
| | | No | 0 | 2 | 2 |
| Abnormal Sweating | Placebo/r-hαGal | Yes | 19 | 1 | 20 |
| | | No | 2 | 3 | 5 |
| | R-hαGal / r-hαGal | Yes | 19 | 1 | 20 |
| | | No | 1 | 4 | 5 |
| Abdominal Pain | Placebo/ r-hαGal | Yes | 3 | 1 | 4 |
| | | No | 4 | 17 | 21 |
| | R-hαGal /r-hαGal | Yes | 5 | 1 | 6 |
| | | No | 5 | 14 | 19 |

- Changes in gastrointestinal QoL scores (U.S. subjects only)

Genzyme states the changes were "unremarkable." The data were not reviewed.

- Plasma GL-3 (12-month results)

For subjects who remained on r-hαGal from AGAL-1-002-98, the mean value decreased from 2.3 ng/µl at entry to AGAL-005-99 to 1.4 ng/µl; for those who started on r-hαGal in AGAL-005-99, mean values were 15.3 ng/µl and 0.6 ng/µl, respectively.

- Ophthalmic changes (12-month results)

Genzyme states that no clinically significant changes were seen in either treatment group. The data were not reviewed.

- Urinary GL-3

Variable collection of 24-hour urines rendered the 12-month data invalid; therefore, data are only presented for the 6-month time point. There was a great degree of variability, and for the r-hαGal/r-hαGal group, the median and mean percent change behaved differently (Table 27). The individual

results were not examined. These results cannot be interpreted to show a definite benefit of treatment.

**Table 27. Urinary GL-3 at 6 months of AGAL-005-99**

| Treatment Group | Statistic | Entry | 6 months post entry | % Change: Entry to 6-Months post entry |
|---|---|---|---|---|
| Placebo/r-hαGal | *n* | *22* | *22* | *22* |
| | Mean | 5357 | 2546 | -43 |
| | Median | 3539 | 1761 | -56 |
| | Std. Dev. | 3812 | 2457 | 64 |
| | Min/Max | 96, 12780 | 81, 8643 | -94, 209 |
| R-hαGal/r-hαGal | *n* | *23* | *23* | *23* |
| | Mean | 4091 | 3050 | 28 |
| | Median | 3323 | 1966 | -27 |
| | Std. Dev. | 3190 | 3294 | 254 |
| | Min/Max | 38, 11079 | 5.0, 14353 | -96, 1170 |

### Summary comments on secondary and other outcomes

The data are consistent with the lack of responses in clinical measures as seen in the 6-month report. Renal function has not changed for either group as a whole (with 3 noted exceptions). Plasma GL-3 drops during treatment with r-hαGal. Overall, these data do not suggest that Genzyme's r-hαGal has demonstrated clinical efficacy. However, neither do these data refute the hypothesis of clinical benefit with treatment. Rather, these trials were not designed to assess the question of clinical benefit.

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## SAFETY

The following review of safety contains data up to infusion 42 of AGAL-005-99. Some of the 6-month data from AGAL-005-99 is repeated here for clarity.

### Safety in AGAL-005-99 (up to 18 months)

The design of this trial has been discussed elsewhere. All subjects from AGAL-1-002-98 were started on r-hαGal, 1 mg/kg every other week.

**Dropouts and exposure**

Twenty-nine subjects started the trial from each treatment group from AGAL-1-002-98 placebo and r-hαGal). Through February 28, 2002, 6 subjects dropped out or were withdrawn:

Placebo/r-hαGal:

Subject 401: after infusion 41, to receive commercial product

Subject 304: after infusion 8, due to skin test reaction to r-hαGal

Subject 506: after infusion 18, due to death

R-hαGal/r-hαGal:

Subject 702: after infusion 41, to receive commercial product

Subject 104: after infusion 23, due to multiple relocations

Subject 806: after infusion 36, due to skin test reaction to r-hαGal

Very few participating subjects missed infusions.

A recently received 24-month report listed some additional dropouts: Subject 705 (r-hαGal/r-hαGal group) was withdrawn at visit 54 for development of serum IgE at visit 52. Subject 606 (r-hαGal/r-hαGal group) voluntarily withdrew for travel "based on improvements in her health and

Fabry disease." Subject 803 (placebo/r-hαGal) was withdrawn after infusion 77 for development of a skin reaction to r-hαGal.

**Deaths**

There has been one death reported up to infusion 42 of AGAL-005-99. This was a 43 year-old man who had been on placebo during AGAL-1-002-98, who suffered a cardiac arrest and dysrhythmia 400 days after being on r-hαGal. His medical history is stated as "severe heart disease associated with marked acute heart failure and findings consistent with Fabry disease."

**Adverse events**

Serious adverse events

Twenty-three of the 58 subjects experienced serious adverse events. Counting terms that were related to each other that occurred on the same day as the same event, the serious adverse events may be grouped as follows:

- Related to biopsy: 3 subjects, 3 events
- Related to infusion: 6 subjects, 7 events. As Table 28 shows, serious infusion-related events may occur late in treatment.

**Table 28. Infusion-associated serious adverse events in AGAL-005-99**

| subject | term | days after treatment |
|---|---|---|
| 201 | tachycardia | 32 |
| | hypertension | 33 |
| 304 | pruritic urticaria | 98 |
| 306 | tightness in chest | 55 |
| | tightness in throat | 55 |
| 705 | swelling and erythema in ear, warmth in face | 881* |
| 805 | fever | 128 |
| | very intense shivering | 128 |
| | tachycardia | 128 |
| 806 | abdominal pain | 582 |
| | cutaneous rash | |
| | skin redness | |
| | vomiting | |
| | pruritis | |
| | nausea | |
| | shivering | |

*post-18-month data

- Cardiac/neurologic events: 6 subjects, 7 events. Serious cardiac and neurologic events occurred mostly several to many months after the first infusion of r-hαGal (Table 29). Two strokes occurred in subjects with no prior history, but stroke is a known complication of Fabry's disease. Subject 603 had an episode of chest pain during this trial, with no documented cardiac abnormality. An additional, ischemic event occurred: hand ischemia in a 41 year-old subject (subject 708) 175 days after the start of treatment, in a subject with no relevant medical history.

**Table 29. Serious cardiac and neurologic adverse events in AGAL-005-99***

| Subject | Term | Age | Days after treatment | Relevant history |
|---|---|---|---|---|
| 109 | Stroke | 37 | 770 | no |
| 112 | Stroke | 25 | 870 | no |
| 501 | Stroke | 42 | 611 | yes |
| 502 | Worsened angina | 62 | 53 | yes |
| 506 | Bradycardia | 43 | 242 | yes |
| | Decreased cardiac output | | 242 | |
| | Cardiac arrest** | | 400 | |
| | Dysrhythmia** | | 400 | |

* See text for additional ischemic/possibly ischemic events
**reported as death

- Miscellaneous: See Table 30.

**Table 30. AGAL-005-99: Miscellaneous serious adverse events (one row per subject)**

| Event | Medical history |
|---|---|
| Viral pericarditis | none related |
| Hand injury | none related |
| Suicide attempt | none related |
| Head and hand injury | none related |
| Bronchitis | asthma, tobacco use |
| Vertigo (twice) and hypoacousia | vestibulocochlear disorders, tinnitus, bilateral hearing loss, vertigo |
| Carpal tunnel syndrome | none related |
| Herpes labialis of leg with erysipelas | none related |
| Suicide attempt | none related |
| Basal cell carcinoma | none related |
| Basal cell carcinoma<br>Nephrotic syndrome | No cancer related history<br>Fabry related-proteinuria, extensive baseline glomerular scarring |
| Loss of visual acuity, macular edema, retinal white dots syndrome | inflammatory syndrome |
| First metatarsal osteitis | cutaneous wound ulcer |

*Comments*

*The group switched to r-hαGal experienced several serious cardiac adverse events, but serious adverse events of this nature did not occur in the r-hαGal-treated group in AGAL-1-002-98, so they do not constitute a strong pattern. There is no clear pattern of serious events other than those associated with biopsy and infusion.*

Trends relating to infusion reactions during the first 12 months of AGAL-005-99

Table 31 is a summary of infusion-related adverse events for the first 12 months of AGAL-005-99.

**Table 31. Proportions of r-hαGal-treated subjects with infusion-related adverse events over time**

| AGAL-1-002-98 | AGAL-005-99 1st 6 months | | AGAL-005-99 2nd 6 months | |
|---|---|---|---|---|
| R-hαGal | Placebo/r-hαGal | R-hαGal/r-hαGal | Placebo/r-hαGal | R-hαGal/r-hαGal |
| 19/29 | 18/29 | 16/29 | 11/28 | 13/29 |

*Comment*

*-These data show a trend toward a reduction of overall infusion-related events over time. However, the proportions of subjects with infusion reactions was still nearly 50% in the subset of subjects in their 3rd 6-month period of treatment.*

Testing for IgE in the event of infusion reactions was done by prespecified clinical criteria.

The following is a summary of the testing of serum samples for IgE for the first 12 months of AGAL-005-99:

- 12/29 (41%) r-hαGal subjects in AGAL-1-002-98 had serum tested for IgE (all negative)
- 18/58 (31%, all r-hαGal) in the 1st 6 months of AGAL-005-99 were tested for IgE (all negative)
- 3/58 (all r-hαGal) in the 2nd 6 months of AGAL-005-99 were tested for IgE (all negative)

Genzyme states that skin testing, done at the discretion of the investigator for the suspicion of an IgE-mediated hypersensitivity reaction, was rarely done: never during AGAL-1-002-98 and 3 times through 12 months of AGAL-005-99. The skin test was "consistent with a positive test" in 1 of these subjects.

Genzyme states that serum IgE testing was supposed to be performed on preinfusion samples (while the post infusion plasma was tested for complement activation). The serum IgE data for AGAL-1-002-98 were developed from 10 preinfusion samples, and 2 postinfusion samples with confirmation using a sample prior to another infusion. The serum IgE data for AGAL-005-99 derive from 17 preinfusion sera and 3 postinfusion sera.

*Comments*

*Four of 12 subjects with serum testing for IgE in AGAL-1-002-98 were retested in the 1st 6 months of AGAL-005-99, and 1/12 was retested in the 2nd half of AGAL-005-99. 14/29 subjects switched from placebo in AGAL-005-99 were serum tested, a similar rate to that of the r-hαGal-treated subjects in AGAL-1-002-98.*

*Two thirds of the subjects with serum tests in the 2nd half of AGAL-005-99 had been switched from placebo to r-hαGal at the time of entry to AGAL-005-99: 1 had been tested during the 1st half of AGAL-005-99, and the other had not been tested until the 2nd half.*

*Suspected IgE-mediated infusion reactions appear to decrease over time. The exact nature of each infusion reaction is not given, leaving the possibility that some bias exists against testing individuals repeatedly for certain reactions. However, this bias is unlikely to account substantially for the drop in testing, given the drastic consequences of missing an IgE-mediated reaction.*

Trends relating to infusion reactions during the first 18 months of AGAL-005-99

CBER examined summaries of adverse events classified as related to treatment that occurred on the same day as infusion, divided by approximate 6-month time periods: baseline to visit 11 (5 months) of AGAL-1-002-98, entry to AGAL-005-99 to 6 months of the trial, 28 weeks to 1 year after entry to AGAL-005-99, and 54 weeks to 18 months after entry to AGAL-005-99. The incidence of infusion-related events generally decreased over time, and there is no event with a reliable increase in incidence. In the period from about 18-24 months after initiation of treatment (subjects on r-hαGal in AGAL-1-002-98), 4 subjects had infusion-associated nausea and 2 subjects

each had the following events: rigors, hypertension, and vomiting. One subject each had paresthesia, abdominal pain, tachycardia, arthrosis, rash, ECG abnormal, hypotension, skin discoloration, anxiety, cardiac failure, hypertonia, and myalgia (the same subject may have had more than one event).

In trial AGAL-005-99 several subjects were withdrawn for evidence of development of IgE to r-hαGal (see tabulation in the section on dropouts and exposure). It is important to note that these reactions could occur out to infusion 52 of the trial.

*Comment*

*Infusion reactions to r-hαGal decrease in incidence with time. It is important to note that severe reactions may occur after extended durations of treatment (up to 881 days after initiation of treatment). To date, there is no predictive factor for the development of infusion reactions. Because nearly all subjects were IgG antibody (+) during the trial, testing for IgG antibody would not allow determination of subjects at risk for development of infusion reactions.*

*Development of anti-r-hαGal IgE may occur. The rarity of discontinuations due to the development of anti-r-hαGal IgE may be due in large part to the lack of therapeutic options for the subjects. Development of anti-r-hαGal IgE may pose a risk to future administration of r-hαGal.*

Serum creatinine deteriorations

There were no changes in means or medians in serum creatinine for either group out to 18 months. However, Genzyme points to 3 subjects who had deteriorations in serum creatinine (Table 32).

**Table 32. Subjects with a > 33% Increase in serum creatinine from the start of treatment and last value above normal range (1.4 mg/dl)**

| Patient | Treatment arm (As Treated) | AGAL-1-002-98 | | AGAL-005-99 | | |
|---|---|---|---|---|---|---|
| | | Baseline | Week 20 | 6 Months | 12 Months | 18-Months |
| 707 | R-hαGal/r-hαGal | 0.7 | 1.3 | 1.3 | 1.4 | 1.6 |
| 804 | R-hαGal/r-hαGal | 1.1 | 1.2 | 1.4 | 1.8 | 1.9 |
| 119 | Placebo/r-hαGal | 1.3 | 1.6 | 1.8 | 2.1 | 2.2 |

Genzyme states that possible contributing factors to the rise in these subjects' serum creatinines were advanced age (age 42.7-48.5, with mean of entire population 31). Genzyme states that these subjects were "among a small subset of patients who had prominent glomerular sclerosis at Baseline."

The 3 pathologists who performed the reading of slides assessed the number of glomeruli showing focal segmental glomerulosclerosis, global glomerulosclerosis, and the number that appeared normal. Forty-eight subjects had renal biopsies at baseline, end-of-AGAL-1-002-98, and 6 months of AGAL-005-99; 43 of these had glomeruli at baseline. It is from this group of 43 that Genzyme derives its number (6) who had "prominent glomerulosclerosis."

Genzyme shows that the 3 subjects were among 10 with a serum protein:creatinine ratio >1.0. In addition, these 3 subjects were among 4 with a combination of "prominent glomerulosclerosis" and serum protein:creatinine ratio >1.0.

*Comment*

*Review of the listings of the glomerular analysis shows that many of the biopsies had very few glomeruli: 37 subjects had biopsies with 10 glomeruli or fewer. Subjects 119, 707, and 804, had 8, 8, and 2 glomeruli at baseline). It is very problematic to infer the proportions of sclerotic glomeruli from many of the specimens.*

*The basis for the use of the criterion ratio over 1.0 is not presented; there does not appear to be a clear separation of the data at 1.0.*

*The data are too weak to be a compelling case for Genzyme's hypothesis at this date.*

Comments on tinnitus as an adverse event

Genzyme's data base on 12 months of AGAL-005-99, submitted with their response to the complete review letter, had identified 1 subject in placebo/r-hαGal and 4 subjects in r-hαGal/r-hαGal who reported tinnitus (discounting a placebo/r-hαGal subject who had tinnitus with an unknown start date). The 18-month data base submitted currently shows that of 5 subjects reporting tinnitus, 1 was on placebo and 3 were on r-hαGal during AGAL-1-002-98 (also discounting a placebo/r-hαGal subject who had tinnitus with an unknown start date). The difference between the data bases is small, and so is the discrepancy between the treatment groups.

Immune complex disease

Genzyme provides a summary of an examination for immune complexes in frozen sections of renal biopsies that contained glomeruli from week 20 of AGAL-1-002-98 (13 subjects), evaluated by Dr. Colvin, one of the pathologists from the evaluation of the primary endpoint. The data are not provided. The samples were distributed as follows:

1. R-hαGal-treated, seronegative subjects (n=3)
2. R-hαGal-treated subjects with titers ≥12800 (n=5)
3. Placebo, seronegative subjects (n=5)

Genzyme states that 12 of the 13 patient specimens were negative for IgG in the glomerulus, and their corresponding complement (C3) levels were recorded as either negative or trace by immunofluorescence. One subject (subject 801,in group 2) had trace amounts of IgG in the glomerulus. This subject's serum creatinines were stable for the 18 months of observation and he has had no hematuria. Genzyme states that his protein excretion has been stable, but the evidence on progression of proteinuria depends on an estimated protein excretion at baseline and is only suggestive.

Genzyme had submitted information to the IND concerning a subject who developed nephrotic range proteinuria around visit 33. Genzyme's discussion of the details of this subject makes the following points:

1. Review of baseline biopsy showed "extensive glomerular sclerosis."
2. Review of biopsy done in workup for worsened proteinuria showed "severe glomerulonephritis," but no testing for immune complexes was done.
3. 6-, 12-, and 18-month 24-hour urine proteins rose then fell (the value provided at baseline is an estimate).
4. Serum creatinine has risen: 1.1 at baseline to AGAL-1-002-98 to 1.8 at 18 months of AGAL-005-99.
5. Month 24 laboratory studies demonstrated increased proteinuria, serum creatinine and decreased creatinine, but the values are not shown.

*Comments*

*The pathological data on the incidence of immune complex deposition in the kidney are very sparse, but suggest that it would not be common (1/8 subjects treated, 1/5 seroconverters). There is little direct evidence cited to determine if the subject with nephrotic range proteinuria did or didn't*

*develop immune complex disease, and there remains concern over the rate of deterioration of the renal function in the subject.*

Adverse events and laboratory abnormalities to 12 months

Table 33 shows the numbers of subjects with adverse events occurring at or after the first infusion of AGAL-005-99 to 12 months. In it a subject appears only once for any term, according to the worst severity of the event experienced.

**Table 33. AGAL-005-99: Numbers of subjects with adverse events by preferred term occurring at or after first infusion to 12 months, by worst severity (in at least 3 subjects in each treatment group)**

| Preferred term | Placebo/r-hαGal *n=29* | | | | r-hαGal/r-hαGal *n=29* | | | |
|---|---|---|---|---|---|---|---|---|
| | Mild | Moder. | Severe | **Total** | Mild | Moder. | Severe | **Total** |
| Rigors | 11 | 3 | 1 | **15** | 9 | 5 | 2 | **16** |
| Rhinitis | 9 | 4 | 0 | **13** | 13 | 0 | 0 | **13** |
| Temperature changed sensation | 11 | 2 | 0 | **13** | 8 | 2 | 0 | **10** |
| Albuminuria | 9 | 3 | 0 | **12** | 9 | 2 | 1 | **12** |
| Fever | 11 | 0 | 1 | **12** | 7 | 2 | 1 | **10** |
| Chest pain | 6 | 2 | 2 | **10** | 4 | 0 | 1 | **5** |
| Pain | 5 | 3 | 2 | **10** | 4 | 4 | 0 | **8** |
| Headache | 6 | 2 | 1 | **9** | 12 | 4 | 1 | **17** |
| Upper respiratory tract infection | 9 | 0 | 0 | **9** | 8 | 0 | 0 | **8** |
| Influenza-like symptoms | 7 | 1 | 0 | **8** | 0 | 5 | 0 | **5** |
| Edema dependent | 8 | 0 | 0 | **8** | 4 | 2 | 0 | **6** |
| Vomiting | 6 | 2 | 0 | **8** | 8 | 2 | 1 | **11** |
| Fabry pain | 3 | 3 | 1 | **7** | 2 | 2 | 3 | **7** |
| Abdominal pain | 6 | 0 | 0 | **6** | 6 | 3 | 1 | **10** |
| Back pain | 2 | 2 | 2 | **6** | 1 | 2 | 2 | **5** |
| Dyspnea | 5 | 1 | 0 | **6** | 3 | 2 | 0 | **5** |
| Flushing | 3 | 3 | 0 | **6** | 1 | 0 | 0 | **1** |
| Heart valve disorders | 4 | 2 | 0 | **6** | 6 | 0 | 0 | **6** |
| Nausea | 4 | 2 | 0 | **6** | 9 | 2 | 0 | **11** |
| Paraesthesia | 4 | 1 | 1 | **6** | 5 | 0 | 2 | **7** |
| Post-operative pain | 4 | 2 | 0 | **6** | 7 | 1 | 0 | **8** |
| Pruritus | 6 | 0 | 0 | **6** | 2 | 0 | 0 | **2** |
| Diarrhea | 5 | 0 | 0 | **5** | 6 | 2 | 1 | **9** |
| Pharyngitis | 5 | 0 | 0 | **5** | 6 | 0 | 0 | **6** |
| Renal function abnormal | 3 | 2 | 0 | **5** | 4 | 1 | 0 | **5** |
| Asthenia | 2 | 2 | 0 | **4** | 3 | 1 | 2 | **6** |
| Bronchospasm | 4 | 0 | 0 | **4** | 2 | 1 | 0 | **3** |
| Cardiomegaly | 4 | 0 | 0 | **4** | 4 | 3 | 0 | **7** |
| Dyspepsia | 3 | 0 | 1 | **4** | 1 | 2 | 0 | **3** |
| Fatigue | 3 | 1 | 0 | **4** | 1 | 0 | 0 | **1** |
| Heart block | 4 | 0 | 0 | **4** | 3 | 0 | 0 | **3** |
| Myalgia | 3 | 1 | 0 | **4** | 1 | 2 | 1 | **4** |
| Somnolence | 4 | 0 | 0 | **4** | 3 | 0 | 0 | **3** |
| Tremor | 3 | 1 | 0 | **4** | 2 | 0 | 0 | **2** |
| Anxiety | 1 | 1 | 1 | **3** | 0 | 1 | 0 | **1** |
| Arthralgia | 2 | 1 | 0 | **3** | 0 | 0 | 0 | **0** |
| Bundle branch block | 3 | 0 | 0 | **3** | 1 | 0 | 0 | **1** |
| Cardiac failure | 2 | 0 | 1 | **3** | 3 | 0 | 0 | **3** |
| Coughing | 3 | 0 | 0 | **3** | 6 | 0 | 0 | **6** |
| Dizziness | 2 | 1 | 0 | **3** | 4 | 1 | 0 | **5** |
| ECG abnormal | 3 | 0 | 0 | **3** | 5 | 0 | 0 | **5** |
| Leg pain | 2 | 1 | 0 | **3** | 2 | 0 | 1 | **3** |
| Malaise | 3 | 0 | 0 | **3** | 1 | 0 | 0 | **1** |

**Table 33 (continued). Numbers of subjects with adverse events by preferred term occurring at or after first infusion to 12 months of AGAL-005-99, by worst severity (in at least 3 subjects in each treatment group)**

| Preferred term | Placebo/r-hαGal | | | | r-hαGal/r-hαGal | | | |
|---|---|---|---|---|---|---|---|---|
| | Mild | Moder. | Severe | **Total** | Mild | Moder. | Severe | **Total** |
| Otitis media | 3 | 0 | 0 | **3** | 0 | 0 | 0 | **0** |
| Palpitation | 3 | 0 | 0 | **3** | 0 | 1 | 0 | **1** |
| Syncope | 3 | 0 | 0 | **3** | 1 | 1 | 0 | **2** |
| Throat tightness | 1 | 1 | 1 | **3** | 0 | 0 | 0 | **0** |
| Anemia | 1 | 1 | 0 | **2** | 5 | 0 | 0 | **5** |
| Bradycardia | 1 | 0 | 1 | **2** | 4 | 0 | 0 | **4** |
| Bronchitis | 1 | 1 | 0 | **2** | 1 | 3 | 0 | **4** |
| Hematuria | 2 | 0 | 0 | **2** | 2 | 1 | 1 | **4** |
| Hypertension | 1 | 1 | 0 | **2** | 2 | 2 | 0 | **4** |
| Tinnitus | 0 | 1 | 0 | **1** | 3 | 1 | 0 | **4** |
| Inflicted injury | 2 | 0 | 0 | **2** | 2 | 1 | 0 | **3** |
| Skeletal pain | 2 | 0 | 0 | **2** | 3 | 0 | 0 | **3** |
| Arthrosis | 0 | 0 | 0 | **0** | 1 | 1 | 1 | **3** |
| Ear disorder | 0 | 0 | 0 | **0** | 3 | 0 | 0 | **3** |

Comparison of events between the 6- and 12-month data bases is problematic due to Genzyme's ongoing revisions of the data base.

Using a criterion of 3 or more subjects, the r-hαGal/r-hαGal group had a larger proportion of subjects who experienced headache, gastrointestinal disorders (abdominal pain, diarrhea, vomiting, and nausea), cardiomegaly, anemia, and arthrosis as adverse events. However, the increase in incidence of these events is not associated with an increase in severity. In addition, the following are notable:

- There was no notable increase in hypertension as an adverse event among those on r-hαGal for a longer period of time.
- The increase in headaches in the group with longer r-hαGal exposure is not associated with an increase in neurological events. The discrepancy between the groups had been noted in the first 6 months of AGAL-005-99, and its etiology is unclear.
- The increase in cardiomegaly in the group with longer r-hαGal exposure is not associated with a trend toward an increase in cardiac adverse events generally.
- 1 subject in each treatment group was noted to have recovered from anemia as an adverse event, leaving a discrepancy of 3 more r-hαGal-treated subjects with unrecovered anemias. None of the anemias was treated.
- The increase in arthrosis in the group with longer r-hαGal exposure was not accompanied by an increase in albuminuria, fever, or rash, suggesting that it is not a signal event for an increase in immune complex disease among those exposed for the longer period of time.

*Comments*

*The 12-month data do not suggest that there is a significant toxicity associated with the greater length of exposure of the r-haGal/r-haGal group (12 months vs. 6 months).*

Adverse events and laboratory abnormalities to 18 months

There has been no increase in particular adverse events in the continuers on r-hαGal compared to those who were switched from placebo to r-hαGal. Severities of events are generally

similar (not shown). Adverse events have been generally consistent with the course of Fabry's disease. There was no remarkable laboratory toxicity.

**Concomitant pain medication**

There were no notable intertreatment group differences in the use of medications used for pain over the first 24 months of AGAL-005-99.

*Conclusions regarding 18-month data on AGAL-005-99*

*The additional 12 months of experience beyond the original submission of 6 months of data has shown that infusion reactions generally diminish in frequency, but that severe reactions, and the development of anti-r-hαGal-IgE, may occur late. Vascular serious adverse events have occurred, but are consistent with the course of Fabry's disease generally. Neither clinical efficacy nor a change in renal course have been demonstrated.*

## Safety data in trials other than AGAL-005-99 and AGAL-007-99

Serious adverse event and death data related to additional trials and experience through February 28, 2002 are reviewed here. The following trials and experience were submitted:

- Ongoing open-label extension study AGAL-006-99: single-arm open-label extension to the original safety trial (15 subjects), with duration of exposure not shown.
- Ongoing, 2:1 randomized, double-blind, placebo-controlled trial AGAL-008-00 (around 58 subjects), with duration of exposure not shown.
- Special access and other programs in the U.S. and Europe (number of subjects not specified).
- Postmarketing experience. The number of patients is not shown (there were approximately 176 patients worldwide who receive Genzyme's commercial r-hαGal as of August 14, 2002).

All treated subjects have received r-hαGal at 1 mg/kg every other week.

## Deaths

Table 34 shows deaths as of February 28, 2002.

**Table 34. Deaths as of February 28, 2002***

| Study/ Patient | Age/ Sex | Treatment group/ Dose q14d | Date of First Infusion/ Date of Onset/ Date of Death | Duration of R-hαGal treatment before SAE (days) | Verbatim Term | Medical History |
|---|---|---|---|---|---|---|
| AGAL-008-00/ 18041 | 51/M | Placebo/ R-hαGal 1.0 mg/kg (Blinded) | 03OCT2001/ 30OCT2001/ 30OCT2001/ | 25 (blinded) | Cardiac arrest | Hyperlipidemia, gout, and kidney stones and findings consistent with history of Fabry disease |
| AGAL-008-00/ 12041 | 55/M | Placebo/ R-hαGal 1.0 mg/kg (Blinded) | 05FEB2002/ 06FEB2002/ 13-Feb-02 | 2 (blinded) | Stroke | Ischemic heart disease, decreased left ventricular function, and renal impairment |
| US Single Patient Exemption AGAL-010-00/ Single patient | 59/M | R-hαGal 1.0 mg/kg | 18SEP2000/ 18SEP2000/ 24-Sep-00 | 1 | Anasarca | Severe Fabry disease associated with severe renal, cardiac and pulmonary involvement; also central nervous system involvement with a past cerebrovascular accident and residual hemiparesis. |
| | | | | UNK | Sepsis | |
| Europe Compassionate Use (Netherlands) | 48/M | R-hαGal 1.0 mg/kg | 05APR2001/ 24APR2001/ 24-Apr-01 | 5 | Cardiac Arrest | Four myocardial infarctions (1986, 1989, 1997, 1998). |
| Japan Compassionate Use/ AGAL-011-00 | 63/M | R-hαGal 1.0 mg/kg | 28DEC2000/ 16SEP2001/ 16-Sep-01 | 263 | Ventricular Tachycardia | Extensive cardiac history including sick sinus syndrome, left ventricular hypertrophy, and congestive heart failure |
| Europe Compassionate Use (under French ATU) | 53/M | R-hαGal 1.0 mg/kg | 06JUN2001/ 18JUL2001/ 18-Jul-01 | 42 | Ischemic colitis, Multiple organ failure | Hemodialysis 3 times a week, long history of abdominal pain |

*excludes the death in AGAL-005-99 described previously in this review.

A recently received report of deaths as of November 30, 2002 lists 6 additional deaths, 5 occurring post approval, and 1 during "compassionate use". These deaths occurred in subjects receiving 1 mg/kg every other week, at a minimum of 257 days after start of treatment. The causes of death were: 1) cardiac arrest, 2) brain stem disorder, 3) cerebrovascular disorder, 4) intracranial hemorrhage, 5) arteriosclerosis and pneumonia, and a 6) cerebrovascular disorder, urinary tract infection, pulmonary embolism, bacterial infection, gastric ulcer, moniliasis, and anemia.

*Comments*

*The deaths are consistent with vasculopathy, and possibly with the natural course of Fabry's disease. Four of the events, two of which were blinded, occurred at or within 6 weeks of the start of treatment. The evidence implicating treatment is weak, but is cause for being watchful.*

**Serious adverse events (excluding deaths)**

*Trial FB9702-01*

The events submitted in this report are as reported in the review of FB9702-01 as originally submitted. Two serious adverse events were reported in this trial among 15 subjects. One was an infusion reaction with "symptoms suggestive of an allergic-type reaction" at 40 days of treatment with 1 mg/kg every 14 days. The other was pulmonary emboli at 12 days of treatment in a subject with a history of deep venous thrombosis whose warfarin had been stopped for the trial. This subject was treated with r-hαGal at 3 mg/kg every 48 hours.

*Trial AGAL-1-002-98*

The events submitted in this report are as reported in the review of AGAL-1-002-98 as originally submitted. Two events occurred in r-hαGal-treated subjects (n=29): worsening of depression in a subject on treatment for depression, and cellulitis in a subject with a history of osteomyelitis.

*Trial AGAL-006-99*

Five subjects had serious adverse events. Times to event do not precisely reflect time from the start of treatment, since subjects had spent variable times on r-hαGal during the core trial, FB9702-01. These events are of miscellaneous natures. Detailed information is available only for the last event, as the others were not deemed related to treatment.

1) vomiting in a subject with a history of irritable bowel (at 8 days of treatment)
2) atrial fibrillation in a subject with a history of junctional rhythm and SVT (at 76 days of treatment)
3) uvula edema in a subject with family member with a "similar condition" (at 92 days of treatment)
4) perforated diverticulitis and peritonitis in a subject with a history of cramping and diarrhea (at 1242 days of treatment)
5) chest pain, fatigue, and dyspnea in a subject with a history of cardiac disease and pacemaker (at 32 days of treatment). The subject was discontinued from treatment.

*AGAL-008-00*

The events from this trial are blinded.

Thirteen subjects experienced serious adverse events after initiating treatment. Counting terms that occurred on different days as separate events, the serious adverse events may be grouped as follows:

- "Probable" relationship to infusion: 1 subject, 1 event: angioedema, flushing, wheezing, urticaria, and cough 43 days after start of treatment.
- "Definite" relationship to infusion: 1 subject, 1 event: hypotension, at 54 days of treatment (infusion 5). This subjects had IgE to r-hαGal and was withdrawn from the trial.
- Possibly cardiac/neurologic: 6 subjects, 6 events (Table 35). Narratives are not available to discern details of these cases, as the events were not deemed to be due to treatment.

**Table 35. Serious possibly* cardiac and neurologic adverse events in AGAL-008-00 (blinded treatment)**

| Subject | Term | Age | Days after treatment | History |
|---|---|---|---|---|
| 20041 | Chest pain | 36 | 40 | Cardiac disease |
| 20047 | Atrial fibrillation | 52 | 68 | Pacemaker |
| 24041 | Chest pain | 54 | 105 | Cardiac disease |
| 27041 | Stroke | 59 | 42 | Cardiac disease |
| 34042 | Auricular disease | 54 | 43 | Cardiovascular; hypertension, left AV bundle branch block |
| 12041 | Stroke | 55 | 2 | Ischemic heart disease; decrease LV function; and renal impairment |

*Narratives not available to determine details of the diagnoses and treatments

- Miscellaneous: 4 subjects, 5 events:
  --an acute attack of Meniere's syndrome in a subject with history of stroke, angina
  --syncope in a subject with asthma
  --mood disorder and medication adjustment in subject with post-traumatic stress disorder and depression
  --fever in subject with "similar febrile reactions, although not in the past year"

*Comments*

*Importantly, trial AGAL-008-00 allows enrollment of subjects with potentially moderately advanced renal disease, which may also include more advancement of cardiac and neurological manifestations of their disease. This may account for the large number of relatively early cardiac and neurological events.*

*Serious adverse events from special access programs*

Subject characteristics from these programs are not presented, and details are not available for all events.

Three subjects had 5 miscellaneous serious adverse events:

--anemia, elevated C-reactive protein, and ileus in a subject with end-stage renal disease and cardiovascular disease

--musculoskeletal pain in the upper abdomen/chest in a subject with no related medical history

--rhabdomyolysis; subject noted to have had red discoloration of the urine thought due to rifampicin (not clear if applicant's submission describes event or medical history)

Possible or diagnosed cardiac or neurological events are shown in Table 36. All but the stroke were thought possibly (------ and ------) or probably (------) to be due to r-hαGal.

**Table 36. Serious possible or diagnosed cardiac and neurologic adverse events in special access programs**

| Subject | Term | Age | Days after treatment | Relevant history |
|---|---|---|---|---|
| ---------- | Myocardial infarction | 36 | Unknown | Mild chest pain |
| ---------- | Ataxia; urosepsis, disorientation | 44 | 6 | Cerebellar stroke |
| ---------- | Stroke | 44 | 264 | 3 left hemispheric strokes |
| --------- | Retrosternal chest pain** | 63 | 170 | Cardiomyopathy, stroke, peripheral vascular disease |

*Details not available in submission

**Responded to nitroglycerin, but not diagnosed conclusively

*Post-marketing serious adverse events*

Three serious adverse events are presented, all in subjects on the proposed dose. Only the last was deemed due to treatment.

1) Toe infection in a 41 year-old subject with no relevant medical history, 121 days after the start of treatment
2) Umbilical hernia in a 47 year-old subject with a history of peritoneal dialysis, 71 days after start of treatment
3) Infusion-related reduced blood pressure, increased sweating, bronchospasm, and somnolence in a 14 year-old subject 43 days after the start of treatment.

Recently received reports of serious adverse events

A recently received report of serious adverse events occurring through November 30, 2002, lists approximately 33 new serious adverse events. These events have not been reviewed in detail. About 13 of these events were in subjects on blinded treatment in AGAL-008-00, the rest were on open-label treatment, including about 16 in "special access" or postmarketing situations. The spectrum of events was not significantly different from events previously described in this review.

### Summary comments on additional safety data

The largest single group of events included possibly vascular: cardiac and neurological events. Some of these events occurred shortly after treatment. However, because of the lack of a control group, the predisposition of patients with Fabry's disease to vascular events, and the documented history of cardiac and neurological events in some of the subjects, there is not a strong safety concern at this time.

Infusion-related events were consistent with those in the clinical trial data presented earlier, and merit continued concern.

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## ANALYSES OF ANTIBODY EFFECTS

In Genzyme's antibody assay, serial dilutions start at 1/100, which Genzyme had determined from normal controls to be equivalent to a background signal. Genzyme judges that a 4-fold titer change, i.e., 2 dilutions, indicates a meaningful change. Genzyme states that the 1:800 titer "was chosen as the upper dilution that encompasses a less than 4-fold change from background signal."

**Genzyme's presentation of titer**

Genzyme creates a classification system for antibody titer among the 58 subjects from AGAL-1-002-98 and AGAL-005-99 and shows the numbers of subjects in each category. The duration of follow-up is not clear (it is noted as "last visit"). Each category in the list excludes the category that follows it:

- Withdrawn after 14 weeks of AGAL-005-99 not included: 1/58 (subject 304)
- Seronegative = never seroconverted ("up to 24 months"): 6/57
- "Low titer" = ≤800: 8/51
- Highest titer at last visit: 3/43
- Downward trend, ≥4-fold lower titer from peak: 28/40
  Plateau: 12/40

Genzyme describes their rationale for their choice of meaningful titers and changes in titer.

*Comments*

*If the 2/8 subjects in the "low responders" group who also showed a ³4-fold reduction in titer are included in the totals of those with such reductions, about 60% of all subjects showed a*

*reduction in titer, and 40% showed either no reduction or an increase in titer. However, a reduction of some degree from a peak value is expected.*

*Genzyme reports that as of the 24-month time point, 7 subjects who previously seroconverted had had two consecutive RIP assays that failed to reveal antibody. These results have not been reviewed in detail. The importance of these data to the chronic (years-long) administration of r-hαGal is unclear, as the possibility of resensitization has not been studied.*

**CBER analysis of data to 18 months of AGAL-005-99**

Table 37 and Table 38 show the titers of antibody to r-hαGal through the first 18 months of AGAL-005-99. The majority of subjects in the placebo/r-hαGal group seroconverted (25/28, with one additional subject from the placebo group in AGAL-1-002-98 remaining seropositive). Among the subjects who remained on r-hαGal from AGAL-1-002-98, 27/29 seroconverted at some point before or at infusion 41, and 26/29 subjects were seropositive at infusion 41 (with 1 missing observation).

**Table 37. Titers in those originally on placebo (“.” signifies 0 titer; “M” signifies missing)**

| | AGAL-1-002-98* | AGAL-005-99 | | |
|---|---|---|---|---|
| Subject ID | End | 6 months | 12 months | 18 months |
| 102 | . | 25600 | 25600 | 25600 |
| 103 | . | 400 | 800 | 1600 |
| 105 | . | 25600 | M | 3200 |
| 106 | . | 200 | 200 | 100 |
| 110 | . | 6400 | 1600 | 3200 |
| 111 | . | . | . | . |
| 113 | . | 200 | M | 100 |
| 116 | 6400 | 12800 | M | 51200 |
| 118 | . | 100 | 200 | 100 |
| 119 | . | 3200 | M | 1600 |
| 201 | . | 25600 | 204800 | 102400 |
| 303 | . | . | . | . |
| 304 | . | . | M | M |
| 306 | . | 12800 | 3200 | 1600 |
| 401 | . | 12800 | 6400 | 25600 |
| 502 | . | 3200 | 800 | 400 |
| 503 | . | 6400 | M | 1600 |
| 505 | . | 1600 | 1600 | 1600 |
| 506 | . | 6400 | 800 | M |
| 601 | . | 1600 | 400 | 400 |
| 603 | . | 6400 | 1600 | 1600 |
| 701 | . | 1600 | 3200 | 1600 |
| 703 | . | . | . | . |
| 704 | . | 12800 | . | . |
| 708 | . | 800 | 200 | 100 |
| 709 | . | 12800 | 12800 | 12800 |
| 802 | . | 3200 | 1600 | 1600 |
| 803 | . | 3200 | 1600 | 1600 |
| 805 | . | 12800 | 6400 | 6400 |

* All titers were 0 at baseline

**Table 38. Titers in those originally on r-hα Gal (“.” signifies 0 titer; “M” signifies missing)**

| | AGAL-1-002-98* | AGAL-005-99 | | |
|---|---|---|---|---|
| Subject ID | End | 6 months | 12 months | 18 months |
| 101 | 25600 | 3200 | 6400 | 6400 |
| 104 | 25600 | 12800 | M | M |
| 107 | 6400 | 6400 | 25600 | 51200 |
| 108 | 6400 | 3200 | 1600 | 1600 |
| 109 | 200 | . | . | 200 |
| 112 | 25600 | 6400 | 6400 | 25600 |
| 114 | 1600 | 800 | 1600 | 800 |
| 115 | 6400 | 12800 | M | 12800 |
| 117 | 12800 | 12800 | 12800 | 6400 |
| 120 | 12800 | M | M | 3200 |
| 202 | . | . | M | . |
| 203 | 200 | 400 | 800 | 200 |
| 301 | . | 400 | M | 200 |
| 302 | 12800 | 3200 | 3200 | 3200 |
| 305 | . | . | . | 100 |
| 307 | 12800 | 3200 | 3200 | 3200 |
| 402 | 12800 | 3200 | 3200 | 1600 |
| 501 | 6400 | 3200 | 1600 | 1600 |
| 504 | 6400 | 3200 | 400 | 800 |
| 602 | . | 200 | 200 | 200 |
| 604 | 12800 | 1600 | 3200 | 800 |
| 605 | . | . | . | . |
| 702 | 3200 | 100 | M | 100 |
| 705 | 25600 | . | 6400 | 25600 |
| 706 | 12800 | 3200 | 25600 | 6400 |
| 707 | 400 | 100 | 100 | 100 |
| 801 | 25600 | 25600 | 25600 | 12800 |
| 804 | 12800 | 3200 | 1600 | 3200 |
| 806 | 3200 | 3200 | 3200 | 3200 |

*Al titers were 0 at baseline except subject 115 (missing)

Genzyme’s choice of a titer of 800 as a threshold titer was based upon performance data from the assay, and were not based upon clinical criteria. CBER compared titers at 18 months of AGAL-005-99 to titers after about 5-6 months of treatment, using a measure that was not dependent upon the titer of 800. Table 39 shows the relationship of the 18-month titer in AGAL-005-99 to either the 6-month titer (subjects who were switched to r-hαGal from placebo in AGAL-005-99) or to end-of-trial titer in AGAL-1-002-98 in subjects who started on r-hαGal in AGAL-1-002-98. The trends are similar for the two groups. A substantial number of subjects had stable titers at 18 months.

**Table 39. Relation of AGAL-005-99 18-month titer to selected titers**

| | Placebo/r-hαGal *n=29* | R-hαGal/r-hαGal *n=29* |
|---|---|---|
| | 18 months to 6 months of AGAL-005-99 | 18 months to AGAL-1-002-98 end |
| Within 1 dilution | 13 | 11 |
| 2 or more dilutions less | 8 | 12 |
| 2 or more dilutions more | 3 | 3 |
| Missing | 2 | 1 |
| Never converted | 3 | 2 |

*Comment*

*A substantial number of subjects had stable titers at 18 months.*

## Analysis of antibody and histological and clinical effects

Adverse events related to infusion and development of antibody

Genzyme submits a graph of the proportion of subjects with adverse experiences related to infusion and proportion of subjects who have seroconverted. A spike in the proportion of subjects with related infusion reactions (to about 35-40%) occurs after the spike in seroconversion for each group. After the spike the proportion of subjects tapers at a somewhat different rate for each group, with small proportions (≤ about10%) of subjects experiencing related infusion reactions out to 18 months of AGAL-005-99. Genzyme states, "Analysis of the patients who experience the most common adverse events (e.g. rigors) does not indicate a correlation with antibody titer value." However, the analysis is not provided.

**Analyses of adverse events by titer**

Genzyme upon request provides analyses of adverse events using different means of describing antibody levels.

Table 40 shows the five most common infusion-related events by area-under-the-curve (AUC) of titer. Subjects are included in the analysis only if they were seropositive at some point (6 subjects remained seronegative) and had a titer measured at 18 months. Note that the value for the AUC of titer that defines each quartile differs between the two treatment arms, and that Genzyme omitted from this analysis subjects with no development of antibody (these results are seen in Table 42). Subjects in the placebo/r-hαGal group had a maximum of 18 months of treatment; those on r-hαGal, 23 months.

**Table 40. Numbers (%) of subjects with 5 most common adverse events, by treatment arm and AUC* of antibody**

| Placebo/r-hαGal | | | | |
|---|---|---|---|---|
| Adverse event | AUC Q1 N=5 | AUC Q2 N=5 | AUC Q3 N=5 | AUC Q4 N=6 |
| Rigors | 1 ( 20) | 3 ( 60) | 5 (100) | 4 ( 67) |
| Temperature changed sensation | 1 ( 20) | 1 ( 20) | 5 (100) | 1 ( 17) |
| Fever | 0 | 1 ( 20) | 3 ( 60) | 3 ( 50) |
| Flushing | 0 | 1 ( 20) | 2 ( 40) | 2 ( 33) |
| Chest pain | 0 | 2 ( 40) | 1 ( 20) | 1 ( 17) |
| R-hαGal/ r-hαGal | | | | |
| Adverse event | AUC Q1 N=6 | AUC Q2 N=6 | AUC Q3 N=6 | AUC Q4 N=6 |
| Rigors | 2 ( 33) | 5 ( 83) | 4 ( 67) | 4 ( 67) |
| Fever | 1 ( 17) | 3 ( 50) | 2 ( 33) | 3 ( 50) |
| Headache | 0 | 2 ( 33) | 2 ( 33) | 4 ( 67) |
| Temperature changed sensation | 2 ( 33) | 2 ( 33) | 1 ( 17) | 3 ( 50) |
| Nausea | 1 ( 17) | 1 ( 17) | 3 ( 50) | 2 ( 33) |

*AUC of titer by group:

placebo/r-hαGal: 63500 to <772000; 772000 to <1280000; 1280000 to <4854000; 4854000 to 41984000

r-hαGal/r-hαGal: 26000 to <1095000; 1095000 to <2556000; 255600 to <6032000; 6032000 to 10592000

Subjects were included if seropositive at some point, and had a titer at 18 months.

There tended to be fewer events in the lowest AUC group, regardless of duration of treatment. Relative incidences of the numbers of nonlisted events were more difficult to assess due to small numbers.

The same events were tabulated by peak titer (Table 41). Note that the titer groups could not be segregated into exactly equal numbers of subjects. Genzyme omitted subject 304 due to early discontinuation, and again omitted subjects with no development of antibody. The analysis combines subjects with about 23 months of active treatment (those who started on active treatment in AGAL-1-002-98) and subjects with 18 months of treatment (subjects who started on r-hαGal in AGAL-005-99).

**Table 41. Numbers (%) of subjects with the five most common infusion-related adverse events by peak titer, from start of treatment to 18 months of AGAL-005-99**

| Adverse event | titer 100-3200 N=15 | titer >3200-12800 N=15 | titer >12800-25600 N=12 | titer >25600-204800 N=9 |
|---|---|---|---|---|
| Rigors | 5 ( 33) | 12 ( 80) | 10 ( 83) | 6 ( 67) |
| Temperature changed sensation | 3 ( 20) | 7 ( 47) | 6 ( 50) | 2 ( 22) |
| Fever | 1 ( 7) | 5 ( 33) | 7 ( 58) | 4 ( 44) |
| Nausea | 2 ( 13) | 3 ( 20) | 6 ( 50) | 1 ( 11) |
| Headache | 0 | 5 ( 33) | 3 ( 25) | 3 ( 33) |

Subject 304 is excluded from this table. He was discontinued from the trial and antibody data were only available up to 14 weeks.

The five most common infusion-related events in AGAL-005-99 by Genzyme antibody response category are shown in Table 42.

**Table 42. Numbers (%) of subjects with the five most common infusion-related adverse events by Genzyme antibody response category from start of treatment to 18 months of AGAL-005-99**

| Adverse event | No response N=6 | Low response N=8 | Downward trend N=28 | Plateau N=12 | Highest at last visit N=3 |
|---|---|---|---|---|---|
| Rigors | 1 ( 17) | 2 ( 25) | 21 ( 75) | 8 ( 67) | 2 ( 67) |
| Temperature changed sensation | 1 ( 17) | 1( 13) | 11 ( 39) | 5 ( 42) | 1 ( 33) |
| Fever | 0 | 1 ( 13) | 9( 32) | 5 ( 42) | 2 ( 67) |
| Nausea | 1 ( 17) | 2 ( 25) | 8 ( 29) | 2 ( 17) | 0 |
| Headache | 1( 17) | 0 | 6 ( 21) | 4 ( 33) | 1 ( 33) |

*Subject 304 is excluded from this table. He was discontinued from the trial and antibody data were only available up to 14 weeks.

*Summary comments*

*The combining of groups with possibly different durations of time on treatment makes quantitative evaluation of the data using Genzyme's categories and peak titer problematic. In addition, numbers of subjects in the categories of titer are small. Given this marked limitation, combining all 3 analytical methods, there does seem to be a trend toward a lower incidence of infusion-related events in the lowest titer or no titer groups. The analyses are consistent with the evidence, previously presented by Genzyme, of the increased incidence of infusion-related events after the first occurrence of IgG antibody.*

**Analyses of creatinine by titer**

Table 43 shows creatinine change categorizations by AUC of titers. In this and the following creatinine analyses, it is remarkable that there is very little change in creatinine in any subject.

**Table 43. Creatinine changes from baseline of AGAL-1-002-98 to 18 months of AGAL-005-99 by AUC titer group**

| Placebo/r-hαGal | | | | |
|---|---|---|---|---|
| Category of creatinine change | AUC Q1 N=5 | AUC Q2 N=5 | AUC Q3 N=5 | AUC Q4 N=6 |
| No Change | 2 ( 40) | 2 ( 40) | 1 ( 20) | 3 ( 50) |
| < 0.5 Increase | 3 ( 60) | 1 ( 20) | 2 ( 40) | 2 ( 33) |
| >= 0.5 but < 1 Increase | 0 | 0 | 1 ( 20) | 0 |
| < 0.5 Decrease | 0 | 1 ( 20) | 0 | 1 ( 17) |
| R-hαGal/ r-hαGal | | | | |
| Category of creatinine change | AUC Q1 N=6 | AUC Q2 N=6 | AUC Q3 N=6 | AUC Q4 N=6 |
| No Change | 1 ( 17) | 1 ( 17) | 4 ( 67) | 2 ( 33) |
| < 0.5 Increase | 3 ( 50) | 2 ( 33) | 2 ( 33) | 4 ( 67) |
| >=0.5 but < 1 Increase | 1 ( 17) | 1 ( 17) | 0 | 0 |
| < 0.5 Decrease | 1 ( 17) | 2 ( 33) | 0 | 0 |

Table 44 shows creatinine patterns expressed in groups of peak titer. The results are consistent with the AUC analysis.

**Table 44. Creatinine changes from baseline of AGAL-1-002-98 to 18 months of AGAL-005-99 by peak titer group**

| Category of creatinine change | titer 100-3200 N=15 | titer >3200-12800 N=15 | titer >12800-25600 N=12 | titer >25600-204800 N=9 |
|---|---|---|---|---|
| No Change | 4 (27) | 4 (27) | 4 (33) | 2 ( 22) |
| < 0.5 Increase | 7 (47) | 6 (40) | 5 (42) | 6 ( 67) |
| >= 0.5 but < 1 Increase | 1 (7) | 1 (7) | 1 (8) | 0 |
| < 0.5 Decrease | 3 (20) | 3 (20) | 2 (17) | 0 |

Table 45 shows creatinine patterns by Genzyme categories of titer.

**Table 45. Creatinine changes from baseline of AGAL-1-002-98 to 18 months of AGAL-005-99, by Genzyme antibody category**

| Category of creatinine change | No response N=6 | Low response N=8 | Downward trend N=28** | Plateau N=12 | Highest at last visit N=3 |
|---|---|---|---|---|---|
| No Change | 3 ( 50) | 2 ( 25) | 8 (29) | 4 ( 33) | 0 |
| < 0.5 Increase | 1 ( 17) | 3 ( 38) | 12 (43) | 6 ( 50) | 3 (100) |
| >= 0.5 but < 1 Increase | 0 | 1 ( 13) | 2 (7) | 0 | 0 |
| < 0.5 Decrease | 2 ( 33) | 2 ( 25) | 4 (14) | 2 ( 17) | 0 |

*Subject 304 is excluded from this table. He was discontinued from the trial and antibody data were only available up to 14 weeks.
**Genzyme's tabulation does not include 28 subjects

*Comment*

*There was so little change in serum creatinine in any subject that it is impossible to measure an effect of antibody.*

**Analyses of capillary endothelium substrate accumulation scores and titer**

The effect of antibody titer on histology score in superficial capillary endothelium of the skin, interstitial capillary endothelium of kidney, and capillary endothelium of the heart was analyzed. However, these analyses were problematic due to small numbers of subjects with non-0 biopsies at the time points analyzed (6 months for kidney and heart; 18 months for skin). In addition, 30 month analyses of skin data suggest that the non-0 determinations may have been due to chance.

*Comments*

*None of the small number of subjects with non-0 scores for skin, heart, and kidney were in the group of subjects in the lowest antibody group. However, considering the limitations of these data, especially the small numbers of subjects with non-0 scores overall, this does not implicate the role of antibody notably.*

**Analyses of GFR and titer**

Table 46 shows glomerular filtration rate as a function of AUC of titer, measured at baseline and visit 11 of AGAL-1-002-98 and at 6, 12, and 18 months of AGAL-005-99, separated by treatment arm. Subjects are included only if they have both an inulin measurement and an antibody measurement. It should be noted that baseline values vary by antibody grouping. There is no pattern for the change from baseline based on AUC of titer for either treatment arm, but the numbers of subjects is too small to generate definitive conclusions.

**Table 46. Inulin-based GFR by AUC of antibody**

| Placebo/r-hαGal | | | | | | |
|---|---|---|---|---|---|---|
| Trial | Visit | | AUC Group 1 | AUC Group 2 | AUC Group 3 | AUC Group 4 |
| AGAL-1-002-98 | Baseline | *n* | *5* | *5* | *5* | *5* |
| | | Mean ± s.d. | 97 ± 23 | 105 ± 55 | 86 ± 38 | 103 ± 30 |
| | | Median | 102 | 130 | 86 | 111 |
| | Visit 11 | *n* | *4* | *5* | *3* | *3* |
| | | Mean ± s.d. | 86 ± 16 | 102 ± 52 | 117 ± 42 | 110 ± 38 |
| | | Median | 85 | 118 | 136 | 121 |
| AGAL-005-99 | 6 Mo | *n* | *5* | *5* | *4* | *6* |
| | | Mean ± s.d. | 111 ± 18 | 106 ± 38 | 101 ± 43 | 137 ± 64 |
| | | Median | 106 | 112 | 113 | 112 |
| | 12 Mo | *n* | *4* | *5* | *4* | *3* |
| | | Mean ± s.d. | 117 ± 32 | 112 ± 35 | 93 ± 47 | 79 ± 12 |
| | | Median | 105 | 113 | 114 | 84 |
| | 18 Mo | *n* | *4* | *3* | *3* | *2* |
| | | Mean ± s.d. | 96 ± 33 | 119 ± 37 | 132 ± 8 | 153 ± 122 |
| | | Median | 86 | 134 | 134 | 153 |
| R-hαGal/r-hαGal | | | | | | |
| Trial | Visit | | AUC Group 1 | AUC Group 2 | AUC Group 3 | AUC Group 4 |
| AGAL-1-002-98 | Baseline | *n* | *6* | *6* | *6* | *6* |
| | | Mean ± s.d. | 81 ± 22 | 65 ± 23 | 96 ± 20 | 84 ± 19 |
| | | Median | 82 | 69 | 99 | 77 |
| | Visit 11 | *n* | *4* | *4* | *2* | *4* |
| | | Mean ± s.d. | 83 ± 42 | 80 ± 30 | 104 ± 1 | 93 ± 31 |
| | | Median | 71 | 70 | 104 | 88 |
| AGAL-005-99 | 6 Mo | *n* | *4* | *6* | *6* | *5* |
| | | Mean ± s.d. | 72 ± 28 | 57 ± 12 | 100 ± 29 | 87 ± 21 |
| | | Median | 69 | 58 | 92 | 88 |
| | 12 Mo | *n* | *6* | *6* | *6* | *6* |
| | | Mean ± s.d. | 70 ± 22 | 86 ± 33 | 74 ± 21 | 78 ± 21 |
| | | Median | 67 | 84 | 68 | 76 |
| | 18 Mo | *n* | *3* | *4* | *2* | *4* |
| | | Mean ± s.d. | 68 ± 31 | 51 ± 23 | 91 ± 19 | 80 ± 12 |
| | | Median | 68 | 48 | 91 | 79 |

Table 47 shows inulin-based GFR by peak titer category as values at baseline and 18 months of AGAL-005-99, and change from visit 11 to 18 months of AGAL-005-99.

**Table 47. Inulin-based GFR based on groups of peak titer**

| | | | titer 100-3200 | titer >3200-12800 | titer >12800-25600 | titer >25600-204800 |
|---|---|---|---|---|---|---|
| Baseline AGAL-1-002-98 | Actual Value | *n* | *15* | *15* | *11* | *9* |
| | | Mean ± s.d. | 95±27 | 76±36 | 92±20 | 93±28 |
| | | Median | 99 | 68 | 96 | 77 |
| 18 Months Post Entry | Actual Value | *n* | *10* | *7* | *6* | *4* |
| | | Mean ± s.d. | 94±39 | 93±40 | 110±74 | 80±12 |
| | | Median | 86 | 78 | 95 | 79 |
| | % Change from Visit 11 | *n* | *7* | *5* | *4* | *4* |
| | | Mean ± s.d. | -18±22 | -27±18 | -18±27 | -11±18 |
| | | Median | -17 | -35 | -6 | -13 |

Numbers of subjects at later time points are small and firm conclusions are impossible to make. There is no apparent correlation with peak antibody titer and change in GFR.

Table 48 shows GFR by Genzyme antibody category. The numbers of subjects in most groups is very small, and baseline values differ from group to group; median values differ markedly from the mean in some cases. No trend is evident.

**Table 48. Inulin-based GFR based on Genzyme's categories of antibody response**

| | | | No response | Low response | Downward trend | Plateau | Highest at last visit |
|---|---|---|---|---|---|---|---|
| Baseline AGAL-1-002-98 | Actual Value | *n* | *6* | *8* | *28* | *11* | *3* |
| | | Mean ± s.d. | 94±23 | 91±23 | 82±30 | 92±31 | 120±5 |
| | | Median | 86 | 97 | 82 | 77 | 118 |
| 18 Months Post Entry | Actual Value | *n* | *4* | *5* | *14* | *6* | *2* |
| | | Mean ± s.d. | 121±25 | 100±50 | 86±37 | 112±67 | 95±1 |
| | | Median | 124 | 98 | 77 | 81 | 95 |
| | % Change from Visit 11 | *n* | *3* | *2* | *11* | *5* | *2* |
| | | Mean ± s.d. | 7±51 | -39±23 | -22±19 | -7±16 | -9±29 |
| | | Median | 6 | -39 | -14 | -3 | -9 |

*Comments*

*Analysis of GFR data is complicated by the dwindling numbers of observations at later time points, with potential for changes in subject characteristics. Consistent trends were not seen based on the categorizations requested.*

*Analyses of antibody effect on creatinine clearance was affected by sporadic determinations of creatinine clearance. These results were not reviewed in detail.*

## Summary comments on antibody data

Antibody development is nearly universal among subjects treated with r-hαGal. There is a temporal relationship to the development of IgG antibodies to the subsequent occurrence of infusion reactions.

The analyses of antibody titer were limited by the small subject numbers in the trials and are insufficient to generate conclusions about the effect of titer on various histological or clinical outcomes. Infusion-related event analyses suggested that the subjects with the lowest titers were the least prone to be affected. Biopsy data were difficult to assess due to the small numbers of non-0 scores; available longer term data on subjects with skin biopsies show that regressions seen in the 18-month data may have been chance observations. Serum creatinine did not change for subjects, so an effect of antibody could not be measured; GFR measurements were based on dwindling numbers

of subjects, with problems of interpretability. It is important to note that overall there appeared to be no change in GFR in either group, so a lack of effect in subgroups is not surprising.

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## CONCLUSIONS

I conclude the following from the additional clinical data, in conjunction with the data reviewed in my previous document:

- A treatment effect on a surrogate reasonably likely to predict benefit has been demonstrated.
- The lack of an observation of clinical benefit in the submitted trials does not negate the likelihood of the surrogate to predict clinical benefit, as prior trials were not designed with clinical efficacy as a goal. These trials were not well-suited to detect clinical efficacy effects.
- Safety events do not preclude the marketing of Genzyme's r-hαGal.

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## RECOMMENDATIONS

Approval under the Accelerated Approval regulations is appropriate. Under Accelerated Approval, a clinical trial is needed to verify that the product confers a clinical benefit. R-hαGal is expected to be given as a chronic treatment, so it will be especially important to monitor long-term effects of treatment. Given the widespread development of antibodies to the product, it will also be important to monitor for long-term antibody effects.