National PBM Drug Monograph
Agalsidase beta (Fabrazyme®)
July 2003

Introduction

Agalsidase beta (Fabrazyme®, Genzyme) received FDA approval for marketing in the U.S. on April 24, 2003. Agalsidase beta is the first treatment approved in the U.S. for patients with Fabry disease. It has also been approved in the European Union and six other countries.

Pharmacology[1-14]

Fabry disease (also referred to as Anderson-Fabry disease) is a rare X-linked recessive genetic disorder in which there is a deficiency of the lysosomal enzyme, α-galactosidase A (α-gal A). This enzyme is responsible for the degradation of glycosphingolipids with a terminal galactose molecule. In Fabry disease, there is a predominant accumulation of globotriaocylceramide (GL-3, also referred to as Gb_3) in many cell types of the kidneys, heart, skin, eyes, gastrointestinal system, and central and peripheral nervous systems. Patients may have the classic phenotype, where levels of α-gal A activity are low or not detectable or the variant phenotype, with detectable levels of enzyme activity.

The incidence of Fabry disease is reported to be 1 in 40,000 to 60,000 and is most typically seen in males, although some heterozygous females will also present with signs and symptoms of the disease. In a study of lysosomal storage disorders diagnosed in Australia, the incidence of Fabry disease was reported as 1 in 117,000, with a median diagnosis at age 28.6 years (range 0-55.7).

In patients with classic Fabry disease, accumulation of GL-3 is progressive with initial symptoms presenting during childhood, including burning pain in the hands and feet that is precipitated by exercise, fever, or stress. There may also be complaints of gastrointestinal symptoms and a rash consisting of angiokeratomas in the lower abdominal and thigh area. Hypohydrosis is a common symptom and anhidrosis may also occur. Corneal opacities may also be seen by slit-lamp examination. After the third decade, morbidity results from chronic deposition of GL-3 in the kidney, and cardiovascular and cerebrovascular systems. Initially, proteinuria may be seen with a progressive decline in kidney function resulting in end stage kidney failure, requiring dialysis or kidney transplantation. Cardiovascular manifestations include left ventricular enlargement, valvular abnormalities, and arrhythmias with mortality resulting from cardiomyopathy or myocardial infarction. Cerebrovascular manifestations of the disease include seizures, transient ischemic attacks, hemiplegia, and labyrinthe dysfunction. Patients with a variant form of Fabry disease may have more mild symptoms and typically present after the fourth decade primarily with cardiac manifestations and some with mild kidney involvement. It has been reported that treatment with galactose infusions may provide benefit in patients with this form of the disease. Treatment for patients with Fabry disease has typically been palliative or directed toward the resulting morbidity from the disease.

More recently, enzyme replacement therapy for Fabry disease has been shown to increase clearance of endothelial deposits of GL-3 in the kidney, liver, heart, and skin. Treatment has also been associated with a reduction in plasma GL-3 levels, a reduction in pain, and an improvement in quality of life indices. An improvement in kidney and cardiac measures also suggest enzyme replacement therapy may have long-term benefits although this has yet to be determined.

Agalsidase beta (Fabrazyme®) is a recombinant human α-galactosidase A enzyme, manufactured in Chinese hamster ovary cells, that provides an exogenous replacement of the enzyme to catalyze the hydrolysis of glycosphingolipids, including GL-3. Agalsidase alpha (Replagal™), a gene-activated human α-galactosidase A, obtained from human fibroblasts, has been approved in the European Union and eleven other countries, and a Biological License Application has been submitted for approval by the U.S. FDA. Biochemical comparisons of the two α-gal A enzyme replacement products found them to have comparable glycosylation and specific activities and were not able to provide an explanation for the differences in recommended doses of agalsidase beta (1 mg/kg) and agalsidase alpha (0.2 mg/kg). There have been no head to head clinical trials of the agents and the endpoints of the individual studies do not allow for a direct comparison. A clinical trial with agalsidase alpha demonstrated an improvement in neuropathic pain as the primary outcome with an improvement in kidney pathology and decrease in plasma GL-3 as secondary endpoints. The pivotal trial with agalsidase beta evaluated the primary endpoint of clearance of microvascular endothelial deposits of GL-3 from kidney biopsy specimens, the effect of which was sustained in an open-label extension trial.

Pharmacokinetics[4]

Pharmacokinetic studies of different doses of agalsidase beta (e.g., 0.3, 1.0, 3.0 mg/kg) in 15 patients with Fabry disease showed that the area under the plasma concentration-time curve (AUC) and clearance did not increase proportionately as the dose was increased and the enzyme follows non-linear pharmacokinetics. The terminal half-life was not dose-related and ranged from 45-102 minutes.

A varying pharmacokinetic response was found in a study of 11 patients with Fabry disease who were administered 1.0mg/kg agalsidase beta every 2 weeks. Some patients showed pharmacokinetic responses that were maintained with repeated dosing; some demonstrated a decrease from baseline at infusion 7, with a return to baseline by infusion 11 (the average AUC was 25% of baseline); some with elevated antibody titers to agalsidase beta were among the patients with an average decrease in AUC. The development of antibodies reduced C_{max} and AUC, but it did not affect half-life. It is unknown how developing antibodies will affect pharmacokinetic parameters on a chronic basis.

FDA Approved Indications and Off-label Uses[4]

Agalsidase beta (Fabrazyme®) is indicated for use in patients with a diagnosis of Fabry disease. It reduces deposition of GL-3 in kidney capillary endothelium and other cell types.

Dosage and Administration[4]

Dosage and infusion rate:

- The recommended dosage is 1.0 mg/kg by IV infusion every 2 weeks.
- Initial infusion rate should not exceed 0.25 mg/min (15 mg/hr). The infusion rate should be slowed if the patient develops infusion-associated reactions. Once patient tolerance has been determined, the infusion rate may be increased by increments of 0.05 to 0.08 mg/min (3 to 5 mg/hr) for each infusion thereafter. The manufacturer's prescribing information states that 31 of 58 patients (53%) received infusions of rates $\geq$ 33 mg/hr.
- Due to the high potential for infusion reactions, the patient should be given antipyretics prior to infusion (see **Warnings**).

Instructions for reconstitution and dilution:

- Reconstitution and dilution should be performed by aseptic technique.
- The product is supplied as a single-use 20 ml vial with 37 mg agalsidase beta (5 mg/ml with a total 35 mg per vial upon reconstitution). The number of vials needed should be determined based on the patient's weight. The vial should be stored in the refrigerator and allowed to come to room temperature (approximately 30 minutes) prior to reconstitution.
- Each vial should be reconstituted by slowly injecting 7.2 ml Sterile Water for Injection, USP down the inside wall of the vial. Gently roll and tilt each vial. Avoid shaking or agitating the product.
- The reconstituted solution should be clear and colorless. Do not use the solution if there is particulate matter or if it is discolored.
- Upon reconstitution, each vial will contain 5 mg/ml agalsidase beta with 7 ml total for extraction (35 mg).
- The reconstituted solution should then be diluted to a final total volume of 500 ml with 0.9% Sodium Chloride Injection, USP. The volume of 0.9% Sodium Chloride for Injection, USP equal to the volume of the reconstituted agalsidase beta patient dose should first be removed from 500 ml infusion bag and then the dose can be added for dilution.
  - Example: Patient weight = 80 kg; dose =80 mg
  - 80mg divided by 5 mg/ml = 16 ml agalsidase beta
  - Therefore, remove 16 ml Sodium Chloride solution from bag
- Slowly withdraw reconstituted agalsidase beta from each vial to obtain total patient dose. Inject dose directly into Sodium Chloride solution (do not inject into airspace).
- Invert bag gently to mix solution.
- Do not infuse solution in the same IV line with other products.
- The solution should be used immediately. If it is not possible to use immediately, the reconstituted and diluted solution may be stored at 36°-46°F for up to 24 hours. Discard any unused portion.

- It is recommended not to use filter needles during preparation.
- The manufacturer's product information states that an in-line low protein-binding 0.2μm filter may be used to filter the diluted solution during administration.

Pediatric Use: The safety and effectiveness of agalsidase beta have not been established in the pediatric patient population.

Geriatric Use: Sufficient numbers of patients age 65 or over were not included in the clinical trials to determine whether this patient population responds differently to those included in the trials.

Adverse Events (Safety Data)[4]

The most common and severe adverse effects with agalsidase beta are infusion reactions. The reactions were reported to include fever, rigors, tachycardia, hypertension, hypotension, chest pain, dyspnea, pruritus, urticaria, rash, throat tightness, lip or ear edema, headache, nausea, vomiting, abdominal pain. Patients were pretreated with acetaminophen and an antihistamine. Some patients experienced reactions despite pretreatment with an antipyretic, antihistamine, and oral steroid. The frequency of infusion reactions decrease with chronic therapy, although serious reactions may still occur after prolonged duration of treatment.

Additional serious adverse events included stroke, pain, ataxia, vertigo, bradycardia, cardiac arrest, arrhythmia, decreased cardiac output, hypoacusia, and nephrotic syndrome. Since these symptoms can also be a result of Fabry disease, there is not enough information to determine whether the frequency or severity of these adverse events were changed as a result of treatment with agalsidase beta.

Adverse events that were reported in at least 2 more patients on treatment compared to placebo during a placebo-controlled trial of 29 patients receiving 1mg/kg agalsidase beta every 2 weeks for 5 months are included in the table below.

Adverse Event	Placebo N=29 (%)	Agalsidase beta N=29 (%)
Body as a Whole		
Chest pain	3 (10)	5 (17)
Fever	5 (17)	14 (48)
Pain	3 (10)	6 (21)
Pallor	1 (3)	4 (14)
Rigors	4 (14)	15 (52)
Sensation of temperature change	1 (3)	5 (17)
Cardiovascular		
Cardiomegaly	1 (3)	3 (10)
Hypertension	0	3 (10)
Hypotension	2 (7)	4 (14)
Edema dependent	1 (3)	6 (21)
Central and Peripheral Nervous System		
Dizziness	2 (7)	4 (14)
Headache	11 (38)	13 (45)
Paresthesia	2 (7)	4 (14)
Gastrointestinal		
Dyspepsia	1 (3)	3 (10)
Nausea	4 (14)	8 (28)
Musculoskeletal		
Arthrosis	0	3 (10)
Skeletal pain	0	6 (21)
Psychiatric		
Anxiety	5 (17)	8 (28)
Depression	1 (3)	3 (10)
Reproductive		
Testicular pain	0	2 (7)
Respiratory		
Bronchitis	3 (10)	1 (3)
Bronchospasm	0	2 (7)
Laryngitis	0	2 (7)
Pharyngitis	2 (7)	8 (28)
Rhinitis	7 (24)	11 (38)
Sinusitis	0	2 (7)

Contraindications[4]

There are no known contraindications.

Warnings[1,4]

Due to the common occurrence of infusion reactions with agalsidase beta (see **Adverse Events**), it is recommended that patients receive antipyretics prior to infusion. If a patient experiences a reaction, recommended interventions include decreasing the rate of or temporarily stopping the infusion, and/or giving antipyretics (regardless of pretreatment), antihistamines, and/or steroids. Since some infusion reactions have been severe, it is important to have appropriate medical support available when administering agalsidase beta, at least for the first 6 months of therapy.

Precautions[4]

Patients with advanced Fabry disease and/or compromised cardiac function should be monitored closely if it is decided to administer agalsidase beta since these patients may be predisposed to severe complications from infusion reactions.

Patients with suspected allergic reactions may be considered for IgE testing and the risk vs. benefit of continued therapy be considered in patients who develop IgE or skin test reactivity specific to agalsidase beta. Most patients will develop IgG antibodies to agalsidase beta. According to prescribing information, 89% of patients in clinical studies have developed antibodies to agalsidase beta (most within the first 3 months of treatment).

Pregnancy Category B: There have been no adequate or well-controlled trials conducted in pregnant women. Studies in rats at a dose up to 30 times the human dose have not demonstrated impaired fertility or adverse effects on embryo fetal development. The manufacturer recommends that agalsidase beta be used during pregnancy only if clearly needed.

Nursing Mothers: Use caution in nursing women since it is unknown whether agalsidase beta is excreted in human breast milk.

Registry: Patients with Fabry disease should be informed of the established Registry to evaluate disease progression and chronic treatment with agalsidase beta. The effects of agalsidase beta on pregnant women and their offspring are being monitored as well as whether agalsidase beta is excreted in breast milk. Information is available at **www.fabryregistry.com** or (800) 745-4447.

Drug Interactions[1,4]

No drug interaction studies have been performed.

Due to the theoretical inhibition of intracellular α-gal A activity, agalsidase beta should not be administered concomitantly with amiodarone, chloroquine, gentamicin, or monobenzone.

Efficacy Measures

Primary Endpoints (in pivotal trial)
- Percent of patients without microvascular endothelial deposits of GL-3 in kidney biopsy specimens

Secondary Endpoints
- Composite score of kidney, heart, and skin microvascular endothelial deposits of GL-3
- Change from baseline of GL-3 in kidney specimens and urinary sediment
- Level of pain (assessed by Short Form McGill Pain Questionnaire)

Clinical Trials[5-7]

<table>
<tr><td>Citation[5]</td><td>Eng CM, Banikazemi M, Gordon RE, et al. A phase 1/2 clinical trial of enzyme replacement in Fabry disease: pharmacokinetic, substrate clearance, and safety studies. Am J Hum Genet 2001;68:711-22.</td></tr>
<tr><td>Study Goals</td><td>• To evaluate the safety and pharmacokinetics of agalsidase beta infusions
• To provide preliminary efficacy data for enzyme replacement therapy in Fabry disease</td></tr>
<tr><td>Methods</td><td>• Study Design
➢ Single-center, open-label, multi-dose, dose escalation
➢ Patients were enrolled sequentially into the following 5 different dosing regimens of agalsidase beta with 3 patients in each treatment group. Agalsidase beta was diluted with saline to 100 ml with an IV infusion rate of 0.83 ml/min.
♦ Group A: 0.3 mg/kg biweekly
♦ Group B: 1.0 mg/kg biweekly
♦ Group C: 3.0 mg/kg biweekly
♦ Group D: 1.0 mg/kg q48h
♦ Group E: 3.0 mg/kg q48h
➢ Medical history, physical examination, vital signs, serum and urine chemistries, hematology indices and ECGs were obtained at baseline, before each infusion, and after infusion 5. An echocardiogram and renal MRI were also obtained at baseline and after infusion 5. Quality of life (QOL) measures were assessed at baseline and after infusion 5 using the Short Form McGill Pain Survey and Short Form-36 Health Survey. Patients continued any prophylactic and analgesic pain medications. Antibody response was assessed at baseline, before each infusion, and after infusion 5.
➢ Plasma levels of GL-3 were obtained at baseline, prior to each infusion, and either 14 days (Groups D and E) or 21-28 days (Groups A-C) after infusion 5.
➢ Tissue biopsies of liver and skin were taken at baseline and 2 to 3 days after infusions 1 and 5.
➢ A subset of patients in Groups C-E had optional endomyocardial and kidney biopsies at baseline and after treatment.
➢ Blood samples were obtained at 30, 60, and 90 minutes during the infusions 1 and 5, and at additional time points 0 to 480 minutes after the infusions. Area under the curve (AUC), area under the moment (AUMC), peak concentration of α-gal A (C_{max}), time to peak (T_{max}), terminal elimination half-life ($t_{½}$), steady-state volume of distribution (VSS), clearance, mean residence time extrapolated to infinity (MRT), and elimination rate constant (λ_z) were determined.
➢ A four-point scoring system of 0 (normal to near normal) to 3 (severe) was used to evaluate GL-3 content in tissue samples. A range of 0 to 5 was used to evaluate vascular endothelium of the skin.
• Statistical Analysis
➢ Data was analyzed using the Statistical Software System (SAS Institute). The SF-36 health scoring system was used to analyze the SF-36 questionnaire. The change from baseline for QOL and pain was calculated using a Wilcoxan signed rank test.</td></tr>
<tr><td>Criteria</td><td>• Inclusion criteria
➢ Men age ≥ 16 years with a diagnosis of classic Fabry disease
➢ Plasma α-gal A activity < 1.5 nmol/h/ml
➢ Plasma GL-3 concentration ≥ 5.0 ng/μl
➢ Serum creatinine < 2.5 mg/dl
• Exclusion criteria
➢ History of renal disease or transplantation</td></tr>
<tr><td>Results</td><td>• Table 1. Plasma GL-3 Clearance
<table>
<tr><th>Dose</th><th>Plasma GL-3 Concentration</th></tr>
<tr><td>Baseline</td><td>2.0-53.9 ng/μl (mean 17.1 ± 12.8 ng/μl)</td></tr>
<tr><td>Group A</td><td>↓ with each treatment; lowest value at infusion 5</td></tr>
<tr><td>Group B</td><td>Infusion 1: Clearance in 2 of 3 patients; 1 of 3 patients ↓ but never undetectable</td></tr>
<tr><td>Group C</td><td>Infusion 1: Completely cleared
Infusion 5: Continued to be undetectable</td></tr>
<tr><td>Groups D&E</td><td>Lowest at infusion 4; not as low as biweekly dosing (data not shown)</td></tr>
</table>
• Table 2. Tissue GL-3 Clearance
<table>
<tr><th>Organ</th><th>Group A</th><th>Group B</th><th>Group C</th><th>Group D</th><th>Group E</th></tr>
<tr><td>Liver</td><td>↓ 93.5%</td><td>↓ 66.7%</td><td>↓ 92%</td><td>↓ 81.7%</td><td>↓ 94%</td></tr>
<tr><td>Heart</td><td>NA</td><td>NA</td><td>↓ 15%</td><td>↑ 1.3%</td><td>↑ 93%</td></tr>
<tr><td>Kidney</td><td>NA</td><td>NA</td><td>↓ 95%</td><td>↓ 69%</td><td>↑ 203%</td></tr>
</table>
➢ Histologic scores
♦ Liver
o Sinusoid endothelial GL-3 accumulation scores: ↓ from baseline 2.4 ± 0.74 (n=15) to 0.5 ± 0.52 after infusion 5 (n=14). A dose effect was noted for patients in Groups A, B, and C.
o Mean Kupffer cell scores: ↓ from 2.8 ± 0.56 (n=15) to 1.07 ± 0.27 (n=14)
♦ Heart
o Mean capillary endothelium scores: ↓ from baseline 1.75 ± 0.89 (n=7) to 0.57 ± 0.79 after treatment (n=7); biopsies obtained by patients from Groups C, D, and E. A dose effect was noted for patients in</td></tr>
</table>

	Groups A, B, and C. o Mean Kupffer cell scores: ↓ from 2.8 ± 0.56 (n=15) to 1.07 ± 0.27 (n=14) ♦ Kidney o Endothelium of interstitial capillaries: ↓ in 4 of 5 patients, ↑ in 1 patient. o Reductions were seen in the glomerular mesangial cells, cortical interstitial cells. There was a trend toward ↓ scores in the distal convoluted tubules and collecting ducts. o Deposits in the glomerular podocytes did not appear to respond to treatment. • Pharmacokinetic Data ➢ Clearance: via saturable and nonsaturable pathways; decreased with increasing doses (from 4 ml/min/kg to ~ 1 ml/min/kg) and was independent of concentration ➢ AUC: Did not increase proportionally with dose (from ~ 80 to ~ 500 to ~ 4000 μg/min/ml) ➢ Mean VSS: 80-330 ml/kg ➢ Terminal $t_{½}$: Not affected by dose • Clinical Findings ➢ No a change in ECG, echocardiogram, or renal MRI. ➢ Anecdotal reports of less fatigue and an increased ability to sweat. ➢ Overall Pain and Present Pain Intensity scores improved from baseline to final treatment (P=0.03, P=0.004, respectively) for all doses. ➢ Improvements in Bodily Pain, General Health, and Vitality were seen as measured by the SF-36. • Safety ➢ Thirteen patients completed the treatment protocol. ➢ The most common adverse event was a transient, mild to moderate increase in blood pressure during infusion (treatment was not required). ➢ Four patients experienced hypersensitivity-type symptoms. Two of which had transient fever and chills, 1 with hives, and 1 with tachycardia. Two of the 4 patients were unable to tolerate infusion 5. ➢ Eight patients developed IgG antibodies to agalsidase beta. ➢ One patient was diagnosed with a pulmonary embolus after stopping 7 months of anticoagulant therapy for a deep vein thrombosis.
Conclusions	• Clearance of GL-3 was dose dependent and also dependent on the organ tissue. • Biweekly dose regimens were more effective than the dose given q48h. • Infusion of agalsidase beta was generally well tolerated with mild reactions that could be managed with conservative treatment. • This study supported follow-up evaluation of enzyme replacement therapy to reverse GL-3 accumulation.
Critique	• Strengths ➢ Supported follow-up evaluation of enzyme replacement therapy to reverse GL-3 accumulation ➢ Gained experience with infusion reactions to guide future studies • Limitations ➢ Open-label, not placebo-controlled ➢ Small number of patients in each group ➢ Inclusion criteria included plasma GL-3 concentration ≥ 5.0 ng/μl, yet baseline values 2.0-53.9 ng/μl (normal undetectable level < 1.2 ng/μl) ➢ Inadequate details of data for q48h dosing ➢ Details on the use of pain medication not included ➢ Details of pain and QOL assessments were limited; authors acknowledged that these measures required further evaluation in a large, double-blind study
Sponsorship	• Grants from the National Institutes of Health, including a Merit Award, a grant for the Mount Sinai General Clinical Research Center, and a grant for the Mount Sinai Child Health Research Center • Research grant from the Genzyme Corporation

Citation[6]	Eng CM, Guffon N, Wilcox WR, et al. for the International Collaborative Fabry Disease Study Group. N Engl J Med 2001;345:9-16.
Study Goals	To test the safety and efficacy of agalsidase beta in patients with Fabry disease
Methods	• Study Design ➢ **Multicenter, randomized, double-blind, placebo-controlled trial for 20 weeks:** 58 patients received either placebo or agalsidase beta 1 mg/kg IV at 0.25 mg/min every other week (11 infusions total); patients received pretreatment with acetaminophen 1000 mg and hydroxyzine 25 to 50 mg (ibuprofen, prednisone, or both were used in a few patients for infusion-related reactions). ➢ **Open-label extension trial of 6 months duration:** all patients received agalsidase beta 1 mg/kg IV every other week with the infusion rate increased as tolerated. ➢ Medical history, physical examination, routine chemical analyses, and hematologic indices were obtained at baseline and prior to each infusion. An echocardiogram and plasma and 24-hour urinary sediments were also obtained at baseline, at the end of the double-blind study, and at 6 months in the extension study. ➢ Inulin clearance was measured at baseline and at 6 months in the extension study to evaluate glomerular filtration rates. ➢ Plasma, tissue, and urinary sediment concentrations of GL-3 were obtained.

- Antibodies to agalsidase beta were assessed prior to each infusion.
- Tissue biopsies of kidney, heart and skin were obtained to assess for microvascular endothelial GL-3 deposits. Specimens were scored according to the following grading scale:
  - 0: none or trace amounts
  - 1: majority of vessels had a single endothelial inclusion
  - 2: several vessels with multiple sites of single or multiple inclusions
  - 3: large accumulations of inclusions with some at the juxtanuclear region and around cytoplasmic borders and bulging vessel lumens
  - Kidney biopsy specimens that were initially graded as 0 or 1 were reevaluated with a similar scoring system with slight modifications
- The primary endpoint was the percent of patients without microvascular endothelial deposits of GL-3 in kidney biopsy specimens after 20 weeks of treatment.
- Secondary endpoints included composite score for microvascular endothelial deposits of GL-3 in heart, kidney, and skin; change in GL-3 concentrations from baseline in kidney specimens and urinary sediment; level of pain as assessed using the Short Form McGill Pain Questionnaire.

- Data Analysis
  - Chi-square analysis was conducted to compare the percent of patients with a kidney biopsy score of 0 after 20 weeks of treatment with agalsidase beta or placebo, and 6 months after treatment in the open-label extension study. Two-sample, two-tailed tests were used with a P value $\leq$ 0.05 as statistically significant.
  - The rank sum score for each patient was obtained for the changes in concentration of GL-3 in kidney specimens and urinary sediment. A two-sample Wilcoxon rank-sum test was used to evaluate the change from baseline to 20 weeks.
  - The mean change from baseline to 20 weeks in the level of pain for each treatment group was assessed using t-tests. A Wilcoxon signed-rank test was used to compare the mean change from baseline in the SF-36 for each group.
  - An analysis of variance was used to compare the changes between groups in GFR from baseline to 6 months.

Criteria

- Inclusion criteria
  - Patients $\geq$ 16 years of age with an enzymatically confirmed diagnosis of classic Fabry disease
  - Plasma α-gal A activity < 1.5 nmol/h/ml or < 4 nmol/h/mg in leukocytes
- Exclusion criteria
  - Serum creatinine > 2.2 mg/dl
  - Undergoing dialysis or history of kidney transplantation

Results

- Table 1. Baseline Data

Characteristic	Placebo (N=29)	Agalsidase beta (N=29)
Mean age (yrs)	28.4 ± 11.4 (range 17-61)	32.0 ± 9.4 (range 16-48)
Weight (kg)	69.6 ± 13.4	67.3 ± 9.9
Height (cm)	175.6 ± 8.3	175.7 ± 8.3
Gender (number)		
Race (number)		
Plasma GL-3 (ng/ml)	14.6 ± 9.6	14.5 ± 10.5
GFR (ml/min)	96.6 ± 35.3	83.0 ± 22.0
Serum creatinine (mg/dl)	0.8 ± 0.2	0.8 ± 0.2

- Primary Endpoint (% of patients with GL-3 score=0 in kidney biopsy at 20 weeks)
  - Placebo: 0/29 (0%) with score=0
  - Agalsidase beta: 20/29 (69%) with score=0 (P<0.001 vs. placebo); 8/9 remaining patients score=1; 1 patient assigned score=3 due to missing specimen
- Secondary Endpoints
  - Table 2. Mean Change in GL-3 Scores*

	Mean Change 0.1 ± 2.0 -4.2 ± 1.8* *Comparison between placebo and agalsidase beta P < 0.001 ➢ Median % change in GL-3 concentration ♦ Kidney specimen: Placebo ↑42.8%; agalsidase beta ↓23.3% ♦ Urinary sediment: Placebo ↑6.2%; agalsidase beta ↓34.1% ➢ Median change in rank-sum scores for kidney and urinary sediment GL-3 concentration was significantly decreased with agalsidase beta compared to placebo (↓48.0% vs. ↓32.5%; P=0.003) ➢ Pain level using the Short Form McGill Pain Questionnaire ♦ Both treatment groups demonstrated statistically significant decreases in pain scores for all pain parameters (e.g., sensory pain, affective pain, pain measured on visual analogue scale, present pain intensity, and total pain) at week 20; there was not a significant difference between treatment groups. • Other Measures ➢ Plasma GL-3 clearance: All 20 of the patients with GL-3 score=0 in kidney biopsy at 20 weeks had undetectable levels of GL-3 (<1.2 ng/μl); 5 of the 8 patients with a score=1had undetectable levels at week 20 and the remaining 3 demonstrated a decreased (12 to 94% of their baseline levels). The patient with the missing kidney biopsy specimen had a level of 3.9 ng/μl. ➢ QOL: Patients receiving agalsidase beta showed significant improvements in physical role and emotional role of the SF-36; patients on placebo had significant improvements in physical role and body-pain evaluations of the SF-36. • Open-Label Extension Study ➢ All 58 patients were included ➢ At 6 months, 43 patients had a biopsy performed with 42 of 43 (98%) having a score=0 on kidney specimens; 45 of 47 patients (96%) had a score=0 for skin specimen; 24 of 32 patients (75%) had a score=0 for heart specimens. Similar results were seen when only the patients who were previously in the placebo group were analyzed. In 95% of patients previously on active treatment, the kidney scores were maintained or further decreased during the open-label extension. There was not a significant change in GFR from baseline in either the placebo or active treatment group after week 20, or after 6 months of open-label treatment with agalsidase beta. • Safety ➢ Table 3. Adverse Events During 20 Week Trial (in at least 10% patients on agalsidase beta)

Adverse Event	Placebo N=29 (%)	Agalsidase beta N=29 (%)
Rigors	0	14 (48)*
Fever	1 (3)	7 (24)**
Headache	2 (7)	5 (17)
Chills	0	4 (14)
Pain related to disease	1 (3)	3 (10)
Hypertension	3 (10)	3 (10)

*P=0.004 vs. placebo
**P=0.024 vs. placebo

	➢ Infusions were generally well tolerated; transient, mild to moderate infusion reactions were reported in 34 of 58 (59%) of patients during the 20 week and 6 month trials. Symptoms were controlled with preventive medications and/or reducing the infusion rate. Treatment was discontinued in 1 patient who developed a positive skin test to agalsidase beta during the extension trial. ➢ In 51 of 58 patients (88%), IgG seroconversion occurred. This was reported not to affect the endpoints of the study. In 15 of 26 patients (58%) in the active treatment group during the 20 week study, IgG titers decreased after 12 months of treatment. One patient with low titers became seronegative. ➢ There were no significant changes in echocardiograms or ECGs compared to baseline in either trial.
Conclusions	• Treatment with agalsidase beta resulted in clearance of microvascular endothelial deposits of GL-3 in kidney (ARR 69%; NNT 1.45), heart, and skin. • Clearance was maintained or further decreased during the extension trial.
Critique	• Strengths ➢ Relatively large number of patients considering prevalence of disease ➢ Double-blind, randomized, placebo-controlled trial for 20 weeks ➢ Long-term extension study for 6 months • Limitations ➢ Unclear as to whether results translate into long-term positive outcomes in patients with Fabry disease ➢ Treatment did not appear to have a significant impact on pain or QOL ➢ Patients were allowed to continue prophylactic or analgesic medications during the study ➢ Criteria for biopsy selection in open-label extension study not described
Sponsorship	• Merit Award from the National Institutes of Health • Grants from the National Institutes of Health to the General Clinical Research Centers at the Mount Sinai School of Medicine and Cedars-Sinai Medical Center, and to the Mount Sinai Child Health Research Center • Grant from the Genzyme Corporation
Additional analyses[7]	• Details of pathologic changes in the distribution of glycosphingolipids and post-treatment kidney clearance were reported with the following observations:

	➢ Accumulations of GL-3 were seen in kidney vascular endothelial cells, vascular smooth muscle cells, mesangial cells, insterstitial cells, with dense accumulations in podocytes and distal tubular epithelial cells at baseline. ➢ After treatment for 11 months with agalsidase beta (according to the study design described above), there was complete clearance of GL-3 from all vascular endothelial cells, mesangial cells of the nucleus, and interstitial cells of the renal cortex. Clearance was also seen in the smooth muscle cells of arterioles and small arteries. Limited clearance was seen in podocytes and distal tubular epithelial cells. ➢ The conclusions of this paper were that treatment with agalsidase beta may prevent the kidney failure seen in patients with classic Fabry disease by stopping the pathologic changes caused by GL-3 accumulation. • Sponsorship included grants from the National Institutes including a Merit Award, a grant for the Mount Sinai General Clinical Research Center Program from the National Center of Research Resources, a grant for the Mount Sinai Child Health Research Center, and a research grant from the Genzyme Corporation

Abstracts[14-22]

Agalsidase beta[14-21]

Abstract[4] Desnick RJ. Enzyme replacement therapy in Fabry disease: pathologic, biochemical, and immunologic results at 6 and 12 months of Phase 3 extension study. Presented at the Meeting of the American Society of Human Genetics 2001.
• Additional results from phase 3 extension study • Abstract states that infusion times have been decreased to 3h • Reductions in GL-3 were seen in endothelial cells of deep skin vessels and from perineurium cells • In most patients, plasma GL-3 levels were cleared to below detectable limits at 6 and 12 months • After 12 months, 7 of 58 patients (12%) were seronegative, 8 of 58 patients (14%) that seroconverted were low responders, and 29 of 43 patients (67%) had IgG titers that were decreased by more than two-fold • These and other reported results of the phase 3 extension study show that agalsidase beta is safe and effective in patients with Fabry disease

Abstract[15] Germain DP, Caplan L, Eng C, et al. Long-term efficacy and safety of enzyme replacement therapy in Fabry disease. Eur J Hum Genet 2002;10:70.
• Results at 12 months of phase 3 extension study • 55 of 58 patients (95%) continued on treatment for 12 months • Mean infusion time was 2.25h • Agalsidase beta was well tolerated with some minor infusion reactions that were managed conservatively; the incidence of infusion reactions decreased over time • The infusion reactions were associated with IgG antibody seroconversion (this did not affect the results). In 50% of patients, IgG titers decreased over time (by at least four-fold) • Kidney function was stable during the study. A subgroup of high-risk patients (e.g., > 35yrs of age; creatinine clearance < 80 ml/min) showed stable kidney function at the 18 month evaluation • Plasma GL-3 was reduced 100% after 12 months; GL-3 was also cleared or reduced in kidney and skin cell types evaluated • Pain scores (using the Short Form McGill Pain questionnaire) improved with treatment • It was concluded that long-term therapy with agalsidase beta is well tolerated and safe; treatment reverses that pathology of the disease and provides clinical benefit

Abstract[16] Wilcox W, Germain DP, Banikazemi M, Lee P, and the International Fabry Study Group. Enzyme replacement therapy in Fabry disease: long term safety and efficacy update on a Phase 3 study. Presented at the American Society of Human Genetics 2002.
• Additional 18 month follow-up of phase 3 open-label extension study • All 58 patients were enrolled and treated with agalsidase beta • GFR and average serum creatinine levels remained stable after 18-24 months and average serum creatinine levels have been within normal limits • The overall improvement in pain scores (by the Short Form McGill Pain Questionnaire) have been maintained during the study period • At 18 months, 52 of 58 patients (90%) IgG seroconverted with 44 of 52 patients (85%) seroconverting within 3 months of treatment which did not affect efficacy; the majority of patients that seroconverted patients had a reduction of four-times or more in titer over the length of the study • At 12 months, GL-3 reduction in multiple kidney cell types is sustained with treatment as is GL-3 clearance • The frequency of reactions during infusion has markedly decreased over time; this is in spite of progressive increases in the rate of administration • After 18 months of the extension trial, 50 of 58 patients (86%) completed one or more infusions of agalsidase beta $\leq$ 2.5 hours; 35 of 58 patients (60%) completed one or more infusions $\leq$ 2.0 hours • Long-term treatment with agalsidase beta is safe and effective

Abstract[17] Guffon N, Wilcox W, Banikazemi M, et al. Long term safety and efficacy of enzyme replacement therapy for Fabry disease. Presented at the American College of Medical Genetics 9th Annual Clinical Genetics Meeting 2003.
• Additional 24 month follow-up of phase 3 open-label extension study • All 58 patients were enrolled and treated with agalsidase beta • IgG antibodies developed in 52 of 58 patients (90%), with the median time to seroconversion at 6 weeks • At 24 months, 7 of 52 patients (13.5%) had no detectable IgG antibody • The majority of patients who seroconverted (50%) had a reduction of four-times or more in titer over the 24 month period • The frequency of reactions during infusion has markedly decreased over time; this is in spite of progressive increases in the rate of administration • After 24 months of the extension trial, 53 of 58 patients (91%) completed one or more infusions of agalsidase beta ≤ 2.5 hours; 44 of 58 patients (76%) completed one or more infusions ≤ 2.0 hours • Mean serum creatinine has remained stable after 24-30 months of therapy • Long-term treatment with agalsidase beta continues to be safe and effective

Abstract[18] Eto Y, Ohashi T, Utsunomiya Y, et al. Enzyme replacement therapy in Japanese Fabry disease patients. Presented at the Meeting of the American Society of Human Genetics 2002.
• Open-label, phase 2 study in 13 male Japanese patients 16-34 years of age (mean 26.6) with Fabry disease, treated with 1 mg/kg agalsidase beta biweekly for 20 weeks • Normal to near-normal decrease in GL-3 accumulation in kidney and skin capillary endothelial cells was seen in 12 of 13 patients (92%) at 20 weeks (P<0.001); median GL-3 levels in the kidney decreased by 51.9% (P=0.003) and in plasma by 100% (P<0.001); kidney function, evaluated by serum creatine levels and creatinine clearance, remained normal • Improvement in many categories of pain and QOL as assessed by the Short Form McGill Pain and SF-36 Health Survey questionnaires were seen compared to baseline • Infusion reactions were the most common adverse events and included fever and rigors • IgG antibody formation was seen in 11 of 13 patients (85%) patients, but this did not affect efficacy; IgE antibody formation was not seen • Treatment with agalsidase beta is safe and effective in the study population

Abstract[19] Breunig F, Weidemann F, Strotmann J, Beer M, Krane V, Wanner C. Ambulatory enzyme replacement therapy and clinical evaluation in Fabry's disease. Presented at the Meeting of the American Society of Human Genetics 2002.
• Study to determine feasibility, safety, and side effects of therapy in patients with Fabry disease • Patients with Fabry disease (16 male and 2 female; mean age 42.4 yrs, range 29 to 57) were treated with agalsidase beta 1mg/kg biweekly for 8.2 months (range 3-12); patients received pretreatment with antipyretics and antihistamines • Infusion time was reduced from 240 to 150 min without an increase in reported adverse events • Treatment was well tolerated although fatigue was a frequent side effect after treatment; 3 patients had chills without fever; 1 patient experienced rigor; 1 patient reported leg cramps; 1 patient experienced vertigo; 1 patient began hemodialysis after 2 months of agalsidase beta (baseline creatinine clearance 7 ml/min) • A clinical evaluation program was established to document baseline status and the course of the disease during enzyme replacement therapy • It was concluded therapy with agalsidase beta in patients with Fabry disease is feasible and safe

Abstract[20] Guffon N. The clinical benefit of Fabrazyme® treatment. J Inherit Metab Dis 2002;25:166.
• Retrospective evaluation of clinical benefit in 16 patients mean age 31.4 yrs (range 16 to 54) with Fabry disease treated with agalsidase beta 1mg/kg biweekly for 19.7 months (range 8 to 29) • Patients were asked to complete a 9 item questionnaire on pain, medication use, heat tolerance, physical activity, fatigue, frequency of bowel movements, and psychological status on a scale from 1 (lowest) to 10 (highest) • At baseline, 88% of patients reported hand/feet pain (mean scores 4.3), 75% reported pain crises (mean 5.4 crises per month with 9.6h duration), 56% were on pain medications, carbamazepine dose was 444mg/d; mean score for heat tolerance was 2.8, physical activity 2.8, fatigue 5.9, and psychological status 5.5; average frequency of bowel movements 3.1/d • After treatment, mean scores for hand/feet pain decreased by 2.1 (P=0.027); frequency of pain crises decreased by 2.1 crises per month (P=0.033); mean score for heat tolerance was increased by 2.8 (P=0.000); physical activity increased by 2.3 (P=0.003); and psychological status increased by 2.3 (P=0.001); mean frequency of bowel movements were decreased by 0.8/d (P=0.029); there were no significant differences in fatigue, use of pain medications, or duration of pain crises • Treatment with agalsidase beta appeared to have clinical benefit in patients with Fabry disease

Abstract[21] Germain DP, Bonfils P, Boutouyrie P, et al. Enzyme replacement therapy with recombinant alpha-galactosidase A in Fabry disease: preliminary experience in patents with end-stage renal disease or post transplant. Presented at the Meeting of the American Society of Human Genetics 2001.
• Open-label study of 8 patients with Fabry disease who were not eligible for the phase 3 trial due to serum creatinine > 2.2 mg/dL, dialysis, or post kidney transplant (6 patients with advanced disease including 4 post transplant; 1 patient on peritoneal dialysis; 1patient on hemodialysis)
• Patients were treated with agalsidase beta 0.8-1.2 mg/kg at 0.25 mg/min biweekly for 16 weeks
• At 4 months, there was no report of adverse events or infusion reactions
• Treatment with agalsidase beta appears to be safe in patients with Fabry disease who are on dialysis or post transplant
• The authors plan to evaluate efficacy at 6 and 12 months and immunologic evaluation is ongoing

Comparison of algalsidase beta vs. agalsidase alpha[22]

Abstract[22]Linthorst GE, Speijer D, Hollack CEM, Aerts JMFG. Therapy for Fabry disease: comparison of agalsidase alpha and beta enzyme preparation. J Inherit Metab Dis 2002;25(abstract).
• Biochemical analysis of the 2 α-galactosidase A enzyme replacement products, agalsidase beta and agalsidase alpha
• Comparison found similar enzyme activity per mg protein (7.0 ± 0.5 and 6.6 ± 0.6 mmol/mg/h)
• Analysis did not show amino acid changes due to RNA-editing (as had been previously reported)
• The uptake of both products in Fabry fibroblasts were similar and demonstrated correction of glycosphingolipid storage
• Patients developed cross-reactive antibodies
• The authors report plans to evaluate the safety and efficacy of agalsidase beta and agalsidase alpha both at doses of 0.2 mg/kg in patients with Fabry disease

Acquisition Cost

Drug	Dose	FSS Price/35mg Vial	Drug Cost/70kg Patient/Month	Annual Drug Cost/Patient
Agalsidase beta	1 mg/kg q2wks	$2,888.00	$11,552.00	$138,624.00

Conclusions

Efficacy: Agalsidase beta is an exogenous source of the enzyme α-galactosidase A, used in the treatment of Fabry disease. Clinical trials with agalsidase beta in patients with classic Fabry disease resulted in clearance of microvascular endothelial deposits of GL-3 in kidney, heart, and skin. These effects appear to be maintained with continued therapy reported at 6 months. Plasma GL-3 concentrations were reduced with therapy and this may be correlated with the clearance of microvascular endothelial deposits.

Safety: The adverse event profile primarily includes infusion type reactions. According to the manufacturer, it is recommended that the patient be given antipyretics prior to infusion. Prophylaxis with antihistamines may also be warranted. IgG seroconversion is common but does not appear to have an effect on efficacy and titers may decrease over time.

Long-term outcomes: The trials with agalsidase beta were conducted in patients with the classic form of the disease and whether enzyme replacement therapy decreases morbidity and mortality in these patients is unknown at this time. Patients with the cardiac variant of Fabry disease in general do not exhibit endothelial accumulation of GL-3 (a primary focus of the trial in classically affected patients) and usually do not develop kidney disease but rather present with cardiac complications at a later stage in life. It is also unknown if treatment with agalsidase beta will prevent or minimize the long-term complications of patients with the cardiac variant of this disease.

Abstracts: The abstracts provide limited information but some describe agalsidase beta as having benefit in clinical symptoms of the disease. They also report patient's ability to tolerate treatment with a decreased infusion time. It is unclear as to whether the difference in dose of agalsidase beta (1 mg/kg) and agalsidase alpha (0.2 mg/kg) is warranted and one abstract described comparison results in preparation for a trial with the two products at a dose of 0.2 mg/kg.

Cost: Currently, the annual cost of therapy (for the drug alone) for a 70kg patient is $138,624.00.

Recommendations

Algalsidase beta has been shown to be effective in improving clearance of microvascular endothelial deposits of GL-3 in kidney, heart, and skin in patients with classic Fabry disease, the effect of which appears to be maintained with continued therapy. It is hypothesized that this will translate into improvement in long-term complications of this disease.

Due to the limited patient population, unknown long-term benefit, and high cost of treatment with agalsidase beta, it is recommended that this agent remain non-formulary at the national level. For the same reasons, it is recommended that this agent be available on a non-formulary basis at the VISN level until further research regarding the dose and long-term benefit of this agent are conducted. Agalsidase beta should be restricted to use in patients with a diagnosis of classic Fabry disease (see Criteria for Non-Formulary Use).

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Prepared by: Elaine M. Furmaga, PharmD
Reviewed by: Michael B. Ganz, MD, Associate Professor of Medicine, Case Western Reserve University
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