

Agalsidase Alfa

A Review of its Use in the Management of Fabry Disease

Gillian M. Keating
Adis, Auckland, New Zealand

Various sections of the manuscript reviewed by:
S. Feriozzi, Belcolle Hospital, Nephrology and Dialysis, Viterbo, Italy; *R. Giugliani*, Department of Genetics and Postgraduate Program in Genetics and Molecular Biology, UFRGS, Porto Alegre, Brazil; *A.B. Mehta*, Lysosomal Storage Disorders Unit, Department of Haematology, Royal Free Hospital and University College Medical School, London, UK; *K. Nicholls*, Department of Nephrology, Royal Melbourne Hospital, Parkville, VIC, Australia; *R. Parini*, Rare Metabolic Diseases Unit, Pediatric Clinic, San Gerardo Hospital, University Milano Bicocca, Monza, Italy; *R. Schiffmann*, Institute of Metabolic Disease, Baylor Research Institute, Dallas, TX, USA.

Data Selection

Sources: Medical literature (including published and unpublished data) on 'agalsidase alfa' was identified by searching databases (including MEDLINE and EMBASE) for articles published since 1996, bibliographies from published literature, clinical trial registries/databases and websites (including those of regional regulatory agencies and the manufacturer). Additional information (including contributory unpublished data) was also requested from the company developing the drug.
Search strategy: MEDLINE and EMBASE search terms were 'agalsidase alfa' and 'Fabry disease'. Searches were last updated 20 August 2012.
Selection: Studies in patients with Fabry disease who received agalsidase alfa. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.
Index terms: Agalsidase alfa, Fabry disease, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

Contents

Abstract	336
1. Introduction	337
2. Pharmacologic Properties	337
2.1 Mechanism of Action	337
2.2 Pharmacokinetic Profile	337
2.2.1 Special Patient Populations	338
2.3 Potential Drug Interactions	338
3. Therapeutic Efficacy	339
3.1 Effects on Cardiac Endpoints	340
3.1.1 Comparisons with Placebo	340
3.1.2 Comparisons with Agalsidase Beta	340
3.1.3 Noncomparative Studies	342
3.1.4 Fabry Outcome Survey	342
3.2 Effects on Pain, Disease Severity, and Health-Related Quality of Life	342
3.2.1 Comparisons with Placebo	342
3.2.2 Comparisons with Agalsidase Beta	342
3.2.3 Noncomparative Studies	342
3.2.4 Fabry Outcome Survey	344
3.3 Effects on Renal Endpoints	344
3.3.1 Comparisons with Placebo	344
3.3.2 Comparisons with Agalsidase Beta	344
3.3.3 Noncomparative Studies	346
3.3.4 Fabry Outcome Survey	346

3.4	Effects on Other Endpoints	346
3.4.1	Comparisons with Placebo	346
3.4.2	Comparisons with Agalsidase Beta	347
3.4.3	Noncomparative Studies	348
3.4.4	Fabry Outcome Survey	348
4.	Tolerability	348
4.1	Immunogenicity	349
5.	Dosage and Administration	349
6.	Place of Agalsidase Alfa in the Management of Fabry Disease	349

Abstract

The enzyme replacement therapy agalsidase alfa (Replagal®) has an amino acid sequence identical to that of native α -galactosidase A; intravenous agalsidase alfa 0.2 mg/kg every other week is indicated for the long-term treatment of patients with confirmed Fabry disease. This article reviews the efficacy and tolerability of agalsidase alfa in patients with Fabry disease, as well as summarizing its pharmacologic properties.

Agalsidase alfa had beneficial effects in adult men with Fabry disease, according to the results of two randomized, double-blind, placebo-controlled, 6-month trials ($n=15$ and 26). For example, left ventricular mass index was reduced to a significantly greater extent with agalsidase alfa than with placebo. Although the change in myocardial globotriaosylceramide content (primary endpoint in one study) did not significantly differ between agalsidase alfa and placebo recipients, the change in the Brief Pain Inventory (BPI) 'pain at its worst' score (reflecting neuropathic pain while without pain medications; primary endpoint in the second study) was improved to a significantly greater extent with agalsidase alfa than with placebo. In addition, the change in creatinine clearance, but not inulin clearance, significantly favored agalsidase alfa versus placebo recipients. Abnormalities in functional cerebral blood flow and cerebrovascular responses were also reversed with agalsidase alfa therapy.

In extensions of these placebo-controlled trials, the reduction in left ventricular mass and improvements in BPI pain scores were maintained after longer-term agalsidase alfa therapy. The significant decline in estimated glomerular filtration rate (eGFR) seen after 48 months' agalsidase alfa treatment was mainly driven by a marked decline in eGFR seen in four patients with stage 3 chronic kidney disease at baseline (although the progression of decline appeared slower than that seen in historic controls); renal function appeared stable in patients with stage 1 or 2 chronic kidney disease. Certain benefits of agalsidase alfa became apparent with longer-term therapy. For example, a significant reduction in cold and warm detection thresholds and a significant improvement in sweat function were seen after 3 years' therapy.

Final results from a head-to-head trial comparing the effects of agalsidase alfa and agalsidase beta at approved dosages are not yet available. The only available fully published study compared agalsidase alfa 0.2 mg/kg every other week with an off-label dosage of agalsidase beta 0.2 mg/kg every other week. This randomized, open-label, 24-month trial in adult men and women with Fabry disease generally found no significant differences in outcome between treatment arms. It should be noted that concerns were subsequently raised by the European Medicines Agency regarding the use of agalsidase beta at dosages other than the approved dosage of 1 mg/kg every other week. Preliminary results from an ongoing, randomized, open-label study suggest no differences in outcome between patients with Fabry disease receiving intravenous agalsidase alfa 0.2 mg/kg every other week and those receiving the approved regimen of agalsidase beta 1 mg/kg every other week. In three switching studies, no safety concerns were raised and disease stability was generally maintained following the switch from agalsidase beta 1 mg/kg every other week to agalsidase alfa 0.2 mg/kg every other week.

Agalsidase alfa also demonstrated beneficial effects, including in women and pediatric patients, in non-comparative studies and in the Fabry Outcome Survey.

Agalsidase alfa was generally well tolerated in patients with Fabry disease, with infusion reactions (e.g. rigors, pyrexia, flushing) being the most commonly occurring adverse event. IgG antibodies developed in $\approx 24\%$ of male patients with Fabry disease who received agalsidase alfa. After 12–54 months of treatment, 17% of agalsidase alfa recipients were still IgG antibody positive, with immunologic tolerance developing in

7% of agalsidase alfa recipients. No IgE antibodies have been detected in any patient receiving agalsidase alfa. No antibody formation was reported in women receiving agalsidase alfa in noncomparative studies.

In conclusion, agalsidase alfa is an effective and well tolerated treatment option for use in patients with Fabry disease.

1. Introduction

Fabry disease is a rare, X-linked genetic disorder in which mutations in the gene encoding the lysosomal enzyme α -galactosidase A result in a deficiency of this enzyme.^[1,2] This deficiency leads to intralysosomal deposition of undegraded glycosphingolipid products, mainly globotriaosylceramide (Gb3), in tissues and organs.^[1,2]

The estimated worldwide prevalence of Fabry disease is approximately 1 in 40 000 to 1 in 117 000 live births,^[1] although it appears that late-onset Fabry disease is underdiagnosed.^[3] It is a chronic, progressive, debilitating, multisystem condition. Patients with Fabry disease experience progressive renal and cardiac impairment, as well as transient ischemic attacks, stroke, gastrointestinal (GI) symptoms, neurologic symptoms (e.g. neuropathic pain, autonomic dysfunction), dermatologic signs, and ocular and auditory symptoms.^[1,2] The severity of the disease and its progression are more variable in female heterozygotes than in males with Fabry disease.^[1,2,4]

Enzyme replacement therapy has demonstrated beneficial effects in patients with Fabry disease.^[1,2] One such enzyme replacement therapy, agalsidase alfa (Replagal®), is available in over 40 countries, including the EU and Canada, for the long-term treatment of patients with confirmed Fabry disease. This article reviews the efficacy and tolerability of agalsidase alfa in patients with Fabry disease, as well as summarizing its pharmacologic properties.

2. Pharmacologic Properties

2.1 Mechanism of Action

Agalsidase alfa is a glycosylated protein with both sialic acid and mannose-6-phosphate residues.^[5] It has a molecular weight of $\approx$ 51 kD and is produced in a genetically engineered continuous human cell line.^[5-7] The amino acid sequence of agalsidase alfa is identical to that of native α -galactosidase A.^[6]

Agalsidase alfa binds to cell surface mannose-6-phosphate receptors with subsequent cellular internalization and transport to the lysosome.^[5,7] Within the lysosomes of affected tissues, agalsidase alfa catalyses the hydrolysis of Gb3, cleaving a terminal α -linked galactose residue from the molecule.^[5,7,8]

There are some differences between agalsidase alfa and agalsidase beta (the other enzyme replacement therapy indicated for use in Fabry diseases) in terms of their glycosylation pattern,^[6,9] mannose-6-phosphate receptor binding,^[6] and mannose-6-phosphate receptor-mediated cellular uptake.^[6,9]

Administration of agalsidase alfa reduced the accumulation of Gb3 in a number of cell types, including endothelial and parenchymal cells.^[7] For example, a significant ($p < 0.05$) reduction from baseline in liver Gb3 levels was seen in patients with Fabry disease after the administration of agalsidase alfa.^[10] The approved dosage regimen of agalsidase alfa 0.2 mg/kg every other week (section 5) was sufficient to produce a maximal reduction in plasma Gb3 levels in men with Fabry disease.^[11] The effects of agalsidase alfa on plasma, urine sediment, and myocardial levels of Gb3 in patients with Fabry disease in clinical trials are discussed further in section 3. It should be noted that plasma levels of Gb3 do not correlate with disease severity or therapeutic response in Fabry disease.^[12]

2.2 Pharmacokinetic Profile

The pharmacokinetics of intravenous agalsidase alfa 0.2 mg/kg following a single dose and repeated administration in patients with Fabry disease are shown in table I.

The maximum serum agalsidase alfa concentration corresponds with the end of the intravenous infusion.^[5,11] Agalsidase alfa had a biphasic serum elimination profile following a single intravenous infusion,^[5,10] and elimination of agalsidase alfa from serum was complete within 24 hours in most patients.^[5] A lack of accumulation in serum was seen with repeated administration of agalsidase alfa.^[5]

In a murine model of Fabry disease, administration of a single intravenous dose of agalsidase alfa was associated with specific immunostaining for agalsidase alfa in the liver, kidney, heart, testes, adrenal gland, spleen, and bone marrow.^[14] In the kidney, cytoplasmic staining was observed in cortical tubular cells, but not in glomeruli or podocytes. In the heart, staining was seen in vascular endothelial cells, but not in myocytes. No tissue staining was seen in the brain.^[14]

It is thought that clearance of agalsidase alfa from serum is primarily mediated by its binding to cell surface mannose-6-phosphate receptors with subsequent cellular internalization

Table 1. Pharmacokinetic properties of intravenous agalsidase alfa in patients with Fabry disease. Patients received agalsidase alfa 0.2 mg/kg as a 40-minute intravenous infusion either as a single dose or every other week

Pt population (no. of pts)	Mean C _{max} (U/mL)	Mean AUC (U • min/mL)	Mean CL (mL/min/kg)	Mean t _{1/2} (min)	Mean V _{ss} (L/kg ^[5] or % bodyweight ^[13])
Single-dose pharmacokinetics					
Men ^[5] (18)		256 958	2.5	112	0.16
Women ^[5] (15)		336 736**	2.1	89*	0.16
Boys ^{[5]a} (19)		156 148	3.9	71	0.16
Girls ^{[5]a} (5)		226 860†	2.9	50**	0.12
<i>In pts with ESRD^[13]</i>					
Renal transplant recipients (11)	3478	221 006	3.2	77	17.6
Hemodialysis pts (6)	3887	216 017	3.4	89	19.6
Control pts without ESRD (18)	3710	256 958	2.5	112	16.0
Multiple-dose pharmacokinetics^b					
Adults ^[5] (18)		262 635	12.1	180	1.04
Pediatric pts ^[5] (24)		201 500	4.3	101	0.36

a Mean age was 11.5 y in boys and 13.7 y in girls.

b Results reported after 6 or 12 mo in adults and 25 wk in pediatric pts.

AUC = area under the serum concentration-time curve; **CL** = serum clearance; **C_{max}** = peak serum concentration; **ESRD** = end-stage renal disease; **pt(s)** = patient(s); **t_{1/2}** = elimination half-life; **V_{ss}** = volume of distribution at steady state; * $p < 0.05$, ** $p < 0.01$ vs men following a single dose; † $p < 0.05$, †† $p < 0.01$ vs boys following a single dose.

and transport to the lysosome.^[5] Agalsidase alfa is then degraded within lysosomes.^[5] The efficiency with which mannose-6-phosphate receptors sequester agalsidase alfa within lysosomes means that tissue uptake is not reversed and there is no release into the circulation.^[5]

The elimination half-life ($t_{1/2}$) of agalsidase alfa in tissues appears to be longer than that seen in serum.^[10] Liver biopsies demonstrated that 8–32% of the administered dose was still present in the liver 44 hours post-infusion in patients with Fabry disease who received a single intravenous dose of agalsidase alfa 0.3–4.7 U/kg.^[10]

2.2.1 Special Patient Populations

Following a single dose of agalsidase alfa, the area under the serum concentration-time curve (AUC) was significantly larger in women than in men, and the $t_{1/2}$ was significantly shorter (table I).^[5]

Agalsidase alfa had a typical biphasic serum elimination profile in pediatric patients with Fabry disease.^[5] Similar to the pattern seen in adults, the AUC was significantly larger in girls than in boys, and the $t_{1/2}$ was significantly shorter (table I). Compared with adults, the mean serum clearance of agalsidase alfa was significantly faster in pediatric patients (2.3 vs 3.7 mL/min/kg; $p < 0.0001$).^[5] It has been suggested that the more rapid serum clearance seen in pediatric patients reflects more efficient re-

moval of agalsidase alfa by mannose-6-phosphate receptors from the plasma into lysosomes.^[5] Even though the clearance of agalsidase alfa from plasma is increased in pediatric patients, a higher dosage of agalsidase alfa is not required in this patient group to compensate for this.^[5]

The pharmacokinetics of agalsidase alfa in renal transplant recipients and in patients undergoing hemodialysis were similar to those seen in patients without end-stage renal disease (table I).^[13] A typical biphasic serum elimination profile was seen in patients with end-stage renal disease.^[13] No dosage adjustment is needed in patients with renal impairment, including in renal transplant recipients or in patients undergoing dialysis, according to the EU summary of product characteristics, although extensive renal damage may limit the renal response to enzyme replacement therapy.^[8]

Studies have not been conducted with agalsidase alfa in patients with hepatic impairment, although hepatic impairment is not expected to have a clinically significant effect on agalsidase alfa pharmacokinetics.^[8]

2.3 Potential Drug Interactions

Agalsidase alfa should not be coadministered with drugs (e.g. chloroquine, amiodarone, benoquin, or gentamicin) that have the potential to inhibit intracellular α -galactosidase activity.^[8]

It is unlikely that agalsidase alfa would be involved in drug interactions mediated by cytochrome P450 isoenzymes.^[8]

In clinical trials, no interactions were seen between agalsidase alfa and drugs commonly used to relieve neuropathic pain (e.g. carbamazepine, phenytoin, gabapentin).^[8]

3. Therapeutic Efficacy

Two randomized, double-blind, placebo-controlled, 6-month trials examined the efficacy of intravenous agalsidase alfa 0.2 mg/kg every other week in adult men with Fabry disease (n = 26^[15] and 15^[16]) and have been published in full (see table II for trial design details). The primary endpoints in these studies were the effects of agalsidase alfa therapy on neuropathic pain^[15] and myocardial Gb3 content^[16] (table II), with additional analyses^[16-21] examining other endpoints.

Following completion of the two 6-month, placebo-controlled trials,^[15,16] patients in each trial could enter extension studies in which all patients received treatment with agalsidase alfa 0.2 mg/kg every other week.^[16-18,20,22-24] In one of the extension studies, 22 of 25 patients eventually received agalsidase alfa in a home setting, administered by a nurse.^[22]

Results of a third randomized, double-blind, placebo-controlled, 6-month trial examining the efficacy of agalsidase alfa 0.2 mg/kg every other week in men with Fabry disease have not been published, although a pooled analysis (n = 108)^[25] combining this trial with the other two placebo-controlled trials,^[15,16] and their extensions, is available (see section 3.3.1).

Final results from a head-to-head trial comparing the effects of agalsidase alfa and agalsidase beta at approved dosages are not yet available. The only available fully published study used an off-label dosage of agalsidase beta.^[26] This randomized,

open-label, multicenter, 24-month study included patients aged ≥ 18 years who had Fabry disease confirmed by α -galactosidase A activity (men) or genotyping (women) and who fulfilled criteria for starting enzyme replacement therapy. Fifty percent of agalsidase alfa recipients and 56% of agalsidase beta recipients were men.^[26] Patients were randomized to receive intravenous agalsidase alfa (n = 18) or agalsidase beta (n = 16) at a dosage of 0.2 mg/kg every other week. The agalsidase beta dosage of 0.2 mg/kg every other week used in this study^[26] is off-label, as the approved dosage is 1 mg/kg every other week.^[27,28] The primary endpoint was the reduction in left ventricular mass (it was initially a renal function endpoint, but was changed to left ventricular mass during the study).^[26] It should be noted that concerns were subsequently raised by the European Medicines Agency regarding the use of agalsidase beta at dosages other than the approved dosage of 1 mg/kg every other week (see section 6).^[29]

The Canadian Fabry Disease Initiative (CFDI) is an ongoing, multicenter study involving three patient cohorts.^[30-32] In one of these cohorts (cohort 1B), patients with Fabry disease who had not received prior enzyme replacement therapy were randomized to intravenous agalsidase alfa 0.2 mg/kg every other week or intravenous agalsidase beta 1 mg/kg every other week (i.e. both approved regimens). Endpoints include estimated glomerular filtration rate (eGFR), left ventricular mass index, pain, health-related quality of life (HR-QOL), disease severity, as well as clinical endpoints such as the incidence of stroke/transient ischemic attacks, hospitalization, and death. Preliminary results of the randomized, open-label, cohort 1B study (available as abstracts) are currently available after 24 months (n = 37)^[33] or 30 months (n = 61)^[34] of follow-up. For example, no differences in clinical outcomes were reported between patients receiving the approved intravenous agalsidase

Table II. Design characteristics of randomized, double-blind, placebo-controlled, 6-month trials examining the efficacy of intravenous agalsidase alfa 0.2 mg/kg every other week in adult men with Fabry disease^[15,16]

	Schiffmann et al. ^[15]		Hughes et al. ^[16]	
	AGA-A (n = 14)	PL (n = 12)	AGA-A (n = 7)	PL (n = 8)
Baseline characteristics				
White pts (%)	93	92	100	87.5
Mean duration of illness (y)	12.8	12.1		
Inclusion criteria	Age ≥ 18 y; hemizygous men with Fabry disease confirmed by α -galactosidase A assay; neuropathic pain		Age ≥ 18 y; hemizygous men with Fabry disease confirmed by α -galactosidase A activity and genotyping; increased left ventricular mass	
Exclusion criteria			Permanent cardiac pacemaker; contraindication to cardiac biopsy	
Primary endpoint	Neuropathic pain while without pain medications ^a		Myocardial globotriaosylceramide content	

a Neuropathic pain while without pain medications was assessed using the 'pain at its worst' item of the Brief Pain Inventory (question 3).

AGA-A = agalsidase alfa; **PL** = placebo; **pts** = patients.

alfa regimen and those receiving the approved agalsidase beta regimen after 24 months of follow-up.^[33] Although the cohort 1B study is not discussed further, results of the CFDI switching experience are discussed.^[30]

Cohort 1A of the CFDI included patients who were already receiving enzyme replacement therapy prior to the start of CFDI.^[31] Because of the shortage of agalsidase beta in Canada, cohort 1A included 36 patients who transitioned from the approved dosage of agalsidase beta (1 mg/kg every other week) to the approved dosage of agalsidase alfa (0.2 mg/kg every other week).^[30] The results of switching studies in the US (n = 62)^[35,36] and Japan (n = 11)^[37] are also reported; in these studies, which were prompted by shortages in agalsidase beta, patients with Fabry disease switched from agalsidase beta to agalsidase alfa at approved dosages.^[35,37] The US study, which was initially designed to evaluate safety, also including 29 treatment-naïve patients who received agalsidase alfa.^[35,38] Results are available after 12 months^[35,37] or a mean 15.1 months^[30] of treatment with agalsidase alfa 0.2 mg/kg every other week. Three of these analyses are available as abstracts.^[30,35,36]

Several noncomparative trials examined the efficacy of agalsidase alfa treatment in patients with Fabry disease.^[39–44] Two of these noncomparative studies included only women.^[39,41] To be eligible for the studies, women had to have clinical evidence of Fabry disease^[39,41] (with involvement of at least three organ systems in one study^[39]). Studies were of single-center^[39,41,43,44] or multicenter^[42] design; one study^[40] was a retrospective pooled analysis of four trials (two of which have been published^[15,41]).

The efficacy of agalsidase alfa in pediatric patients with Fabry disease was examined in an initial 26-week, noncomparative, multicenter trial (n = 24),^[45] with 17 patients subsequently participating in a 3.5-year extension study.^[46] A third, small, noncomparative study in pediatric patients with Fabry disease (n = 13), primarily designed to assess the tolerability of agalsidase alfa (see section 4), did not conduct statistical analyses and is not discussed further in this section.^[47]

The Fabry Outcome Survey (FOS) is an international product registry which is open to patients with a confirmed diagnosis of Fabry disease who are receiving, or who are candidates for, enzyme replacement therapy with agalsidase alfa. A number of analyses have examined the efficacy of agalsidase alfa in patients with Fabry disease who are enrolled in FOS.^[48–57]

3.1 Effects on Cardiac Endpoints

3.1.1 Comparisons with Placebo

Agalsidase alfa had beneficial effects on various endpoints in men with Fabry disease, according to the results of placebo-

controlled trials.^[15,16] In terms of cardiac endpoints, the change in myocardial Gb3 content (primary endpoint) did not significantly differ between agalsidase alfa and placebo recipients after 6 months' therapy (table III). However, left ventricular mass and left ventricular mass index were reduced to a significantly greater extent with agalsidase alfa than with placebo (table III); 10 of the 15 patients (67%) included in the study had left ventricular hypertrophy at baseline.^[16] The QRS complex duration was reduced to a significantly greater extent with agalsidase alfa than with placebo in one study,^[15] with no significant between-group difference in the other study^[16] (table III).

Although no further reduction in left ventricular mass was seen after 2 years of treatment with agalsidase alfa, there were significant reductions in the thickness of the left ventricular posterior wall and septum, indicating cardiac remodelling (table III).^[16]

3.1.2 Comparisons with Agalsidase Beta

In general, there were no significant differences in outcome between patients with Fabry disease receiving agalsidase alfa 0.2 mg/kg every other week and those receiving agalsidase beta 0.2 mg/kg every other week.^[26] The change from baseline in left ventricular mass did not significantly differ between agalsidase alfa recipients and agalsidase beta recipients after 12 months' therapy (table III), with a similar pattern seen after 24 months' follow-up.^[26]

Over 24 months of follow-up, treatment failure (defined as progression of renal or cardiac disease or a new cerebrovascular accident) occurred in five agalsidase alfa recipients and three agalsidase beta recipients.^[26] The time to treatment failure did not significantly differ between the two treatment groups. An additional two patients in each treatment group experienced treatment failure when the duration of follow-up was extended beyond 24 months. Patients with more severe disease before starting treatment and those who were older were significantly (p = 0.02) more likely to experience treatment failure.^[26]

Switching Studies

In general, disease stability was maintained following the switch from agalsidase beta to agalsidase alfa at approved dosages.^[30,35,37] For example, there was no significant change in mean left ventricular mass index post-switch in the CFDI^[30] and US^[35] studies, with a significant reduction in mean left ventricular mass index in the Japanese study (from 58.06 g/m^{2.7} pre-switch to 51.59 g/m^{2.7} post-switch; p = 0.0137).^[37] Septal wall thickness was significantly increased (from 1.40 cm pre-switch to 1.49 cm post-switch; p = 0.032) in the CFDI study,^[30] with no significant change in septal wall thickness in the Japanese

Table III. Effects of agalsidase alfa on cardiac endpoints in patients with Fabry disease. Results of randomized, controlled trials^[15,16,26] and extension,^[16] noncomparative studies,^[39–41,45] and analyses from the Fabry Outcome Survey.^[48,56] Most studies were conducted in adults, with one study only including pediatric patients.^[45] Some studies included only men^[15,16] or only women.^[39,41] Intravenous agalsidase alfa was administered at a dosage of 0.2 mg/kg every other week

Study (study duration ^a)	Treatment (no. of pts)	Mean ^[16,39–41,45,48,56] or median ^[26] change from baseline in LVM (g) and/or LVMI (g/m ² ^[16,39] or g/m ^{2.7} ^[40,41,45,48,56]) ^b [baseline value]	Other cardiac endpoints (mean change from baseline ^[15,16,39,41,48,56]) [baseline value]
Comparisons with PL			
Hughes et al. ^[16] (6 mo)	AGA-A vs PL (6–7 vs 7–8)	LVM: –11.5* vs +21.8 [276.2 vs 248.2] LVMI: –6.4* vs +12 [176 vs 186]	Myocardial Gb3 content: –0.13 vs +0.05 nmol/μg protein ^c [0.71 vs 0.58] QRS duration: –12.9 vs +4 msec
Schiffmann et al. ^[15] (6 mo)	AGA-A vs PL (14 vs 12)		QRS duration: –2.4* vs +3.6 msec
<i>Extension study</i>			
Hughes et al. ^[16] (24 mo)	AGA-A (10)	No further reduction in LVM	LV posterior wall thickness: –1.9 mm ^{††} Septal thickness: –3 mm ^{††}
Comparison with AGA-B			
Vedder et al. ^[26] (24 mo)	AGA-A vs AGA-B ^d (10 vs 10)	LVM at 12 mo: –23 vs –46 ^c [288 vs 316]	
Noncomparative studies			
Baehner et al. ^[39] (up to 55 wk)	AGA-A (15)	LVMI at 27 wk: –23.0 ^{††} ; at 41 wk: –25.2 [†] [148.1]	QRS duration at 27 wk: –8.7 msec ^{††} ; at 41 wk: –3.6 msec [100.5 msec]
Kampmann et al. ^{[40]e} (≥36 mo)	AGA-A (45)	LVMI in pts with LVH at 12 mo: –9.2 ^{††} ; at 36 mo: –5.1 [†] [55.4] LVMI in pts without LVH at 12 mo: –3.6 ^{††} ; at 36 mo: –2.1 [39.1]	
Whybra et al. ^[41] (4 y)	AGA-A (36)	LVMI in pts with LVH: –7.3 to –40 ^{†††} [56.0–131.9] ^f LVMI in pts without LVH: –4.5 ^{††} [40.7]	NYHA classification: –0.52 ^{†††} [1.83]
<i>Pediatric pts</i>			
Fries et al. ^{[45]g} (26 wk)	AGA-A (24)	LVMI in boys at 25 wk: –1 [32.4] LVMI in girls at 25 wk: –3.2 [36.0]	Improved heart rate variability indices in boys [†]
Fabry Outcome Survey			
Hughes et al. ^[56] (4 y)	AGA-A (69)	LVMI in women: –4.5 [†] [48.2] LVMI in men: –2.5 [54.7]	MFS in women: +0.7% [15.5] MFS in men: +0.7% [15.6]
Mehta et al. ^[48] (5 y)	AGA-A (50–57)	LVMI in pts with LVH: –7.3 [†] [71.4] LVMI in pts without LVH: +1.8 [38.7]	MFS in pts with LVH: +0.5% [14.1] MFS in pts without LVH: +0.8% [17.0]

a Outcomes were assessed at study end unless specified otherwise.

b LVM was assessed using magnetic resonance imaging^[16] or echocardiography.^[26,39–41,45,48,56]

c Primary endpoint.

d Intravenous AGA-B 0.2 mg/kg every other week (approved dosage is 1 mg/kg every other week).

e A retrospective pooled analysis of four trials (two of which have been published^[15,41]).

f LVMI was evaluated across LVM tertiles in pts with LVH at baseline.

g Mean age at baseline of boys (n = 19) was 11.5 y and of girls (n = 5) was 13.5 y.

AGA-A = agalsidase alfa; **AGA-B** = agalsidase beta; **Gb3** = globotriaosylceramide; **LV** = left ventricular; **LVH** = LV hypertrophy; **LVM** = LV mass; **LVMI** = LV mass index; **MFS** = midwall fractional shortening; **NYHA** = New York Heart Association; **PL** = placebo; **pts** = patients; *p < 0.05 vs PL; †p < 0.05, ††p < 0.01, †††p < 0.001 vs baseline.

study.^[37] Following the switch to agalsidase alfa, there were no significant changes in posterior wall thickness^[30,37] or New York Heart Association class.^[30]

Interim 12-month results from treatment-naïve patients with Fabry disease in the US study found no significant change from baseline in left ventricular mass index with agalsidase alfa therapy.^[35]

3.1.3 Noncomparative Studies

Agalsidase alfa therapy was associated with significant reductions from baseline in left ventricular mass in patients with Fabry disease after 27 weeks to 4 years of follow-up in non-comparative studies;^[39-41] these reductions generally occurred regardless of whether or not patients had left ventricular hypertrophy at baseline^[40,41] (table III). In addition, the duration of the QRS complex was significantly reduced from baseline after 27 weeks, but not 41 weeks, of follow-up,^[39] and there was also a significant improvement from baseline in New York Heart Association classification after 4 years' follow-up^[41] (table III).

Pediatric Patients

In pediatric patients aged ≥ 6.5 years with Fabry disease, left ventricular mass index was in the normal range at baseline and there was no significant change after 25 weeks' therapy (table III),^[45] or after a total of 4 years of treatment (quantitative data not reported).^[46] Measures of heart rate variability were significantly improved from baseline in boys after 25 weeks of treatment with agalsidase alfa (table III),^[45] with significant ($p < 0.05$) improvement in some measures sustained after 4 years' therapy.^[46]

3.1.4 Fabry Outcome Survey

After 4 years of follow-up, left ventricular mass index was significantly reduced from baseline among women receiving agalsidase alfa, but not among men receiving agalsidase alfa (table III).^[56] After 5 years of follow-up, left ventricular mass index was significantly reduced among agalsidase alfa recipients with left ventricular hypertrophy at baseline, and remained within the normal range among those without left ventricular hypertrophy at baseline (table III).^[48] There was no significant change from baseline in midwall fractional shortening in either study (table III).^[48,56]

Pediatric Patients

In pediatric patients with Fabry disease enrolled in FOS, mean left ventricular mass index was $31.7 \text{ g/m}^{2.7}$ after 2 years of agalsidase alfa therapy, compared with $35.7 \text{ g/m}^{2.7}$ at baseline (statistical analysis not reported).^[57]

3.2 Effects on Pain, Disease Severity, and Health-Related Quality of Life

3.2.1 Comparisons with Placebo

Neuropathic pain (primary endpoint; assessed using the Brief Pain Inventory [BPI] 'pain at its worst' score) was decreased to a significantly greater extent with agalsidase alfa than with placebo in men with Fabry disease (table IV);^[15] a 1-unit reduction in the BPI score is considered clinically significant. Of the patients who were receiving neuropathic pain medications at baseline, significantly ($p = 0.03$) more agalsidase alfa recipients (4 of 11; 36%) than placebo recipients (0 of 11) were able to discontinue these pain medications for the duration of the trial. The mean time for which agalsidase alfa recipients were able to remain without pain medication during the study was significantly longer than that seen in placebo recipients (74.5 vs 12.9 days; $p = 0.02$).^[15]

The reduction from baseline in the BPI severity score also significantly favored agalsidase alfa versus placebo recipients, with no significant between-group difference in the change in the BPI pain-related quality-of-life score (table IV).^[15]

Improvements in pain scores were maintained following longer-term therapy with agalsidase alfa (table IV).^[18]

3.2.2 Comparisons with Agalsidase Beta

The change from baseline in the BPI 'pain at its worst' score did not significantly differ between patients with Fabry disease receiving agalsidase alfa 0.2 mg/kg every other week and those receiving agalsidase beta 0.2 mg/kg every other week after 12 months' therapy (table IV), with a similar pattern seen after 24 months' follow-up.^[26]

Switching Studies

The Japanese switching study reported no significant changes in BPI pain scores or in HR-QOL following the switch from agalsidase beta to agalsidase alfa.^[37]

3.2.3 Noncomparative Studies

The BPI score for 'pain at its worst' was significantly reduced from baseline after 12 months' treatment with agalsidase alfa in a noncomparative study (table IV), and remained stable after this time point.^[41]

Significant improvements from baseline in the total Mainz Severity Score Index (MSSI) score (a measure of total disease burden), the neurologic MSSI subscore, and the cardiovascular MSSI subscore were seen in two studies (treatment duration of ≥ 1 year [median of 2.9 years]^[42] or 4 years^[41]) [table IV].^[41,42] One study also showed a significant improvement from baseline

Table IV. Effects of agalsidase alfa on pain, disease severity, and health-related quality-of-life endpoints in patients with Fabry disease. Results of randomized, controlled trials^[15,26] and extension,^[18] noncomparative studies^[39,41,42,45,46] and analyses from the Fabry Outcome Survey.^[48,49,56] Most studies were conducted in adults, with some studies only including pediatric patients.^[45,46] Some trials included only men^[15] or only women.^[39,41] Intravenous agalsidase alfa was administered at a dosage of 0.2 mg/kg every other week

Study (study duration ^b)	Treatment (no. of pts)	Endpoint ^a (mean ^[15,18,39,41,45,46,48,56] or median ^[26,42] change from baseline) [baseline value]
Comparison with PL		
Schiffmann et al. ^[15] (6 mo)	AGA-A vs PL (14 vs 12)	BPI 'pain at its worst' score: -1.9* vs -0.3 ^c [6.2 vs 7.3] BPI severity score: -1.1* vs -0.7 [3.8 vs 5.4] BPI pain-related quality-of-life score: -1.1 vs -0.6 [3.2 vs 4.8]
<i>Extension study</i>		
Schiffmann et al. ^[18] (up to 3 y)	AGA-A (26)	BPI 'pain at its worst' score at 18 mo: -1.9** BPI score for interference in daily life at 12–18 mo: -1.2*
Comparison with AGA-B		
Vedder et al. ^[26] (24 mo)	AGA-A vs AGA-B ^d (15 vs 13)	BPI 'pain at its worst' score at 12 mo: 0 vs -1.5 [4 vs 4]
Noncomparative studies		
Baehner et al. ^[39] (up to 55 wk)	AGA-A (15)	SF-36 physical component summary score at 27 wk: +6.6* [35.1] SF-36 role physical score at 27 wk: +27.3** [25.0] SF-36 general health score at 27 wk: +19.3** [41.1]
Parini et al. ^{[42]e} (≥1 y)	AGA-A (30)	Total MSSI: -4****; general MSSI: -1***; neurologic MSSI: -1**; cardiovascular MSSI: 0*; renal MSSI: 0
Whybra et al. ^[41] (4 y)	AGA-A (36)	↓ Total MSSI***, neurologic MSSI***, and cardiovascular MSSI***, but not general or renal MSSI BPI 'pain at its worst' score at 12 mo: -1.3*** [4.6]
<i>Pediatric pts</i>		
Ries et al. ^{[45]f} (26 wk)	AGA-A (24)	BPI 'pain at its worst' score at 25 wk in boys: -1.64 [6.06]; in girls: -0.92 [5.67]
Schiffmann et al. ^{[46]f} (3.5 y)	AGA-A (17)	BPI 'pain at its worst' score at 1 y: -2.86*** [6.05] BPI 'average' pain score at 1 y: -1.26* [2.96]
Fabry Outcome Survey		
Hoffmann et al. ^[49] (36 mo)	AGA-A (62–81)	Shift to less severe pain for BPI 'pain at its worst', 'pain at its least', and 'average' pain** at 24 and 36 mo
Hughes et al. ^[56] (4 y)	AGA-A (73)	BPI 'pain at its worst' score in women: -0.2 [4.0]; in men: -0.2 [3.7] BPI 'average' pain score in women: -0.5 [3.6]; in men: -0.1 [2.7]
Mehta et al. ^[48] (5 y)	AGA-A (49–53)	BPI 'pain at its worst' score: -1.3* [5.0]; BPI 'average' pain score: -1.2** [3.7] Quality-of-life deviation score: +0.07 ^g [-0.24]

a The BPI scores pain from 0 (no pain) to 10 (worst pain). Total MSSI scores of <20, 20–40, and >40 reflect mild, moderate, and severe disease, respectively.

b Outcomes were assessed at study end unless specified otherwise.

c Primary endpoint. The 'pain at its worst' item of the BPI (question 3) was used to assess the effect of treatment on neuropathic pain while without pain medications. Values in PL recipients were estimated from a graph.

d Intravenous AGA-B 0.2 mg/kg every other week (approved dosage is 1 mg/kg every other week).

e This trial included five boys aged 4–18 y.

f 24 pts were enrolled in the initial 26 wk trial^[45] (mean age at baseline of boys [n=19] was 11.5 y and of girls [n=5] was 13.5 y), with 17 pts enrolled in the subsequent 3.5 y extension study.^[46]

g Deviation scores from EuroQol values for the general population.

AGA-A=agalsidase alfa; **AGA-B**=agalsidase beta; **BPI**=Brief Pain Inventory; **MSSI**=Mainz Severity Score Index; **PL**=placebo; **pts**=patients; **SF-36**=Short-Form 36 Health Survey; ↓ indicates significantly decreased; *p<0.05 vs PL; †p<0.05, ††p<0.01, †††p<0.001, ††††p<0.0001 vs baseline.

in the general MSSSI subscore,^[42] but neither study showed an improvement in the renal MSSSI subscore^[41,42] (table IV).

In terms of HR-QOL, significant improvements from baseline in the Short Form-36 Health Survey (SF-36) physical component summary score, role physical score, and general health score were seen in women after 27 weeks' treatment with agalsidase alfa (table IV), with no significant changes from baseline in the mental component summary score or any of the other domain scores.^[39]

Pediatric Patients

The BPI 'pain at its worst' score had not significantly altered from baseline after 6 months' therapy with agalsidase alfa in pediatric patients aged ≥ 6.5 years with Fabry disease in a noncomparative study;^[45] however, after 1 year's follow-up, both the BPI 'pain at its worst' score and the BPI 'average' pain score were significantly reduced from baseline^[46] (table IV). Significant ($p < 0.05$) reductions from baseline in the BPI 'pain at its worst' score were also seen after 1.5, 2, 2.5, and 3.5 years of therapy.^[46] Six of the 11 patients (55%) who were receiving anticonvulsants for neuropathic pain at baseline were able to stop or reduce their use of these medications.^[45]

3.2.4 Fabry Outcome Survey

Pain was reduced in patients with Fabry disease who received agalsidase alfa in FOS, as indicated by significant reductions in BPI scores for 'pain at its worst' or 'average' pain at 5 years,^[48] or a significant shift to less severe pain at 24 and 36 months^[49] (table IV). However, no significant change from baseline in BPI scores for 'pain at its worst' or 'average' pain were seen among men or women receiving agalsidase alfa for 4 years (table IV).^[56]

3.3 Effects on Renal Endpoints

3.3.1 Comparisons with Placebo

Glomerular histology was improved by agalsidase alfa in men with Fabry disease, with a significant increase in normal glomeruli (mean change of +8.1% with agalsidase alfa vs -16.0% with placebo; $p = 0.01$) and a significant decrease in glomeruli with mesangial widening (mean change -12.5% vs +16.5%; $p = 0.01$) after 6 months' therapy.^[15] Although there was a statistically significant increase in glomeruli with segmental sclerosis with agalsidase alfa versus placebo (mean change +4.0% vs -3.0%; $p = 0.048$), the relative increase was small compared with the improvements seen in normal glomeruli and glomeruli with mesangial widening. There was no significant difference between agalsidase alfa and placebo in obsolescent glomeruli (mean change +0.4% vs +2.5%).^[15]

Renal function tests revealed a significant difference between agalsidase alfa and placebo recipients in creatinine clearance (with improved function in agalsidase alfa recipients and decreased function in placebo recipients), but not in inulin clearance, after 6 months' therapy (table V).^[15]

A significant decrease from baseline in eGFR was seen after 48 months' treatment with agalsidase alfa (table V).^[22] This was mainly driven by a marked decline in eGFR seen in four patients who had stage 3 chronic kidney disease at baseline, although the progression of decline in these patients appeared slower than that seen in a group of untreated historic controls with Fabry disease.^[22] Renal function appeared stable in patients with stage 1 or 2 chronic kidney disease who received agalsidase alfa.^[22]

Twelve patients who experienced a rate of decline in eGFR of ≥ 5 mL/min/1.73 m²/year despite treatment with agalsidase alfa 0.2 mg/kg every other week received weekly treatment with agalsidase alfa 0.2 mg/kg instead.^[24] The annualized rate of decline in eGFR was significantly slower after 2 years of weekly agalsidase alfa administration than during administration of agalsidase alfa every other week (-3.3 vs -8.0 mL/min/1.73 m²/year; $p = 0.01$).^[24]

In the pooled analysis of three placebo-controlled studies, the mean annualized rate of change in eGFR was -2.9 mL/min/1.73 m²/year in agalsidase alfa recipients and -7.0 mL/min/1.73 m²/year in placebo recipients when patients with renal hyperfiltration were excluded from the analysis.^[25] Agalsidase alfa therapy did not significantly alter proteinuria.^[25]

There was no significant difference between agalsidase alfa and placebo recipients in the change in urine sediment or kidney Gb3 levels in one 6-month trial,^[15] although in the second 6-month trial, urine sediment Gb3 levels were reduced to a significantly greater extent with agalsidase alfa than with placebo^[16] (table V). A significant reduction from baseline in urine sediment Gb3 levels was seen after 36 months' treatment with agalsidase alfa in an extension study (table V).^[22]

3.3.2 Comparisons with Agalsidase Beta

The change from baseline in GFR or urine sediment Gb3 levels did not significantly differ between patients with Fabry disease receiving agalsidase alfa 0.2 mg/kg every other week and those receiving agalsidase beta 0.2 mg/kg every other week after 12 months' therapy (table V), with a similar pattern seen after 24 months' follow-up.^[26]

Switching Studies

In terms of renal outcomes, eGFR was significantly decreased (by a mean 3.2 mL/min/1.73 m²; $p = 0.009$) following the

Table V. Effects of agalsidase alfa on renal endpoints in patients with Fabry disease. Results of randomized, controlled trials^[15,16,26] and extension,^[22] noncomparative studies,^[39,41,43,45,46] and analyses from the Fabry Outcome Survey,^[48,52,56,57] Most studies were conducted in adults, with some studies including only pediatric patients.^[45,46,57] Some trials included only men^[15,16] or only women.^[39,41] Intravenous agalsidase alfa was administered at a dosage of 0.2 mg/kg every other week

Study (study duration ^a)	Treatment (no. of pts)	Renal function tests ^b (mean ^c , [15,22,41,43,45,46,57] median, ^[26,56] or mean yearly ^[48,52] change from baseline; mL/min/1.73 m ²) [baseline value]	Other endpoints (mean ^[15,16,41,43,45,46] or median ^[22,26] change from baseline) [baseline value]
Comparison with PL			
Hughes et al. ^[16] (6 mo)	AGA-A vs PL (7 vs 8)		Urine sediment Gb3: -1052* vs -25 nmol/24 h
Schiffmann et al. ^[15] (6 mo)	AGA-A vs PL (11-14 vs 9-11)	CL _{CR} : +2.1* vs -16.1 [92.7 vs 100.6] Inulin clearance: -6.2 vs -19.5 [77.2 vs 90.9]	Urine sediment Gb3: -686 vs +333 nmol/g of creatinine [2369 vs 2162] Kidney Gb3: -4.0 vs -0.9 [19.5 vs 19.0]
Extension study			
Schiffmann et al. ^[22] (up to 4.5 y)	AGA-A (24)	eGFR at 48 mo: -13* [88]	Proteinuria at 36 mo: +7 mg/24 h [353] Urine sediment Gb3 at 36 mo: ↓ by 60% ^{†††}
Comparison with AGA-B			
Vedder et al. ^[26] (24 mo)	AGA-A vs AGA-B ^c (18 vs 16)	GFR at 12 mo: +5 vs +5 [99 vs 108]	No significant changes in proteinuria Urine sediment Gb3 at 12 mo: -284* vs -265 nmol/24 h
Noncomparative studies			
Baehner et al. ^[39] (up to 55 wk)	AGA-A (15)	CL _{CR} remained stable	↓ Urine sediment Gb3 at wk 13*
Thofehrn et al. ^[43] (36 mo)	AGA-A (8)	GFR: +12.3 [110.3]	Proteinuria: +361.3 mg/24 h [194.3]
Whybra et al. ^[41] (4 y)	AGA-A (33-36)	eGFR: 0 [91.0]	Proteinuria: -114 mg/24 h [377]
Pediatric pts			
Ries et al. ^[45] (26 wk)	AGA-A (24)	eGFR: -5 [121]	Urine sediment Gb3: -972 nmol/g of creatinine in boys [1929]; -53 nmol/g of creatinine in girls [141]
Schiffmann et al. ^[46] (3.5 y)	AGA-A (17)	eGFR: +0.7 [121]	↓ Urine sediment Gb3 in boys ^{††} Albuminuria: +4 mg/24 h [7.6]
Fabry Outcome Survey			
Feriozzi et al. ^[52] (≥5 y)	AGA-A (208)	eGFR in men: -2.2 ^{††} ; in women: -0.7	Minimal changes in proteinuria
Hughes et al. ^[56] (4 y)	AGA-A (146)	eGFR in women: -2.2 ^{††} [71.8]; in men: -7.9 ^{†††} [88.2]	No significant changes in proteinuria
Mehta et al. ^[48] (5 y)	AGA-A (150)	eGFR in men: -3.17 ^{††††} ; in women: -0.89 ^{††}	
Pediatric pts			
Ramaswami et al. ^[57] (24 mo)	AGA-A (45)	eGFR: -0.7 [93.2]	
a Outcomes were assessed at study end unless specified otherwise.			
b Where specified, eGFR was estimated using the Modification of Diet in Renal Disease formula,^[22,41,48,56] the Chronic Kidney Disease Epidemiology Collaboration formula,^[52] or the Counahan-Barratt equation.^[45,46,57] In other studies, GFR was measured using iohexolam/hippuran or iohexol infusions^[26] or chromium ethylene diamine tetra-acetate clearance.^[43]			
c Intravenous AGA-B 0.2 mg/kg every other week (approved dosage is 1 mg/kg every other week).			
d 24 pts were enrolled in the initial 24 wk trial^[45] (mean age at baseline of boys [n = 19] was 11.5 y and of girls [n = 5] was 13.5 y), with 17 pts enrolled in the subsequent 3.5 y extension study.^[46]			
e Mean age at the start of AGA-A therapy was 12.6 y in boys and 15.2 y in girls.			
AGA-A = agalsidase alfa; AGA-B = agalsidase beta; CL_{CR} = creatinine clearance; (e)GFR = (estimated) glomerular filtration rate; Gb3 = globotriaosylceramide; PL = placebo; pts = patients; ↓ indicates significantly decreased; * p < 0.05 vs PL; † p < 0.05, †† p ≤ 0.01, ††† p ≤ 0.001, †††† p < 0.0001 vs baseline.			

switch to agalsidase alfa in the US switching study,^[35] with no significant change in the CFDI^[30] or Japanese^[37] studies. When data from the US study were reanalyzed with hyperfiltrators removed, the mean change from baseline in eGFR was no longer statistically significant ($-1.2 \text{ mL/min/1.73 m}^2$).^[36] A significant reduction in creatinine-normalized urine Gb3 levels (by 0.9 nmol/mg ; $p=0.009$) was seen in the US study.^[35] Post-switch, there were no significant changes in proteinuria.^[30,37]

Interim 12-month results from treatment-naïve patients with Fabry disease in the US study showed no significant change from baseline in eGFR after 12 months' agalsidase alfa therapy, although a significant ($p<0.05$) reduction from baseline in creatinine-normalized urine Gb3 levels (by 2.1 nmol/mg) was seen.^[35]

3.3.3 Noncomparative Studies

Renal function remained stable during up to 4 years of agalsidase alfa therapy in noncomparative studies,^[39,41,43] with no significant change in proteinuria^[41,43] (table V). A significant reduction in urine sediment Gb3 was seen after 13 weeks' therapy (table V).^[39]

Pediatric Patients

The eGFR was not significantly altered after 6 months of agalsidase alfa therapy in pediatric patients aged ≥ 6.5 years in a noncomparative study,^[45] and remained stable after an additional 3.5 years of follow-up^[46] (table V). Among a subgroup of five boys with hyperfiltration at baseline, the mean eGFR had significantly ($p<0.05$) decreased from $143.4 \text{ mL/min/1.73 m}^2$ at baseline to $121.3 \text{ mL/min/1.73 m}^2$ after 4 years' treatment.^[46] In addition, after 4 years' therapy, renal function normalized (eGFR of $110 \text{ mL/min/1.73 m}^2$) in a boy with an eGFR of $85.5 \text{ mL/min/1.73 m}^2$ at baseline.^[46] Albuminuria normalized in two boys with microalbuminuria at baseline.^[46]

There was no significant change in urine sediment Gb3 levels after 6 months' therapy,^[45] although a significant reduction from baseline was seen in boys after an additional 3.5 years of follow-up^[46] (table V).

3.3.4 Fabry Outcome Survey

Analysis of data from patients with Fabry disease enrolled in FOS ($n=201$ ^[50] and 165 ^[51]) suggested that deterioration in renal function may be slowed by agalsidase alfa; patients received 2^[50] or 3^[51] years of treatment. However, a significant mean yearly reduction in eGFR was seen in both men and women who received agalsidase alfa for 5 years (table V).^[48] Analysis of FOS data from patients who received agalsidase alfa for ≥ 5 years (mean 7.4 years) showed that although there

was a significant mean yearly reduction in eGFR in men, renal function remained stable in women^[52] (table V). It should be noted that different formulae were used to calculate eGFR in these two longer-term evaluations^[48,52] (table V).

Further analysis revealed that the decline in eGFR was significantly ($p\leq 0.01$) worse in patients with baseline proteinuria of $>1000 \text{ mg/24 hours}$ than in those with baseline proteinuria of <500 or $500\text{--}1000 \text{ mg/24 hours}$.^[52]

An analysis in 20 patients with Fabry disease who had undergone renal transplantation revealed that renal function and proteinuria remained stable after 2 years' therapy with agalsidase alfa.^[53]

Pediatric Patients

In pediatric patients with Fabry disease enrolled in FOS, no significant change in renal function was seen after 2 years' treatment (table V).^[57]

3.4 Effects on Other Endpoints

3.4.1 Comparisons with Placebo

Abnormalities in functional cerebral blood flow and cerebrovascular responses were reversed with agalsidase alfa therapy (table VI).^[19,21] At baseline, patients with Fabry disease had significantly ($p<0.05$) increased resting regional cerebral blood flow, exaggerated cerebrovascular responses, and significantly ($p<0.05$) higher blood flow velocities, compared with healthy controls.^[19–21] Although no significant differences between agalsidase alfa and placebo were seen in cerebral blood flow velocities after 6 months of treatment, significant improvements were seen after 18 months of agalsidase alfa therapy (table VI).^[20]

After 6 months' therapy, there were no significant differences between agalsidase alfa and placebo in sensory modalities (e.g. warm and cold detection thresholds),^[18] although a significant reduction was seen in the cold and warm detection thresholds in the foot after 3 years' agalsidase alfa treatment^[18] (table VI).

No significant differences between agalsidase alfa and placebo in measurements of nerve conduction^[18] or intraepidermal nerve fibre density^[17] were seen after 6 months' therapy, although a significant decline in intraepidermal nerve fibre density was seen after 18 months' agalsidase alfa treatment^[17] (table VI).

A significant deterioration from baseline in high-frequency sensorineural hearing loss was seen in both agalsidase alfa and placebo recipients after 6 months' therapy (table VI).^[58] However, high-frequency sensorineural hearing loss improved with longer-term agalsidase alfa therapy, with a significant improvement in high-frequency hearing loss seen after 30 and

Table VI. Effects of agalsidase alfa on additional endpoints in adults with Fabry disease. Results of randomized, controlled trials^[17-21,58] and extensions,^[17,18,20,23] and an analysis from the Fabry Outcome Survey.^[54] Some trials included only men.^[17-21,58] Intravenous agalsidase alfa was administered at a dosage of 0.2 mg/kg every other week

Study (study duration ^a)	Treatment (no. of ears/pts)	Endpoint
Comparisons with PL		
Hajioff et al. ^{[58]b} (6 mo)	AGA-A vs PL (14 vs 16 ears)	Median change in high-frequency SNHL: -5** vs -3.3** dB
Moore et al. ^{[19-21]c,d} (6 mo)	AGA-A vs PL (14 vs 12 pts)	Change in resting global CBF: -3.48 [†] vs +1.25 mL/min/100 g of tissue ↓ Resting regional CBF with AGA-A [†] vs PL ↓ Absolute regional CBF during visual stimulation with AGA-A ^{††} vs PL ↓ Regional CBF after acetazolamide infusion with AGA-A ^{††} vs PL No significant between-group differences in blood flow velocities
Schiffmann et al. ^{[17,18]c} (6 mo)	AGA-A vs PL (14 vs 12 pts)	No significant between-group differences in sensory modalities, nerve conduction, or intraepidermal nerve fibre density
Extension studies		
Hajioff et al. ^[23] (42 mo)	AGA-A (20–26 ears)	Median change in high-frequency SNHL at 18 mo: +1.5 dB; at 30 mo: +5.0 dB**; at 42 mo: +4.0 dB**
Moore et al. ^[20] (18 mo)	AGA-A (11 pts)	↓ Peak, mean, and end-diastolic velocities in cerebral arteries at 18 mo***
Schiffmann et al. ^[17,18] (3 y)	AGA-A (17–26 pts)	↓ Intraepidermal nerve fibre density at 18 mo: -1.678 fibers/mm* ↓ Cold*** and warm** detection thresholds in the foot Sweat function ↑ from mean 0.24 μL/mm ² pre-infusion to mean 0.57 μL/mm ² 24–72 h post-infusion*
Fabry Outcome Survey		
Hajioff et al. ^[54] (12 mo)	AGA-A (26 pts)	No change in ears with normal hearing or severe hearing loss Median change in hearing threshold of -4 to -7 dB* in ears with mild to moderate hearing loss ^e

a Outcomes were assessed at study end unless specified otherwise.

b An additional analysis of the study by Hughes et al.^[16]

c Additional analyses of the study by Schiffmann et al.^[15]

d Functional cerebral blood flow and cerebrovascular responses were assessed using positron emission tomography,^[19,21] and blood flow velocity was assessed using transcranial Doppler.^[20]

e Statistically significant improvements were seen at 250, 500, 4000, and 8000 Hz, but not at 1000 or 2000 Hz.

AGA-A=agalsidase alfa; **CBF**=cerebral blood flow; **PL**=placebo; **pts**=patients; **SNHL**=sensorineural hearing loss; ↓ indicates significantly decreased; ↑ indicates significantly increased; * $p \leq 0.05$, ** $p \leq 0.01$, *** $p < 0.001$ vs baseline; † $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$ vs PL.

42 months' treatment with agalsidase alfa (table VI).^[23] Low-frequency hearing loss was not significantly altered during the study.^[23,58]

After 3 years of follow-up, sweat function had significantly improved in agalsidase alfa recipients (table VI).^[18] Of the 17 evaluable patients, four patients experienced normalization of sweat function, although seven patients did not respond to agalsidase alfa. The beneficial effect of agalsidase alfa on the sweat response persisted for ≈7 days after the infusion, after which there was a return to the preinfusion level of sweat response.^[18]

At 6 months, plasma Gb3 levels were reduced from baseline to a significantly ($p \leq 0.005$) greater extent in agalsidase alfa recipients than in placebo recipients in both trials (-6.22 vs -0.55 nmol/mL^[16] and -6.56 vs -0.77 nmol/mL^[15]). After

48 months' treatment with agalsidase alfa, mean plasma Gb3 levels were significantly ($p < 0.001$) reduced from baseline by 65%.^[22]

3.4.2 Comparisons with Agalsidase Beta

Plasma Gb3 levels were significantly ($p < 0.05$) reduced from baseline in patients receiving agalsidase alfa 0.2 mg/kg every other week or agalsidase beta 0.2 mg/kg every other week after 12 months' treatment (-2.56 vs -1.84 nmol/mL), with no significant between-group difference.^[26]

Switching Studies

A significant reduction in plasma Gb3 levels (by 2.6 nmol/mL; $p < 0.001$) was seen in the US switching study,^[35] with no significant change in plasma Gb3 levels in the Japanese study.^[37]

Among treatment-naïve patients with Fabry disease in the US study, significant ($p < 0.05$) reductions from baseline in plasma Gb3 levels (by 6.7 nmol/mL) and plasma globotriaosylsphingosine levels (by 37.8 nmol/L) were seen.^[35]

3.4.3 Noncomparative Studies

GI symptoms improved with agalsidase alfa therapy in adults with Fabry disease ($n = 10$), according to the results of a noncomparative study.^[44] Significant ($p < 0.02$) improvements from baseline in abdominal pain severity and frequency scores were seen after 6 months' agalsidase alfa treatment, with these improvements generally maintained after 1 year's therapy.^[44]

Pediatric Patients

Three pediatric patients with anhidrosis at baseline had measurable sweating after 25 weeks' agalsidase alfa therapy.^[45]

A significant ($p < 0.001$) reduction in mean plasma Gb3 levels from 7.91 nmol/mL at baseline to 4.21 nmol/mL at 6 months was seen in boys with Fabry disease, with a significant ($p < 0.05$) reduction maintained after an additional 3.5 years of treatment.^[46] Plasma Gb3 levels were not elevated at baseline in girls.^[46]

3.4.4 Fabry Outcome Survey

A significant improvement in hearing was seen in patients with Fabry disease enrolled in FOS who had mild to moderate hearing loss at baseline and received agalsidase alfa for 12 months, with no significant change in hearing seen in patients with normal hearing or severe hearing loss at baseline (table VI).^[54]

The prevalence of abdominal pain was significantly reduced by agalsidase alfa therapy among 58 evaluable patients with Fabry disease (from 43% at baseline to 29% after 24 months' therapy; $p < 0.05$).^[55] The prevalence of diarrhea was 28% at baseline and 26% after 24 months' treatment with agalsidase alfa.^[55]

4. Tolerability

Data concerning the tolerability of intravenous agalsidase alfa 0.2 mg/kg every other week in patients with Fabry disease were obtained from clinical trials discussed in section 3, supplemented by information from the EU summary of product characteristics.^[8]

Intravenous agalsidase alfa was generally well tolerated in patients with Fabry disease,^[15,16,43] including in women^[39,41] and pediatric patients.^[46,47]

Aside from infusion reactions, the majority of adverse events reported in agalsidase alfa recipients appeared to be associated with the underlying disease, rather than with treatment (e.g. hearing loss,^[15,39] abdominal pain crisis,^[15] constipation^[15]).

Infusion reactions (e.g. rigors, pyrexia, flushing, headache, nausea, and/or fatigue) were the most common adverse event.^[8]

Infusion reactions appeared to occur less commonly in women than in men, with infusion reactions reported in 0 of 15 women receiving agalsidase alfa in one noncomparative study,^[39] and in 1 of 36 women in another noncomparative study.^[41]

Among pediatric patients with Fabry disease, four boys in one noncomparative study experienced mild to moderate infusion reactions (11 events over seven agalsidase alfa infusions), which resolved within 1 day.^[47] No serious, treatment-related adverse events were reported.^[47] In a second noncomparative study, 62 events occurred during 1472 agalsidase alfa infusions (4.2%) among pediatric patients over 4 years of follow-up.^[46] In this study, 93% of adverse events were of mild to moderate severity, with 6.5% and 3.4% considered possibly or probably related to treatment; there were no reports of life-threatening treatment-related adverse events and no deaths.^[46]

Agalsidase alfa was also well tolerated in patients with Fabry disease who had end-stage renal disease.^[13] Mild to moderate infusion reactions were reported in 8 of 21 patients (38%).^[13]

Long-term treatment with intravenous agalsidase alfa was well tolerated, according to the results of an extension study in which 25 men with Fabry disease were treated for 4–4.5 years.^[22] Most adverse events (e.g. cerebrovascular accident, transient ischemic attack, myocardial infarction) reflected the natural history of Fabry disease, and were not attributed to treatment with agalsidase alfa. In this extension study, infusion reactions (usually comprising facial flushing and rigors) occurred during or shortly after at least one agalsidase alfa infusion in 13 of 25 (52%) patients. Patients who experienced infusion reactions received premedication with oral histamine H_1 - and H_2 -receptor antagonists and/or a corticosteroid prior to subsequent infusions. No patients permanently discontinued treatment with agalsidase alfa because of infusion reactions.^[22]

No new safety concerns were identified in 555 agalsidase alfa recipients enrolled in FOS during 5 years of follow-up (mean duration of therapy of 3.1 years).^[48] During follow-up, 826 adverse events were reported in 188 patients, with the most commonly reported adverse events including infusion reactions ($n = 35$ patients), cerebrovascular accident ($n = 12$), pyrexia ($n = 12$), dizziness ($n = 11$), transient ischemic attack ($n = 11$), headache ($n = 10$), and nausea ($n = 10$). None of the 32 deaths that occurred during follow-up were considered related to treatment.^[48]

Agalsidase alfa did not affect vital signs,^[39,47] laboratory parameters,^[39] or ECG recordings,^[39] according to the results of noncomparative studies conducted in women^[39] and in pediatric patients.^[47]

In the 24-month study, the tolerability profile of agalsidase alfa 0.2 mg/kg every other week and agalsidase beta 0.2 mg/kg every other week appeared generally similar, with a low incidence of mild to moderate adverse events (e.g. grade 1 or 2 nausea, dizziness, headache, and diarrhea), reported in both treatment groups.^[26] Infusion reactions (chills and fever) were reported in one of four antibody-positive men who received agalsidase alfa and in two of six antibody-positive men who received agalsidase beta.^[26] Although comparisons across trials should be made with caution, the EU summary of product characteristics reported infusion-related reactions in 13.7% of adults who received agalsidase alfa in clinical trials,^[8] whereas 67% of agalsidase beta recipients experienced at least one infusion-associated reaction.^[28]

No safety concerns were raised following the switch from agalsidase beta to agalsidase alfa.^[37] In the Japanese switching study, worsening allergic rhinitis was reported in one patient after administration of agalsidase beta, but not after the switch to agalsidase alfa.^[37] No allergic symptoms were reported in the other ten patients. No treatment-related laboratory abnormalities were reported, and no cardiac events (e.g. atrial fibrillation, ventricular premature beats, tachyarrhythmias, cardiac failure) were reported within 24 hours of enzyme replacement therapy administration.^[37]

4.1 Immunogenicity

IgG antibodies developed in ≈24% of male patients with Fabry disease who received agalsidase alfa.^[8] Limited data indicate IgG antibody development in 7% of agalsidase alfa recipients in the male pediatric population. IgG antibodies appeared to develop after ≈3–12 months of agalsidase alfa therapy. After 12–54 months of treatment, 17% of agalsidase alfa recipients were still IgG antibody positive, with immunologic tolerance developing in 7% of agalsidase alfa recipients, based on the disappearance of IgG antibodies over time. No IgE antibodies have been detected in any patient receiving agalsidase alfa.^[8]

The antibody status of patients did not appear to influence changes in renal function in one of the placebo-controlled studies and its extension (treatment duration of 4–4.5 years).^[22] The presence or absence of persistently positive IgG antibodies did not appear to correlate with eGFR changes in individual patients. However, the eight men who had persistently positive IgG antibodies did exhibit increased urine sediment Gb3 levels, with a return to almost baseline levels seen after 12 months of agalsidase alfa therapy.^[22]

In the 24-month study, there was no significant difference between patients receiving agalsidase alfa 0.2 mg/kg every other

week and those receiving agalsidase beta 0.2 mg/kg every other week in the incidence of antibody formation, with antibodies reported in four of eight men receiving agalsidase alfa (50%) and in six of eight men receiving agalsidase beta (75%); no antibody formation was reported in women.^[26] The EU summary of product characteristics reports the development of IgG antibodies in the majority of agalsidase beta recipients.^[28]

In addition, no antibody formation was reported in women receiving agalsidase alfa in noncomparative studies to date.^[39,41]

5. Dosage and Administration

Agalsidase alfa is approved in over 40 countries, including the EU and Canada, for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease. Treatment with agalsidase alfa should be supervised by a clinician who is experienced in the management of patients with Fabry disease or other inherited metabolic disorders.^[8]

The recommended agalsidase alfa regimen is 0.2 mg/kg administered every other week by intravenous infusion over 40 minutes.^[8,59]

In patients who experience infusion reactions, administration of antihistamines and/or corticosteroids prior to agalsidase alfa infusion may prevent subsequent reactions.^[8,59]

Local prescribing information should be consulted for contraindications, special warnings, and precautions for use, as well as for further information regarding the method of administration.

6. Place of Agalsidase Alfa in the Management of Fabry Disease

It is of great importance that patients with Fabry disease are diagnosed early and receive comprehensive treatment, especially considering that disease progression can be rapid in some patients.^[60] Various supportive and adjunctive therapies are used to treat the complications of Fabry disease.^[2] For example, ACE inhibitors and angiotensin receptor antagonists are used in patients with proteinuria as antiproteinuric agents and to control hypertension, although renal involvement may eventually necessitate dialysis or renal transplantation.^[1] Standard therapies should be used in patients with cardiovascular manifestations of Fabry disease, including β -adrenergic receptor antagonists, ACE inhibitors, angiotensin receptor antagonists, and diuretics.^[1] In addition, anticonvulsants (e.g. phenytoin, carbamazepine, topiramate, gabapentin) and tricyclic antidepressants may be helpful in managing pain.^[1,2]

Although the use of adjunctive therapy remains important (particularly for the control of proteinuria), the current main

focus of treatment in Fabry disease is the use of enzyme replacement therapy.^[1] The aim of enzyme replacement therapy is to prevent disease progression and to stabilize, or even reverse, disease that is already manifest.^[2] It is generally thought that enzyme replacement therapy will be most effective when started early in the course of the disease,^[2,4,61] although the optimal time at which to start treatment (e.g. after diagnosis or after the emergence of complications) remains a matter of debate.^[62] Although most of the available treatment guidelines regarding the use of enzyme replacement therapy in Fabry disease need updating,^[2,63,64] the most recent guidelines suggest starting enzyme replacement therapy as early as possible (i.e. as soon as clinical symptoms or signs are observed) in order to delay further organ damage, particularly in males who have no residual α -galactosidase A activity.^[4] Females should be treated in the same way as males, taking into account that the onset of disease complications tends to occur at a later age in females than in males.^[4]

Gb3 accumulation in myocytes, coronary endothelium, intimal and medial cells, and valve tissue leads to complications such as left ventricular hypertrophy, conduction abnormalities, valve thickening, heart failure, and coronary artery disease in patients with Fabry disease.^[16] At 6 months, myocardial Gb3 content was not reduced to a significantly greater extent with agalsidase alfa versus placebo (section 3.1.1), possibly reflecting the short duration of the study or that it was underpowered (the study was designed with a target of 24 patients, whereas only 15 were enrolled).^[16] However, left ventricular mass was reduced to a significantly greater extent with agalsidase alfa than with placebo after 6 months' treatment; this improvement was maintained after 2 years' treatment with agalsidase alfa in an extension study (section 3.1.1). These findings are supported by the results of noncomparative studies (section 3.1.3), and FOS, in which the beneficial effect of agalsidase alfa on left ventricular mass among patients with left ventricular hypertrophy at baseline was sustained for 5 years (section 3.1.4).

Patients with Fabry disease experience recurrent episodes of neuropathic pain in the extremities that are severe and debilitating.^[18] Agalsidase alfa improved neuropathic pain to a significantly greater extent than placebo, with some agalsidase alfa recipients able to discontinue their neuropathic pain medications; the improvement was sustained in the longer term (section 3.2.1). Improvements in BPI scores were also seen in agalsidase alfa recipients in noncomparative studies (section 3.2.3) and FOS, including in FOS patients who were followed up for 5 years (section 3.2.4).

The neuropathic pain syndrome seen in patients with Fabry disease is thought to be secondary to small-fiber neuropathy arising from the deposition of Gb3 in dorsal root ganglia; this

small-fiber neuropathy is also associated with decreased thermal sensation.^[18] Improvements in cold and warm perception in the foot were seen after 3 years' treatment with agalsidase alfa (section 3.4.1).

Certain measures of disease severity and HR-QOL (section 3.2), and certain GI symptoms (section 3.4), were also improved by agalsidase alfa therapy in various studies.

Almost all men with Fabry disease develop progressive renal deterioration and proteinuria.^[24] This arises from intraglomerular Gb3 deposition, which is associated with mesangial widening and, eventually, segmental and global glomerulosclerosis.^[24] Ischemic damage may also contribute to glomerular changes in patients with Fabry disease.^[15] Sustained reductions in urine sediment Gb3 were seen in agalsidase alfa recipients (section 3.3). There was also a significant increase in normal glomeruli and a significant decrease in glomeruli with mesangial widening with agalsidase alfa versus placebo, although there was a significant increase in glomeruli with segmental sclerosis (section 3.3.1).

It has been suggested that enzyme replacement therapy has limited efficacy in adults with advanced Fabry disease, in whom irreversible organ damage may have already occurred.^[45] However, agalsidase alfa may be able to slow the rate of decline in renal function even in patients with more advanced renal impairment. For example, although a significant reduction in eGFR was seen after 48 months' treatment with agalsidase alfa, mainly driven by a marked reduction among patients who had stage 3 chronic kidney disease, the progression of decline seemed slower than that seen in untreated historic controls with Fabry disease (section 3.3.1). Similarly, data from FOS showed that although a significant decline in renal function occurred over 5 years' treatment with agalsidase alfa (section 3.3.4), the rate of decline was slower than that generally seen in historic controls, particularly in patients with more advanced chronic kidney disease (e.g. stage 3).^[48] Renal function tended to remain stable amongst agalsidase alfa recipients with less severe renal disease (section 3.3.1), and in women who were followed in FOS and had received agalsidase alfa for 5 years (section 3.3.4). Administering agalsidase alfa on a weekly basis, rather than every other week, slowed the annualized rate of decline in eGFR in a small cohort of patients experiencing a rapid decline in eGFR with the approved treatment regimen (section 3.3.1).

A faster decline in eGFR was seen in patients with more advanced proteinuria (section 3.3.4), highlighting the importance of reducing proteinuria as much as possible with the use of antiproteinuric agents.^[52]

Both structural and functional abnormalities of the cerebral circulation are seen in patients with Fabry disease.^[22] Indeed,

the increased incidence of stroke in patients with Fabry disease may be related to progressive accumulation of glycosphingolipid products in cerebral vessels or to vessel function abnormalities.^[21] Agalsidase alfa improved functional cerebral blood flow abnormalities (section 3.4.1). It has been suggested that these improvements may help reduce the risk of stroke, although this still needs to be demonstrated clinically.^[2] Four agalsidase alfa recipients experienced a cerebrovascular accident or transient ischemic attack during 4–4.5 years of follow-up in the extension of the study from which the functional cerebral blood flow data were obtained.^[22]

Patients with Fabry disease may experience hypohidrosis which, along with neuropathic pain, contributes to poor tolerance to exercise and heat.^[24] An improvement in sweat function, persisting for ≈ 7 days after each infusion, was seen in patients receiving longer-term agalsidase alfa therapy (section 3.4.1).^[18]

Neuropathic pain is often one of the first symptoms to emerge in pediatric patients with Fabry disease;^[45,46] improvements in the BPI 'pain at its worst' score were seen after 1 year's treatment with agalsidase alfa in pediatric patients (section 3.2.3). In addition, heart rate variability indices were significantly improved by agalsidase alfa therapy in boys with Fabry disease (section 3.1.3), suggesting a long-term beneficial effect on cardiac autonomic innervation.^[46] Major organ dysfunction is usually absent in pediatric patients with Fabry disease, with a deterioration in renal function, for example, often not seen until the third or fourth decade of life.^[45] However, some pediatric patients may present with mild renal impairment,^[65] and agalsidase alfa appears beneficial in these patients.^[46,61] For example, after 4 years of agalsidase alfa therapy, the eGFR normalized among boys with hyperfiltration or deficits in eGFR at baseline, and albuminuria normalized in boys with microalbuminuria at baseline (section 3.3.3). This suggests that early initiation of agalsidase alfa therapy may stabilize renal function in pediatric patients with Fabry disease, although longer-term data are needed.^[46,61] Indeed, data examining the early initiation of enzyme replacement therapy in pediatric patients with Fabry disease are generally lacking.

Agalsidase beta, the other enzyme replacement therapy available for use in Fabry disease, is approved in the EU^[28] and the US.^[27] Agalsidase alfa is produced in a genetically engineered continuous human cell line (section 2.1), whereas agalsidase beta is produced using recombinant DNA technology in mammalian Chinese hamster ovary cell culture.^[66] Although the amino acid sequence of both agalsidase alfa and agalsidase beta is identical to that of native α -galactosidase A, there are differences between the enzyme replacement therapies in terms of their glycosylation pattern, mannose-6-phosphate

receptor binding, and mannose-6-phosphate receptor-mediated cellular uptake (section 2.1). Whether or not these differences are of clinical relevance has been a matter of debate.

Indeed, it is currently difficult to draw conclusions regarding the relative efficacy of agalsidase alfa versus agalsidase beta. The only fully published head-to-head trial comparing these two agents used an off-label dosage of agalsidase beta 0.2 mg/kg every other week (section 3).^[27,28] Although agalsidase alfa and agalsidase beta at a dosage of 0.2 mg/kg every other week appeared to have similar efficacy in this 24-month trial, concerns have been raised by the European Medicines Agency regarding the use of agalsidase beta at dosages lower than the approved dosage of 1 mg/kg every other week.^[29] Clinical deterioration was seen in some patients receiving lower dosages of agalsidase beta, with increased reporting of symptoms (including pain, paresthesia, diarrhea, and cardiac, CNS, and renal manifestations) in some patients receiving reduced agalsidase beta dosages for an extended period; these symptoms resemble the natural course of Fabry disease.^[8,29] Results of an exploratory study also found that an off-label dosage of agalsidase beta 0.3 mg/kg every other week (reduced from 1 mg/kg every other week) was insufficient to maintain cellular clearance of Gb3 in some patients.^[67] Preliminary results from an ongoing CFDI trial suggest that agalsidase alfa and agalsidase beta at approved dosages had similar efficacy in patients with Fabry disease (section 3).^[33,34]

It is worth noting that in the head-to-head trial, treatment failure was more likely in patients with more severe disease and in older patients (section 3.1.2), supporting the hypothesis that starting enzyme replacement therapy early in the course of the disease may yield the greatest benefits.^[26]

There have been supply problems with agalsidase beta in recent years (although these supply difficulties are now being resolved^[68]), meaning that some agalsidase beta recipients were switched over to agalsidase alfa.^[69] Results of switching studies support these two agents having similar safety (section 4), and disease stability was generally maintained following the switch from agalsidase beta to agalsidase alfa (section 3), although patients had only received agalsidase alfa for ≈ 12 –15 months at the time of analysis.

Agalsidase alfa was generally well tolerated in patients with Fabry disease, with infusion reactions being the most commonly occurring adverse event (section 4). Infusion reactions are usually of mild to moderate severity and decrease in frequency with ongoing agalsidase alfa therapy.^[11] A slowing of the infusion rate or temporary interruption of the infusion may be required to manage infusion reactions; however, treatment withdrawal is rarely needed.^[11] The use of premedication (e.g.

antihistamines, corticosteroids) may also help manage such reactions.^[1]

Infusion reactions often coincide with seroconversion and the development of IgG antibodies.^[1] Formation of IgG antibodies has been reported with both agalsidase alfa and agalsidase beta administration.^[70] Although comparisons across studies should be made with caution, the incidence of IgG antibody formation appears higher in patients receiving agalsidase beta than in those receiving agalsidase alfa.^[70,71] IgE antibodies have also been reported in a small proportion of agalsidase beta recipients, with no reports to date of IgE antibody formation in agalsidase alfa recipients.^[70] It should be noted that antibody formation is most commonly reported in men. IgG antibody formation has occasionally been reported in women receiving agalsidase beta, with no reports of IgG antibodies in women receiving agalsidase alfa to date.^[70] IgG antibodies to agalsidase alfa or agalsidase beta were cross reactive *in vitro*.^[72]

Although antibodies formed against agalsidase alfa or agalsidase beta have been shown to have neutralizing effects *in vitro*, their clinical importance is more difficult to assess.^[70] While men with persistently positive IgG antibodies following agalsidase alfa treatment exhibited increased urine sediment Gb3 levels, the presence or absence of persistently positive IgG antibodies did not appear to correlate with eGFR changes in individual patients (section 4.1). Different assays are currently used to measure antibody formation in patients receiving agalsidase alfa and agalsidase beta. The Fabry Disease Antibody Standardization Initiative is working on standardizing the assay used to measure anti-drug antibodies in patients receiving these enzyme replacement therapies.^[73] The CFDI also intends to compare antibody formation in agalsidase alfa recipients with that in agalsidase beta recipients.^[31]

Data are limited regarding the use of agalsidase alfa during pregnancy, although no adverse effects on the mother or child have been reported to date.^[8,74-76]

The agalsidase alfa administration schedule (i.e. an intravenous infusion every other week) can pose a significant treatment burden, which may be reduced by administration in a home setting.^[1] Home administration was shown to be a feasible and safe option in a long-term extension study in which 22 patients received a total of 1528 agalsidase alfa infusions (42–73 infusions per patient) in a home setting.^[22] Patients were eligible for treatment at home after they had received open-label agalsidase alfa for 1 year in a hospital setting. None of the patients experienced new-onset infusion reactions after switching to treatment at home.^[22]

There are certain limitations regarding the data supporting the use of agalsidase alfa (and agalsidase beta) in the treatment of Fabry disease. For example, randomized trials are of small

size, and the placebo-controlled agalsidase alfa trials did not include a control arm beyond 6 months.^[22] Although data are available from larger numbers of ‘real world’ patients included in disease registries such as FOS, the observational nature of these studies represents a limitation. In addition, much of the data pertaining to agalsidase alfa therapy relates to surrogate endpoints (e.g. left ventricular mass, eGFR). Data are currently lacking regarding the ability of agalsidase alfa to reduce the incidence of clinical events (e.g. cardiac events, stroke, and the need for dialysis and transplantation). One of the primary objectives of the CFDI is to examine the ability of enzyme replacement therapy to prevent clinical events (see section 3);^[31] results are awaited with interest.

The addition of substrate reduction therapy to enzyme replacement therapy may further improve the outcome of patients with Fabry disease.^[77] Substrate reduction therapies inhibit glucosylceramide synthase, which catalyzes the first step in the synthesis of glycosphingolipids, and have shown potential in mouse models of Fabry disease,^[77,78] particularly when used in combination with enzyme replacement therapy.^[77]

In conclusion, intravenous agalsidase alfa 0.2 mg/kg every other week is effective and generally well tolerated in the treatment of Fabry disease. In randomized, double-blind, placebo-controlled, 6-month trials, agalsidase alfa showed beneficial effects on left ventricular mass and neuropathic pain, which were maintained in longer-term extension studies. The significant decline in eGFR seen after 48 months’ agalsidase alfa treatment was mainly driven by a marked decline in GFR seen in patients with stage 3 chronic kidney disease (although the progression of decline appeared slower than that seen in historic controls); renal function appeared stable in patients with stage 1 or 2 chronic kidney disease. In general, there were no significant differences in outcome between patients with Fabry disease receiving agalsidase alfa and those receiving agalsidase beta. No safety concerns were raised following the switch from agalsidase beta to agalsidase alfa in switch studies, and disease stability was generally maintained. Agalsidase alfa also demonstrated beneficial effects, including in women and pediatric patients, in noncomparative studies and in FOS. Thus, agalsidase alfa is an effective and well tolerated treatment option for use in patients with Fabry disease.

Disclosure

The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article. Changes resulting from comments received were made by the author on the basis of scientific and editorial merit.

References

- Mehta A, Beck M, Eyskens F, et al. Fabry disease: a review of current management strategies. *QJM Mon J Assoc Physicians* 2010 Sep; 103 (9): 641-59
- Hughes DA, Ramaswam U, Elliott P, et al. Guidelines for the diagnosis and management of Anderson-Fabry disease [online]. Available from URL: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4118408.pdf [Accessed 2012 May 3]
- Spada M, Pagliardini S, Yasuda M, et al. High incidence of later-onset Fabry disease revealed by newborn screening. *Am J Hum Genet* 2006 Jul; 79 (1): 31-40
- Ortiz A, Oliveira JP, Wanner C, et al. Recommendations and guidelines for the diagnosis and treatment of Fabry nephropathy in adults. *Nat Clin Pract Nephrol* 2008 Jun; 4 (6): 327-36
- Ries M, Clarke JT, Whybra C, et al. Enzyme replacement in Fabry disease: pharmacokinetics and pharmacodynamics of agalsidase alfa in children and adolescents. *J Clin Pharmacol* 2007 Oct; 47 (10): 1222-30
- Lee K, Jin X, Zhang K, et al. A biochemical and pharmacological comparison of enzyme replacement therapies for the glycolipid storage disorder Fabry disease. *Glycobiology* 2003 Apr; 13 (4): 305-13
- European Medicines Agency. European public assessment report for Replagal: scientific discussion [online]. Available from URL: <http://www.ema.europa.eu> [Accessed 2012 Apr 24]
- European Medicines Agency. Replagal (agalsidase alfa): EU summary of product characteristics [online]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000369/WC500053612.pdf [Accessed 2012 Apr 24]
- Sakuraba H, Murata-Ohsawa M, Kawashima I, et al. Comparison of the effects of agalsidase alfa and agalsidase beta on cultured human Fabry fibroblasts and Fabry mice. *J Hum Genet* 2006 Mar; 51 (3): 180-8
- Schiffmann R, Murray GJ, Treco D, et al. Infusion of α -galactosidase A reduces tissue globotriaosylceramide storage in patients with Fabry disease. *Proc Natl Acad Sci U S A* 2000 Jan 4; 97 (1): 365-70
- Clarke JTR, West ML, Bultas J, et al. The pharmacology of multiple regimens of agalsidase alfa enzyme replacement therapy for Fabry disease. *Genet Med* 2007 Aug; 9 (8): 504-9
- Gal A, Hughes DA, Winchester B. Toward a consensus in the laboratory diagnostics of Fabry disease: recommendations of a European expert group. *J Inher Metab Dis* 2011 Apr; 34 (2): 509-14
- Pastores GM, Boyd E, Crandall K, et al. Safety and pharmacokinetics of agalsidase alfa in patients with Fabry disease and end-stage renal disease. *Nephrol Dial Transplant* 2007 July; 22 (7): 1920-5
- Murray GJ, Anver MR, Kennedy MA, et al. Cellular and tissue distribution of intravenously administered agalsidase alfa. *Mol Genet Metab* 2007 Mar; 90 (3): 307-12
- Schiffmann R, Kopp JB, Austin III IHA, et al. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. *JAMA* 2001 Jun 6; 285 (21): 2743-9
- Hughes DA, Elliott PM, Shah J, et al. Effects of enzyme replacement therapy on the cardiomyopathy of Anderson-Fabry disease: a randomised, double-blind, placebo-controlled clinical trial of agalsidase alfa. *Heart* 2008 Feb; 94 (2): 153-8
- Schiffmann R, Hauer P, Freeman B, et al. Enzyme replacement therapy and intraepidermal innervation density in Fabry disease. *Muscle Nerve* 2006 Jul; 34 (1): 53-6
- Schiffmann R, Floeter MK, Dambrosia JM, et al. Enzyme replacement therapy improves peripheral nerve and sweat function in Fabry disease. *Muscle Nerve* 2003 Dec; 28 (6): 703-10
- Moore DF, Scott LTC, Gladwin MT, et al. Regional cerebral hyperperfusion and nitric oxide pathway dysregulation in Fabry disease: reversal by enzyme replacement therapy. *Circulation* 2001 Sep 25; 104 (13): 1506-12
- Moore DF, Altarescu G, Ling GSF, et al. Elevated cerebral blood flow velocities in Fabry disease with reversal after enzyme replacement. *Stroke* 2002 Feb; 33 (2): 525-31
- Moore DF, Altarescu G, Herscovitch P, et al. Enzyme replacement reverses abnormal cerebrovascular responses in Fabry disease. *BMC Neurol* 2002 Jun 18; 2: 4
- Schiffmann R, Ries M, Timmons M, et al. Long-term therapy with agalsidase alfa for Fabry disease: safety and effects on renal function in a home infusion setting. *Nephrol Dial Transplant* 2006 Feb; 21 (2): 345-54
- Hajioff D, Goodwin S, Quiney R, et al. Hearing improvement in patients with Fabry disease treated with agalsidase alfa. *Acta Paediatr Suppl* 2003 Dec; 92 (443): 28-30
- Schiffmann R, Askari H, Timmons M, et al. Weekly enzyme replacement therapy may slow decline of renal function in patients with Fabry disease who are on long-term biweekly dosing. *J Am Soc Nephrol* 2007 May; 18 (5): 1576-83
- West M, Nicholls K, Mehta A, et al. Agalsidase alfa and kidney dysfunction in Fabry disease. *J Am Soc Nephrol* 2009 May; 20 (5): 1132-9
- Vedder AC, Linthorst GE, Houge G, et al. Treatment of Fabry disease: outcome of a comparative trial with agalsidase alfa or beta at a dose of 0.2 mg/kg. *PLoS One* 2007 Jul; 2 (7): e598
- Genzyme Corporation. Fabrazyme (agalsidase beta): US prescribing information [online]. Available from URL: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103979s51351bl.pdf [Accessed 2012 May 3]
- European Medicines Agency. Fabrazyme (agalsidase beta): EU summary of product characteristics [online]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000370/WC500020547.pdf [Accessed 2012 May 3]
- European Medicines Agency. Assessment report for Fabrazyme (agalsidase beta) [online]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/11/WC500099241.pdf [Accessed 2012 Jul 10]
- West M, Bichet DG, Casey R, et al. Prospective results of switching enzyme replacement therapy from agalsidase beta to agalsidase alfa in the Canadian Fabry Disease Initiative study [abstract no. 197]. 8th Annual Lysosomal Disease Network World Symposium; 2012 Feb 8-10; San Diego (CA)
- Sirrs S, Clarke JTR, Bichet DG, et al. Baseline characteristics of patients enrolled in the Canadian Fabry Disease Initiative. *Mol Genet Metab* 2010 Apr; 99 (4): 367-73
- Canadian Fabry Research Consortium. Canadian Fabry Disease Initiative (CFDI) enzyme replacement therapy (ERT) study [ClinicalTrials.gov identifier NCT00455104]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: <http://www.clinicaltrials.gov> [Accessed 2012 May 4]
- West M, LeMoine K, Bichet D, et al. A randomized controlled trial of enzyme replacement therapy in Fabry nephropathy: the Canadian Fabry Disease Initiative at year two [abstract]. *Clin Ther* 2010; 32 Suppl. C: S115-S6
- West M, Bichet D, Casey R, et al. Agalsidase alfa and agalsidase beta have similar effects on outcomes in Fabry disease: results from the Canadian Fabry Disease Initiative [abstract]. *Mol Genet Metab* 2011; 102: S46
- Alpan-Goker O, Nedd K, Shankar S, et al. Effect and tolerability of agalsidase alfa in patients with Fabry disease who were treatment-naïve or formerly treated with agalsidase beta [abstract]. Annual Clinical Genetics Meeting; 2012 Mar 27-31; Charlotte (NC)
- Goker-Alpan O, Nedd K, Shankar S, et al. Effect and tolerability of agalsidase alfa in patients with Fabry disease [abstract]. Society for the Study of Inborn Errors of Metabolism Annual Symposium; 2012 Sep 4-7; Birmingham
- Tsuboi K, Yamamoto H. Clinical observation of patients with Fabry disease after switching from agalsidase beta (Fabrazyme) to agalsidase alfa (Replagal). *Genet Med. Epub* 2012 Apr 12
- Shire Human Genetic Therapies, Inc. Treatment protocol of Replagal for patients with Fabry disease [ClinicalTrials.gov identifier NCT01031173]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: <http://www.clinicaltrials.gov> [Accessed 2012 Aug 7]

39. Baehner F, Kampmann C, Whybra C, et al. Enzyme replacement therapy in heterozygous females with Fabry disease: results of a phase IIIB study. *J Inherit Metab Dis* 2003; 26 (7): 617-27
40. Kampmann C, Linhart A, Devereux RB, et al. Effect of agalsidase alfa replacement therapy on Fabry disease-related hypertrophic cardiomyopathy: a 12- to 36-month, retrospective, blinded echocardiographic pooled analysis. *Clin Ther* 2009 Sep; 31 (9): 1966-76
41. Whybra C, Miebach E, Mengel E, et al. A 4-year study of the efficacy and tolerability of enzyme replacement therapy with agalsidase alfa in 36 women with Fabry disease. *Genet Med* 2009 Jun; 11 (6): 441-9
42. Parini R, Rigoldi M, Santus F, et al. Enzyme replacement therapy with agalsidase alfa in a cohort of Italian patients with Anderson-Fabry disease: testing the effects with the Mainz Severity Score Index. *Clin Genet* 2008; 74 (3): 260-6
43. Thofehrn S, Netto C, Cecchin C, et al. Kidney function and 24-hour proteinuria in patients with Fabry disease during 36 months of agalsidase alfa enzyme replacement therapy: a Brazilian experience. *Ren Fail* 2009 Oct; 31 (9): 773-8
44. Dehout F, Roland D, Treille de Granseigne S, et al. Relief of gastrointestinal symptoms under enzyme replacement therapy in patients with Fabry disease. *J Inherit Metab Dis* 2004; 27 (4): 499-505
45. Ries M, Clarke JTR, Whybra C, et al. Enzyme-replacement therapy with agalsidase alfa in children with Fabry disease. *Pediatrics* 2006 Sep; 118 (3): 924-32
46. Schiffmann R, Martin RA, Reimschisel T, et al. Four-year prospective clinical trial of agalsidase alfa in children with Fabry disease. *J Pediatr* 2010 May; 156 (5): 832-7
47. Ramaswami U, Wendt S, Pintos-Morell G, et al. Enzyme replacement therapy with agalsidase alfa in children with Fabry disease. *Acta Paediatr* 2007 Jan; 96 (1): 122-7
48. Mehta A, Beck M, Elliott P, et al. Enzyme replacement therapy with agalsidase alfa in patients with Fabry's disease: an analysis of registry data. *Lancet* 2009 Dec 12; 374 (9706): 1986-96
49. Hoffmann B, Beck M, Sunder-Plassmann G, et al. Nature and prevalence of pain in Fabry disease and its response to enzyme replacement therapy: a retrospective analysis from the Fabry outcome survey. *Clin J Pain* 2007 Jul/Aug; 23 (6): 535-42
50. Schwarting A, Dehout F, Feriozzi S, et al. Enzyme replacement therapy and renal function in 201 patients with Fabry disease. *Clin Nephrol* 2006 Aug; 66 (2): 77-84
51. Feriozzi S, Schwarting A, Sunder-Plassmann G, et al. Agalsidase alfa slows the decline in renal function in patients with Fabry disease. *Am J Nephrol* 2009 April; 29 (5): 353-61
52. Feriozzi S, Torras J, Cybulla M, et al. The effectiveness of long-term agalsidase alfa therapy in the treatment of Fabry nephropathy. *C J Am Soc Nephrol* 2012 Jan; 7 (1): 60-9
53. Cybulla M, Walter KN, Schwarting A, et al. Kidney transplantation in patients with Fabry disease. *Transpl Int* 2009 Apr; 22 (4): 475-81
54. Hajioff D, Hegemann S, Conti G, et al. Agalsidase alpha and hearing in Fabry disease: data from the Fabry Outcome Survey. *Eur J Clin Invest* 2006; 36: 663-7
55. Hoffmann B, Schwarz M, Mehta A, et al. Gastrointestinal symptoms in 342 patients with Fabry disease: prevalence and response to enzyme replacement therapy. *Clin Gastroenterol Hepatol* 2007 Dec; 5 (12): 1447-53
56. Hughes DA, Barba Romero M-A, Hollak CEM, et al. Response of women with Fabry disease to enzyme replacement therapy: comparison with men, using data from FOS (the Fabry Outcome Survey). *Mol Genet Metab* 2011 Jul; 103 (3): 207-14
57. Ramaswami U, Parini R, Pintos-Morell G, et al. Fabry disease in children and response to enzyme replacement therapy: results from the Fabry Outcome Survey. *Clin Genet* 2012 May; 81 (5): 485-90
58. Hajioff D, Enever Y, Quiney R, et al. Hearing loss in Fabry disease: the effect of agalsidase alfa replacement therapy. *J Inherit Metab Dis* 2003; 26 (8): 787-94
59. Shire Human Genetic Therapies, Inc. Replagal® (agalsidase alfa): Canadian product monograph [online]. Available from URL: http://www.shirecanada.com/en/shire-canada/Replagal_M_080521_En.pdf [Accessed 2012 May 1]
60. Schaefer RM, Tylki-Szymańska A, Hilz MJ. Enzyme replacement therapy for Fabry disease: a systematic review of available evidence. *Drugs* 2009; 69 (16): 2179-205
61. Ramaswami U. Update on role of agalsidase alfa in management of Fabry disease. *Drug Des Devel Ther* 2011; 5: 155-73
62. Beck M. Agalsidase alfa for the treatment of Fabry disease: new data on clinical efficacy and safety. *Expert Opin Biol Therapy* 2009 Feb; 9 (2): 255-61
63. Desnick RJ, Brady R, Barranger J, et al. Fabry disease, an under-recognized multisystemic disorder: expert recommendations for diagnosis, management, and enzyme replacement therapy. *Ann Intern Med* 2003 Feb 18; 138 (4): 338-46
64. Eng CM, Germain DP, Banikazemi M, et al. Fabry disease: guidelines for the evaluation and management of multi-organ system involvement. *Genet Med* 2006 Sep; 8 (9): 539-48
65. Tøndel C, Bostad L, Hirth A, et al. Renal biopsy findings in children and adolescents with Fabry disease and minimal albuminuria. *Am J Kidney Dis* 2008 May; 51 (5): 767-76
66. Keating GM, Simpson D. Agalsidase beta: a review of its use in the management of Fabry disease. *Drugs* 2007; 67 (3): 435-55
67. Lubanda J-C, Anijalg E, Bzdúch V, et al. Evaluation of a low dose, after a standard therapeutic dose, of agalsidase beta during enzyme replacement therapy in patients with Fabry disease. *Genet Med* 2009 Apr; 11 (4): 256-64
68. Genzyme Corporation. Genzyme announces FDA approval of Framingham manufacturing plant [media release]. Available from URL: <http://www.businesswire.com/news/genzyme/20120123006531/en> [Accessed 2012 May 4]
69. Linthorst GE, Germain DP, Hollak CEM, et al. Expert opinion on temporary treatment recommendations for Fabry disease during the shortage of enzyme replacement therapy (ERT). *Mol Genet Metab* 2011 Jan; 102 (1): 99-102
70. Deegan PB. Fabry disease, enzyme replacement therapy and the significance of antibody responses. *J Inherit Metab Dis* 2012 Mar; 35 (2): 227-43
71. Vedder AC, Breunig F, Donker-Koopman WE, et al. Treatment of Fabry disease with different dosing regimens of agalsidase: effects on antibody formation and GL-3. *Mol Genet Metab* 2008 Jul; 94 (3): 319-25
72. Linthorst GE, Hollak CEM, Donker-Koopman WE, et al. Enzyme therapy for Fabry disease: neutralizing antibodies toward agalsidase alpha and beta. *Kidney Int* 2004 Oct; 66 (4): 1589-95
73. Brinks V, Richards S, Ruiz J, et al. Fabry disease antibody standardization initiative (FASI) [abstract]. *Mol Genet Metab* 2012; 105: S22-S3
74. Wendt S, Whybra C, Kampmann C, et al. Successful pregnancy outcome in a patient with Fabry disease receiving enzyme replacement therapy with agalsidase alfa. *J Inherit Metab Dis* 2005; 28 (5): 787-8
75. Dehout F, Roland D, Henry F. Successful pregnancy in a patient with Fabry disease receiving enzyme replacement therapy [abstract]. *Acta Paediatr* 2006; 95 Suppl. 451: 137-8
76. Kalkum G, Macchiella D, Reinke J, et al. Enzyme replacement therapy with agalsidase alfa in pregnant women with Fabry disease. *Eur J Obstet Gynecol Reprod Biol* 2009 May; 144 (1): 92-3
77. Marshall J, Ashe KM, Bangari D, et al. Substrate reduction augments the efficacy of enzyme therapy in a mouse model of Fabry disease. *PLoS One* 2010; 5 (11): e15033
78. Abe A, Gregory S, Lee L, et al. Reduction of globotriaosylceramide in Fabry disease mice by substrate deprivation. *J Clin Invest* 2000 Jun; 105 (11): 1563-71

Correspondence: Gillian M. Keating, Adis, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand.
E-mail: demail@springer.com

Copyright of BioDrugs is the property of ADIS International Limited and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.