Annals of Internal Medicine | ARTICLE

Agalsidase-Beta Therapy for Advanced Fabry Disease

A Randomized Trial

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Background: Fabry disease (α-galactosidase A deficiency) is a rare, X-linked lysosomal storage disorder that can cause early death from renal, cardiac, and cerebrovascular involvement.

Objective: To see whether agalsidase beta delays the onset of a composite clinical outcome of renal, cardiovascular, and cerebrovascular events and death in patients with advanced Fabry disease.

Design: Randomized (2:1 treatment-to-placebo randomization), double-blind, placebo-controlled trial.

Setting: 41 referral centers in 9 countries.

Patients: 82 adults with mild to moderate kidney disease; 74 of whom were protocol-adherent.

Intervention: Intravenous infusion of agalsidase beta (1 mg per kg of body weight) or placebo every 2 weeks for up to 35 months (median, 18.5 months).

Measurements: The primary end point was the time to first clinical event (renal, cardiac, or cerebrovascular event or death). Six patients withdrew before reaching an end point: 3 to receive commercial therapy and 3 due to positive or inconclusive serum IgE or skin test results. Three patients assigned to agalsidase beta elected to transition to open-label treatment before reaching an end point.

Results: Thirteen (42%) of the 31 patients in the placebo group and 14 (27%) of the 51 patients in the agalsidase-beta group experienced clinical events. Primary intention-to-treat analysis that adjusted for an imbalance in baseline proteinuria showed that, compared with placebo, agalsidase beta delayed the time to first clinical event (hazard ratio, 0.47 [95% CI, 0.21 to 1.03]; $P = 0.06$). Secondary analyses of protocol-adherent patients showed similar results (hazard ratio, 0.39 [CI, 0.16 to 0.93]; $P = 0.034$). Ancillary subgroup analyses found larger treatment effects in patients with baseline estimated glomerular filtration rates greater than 55 mL/min per 1.73 m^2 (hazard ratio, 0.19 [CI, 0.05 to 0.82]; $P = 0.025$) compared with 55 mL/min per 1.73 m^2 or less (hazard ratio, 0.85 [CI, 0.32 to 2.3]; $P = 0.75$) (formal test for interaction, $P = 0.09$). Most treatment-related adverse events were mild or moderate infusion-associated reactions, reported by 55% of patients in the agalsidase-beta group and 23% of patients in the placebo group.

Limitations: The study sample was small. Only one third of the patients experienced clinical events, and some patients withdrew before experiencing any event.

Conclusions: Agalsidase-beta therapy slowed progression to the composite clinical outcome of renal, cardiac, and cerebrovascular complications and death compared with placebo in patients with advanced Fabry disease. Therapeutic intervention before irreversible organ damage may provide greater clinical benefit.

Ann Intern Med. 2007;146:77-86. www.annals.org

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*For a list of members of the Fabry Disease Clinical Trial Study Group, see the Appendix (available at www.annals.org).

ClinicalTrials.gov identifier: NCT00074984.

Fabry disease is a rare, X-linked lysosomal storage disorder caused by deficient activity of the lysosomal enzyme α-galactosidase A (α-Gal A). The resultant progressive accumulation of its substrates (globotriaosylceramide and related glycosphingolipids) has profound clinical consequences, particularly in the vascular endothelial cells of the kidney and heart (1, 2). Early manifestations typically include debilitating chronic acroparesthesias, episodic excruciating pain "crises," hypohidrosis, and abdominal pain and diarrhea. Subsequent kidney failure, heart disease, and strokes lead to early death, typically at age 40 to 50 years (1, 3–5). Heterozygous females can have serious disease manifestations due to nonrandom X-chromosomal inactivation (6–8). Late-onset variants have been described (9–11).

Two clinical trials in patients with Fabry disease demonstrated that enzyme replacement with agalsidase beta (recombinant human α-Gal A, Fabrazyme, Genzyme Corp., Cambridge, Massachusetts) (12–16) clears globotriaosylceramide from the capillary endothelia of the kidney, heart, and skin—the major sites of pathology in Fabry disease. On the basis of the results of these trials, agalsidase beta was approved in Europe in 2001 and in the United States by the U.S. Food and Drug Administration (FDA), under its accelerated approval program, in 2003. Since approval was based on a surrogate marker, the FDA required an additional trial to demonstrate clinical benefit. Thus, our objective was to evaluate the effect of agalsidase beta on disease progression by a time-to-event analysis of renal, cerebrovascular, and cardiac events or death in patients with advanced Fabry disease in a placebo-controlled trial.

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Context

Fabry disease is an X-linked storage disorder characterized by deficient lysosomal enzyme activity and excessive deposition of glycosphingolipids in vascular endothelial cells.

Contribution

In this double-blind multicenter trial, 82 adults with kidney dysfunction from Fabry disease were randomly assigned to infusions of enzyme replacement with agalsidase beta or placebo every 2 weeks for up to 35 months. Agalsidase beta reduced the frequency of and delayed the time to clinical events (composite outcome of renal, cardiac, and cerebrovascular events and death) and caused infusion reactions more often than placebo.

Caution

Most clinical events in the small trial were worsening kidney function.

Implication

Agalsidase beta may slow disease progression in patients with advanced Fabry disease.

—The Editors

METHODS

Design Overview

This multicenter, randomized, double-blind, placebo-controlled study began in February 2001 and ended in January 2004. We used a 2:1 treatment-to-placebo randomization ratio to give more patients access to treatment (**Figure 1**). Because Fabry disease is multisystemic, we chose a composite primary end point. Natural history data related to clinical events in Fabry disease are limited; thus, we planned 2 interim analyses (which did not require unblinding the study) to evaluate whether trial duration and patient numbers were adequate. Institutional review boards at all sites approved the protocol. All patients gave written informed consent at trial entry and were informed in April 2003 that the commercial drug had become available in the United States.

Setting and Participants

Physicians who were experienced in treating Fabry disease were contacted at 41 university or research hospitals in 9 countries in North America and Europe. Patients were recruited through mailings, advertisements, Web site postings, physician-to-physician and physician-to-patient information letters, and patient meetings. Eligible patients were at least 16 years of age with clinical evidence of Fabry disease; α-Gal A activity less than 1.5 nmol/h per mL of plasma (normal mean, 8.1 nmol/h per mL of plasma [SD, 3.2] [$n = 218$]) or less than 4 nmol/h per mg of leukocyte protein (normal mean, 97.5 nmol/h per mg of leukocyte protein [SD, 16.4] [$n = 46$]); no previous enzyme replacement therapy; and the following evidence of kidney disease: 2 consecutive serum creatinine measurements of 106 μmol/L or greater ($\geq$1.2 mg/dL) and less than 265 μmol/L ($<$3.0 mg/dL) or, if the serum creatinine measurement was less than 106 μmol/L ($<$1.2 mg/dL), an estimated creatinine clearance less than 1.33 mL/s ($<$80 mL/min) (Cockcroft–Gault equation). We excluded patients who were undergoing dialysis or were scheduled for kidney transplantation; those with documented transient ischemic attacks, ischemic stroke, unstable angina, or myocardial infarction within 3 months of trial entry; and those with confounding conditions or other clinically significant comorbid conditions.

Randomization and Interventions

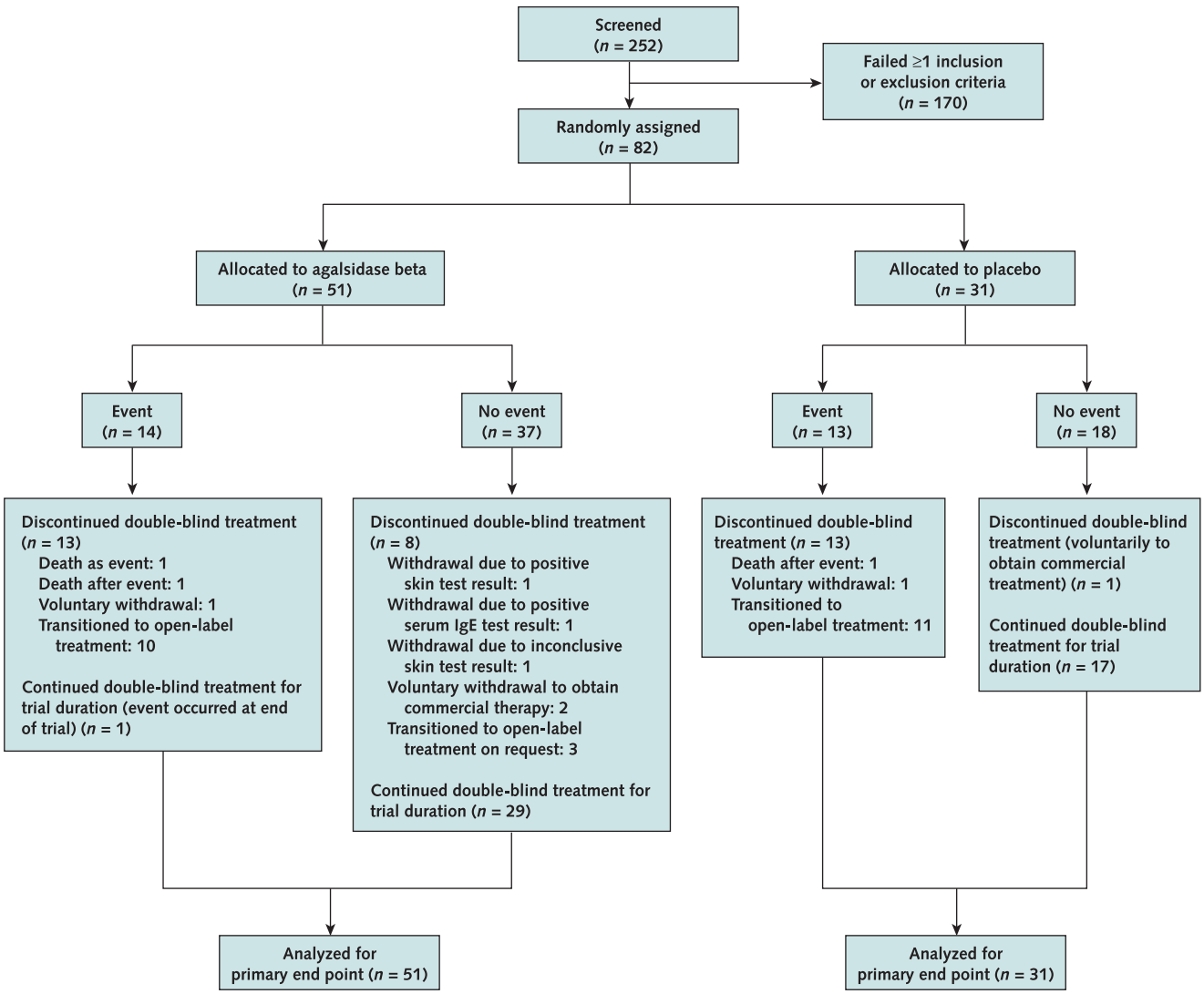
Randomization codes were computer-generated and were maintained centrally at a secure location. The 2:1 randomization scheme was blocked (block size of 3, which was not revealed to investigators) at each site. Study materials were packaged identically, and sponsor staff, investigators, and patients were blinded to treatment allocation. Every 2 weeks, patients received either agalsidase beta (1 mg/kg of body weight) or placebo (phosphate-buffered mannitol) administered intravenously at an initial rate of 0.25 mg/min, which was increased after the eighth infusion as tolerated to decrease the infusion time to a minimum of 90 minutes. All patients were pretreated with acetaminophen or ibuprofen and some patients with an antihistamine to minimize infusion-associated reactions (defined as adverse events on the treatment day considered to be treatment-related) (13).

Outcome and Measurements

The following measures were performed or obtained at baseline and at the final study visit or time of study withdrawal: serum creatinine level, proteinuria (ratio of urinary protein to urinary creatinine [in mg/dL]), ratio of urinary albumin to urinary creatinine (in mg/dL), 12-lead electrocardiography, echocardiography, neurologic examination, head magnetic resonance imaging, Brief Pain Inventory, exercise tolerance, plasma globotriaosylceramide level, Fabry symptom assessment, physical examination, blood chemistries, urinalysis, IgG antibody titers to agalsidase beta, and optional skin biopsy. Every 4 weeks, serum creatinine levels were measured, and all baseline measures were repeated every 12 weeks, except for echocardiography, head magnetic resonance imaging, and exercise tolerance, which were repeated every 24 weeks. The estimated glomerular filtration rate (GFR) was determined by using the 4-variable Modification of Diet in Renal Disease formula (17).

The primary end point was the time to first clinical event (renal, cardiac, or cerebrovascular event or death) in the placebo and agalsidase-beta groups. We defined a renal event as a 33% increase in serum creatinine level from baseline (2 consecutive values) or end-stage kidney disease requiring long-term dialysis or transplantation. We defined

Figure 1. **Study flow diagram.**



a cardiac event as myocardial infarction; new symptomatic arrhythmia requiring antiarrhythmic medication, pacemaker, direct current cardioversion, or defibrillator implantation; unstable angina defined by national practice guidelines (18) and accompanied by electrocardiographic changes resulting in hospitalization; or worsening congestive heart failure requiring hospitalization. We defined a cerebrovascular event as a stroke or transient ischemic attack documented by a physician. Patients were allowed to transition to open-label agalsidase beta after an independent adjudication board confirmed that a primary end point event had occurred.

Safety monitoring included physician evaluation and documentation of adverse events. At each study visit, investigators asked patients an open-ended question about their health status. They also reviewed the results of all physical examinations, electrocardiographies, and laboratory assessments and reported any clinically significant symptom or abnormality as an adverse event. They assessed all adverse events for seriousness, severity, and relatedness to treatment. An independent data monitoring committee, which was authorized to recommend study termination on the basis of the methods of O'Brien and Fleming (19), periodically reviewed safety data.

Serum was collected at baseline and every 4 weeks thereafter for detection and measurement of IgG antibody titers to agalsidase beta at the Genzyme Immunology Laboratory, Framingham, Massachusetts, as described previously (15). If an investigator suspected that an infusion-associated reaction was IgE-mediated, serum IgE tests or skin tests to agalsidase beta were performed. According to

the protocol, we withdrew patients with positive test results from the study.

Follow-up Procedures

On trial completion, patients were eligible to enroll in an 18-month, open-label extension study. We contacted patients for safety follow-up if they withdrew or chose not to continue in the extension study.

Statistical Analysis

We chose a final sample size of 80 patients to provide 80% power for detecting a treatment effect on the basis of log-rank testing by using a 10% drop-out rate; a 14-month enrollment period and 18 months of follow-up; type I error of 0.05 (2-sided); and expected event rates over 2 years of 40% and 10% for patients in the placebo and agalsidase-beta groups, respectively, as predicted by an estimated 20% to 30% decline per year in estimated GFR (3, 20). To ensure that the proposed trial duration and sample size were adequate, the data monitoring committee conducted blinded interim analyses of event rates at 12 months and 18 months, and the study duration was increased from 24 months to 29 months and then to 35 months. Because the trial remained blinded and no hypothesis testing was performed, the type I error rate was not adjusted for the primary end point (21).

Efficacy analyses, which were performed by using SAS, version 8.2 (SAS Institute Inc., Cary, North Carolina), included only data that were obtained while patients received double-blind treatment. To evaluate the treatment effect in the time-to-event analyses, Kaplan–Meier methods were used for unadjusted analyses and the Cox proportional-hazards model was used for proteinuria-adjusted analyses (22, 23). Because of the small sample size, the protocol specified that any imbalance in important prognostic factors after randomization could be adjusted by using the Cox proportional-hazards model (22, 23). More patients in the agalsidase-beta group had elevated baseline proteinuria, which was significantly associated with time to any clinical end point and with time to renal end point. In addition, adding a term for proteinuria to the Cox proportional-hazards model with a term for treatment resulted in a 23% change in the hazard ratio for treatment. Hence, we applied a change in estimate criterion (24) and determined that baseline proteinuria was the most important potential confounder. Adjusted analyses were performed using Cox proportional-hazards models with a term for baseline proteinuria. Because the distribution of baseline proteinuria was skewed, adjusted analyses also were performed using fourth-root transformations of proteinuria values to invoke a normal distribution (25). The proportional-hazards assumptions were tested by assessing the treatment-by-time interaction and the proteinuria-by-time interaction. Both interactions were nonsignificant.

Hazard ratios, 95% CIs, and *P* values were calculated for the treatment effect for the composite outcome and for renal events with and without proteinuria adjustment. Odds ratios for cardiovascular and cerebrovascular events were calculated by Fisher exact test with StatXact, version 3 (Cytel Software Corp., Cambridge, Massachusetts) (26). We conducted the primary end point analyses in the intention-to-treat population and, as secondary analyses, in a prespecified per-protocol population.

We performed ancillary analyses that were not specified by the protocol in the intention-to-treat population. These included time-to-event analyses and formal tests for treatment interaction in subgroups stratified by median baseline proteinuria and by median baseline serum creatinine level and median baseline estimated GFR with adjustment for baseline proteinuria. Proteinuria, serum creatinine levels, and estimated GFR were examined over the course of the study and compared by treatment group by using mixed-model analyses. Linear mixed-effects models were fit with fixed effects for treatment group, time, and treatment-by-time interactions, as well as random intercepts and slopes, for each patient over time.

The investigators asked patients about adverse events and monitored for adverse events during double-blind and open-label treatment. Adverse events were coded using the World Health Organization Adverse Reaction Terminology (WHO-ART) (27). Frequency, severity, and causality data that directly compared events among patients taking agalsidase beta or placebo were assessed during the double-blind treatment period.

Role of the Funding Sources

The Genzyme Corporation and the National Center for Research Resources, a component of the National Institutes of Health, supported the trial. The Genzyme project team participated in the design of the trial in collaboration with the study investigators and the senior author, with input from the FDA (28). A contract research organization performed site monitoring and source data verification. Genzyme, in conjunction with the investigators, performed the data management and statistical analyses. Genzyme provided funding for writing services and reviewed the manuscript for accuracy but had no formative role in data interpretation, writing or revising the manuscript, or the decision to submit the paper for publication.

RESULTS

Of the 252 patients screened, 82 eligible patients (intention-to-treat population) were treated at 26 sites in 6 countries. Fifty-one patients were randomly assigned to the agalsidase-beta group and 31 patients were randomly assigned to the placebo group (**Figure 1**). The baseline characteristics of patients in the 2 groups were similar, except for proteinuria (**Table 1**). Of note, 4 (proteinuria, estimated GFR, hemoglobin level, and serum albumin level) of 15 (serum creatinine level, estimated creatinine clearance, angiotensin-converting enzyme inhibitor use, sex, urinary albumin–urinary creatinine ratio, history of hypertension, race or ethnicity, age, plasma globotriaosylceram-

Table 1. **Baseline Characteristics***

Characteristic	Agalsidase-Beta Group (n = 51)	Placebo Group (n = 31)
Men, %	88	87
Mean age (SD), *y*	46.9 (9.8)	44.3 (9.2)
Mean weight (SD), *kg*	70.5 (11.7)	70.2 (13.3)
Mean height (SD), *cm*	173.2 (8.0)	172.8 (8.2)
Race or ethnicity, %		
Caucasian	88	87
Black	2	0
Hispanic	6	6
Asian	2	3
Other	2	3
History of stroke or TIA, %	14	13
History of cardiac disease, %†	31	36
Treated with ACE inhibitors or ARBs at or before baseline, %	35	36
Mean plasma globotriaosylceramide level (SD), *μg/mL*	9.0 (3.5)	9.1 (3.2)
Mean proteinuria (SD)‡	1.5 (1.5)	1.1 (1.4)
Mean urinary albumin–urinary creatinine ratio (SD)	1.3 (1.8)	0.9 (1.2)
Mean estimated GFR (SD), *mL/min per 1.73 m²*§	53.0 (17.7)	52.4 (17.7)
Mean serum creatinine level (SD)		
mg/dL	1.6 (0.5)	1.6 (0.5)
μmol/L	141 (44.2)	141 (44.2)
Mean systolic blood pressure (SD), *mm Hg*	126 (16)	128 (14)
Mean diastolic blood pressure (SD), *mm Hg*	77 (10)	75 (11)

* ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; GFR = glomerular filtration rate; TIA = transient ischemic attack.
† Myocardial infarction, coronary artery bypass graft, atrial fibrillation, pacemaker, angina, or chest pain.
‡ Urine protein–creatinine ratio.
§ Calculated by using the 4-variable Modification of Diet in Renal Disease equation (17).

ide level, body mass index, and weight) baseline variables were associated with time to clinical event. Of these 4 variables, proteinuria was most strongly associated with any clinical event (hazard ratio, 1.3 [95% CI, 1.1 to 1.6]; $P = 0.005$) and any renal event (hazard ratio, 1.4 [CI, 1.2 to 1.8]; $P < 0.001$).

From the first infusion to the final blinded visit, patients received treatment for up to 35 months. Mean and median treatment durations were 18.4 months (SD, 8.8) and 18.5 months, respectively. At the end of the study, 71 patients were still enrolled, 8 withdrew, and 3 died. Six withdrawals occurred before an end point event: 2 patients in the agalsidase-beta group and 1 patient in the placebo group withdrew to obtain commercial therapy, which became available in the United States during the trial, and 3 patients in the agalsidase-beta group withdrew due to positive or inconclusive skin test results or positive IgE test results. Two withdrawals, 1 from each group, were voluntary and occurred after an end point event. In addition, 3 patients in the agalsidase-beta group who had not met the primary end point elected to transition to open-label treatment after 13 to 17 months. We excluded them from further efficacy analyses upon transition but included them in safety analyses. The deaths of 2 patients, 1 from each group, occurred after a primary end point. The death of 1 patient in the agalsidase-beta group was the primary end point (see Adverse Events section).

Eight patients were excluded in the per-protocol population before unblinding because of major protocol violations: 4 patients in the agalsidase-beta group who missed 22% to 87% of infusions, 1 patient in the placebo group who missed 22% of infusions, 1 patient in the placebo group who did not meet the required clinical inclusion criteria, and 2 patients in the placebo group who received a wrong treatment. Thus, the per-protocol population had 74 patients: 47 patients in the agalsidase-beta group and 27 patients in the placebo group. Of the excluded patients, 1 patient in the agalsidase-beta group had a cardiac event and 1 patient in the placebo group had a renal event.

Primary End Point and Protocol-Specified Secondary Analyses

Thirteen (42%) of 31 patients in the placebo and 14 (27%) of 51 patients in the agalsidase-beta group had clinical events (**Table 2**). The intention-to-treat analysis of time to first clinical event that adjusted for baseline imbalance in proteinuria favored agalsidase beta (hazard ratio, 0.47 [CI, 0.21 to 1.03]; $P = 0.06$) (**Figure 2**, *top*). We observed a similar effect of agalsidase beta when the time-to-event analyses were repeated using fourth-root transformations of proteinuria to normalize the skewed distribution (hazard ratio, 0.49 [CI, 0.22 to 1.1]; $P = 0.07$).

Most clinical events were renal; however, hazard ratios and odds ratios for renal, cardiac, and cerebrovascular events separately were also consistent with a treatment effect (**Table 2**). Secondary analyses of protocol-adherent patients that adjusted for baseline proteinuria demonstrated a more pronounced treatment effect compared with placebo (hazard ratio, 0.39 [CI, 0.16 to 0.93]; $P = 0.034$) (**Figure 2**, *bottom*).

Table 2. **Primary End Point Events in the Intention-to-Treat Population***

Primary End Point Event	Events in the Agalsidase-Beta Group ($n = 51$), n	Events in the Placebo Group ($n = 31$), n	Hazard Ratio or Odds Ratio (95% CI)†	*P* Value
Composite outcome	14	13	0.47 (0.21–1.0)	0.06
Renal	10	7	0.49 (0.17–1.4)	0.18
33% increase in serum creatinine level; ESRD	10; 0	7‡; 0		
Cardiac	3	4	0.42 (0.058–2.7)	0.42
Arrhythmia; angina; MI	2‡; 0; 1	3; 1; 0		
Cerebrovascular	0	2	0 (0–3.2)	0.14
Stroke; TIA	0; 0	2; 0		
Death	1	0	NA	

* ESRD = end-stage renal disease; MI = myocardial infarction; NA = not applicable; TIA = transient ischemic attack.
† Adjusted for baseline imbalance in proteinuria. The unadjusted hazard ratio for a renal event and for any event was 0.73 (95% CI, 0.28–1.9) and 0.57 (CI, 0.27–1.2), respectively. Other values did not change with adjustment. Due to the small number of events, odds ratios were calculated for cardiac and cerebrovascular events by using Fisher exact test with StatXact, version 3 (Cytel Software Corp., Cambridge, Massachusetts) (26).
‡ One of these patients was excluded in the per-protocol population (overall, 2 patients who had end points were excluded in the per-protocol population).

Ancillary Analyses

Figure 3 shows the treatment effects evaluated in subgroups stratified by the median value for each of 3 baseline kidney function measures. Patients with baseline estimated GFRs greater than 55 mL/min per 1.73 m^2 (hazard ratio, 0.19 [CI, 0.05 to 0.82]; $P = 0.025$) had a stronger treatment effect than patients with GFRs of 55 mL/min per 1.73 m^2 or less (hazard ratio, 0.85 [CI, 0.32 to 2.3]; $P = 0.75$) (formal test for treatment interaction using models that adjusted for baseline proteinuria, $P = 0.09$). Patients with baseline serum creatinine levels of 132.6 μmol/L or less ($\leq$1.5 mg/dL) had greater treatment effects (hazard ratio, 0.25 [CI, 0.07 to 0.90]; $P = 0.034$) than those with baseline serum creatinine levels greater than 132.6 μmol/L (>1.5 mg/dL) (hazard ratio, 0.80 [CI, 0.29 to 2.21]; $P = 0.66$) (formal test for treatment interaction, $P = 0.16$). We observed a less pronounced difference in patients with baseline proteinuria of 1 or less (hazard ratio, 0.41 [CI, 0.13 to 1.3]; $P = 0.13$) versus patients with proteinuria greater than 1 (hazard ratio, 0.67 [CI, 0.24 to 1.9]; $P = 0.44$) (formal test for treatment interaction, $P = 0.54$).

Mean serum creatinine level, estimated GFR, and proteinuria did not change between baseline and final assessment in either treatment group. Longitudinal analyses showed nonsignificant decreases in proteinuria and nonsignificant increases in inverse serum creatinine level and estimated GFR over time for the agalsidase-beta group compared with the placebo group (**Appendix Figure**, available at www.annals.org).

Adverse Events

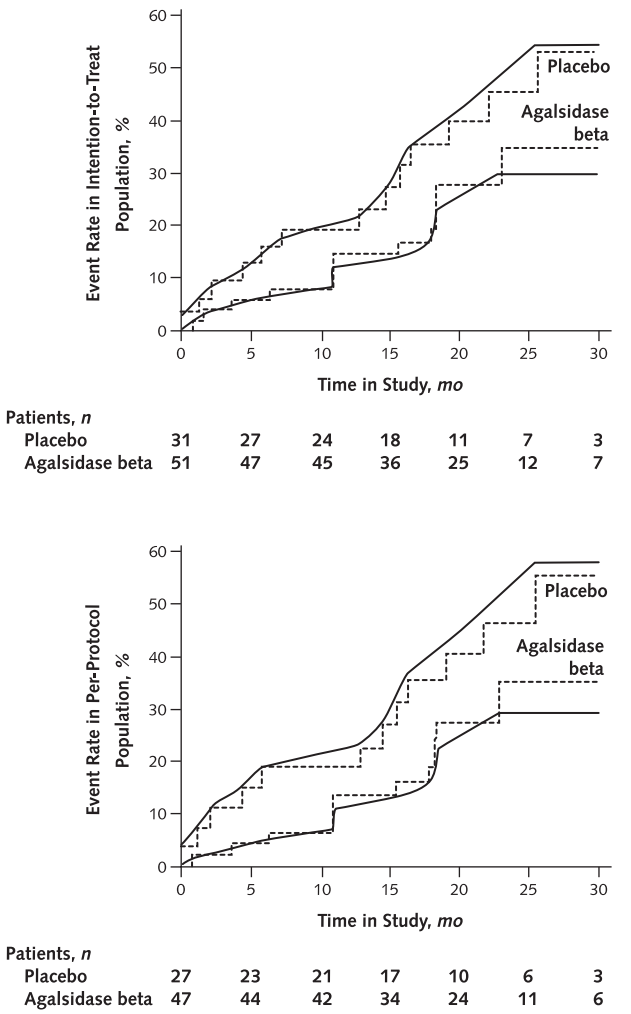
Overall, 99% of trial participants experienced adverse events, such as rhinitis, coughing, or headache, during the trial. Most events occurred in similar frequencies in both groups and seemed to be unrelated to drug treatment (**Appendix Table**, available at www.annals.org). During double-blind treatment, 61% of patients in the agalsidase-beta group and 32% of patients in the placebo group reported treatment-related adverse events (**Table 3**). Most treatment-related events were mild or moderate infusion-associated reactions (most commonly rigors and fever), which occurred in 55% of patients in the agalsidase-beta group and 23% of patients in the placebo group. Most infusion-associated reactions occurred during the first 6 months of treatment.

Of 56 serious adverse events reported for 30 patients, only 3 events were considered to be treatment-related. One patient in the agalsidase-beta group experienced severe hypotension and subsequently had a positive serum IgE test result. We withdrew this patient from the trial. One patient in the agalsidase-beta group developed urticaria and throat congestion, and another patient developed urticaria, rigors, and fever during infusions. Both patients subsequently had positive skin test results. We withdrew 1 patient from the trial, and the other patient continued participation as an institutional review board–approved protocol exception. Both withdrawn patients were subsequently rechallenged and continued receiving the commercial drug. No patient experienced anaphylaxis.

Three patients died during the study. All had clinically significant histories of cardiovascular disease, cerebrovascular disease, or both. The patient in the agalsidase-beta group whose death was a primary end point died of multiple pulmonary emboli. The patient had massive lymphedema and had habitually used methamphetamine. The other 2 patients died secondary to their primary end points: 1 patient in the agalsidase-beta group died of sudden cardiac arrest and 1 patient in the placebo group died of cardiac arrest 1 week after a stroke. The investigators did not consider any death to be related to treatment.

The investigators detected IgG antibodies in 43 (68%) of the 63 patients who received agalsidase beta at any time during the trial. Of the 55 men who received agalsidase beta, 14 (26%) remained seronegative. Titers were not available for 1 man after his transition to open-label therapy. Of the 8 women who received agalsidase beta, 5 (63%) remained seronegative. One seropositive man and

Figure 2. **Analyses of time to first clinical outcome.**



Dashed lines show Kaplan–Meier estimates of time to any clinical event (composite outcome). Solid lines show curves with adjustment for baseline proteinuria (urine protein–creatinine ratio), derived from a Cox regression analysis with baseline proteinuria added as a covariate to the regression equation (22, 23). **Top.** The time-to-event analyses for the composite end point for both treatment groups in the intention-to-treat population are shown. The unadjusted treatment-related hazard ratio associated with agalsidase beta was 0.57 (95% CI, 27.0 to 1.22; $P = 0.14$). With adjustment for baseline proteinuria, the hazard ratio was 0.47 (CI, 0.21 to 1.03; $P = 0.06$). **Bottom.** The time-to-event analyses for the composite end point for both treatment groups in the per-protocol population are shown. The unadjusted treatment-related hazard ratio associated with agalsidase beta was 0.54 (CI, 0.25 to 1.19; $P = 0.12$). With adjustment for baseline proteinuria, the hazard ratio was 0.39 (CI, 0.16 to 0.93; $P = 0.034$).

all 3 seropositive women tolerized. Mean infusion time decreased during the study to almost half of the initial time in both treatment groups.

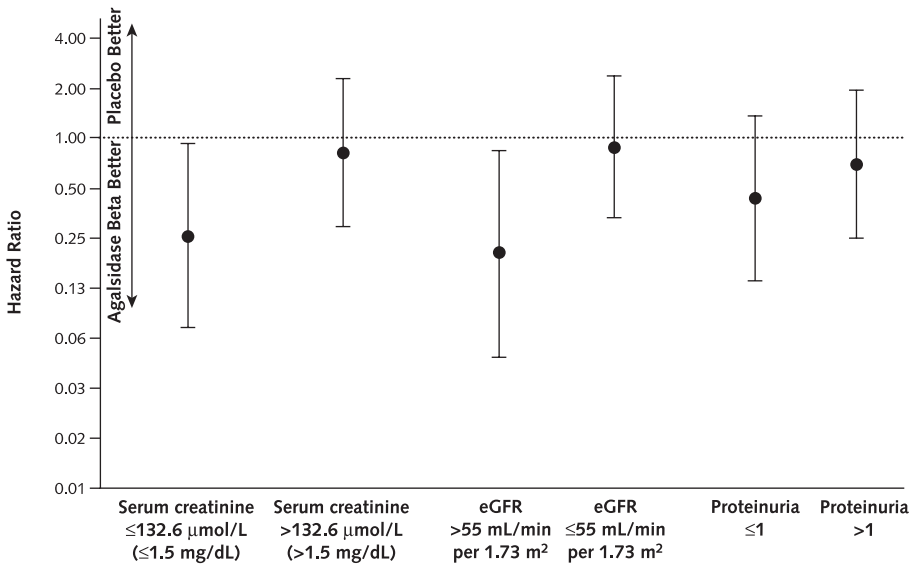
Discussion

This randomized, double-blind, placebo-controlled trial showed that agalsidase-beta therapy reduced the likelihood of any clinical event (composite outcome) in patients with advanced Fabry disease, indicating a slower progression of severe manifestations. Among the renal, cardiac, and cerebrovascular end points monitored in the study, deteriorating kidney function was the most frequent, which is not surprising because mild to moderate kidney disease was required for trial participation. As in earlier studies, agalsidase beta was tolerated reasonably well; transient mild or moderate infusion-associated reactions occurred in 55% of the treated patients and declined in frequency over time (12, 13, 15). The results of our trial support and extend the findings of smaller studies and case reports describing the effects of agalsidase-beta therapy, 1 mg/kg every 2 weeks (15, 29–38). These studies, identified by a MEDLINE search of clinical trials on Fabry disease published between 2000 and October 2006, report improvements in cardiac function (30, 31, 35), gastrointestinal symptoms (36, 38), and heat tolerance and physical activity (33), as well as stabilization of kidney function (15), reduction of pain (30, 33), and reduction of neuropathic abnormalities (32).

In Fabry disease, glycosphingolipid deposition begins before birth (39) and is cumulative. Thus, early intervention with enzyme replacement therapy would be more beneficial than later intervention, when substrate accumulation may have caused irreversible organ damage. More than a decade of experience with enzyme replacement therapy for a related lysosomal storage disease, type 1 Gaucher disease, has clearly demonstrated that early intervention can prevent progressive disease manifestations (40). The patients with Fabry disease who participated in our trial had an average of 45 years of glycosphingolipid accumulation, resulting in significant kidney dysfunction. We observed greater treatment effects in patients with less severe kidney dysfunction at baseline (**Figure 3**), although formal tests for interaction were nonsignificant, perhaps due to the small sample size. This is consistent with the results of a recent open-label, single-center study of 26 patients who received agalsidase beta (1 mg/kg every 2 weeks) for a mean of 23 months. Of the 9 patients who experienced clinical events (death, dialysis initiation, myocardial infarction, coronary artery bypass grafting, cardiac pacemaker implantation, or atrial fibrillation), all had impaired kidney function at study entry (38).

In our trial, proteinuria emerged as a predictor of clinical outcome. Proteinuria is a well-known risk factor for the progression of kidney disease and cardiovascular illness (41–44), and it was recently implicated as a risk factor for progression of kidney involvement in Fabry disease (15). We did not observe a treatment effect with respect to proteinuria, although longitudinal analyses showed a non–statistically significant decrease in proteinuria in patients in the agalsidase-beta group compared with those in the placebo group. These findings suggest that proteinuria should be monitored in patients with Fabry disease. Treatment with antiproteinuria drugs, such as angiotensin-converting

Figure 3. **Hazard ratios for the primary end point stratified by median baseline serum creatinine level, estimated glomerular filtration rate (*eGFR*), and proteinuria.**



Proteinuria denotes the urine protein–creatinine ratio. The *P* values for formal tests for treatment interaction were as follows: baseline serum creatinine level, $P = 0.16$; baseline eGFR, $P = 0.09$; and baseline proteinuria, $P = 0.54$.

enzyme inhibitors and angiotensin-receptor blockers, should be evaluated, because these drugs have been effective in other diseases and chronic conditions that are associated with proteinuria (45, 46). We did not design our trial to evaluate the effects of renoprotective drugs because their potential benefits had not been established when the trial began enrollment. Few patients were taking these drugs at baseline, and the duration of therapy and the specific drugs and dosages prescribed varied considerably. Further studies to evaluate the effect of antiproteinuria drugs on clinical outcome in the setting of enzyme replacement therapy may demonstrate their importance as an adjunctive therapy for Fabry disease.

The major limitation of our trial was the small sample size because of the rarity of Fabry disease and the narrow window of disease severity necessary to quantify clinical benefit within a reasonable time frame. Only one third of the participants experienced clinical events. Six patients

Table 3. **Summary of Adverse Events**

Adverse Event	Agalsidase-Beta Group (*n* = 51), *n* (%)	Placebo Group (*n* = 31), *n* (%)	Patients Who Switched from Placebo to Agalsidase Beta after Event (*n* = 12), *n* (%)	95% CI for Difference between Treatment Groups, *percentage points*
Any adverse event	51 (100)	30 (97)	10 (83)	
Serious adverse events	18 (35)	10 (32)	3 (25)	
Adverse events resulting in adjustment of the infusion rate or temporary interruption of the infusion*	21 (41)	8 (26)	3 (25)	
Adverse events resulting in treatment termination†	4 (8)	1 (3)	0 (0)	
Any treatment-related adverse event	31 (61)	10 (32)		
Rigors	18 (35)	1 (3)		11.4 to 51.1
Fever	14 (27)	1 (3)		3.9 to 43.3
Hypertension	7 (14)	2 (6)		–12.8 to 26.1
Vomiting	6 (12)	0 (0)		–5.8 to 28.5
Temperature changed sensation	5 (10)	1 (3)		–12.1 to 23.9
Chest pain	5 (10)	0 (0)		–7.5 to 26.1
Fatigue	5 (10)	0 (0)		–7.5 to 26.1

* All patients completed their infusions and received the full dose of agalsidase beta.
† Includes 2 patients, 1 patient in each group, who withdrew voluntarily after having a clinical event. The remaining 3 patients in the agalsidase-beta group were withdrawn due to positive or inconclusive skin test result or positive serum IgE test result.

withdrew from the double-blind trial before experiencing any outcome event: 3 to obtain commercial therapy and 3 due to positive or inconclusive skin test results or positive IgE test results. Eight patients had major protocol violations, including 5 patients who missed 22% to 87% of their infusions. The effect of such protocol deviations may be negligible in clinical efficacy trials that involve hundreds of participants in each treatment group, but the effect can be substantial when patient numbers are small, as discussed in recent guidelines prepared by the European Medicines Agency for clinical trials in small study populations (47). In particular, nonsystematic errors introduced by protocol violations, such as missed treatments, can lead to bias toward treatment failure.

In conclusion, our placebo-controlled trial indicates that agalsidase beta, 1 mg/kg every 2 weeks, can slow the progression of the serious, life-threatening complications of Fabry disease, even in patients who already have overt kidney dysfunction. Our results also support the rationale for early treatment and the need to evaluate the potential benefit of renoprotective drugs in Fabry disease.

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Disclaimer: The views expressed herein are those of the authors and do not necessarily reflect those of the National Center for Research Resources or the National Institutes of Health.

Acknowledgments: The authors thank the patients, nurses, and hospital staff who participated in the study, as well as Lisa Underhill for writing assistance.

Grant Support: By the National Center for Research Resources of the National Institutes of Health grants to the Mount Sinai School of Medicine (grant 5 M01 RR00071); Cedars-Sinai Medical Center (grant 5 M01 RR00425); University of Minnesota (grant 5 M01 RR00400); The Children's Hospital of Philadelphia (grant 5 M01 RR00240); University of California, San Francisco (grant 5 M01 RR01271); and University of Alabama at Birmingham (grant 5 M01 RR00032). Additional support came from the National Institutes of Health Merit Award 5 R37 DK34045 (Dr. Desnick) and from the Genzyme Corporation.

Potential Financial Conflicts of Interest: *Consultancies:* J. Bultas (Genzyme Corp.), W.R. Wilcox (Genzyme Corp.), S. Packman (Genzyme Corp.), D.G. Bichet (Genzyme Corp.), D.G. Warnock (Genzyme Corp.), R.J. Desnick (Genzyme Corp., Amicus Therapeutics); *Honoraria:* M. Banikazemi (Genzyme Corp.), S. Waldek (Genzyme Corp.), W.R. Wilcox (Genzyme Corp.), C.B. Whitley (Genzyme Corp.), M. McDonald (Genzyme Corp.), D.G. Bichet (Genzyme Corp.), D.G. Warnock (Genzyme Corp.); *Stock ownership or options (other than mutual funds):* M. McDonald (Genzyme Corp.), R.J. Desnick (Amicus Therapeutics); *Grants received:* S. Waldek (Genzyme Corp., Amicus Therapeutics), W.R. Wilcox (Genzyme Corp.), C.B. Whitley (BioMarin, Genzyme Corp.), M. McDonald (Genzyme Corp.), R. Finkel (Genzyme Corp.), S. Packman (Genzyme Corp.), D.G. Bichet (Genzyme Corp.), D.G. Warnock (Genzyme Corp.), R.J. Desnick (Genzyme Corp.); *Grants pending:* D.G. Warnock (Genzyme Corp.); *Patents received:* R.J. Desnick (Mount Sinai School of Medicine to Genzyme Corp. for Fabrazyme); *Royalties:* R.J. Desnick (Genzyme Corp.).

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Appendix: Fabry Disease Clinical Trial Study Group

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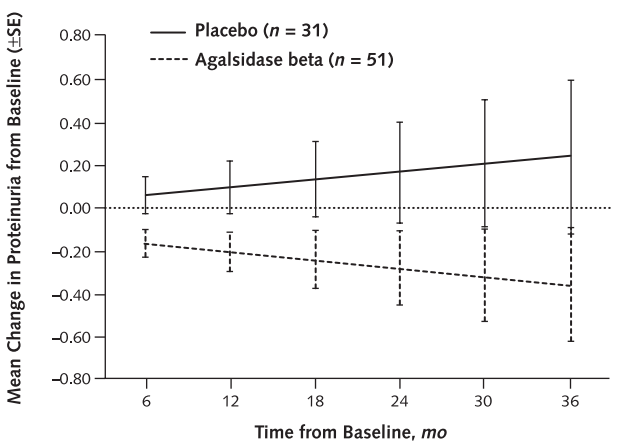
Appendix Figure. **Longitudinal analysis of proteinuria in both groups.**



Data are shown as increases or decreases from baseline proteinuria (urinary protein–urinary creatinine ratio) for the placebo group (*solid line*) and the agalsidase-beta group (*dashed line*). A mixed model with fixed effects for treatment group, time, and treatment-by-time interactions, as well as random intercepts and slopes, for each patient over time was fit. The overall *P* value for treatment effect is 0.32.

Appendix Table. **Adverse Events That Occurred without Regard to Causality in at Least 10% of Patients in the Agalsidase-Beta Group**

Adverse Events	Agalsidase-Beta Group (n = 51), n (%)	Placebo Group (n = 31), n (%)	Patients Who Switched from Placebo to Agalsidase Beta after Event (n = 12), n (%)
Any adverse event	51 (100)	30 (97)	10 (83)
Rhinitis	29 (57)	13 (42)	2 (17)
Coughing	25 (49)	11 (35)	2 (17)
Headache	22 (43)	7 (23)	2 (17)
Upper respiratory tract infection	22 (43)	7 (23)	3 (25)
Rigors	20 (39)	5 (16)	1 (8)
Fever	19 (37)	9 (29)	1 (8)
Back pain	18 (35)	4 (13)	1 (8)
Fatigue	17 (33)	4 (13)	0 (0)
Vomiting	15 (29)	8 (26)	1 (8)
Diarrhea	14 (27)	7 (23)	1 (8)
Myalgia	14 (27)	6 (19)	2 (17)
Pain	14 (27)	6 (19)	2 (17)
Abdominal pain	14 (27)	5 (16)	3 (25)
Fabry pain	13 (25)	7 (23)	2 (17)
Pharyngitis	13 (25)	9 (29)	1 (8)
Dizziness	12 (24)	4 (13)	1 (8)
Nausea	10 (20)	11 (35)	1 (8)
Edema-dependent	10 (20)	2 (6)	4 (33)
Anemia	10 (20)	1 (3)	1 (8)
Sinusitis	9 (18)	6 (19)	1 (8)
Chest pain	9 (18)	6 (19)	0 (0)
Influenza-like symptoms	9 (18)	4 (13)	1 (8)
Rash	9 (18)	4 (13)	0 (0)
Leg pain	9 (18)	2 (6)	0 (0)
Acidosis	8 (16)	5 (16)	1 (8)
Hypertension	8 (16)	3 (10)	3 (25)
Dyspepsia	8 (16)	2 (6)	1 (8)
Paresthesia	8 (16)	1 (3)	1 (8)
Abrasion, not otherwise specified	8 (16)	0 (0)	0 (0)
Skin disorder	7 (14)	0 (0)	2 (17)
Pruritus	7 (14)	1 (3)	1 (8)
Arthralgia	6 (12)	5 (16)	2 (17)
Hypoesthesia	6 (12)	3 (10)	1 (8)
Insomnia	6 (12)	3 (10)	1 (8)
Tachycardia	6 (12)	2 (6)	1 (8)
Nonprotein nitrogen increased	6 (12)	2 (6)	1 (8)
Temperature changed sensation	6 (12)	1 (3)	1 (8)
Syncope	6 (12)	1 (3)	0 (0)
Tinnitus	6 (12)	1 (3)	0 (0)
Injury accident	6 (12)	1 (3)	0 (0)
Abnormal renal function	6 (12)	0 (0)	0 (0)
Anxiety	5 (10)	3 (10)	1 (8)
Tooth disorder	5 (10)	2 (6)	0 (0)
Hearing decreased	5 (10)	2 (6)	0 (0)
Bronchitis	5 (10)	2 (6)	0 (0)
Leg cramps	5 (10)	1 (3)	0 (0)
Arrhythmia	5 (10)	1 (3)	0 (0)
Viral infection	5 (10)	1 (3)	0 (0)
Dyspnea	5 (10)	1 (3)	0 (0)
Flushing	5 (10)	1 (3)	0 (0)
Purpura	5 (10)	0 (0)	2 (17)
Postoperative pain	5 (10)	0 (0)	0 (0)