Effect and Tolerability of Agalsidase Alfa in Patients with Fabry Disease Who Were Treatment Naïve or Formerly Treated with Agalsidase Beta or Agalsidase Alfa

Ozlem Goker-Alpan • Khan Nedd • Suma P. Shankar •
Yeong-Hau H. Lien • Neal Weinreb • Anna Wijatyk •
Peter Chang • Rick Martin

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Abstract Objectives: In a multicenter, open-label, treatment protocol (HGT-REP-059; NCT01031173), clinical effects and tolerability of agalsidase alfa (agal α ; 0.2 mg/kg every other week) were evaluated in patients with Fabry disease who were treatment naïve or switched from agalsidase beta (switch). Over 24 months, data were collected on the safety profile; renal and cardiac parameters were assessed using estimated glomerular filtration rate (eGFR), left ventricular mass index (LVMI), and midwall fractional shortening (MFS).

Results: Enrolled patients included 71 switch (median [range] age, 46.6 [5–84] years; male to female [M:F],

40:31) and 29 treatment naïve (38.7 [12–74] years; M:F, 14:15). Adverse events (AEs) were consistent with the known safety profile of agal α . Two switch patients had hospitalization due to possibly/probably drug-related serious AEs (one with transient ischemic attack, one with infusion-related AEs). One switch and two treatment-naïve patients discontinued treatment because of AEs. Three patients (one each switch, treatment naïve, and previous agal α) died; no deaths were considered drug-related. There was no significant change from baseline in LVMI or MFS in either group. Similarly, eGFR remained stable; mean $\pm$ standard error annualized change in eGFR (mL/min/1.73 m²) was -2.40 ± 1.04 in switch and -1.68 ± 2.21 in treatment-naïve patients.

Conclusions: This is the largest cohort of patients with Fabry disease who were started on or switched to agal α in an FDA-accepted protocol during a worldwide supply shortage of agalsidase beta. Because this protocol was primarily designed to provide access to agal α , there were limitations, including not having stringent selection criteria and the lack of a placebo group.

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O. Goker-Alpan (✉)

Lysosomal Disorders Unit, O&O ALPAN LLC, Fairfax, VA, USA
e-mail: ogokeralpan@oandoalpan.com

K. Nedd

Infusion Associates, Grand Rapids, MI, USA

S.P. Shankar

Department of Human Genetics and Ophthalmology, School of Medicine, Emory University, Atlanta, GA, USA

Y.-H.H. Lien

Arizona Kidney Disease and Hypertension Center, Tucson, AZ, USA

N. Weinreb

University Gaucher Disease–Fabry Disease Treatment Center, University Research Foundation for Lysosomal Storage Disorders, Coral Springs, FL, USA

A. Wijatyk

Global Clinical Development, Shire, Lexington, MA, USA

P. Chang

Biometrics, Shire, Lexington, MA, USA

R. Martin

Global Medical, Shire, Lexington, MA, USA

Introduction

Fabry disease (FD; OMIM number 301500) is a rare, X-linked disorder caused by deficiency of the lysosomal enzyme alpha-galactosidase A (Enzyme Commission number 3.2.1.22) that hydrolyzes the terminal alpha-galactosyl moieties from glycolipids and glycoproteins. FD is a chronic and progressive multiorgan disorder with considerable morbidity and early mortality in both men and clinically affected women (MacDermot et al. 2001). Signs and symptoms of FD include progressive renal insuffi-

ciency and cardiovascular, cerebrovascular, dermatologic, ocular, auditory, and neurologic complications, with consequent reductions in quality of life.

Enzyme replacement therapy (ERT) with agalsidase alfa (agal α) alleviates many of the renal and cardiac signs and symptoms of FD, decreases pain and gastrointestinal symptoms, and improves overall quality of life (Dehout et al. 2003; Beck et al. 2004; Schwarting et al. 2006; Choi et al. 2008; Mehta et al. 2009). In December 2009, because of a worldwide supply shortage of agalsidase beta (agal β), the only ERT then marketed in the United States, the US Food and Drug Administration approved HGT-REP-059, a protocol to allow access to agal α for FD patients who were left without a therapeutic option. FD patients who were ERT treatment naïve (“naïve”), or who were previously treated with agal β (“switch”), were included. Outcome measures focused on agal α safety and tolerability and renal, cardiac, biomarker, and pharmacodynamic parameters. This report of up to 24-month results from HGT-REP-059 is the largest agal β -to-agal α switch experience to date and presents reasonable expectations for FD treatment in real-life clinical settings.

Patients and Methods

Treatment Protocol Design and Data Collection

HGT-REP-059 was a US multicenter, open-label treatment protocol for patients with FD (funded by Shire; ClinicalTrials.gov identifier: NCT01031173). Inclusion criteria were a confirmation of FD diagnosis biochemically (for males) or genetically (for males or females) and required the use of approved birth control methods (if female of childbearing potential) throughout the study and for at least 30 days after the final infusion. Exclusion criteria included prior anaphylactic, anaphylactoid, or other significant infusion-related reactions with agal β ; current pregnancy or breastfeeding; the use of another investigational drug or device within 30 days prior to study entry; concomitant agal β therapy; failure to provide written informed consent; or otherwise considered unsuitable for the study in the judgment of the investigators.

Regardless of prior treatment status, dose, or schedule of administration, patients in these analyses were treated with agal α (0.2 mg/kg body weight, infused intravenously over a 40-min period every other week). The study duration was planned to be 12 months with an option to extend. Thus, data were collected and assessed for up to 24 months of agal α treatment in the safety population (defined as all enrolled patients who received at least one full or partial dose of agal α). The study was initiated in February 2010 and terminated by the sponsor in July 2012.

Clinical effect parameters are presented only for “naïve” patients with no history of prior ERT for FD and for “switch” patients who were treated with agal β before study entry for whom detailed information on prior dosing, gaps in treatment, and prior clinical history was not available.

Adverse events (AEs) in the safety population were recorded and coded using the Medical Dictionary for Regulatory Activities (<http://www.meddras.com/>) from baseline through the end of study. AEs were rated by severity and potential relationship to study drug. Possibly or probably drug-related AEs were considered infusion-related (IRAEs) if they occurred within 12 h from the start of an infusion. Serious AEs (SAEs; i.e., AEs that resulted in death, were life-threatening, caused new or prolonged hospitalization, led to persistent disability or congenital abnormality, or were considered SAEs by the treating investigator) and discontinuations due to AEs were recorded. Blood samples were collected at baseline and months 6, 18, and 24 to analyze for serum antibodies (Abs) against agal α (all assessments) and agal β (at baseline only), using an enzyme-linked immunosorbent assay. Ab-positive samples were isotyped for immunoglobulin (Ig) G, IgA, IgM, and IgE and tested for enzyme-neutralizing activity using an in vitro assay (Schiffmann et al. 2001).

Clinical and Pharmacodynamic Parameters

Renal function was assessed at baseline and at months 1, 3, 6, 9, 12, 18, and 24 using estimated glomerular filtration rate (eGFR) calculated with the Modification of Diet for Renal Disease equation (Levey et al. 2006) or, in patients <18 years of age, the Counahan-Barratt equation (Counahan et al. 1976). Patients were classified at baseline into chronic kidney disease (CKD) stage: 1b (normal kidney function), 2 (mildly reduced kidney function), 3 (moderately reduced kidney function), or 4 (severely reduced kidney function) (Levey et al. 2003). Patients with eGFR >130 ml/min/1.73 m² were classified as hyperfiltrators (CKD stage 1a) (Magee et al. 2009). The first morning's spot urine sample and 24-h urine sample were used to calculate protein-to-creatinine ratio. Patients were evaluated in subgroups of <200 or $\geq$ 200 mg 24-h urine protein at baseline.

Cardiac structure and function were assessed using left ventricular mass indexed to height (LVMI) and midwall fractional shortening (MFS). Echocardiograms at baseline (or within 60 days of the first infusion) and at months 12, 18, and 24 were assessed at a central laboratory. Left ventricular hypertrophy (LVH) was defined as LVMI values >51 g/m^{2.7} in males or >48 g/m^{2.7} in females.

Samples for accumulation of globotriaosylceramide (Gb₃) and globotriaosylsphingosine (lyso-Gb₃) were obtained

after 8 h of fasting. Both plasma and urine samples (Gb₃ only) were analyzed with liquid chromatography–tandem mass spectrometry using a validated assay (Krüger et al. 2010, 2011).

Data and Statistical Analyses

Baseline demographic and other clinical characteristics were summarized with descriptive statistics. A Wilcoxon signed-rank test at 5% significance level was used to analyze the change from baseline through 24 months in the parameters of interest for each of the subpopulations for previous ERT status. No multiplicity adjustment was made. Similar analyses were performed to assess effects within each population stratified by CKD stage (1a, 1b, 2, 3, and 4) for eGFR and by presence or absence of baseline proteinuria (24-h urine protein ≥ 200 mg) and LVH. To

calculate an annualized rate of eGFR change, a statistical model was used to take into account all repeated measurements of eGFR over time (not just computed from the baseline and the last measurement), and the model assumed a linearity of change over time.

Results

Patient characteristics are shown in Table 1. The safety population comprised 132 patients, including 29 naïve and 71 switch patients, plus 32 patients previously treated with either agal α ($n = 22$) or with both agal α and agal β ($n = 10$). Female representation was substantial and comparable in naïve and switch patients. Switch patients tended to be older than naïve patients. In patients with available information on date of diagnosis of FD, the median years

Table 1 Baseline demographic and clinical characteristics

Baseline characteristic	Naïve ($n = 29$)	Switch ($n = 71$)	Safety population ($N = 132$) ^a
Age, years, median (range)	38.7 (12–74)	46.6 (5–84)	45.1 (5–84)
Sex, n (%)			
Male	14 (48.3)	40 (56.3)	81 (61.4)
Female	15 (51.7)	31 (43.7)	51 (38.6)
Race, n (%)			
Caucasian	26 (89.7)	71 (100.0)	128 (97.0)
African-American	1 (3.4)	0	1 (0.8)
Asian	2 (6.9)	0	2 (1.5)
Other	0	0	1 (0.8)
Years since Fabry diagnosis, median (range)	1.1 (0.1–27.4), $n = 28$	7.2 (0.9–49.3), $n = 70$	7.1 (0.1–49.3), $n = 125$
Years of previous agal β treatment, median (range)	NA	4.6 (0.3–12.2)	5.2 (0.3–12.2), $n = 81$
Years of previous agal α treatment, median (range)	NA	NA	7.60 (0.4–12.2), $n = 29$
CKD stage, n (%) ^b			
1A	3 (10.3)	5 (7.0)	16 (12.1)
1B	12 (41.4)	27 (38.0)	50 (37.9)
2	7 (24.1)	21 (29.6)	28 (21.2)
3	4 (13.8)	9 (12.7)	23 (17.4)
4	3 (10.3)	9 (12.7)	15 (11.4)
LVH, n (%) ^c			
Yes	10 (34.5)	27 (38.0)	47 (35.6)
No	15 (51.7)	25 (35.2)	55 (41.6)
Data not available	4 (13.8)	19 (26.8)	30 (22.7)

^a The safety population also includes patients who previously received either agal α or both agal α and agal β prior to baseline. However, these patients were not evaluated as separate subgroups, because of low patient numbers and insufficient pre-baseline data

^b CKD stages were defined by eGFR (ml/min/1.73 m²) standards as follows: stage 1A (>130), stage 1B (90–130), stage 2 (60–89), stage 3 (30–59), and stage 4 (15–29)

^c Patients ($n = 52$ switch and 25 naïve) had sufficient echocardiographic measurements or urine samples to assess baseline LVH or urine protein data, respectively

agal α agalsidase alfa, agal β agalsidase beta, CKD chronic kidney disease, eGFR estimated glomerular filtration rate, LVH left ventricular hypertrophy, NA not applicable, naïve treatment naïve prior to baseline, switch patients formerly treated with agal β

elapsed since diagnosis of FD were considerably fewer in naïve patients compared with switch patients. The majority of both naïve and switch patients had CKD stage 1b or stage 2. Hyperfiltrators (CKD stage 1a) were uncommon (Fig. 1a).

Safety and Tolerability

In the safety population, most patients experienced treatment-emergent AEs ($n = 131$ [99.2%]); however, the majority were considered mild ($n = 23$ [17.4%]) or moderate ($n = 66$ [50.0%]) in severity. Treatment-emergent AEs (TEAEs) occurring in $\geq 15\%$ included nasopharyngitis, nausea, headache, dizziness, fatigue, and vomiting. Approximately half of TEAEs were considered to be possibly or probably drug-related, and approximately one third were deemed IRAEs.

Serious AEs occurred in 47 (35.6%) patients in the safety population; the most common were pneumonia ($n = 5$ [4.3%]); cerebrovascular accident ($n = 4$ [3.4%]); and anemia, congestive cardiac failure, vomiting, asthenia, transient ischemic attack, confusion, and renal impairment (each $n = 3$ [2.6%]). Hospitalizations in two adult switch patients were reported as SAEs possibly or probably drug-related, per investigators. One patient had a transient ischemic attack 13 days after the last agal α infusion; the second patient had an IRAE, with vomiting, asthenia, chills, and increased blood pressure. Both SAEs resolved without sequelae. With respect to AE severity, 31% of the safety population experienced AEs that were reported as severe or life-threatening in intensity (naïve $n = 11$ [37.9%], switch $n = 21$ [29.6%], previous agal α $n = 6$ [27.3%]).

Three adult patients discontinued treatment due to AEs: two naïve patients ($n = 1$ each with arthralgia or chest discomfort and face swelling) and one switch patient (psychotic disorder). Three patients died: a 68-year-old man (naïve) with cardiorespiratory arrest following methicillin-resistant *Staphylococcus aureus* bacteremia; a 55-year-old man (switch) with cardiac arrest; and a 55-year-old man (previous agal α) with cardiorespiratory arrest subsequent to cerebrovascular accident. All three patients had advanced heart and kidney disease at baseline, and no deaths were deemed drug-related.

Treatment adherence was high, with 94 of 132 patients (71.2%) missing no more than one agal α infusion. The mean number of completed infusions per patient was 45.5, with a mean total exposure duration of 638.5 days.

Immunogenicity and Other Safety Parameters

No clinically meaningful changes occurred in laboratory values, vital signs, or physical examination findings in any study subpopulation. Table 2 summarizes agal α antibody

status in patients with available data; 28 of 28 naïve patients were Ab negative at baseline. Two (7.1%) naïve patients converted from seronegative to seropositive during the study without experiencing IRAEs. One naïve patient lacking Ab data had an IRAE.

At baseline, 54.9% of switch patients had anti-agal β Abs. Also at baseline, 35.2% of these anti-agal β Ab-positive switch patients had anti-agal α Abs, and 22.5% had neutralizing Abs despite no prior agal α exposure (Table 2). Among patients who were agal α Ab negative at baseline, 19.6% (9/46) transiently or persistently seroconverted to IgM or IgG, but none developed neutralizing Abs. IRAEs occurred in 27 switch patients overall, and 15 of these were agal α Ab positive at some point.

Renal Function and Cardiac Structure/Function

At month 24, kidney function as assessed by eGFR remained clinically stable in both the naïve and switch subgroups (Fig. 1b). Among those with no dialysis or kidney transplant experience, baseline mean $\pm$ SE eGFR (ml/min/1.73 m²) values were 94.20 ± 7.65 in naïve ($n = 27$) and 87.45 ± 4.40 in switch ($n = 59$) patients. The mean $\pm$ SE annualized rates of eGFR change (ml/min/1.73 m²/year) were switch -2.40 ± 1.04 ($n = 59$) and naïve -1.68 ± 2.21 ($n = 27$). In the total safety population, patients in most CKD stages showed relatively stable eGFR, except for CKD stage 1a (the hyperfiltrator group) and CKD stage 3 (Fig. 1a). The decline in the hyperfiltrator group suggests a trend toward a normal eGFR. There were no significant changes in measures of proteinuria in either naïve or switch patients, regardless of whether baseline 24-h urine protein was less than or greater than 200 mg (Fig. 1c). Mean echocardiographic measurements (LVMI, MFS) did not change significantly in any patient subgroup (Fig. 1d, e). Mean LVMI did not change significantly in patients with or without LVH at baseline (Fig. 1f).

Plasma and Urine Biomarkers

Previous assessments in healthy volunteers have shown that the mean $\pm$ 2 standard deviations normal plasma Gb₃ (nmol/mL) was 4.55 ± 3.90 (observed range, 1.96–7.70; $n = 60$). For naïve patients, mean $\pm$ SE baseline plasma Gb₃ levels (nmol/mL) were 19.02 ± 3.11 for male patients and 13.76 ± 2.32 for female patients. For switch patients, mean $\pm$ SE baseline plasma Gb₃ levels (nmol/mL) were 13.36 ± 0.86 for male patients and 11.46 ± 0.96 for female patients. There was a trend of reduction from baseline in plasma Gb₃ levels in naïve male patients, but not in switch male nor in all female patients (Fig. 2a).

The normal range for creatinine-normalized urine Gb₃ in healthy volunteers is <0.03 nmol/mg creatinine ($n = 60$;

Fig. 1 Renal and cardiac parameters in the safety population. Renal parameters included change over time by treatment group by (a) CKD stage, (b) mean $\pm$ SE eGFR, and (c) early-morning spot urine protein-to-creatinine ratio in patients with baseline 24-h urine protein <200 or ≥ 200 mg. CKD stages defined by eGFR (in ml/min/1.73 m²) standards as follows: stage 1A (>130 [hyperfiltrators]), stage 1B (90–130 [normal kidney function]), stage 2 (60–89 [mildly reduced kidney function]), stage 3 (30–59 [moderately reduced kidney function]), and stage 4 (15–29 [severely reduced kidney function]). eGFR was calculated with the Modification of Diet for Renal Disease or Counahan-Barratt equation in patients aged <18 years. Cardiac

parameters as measured by echocardiography by treatment group included (d) mean $\pm$ SE LVMI (g/m^{2.7}) change over time and (e) mean change over time in MFS (%), as well as by (f) presence or absence of baseline LVH. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$; other data points (without footnotes indicating p -values) were $p \geq 0.05$ versus baseline. *agal* agalsidase alfa, *CFB* change from baseline, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *LVH* left ventricular hypertrophy, *LVMI* left ventricular mass index, *MFS* midwall fractional shortening, *naïve* treatment naïve prior to baseline, *SE* standard error, *switch* patients formerly treated with agalsidase beta

Table 2 Anti-agalsidase alfa antibody status over time by previous treatment group

Status	Baseline		Month 6		Month 12		Month 24	
	Anti-agal α Ab <i>n</i> (%)	NAb <i>n</i> (%)	Anti-agal α Ab <i>n</i> (%)	NAb <i>n</i> (%)	Anti-agal α Ab <i>n</i> (%)	NAb <i>n</i> (%)	Anti-agal α Ab <i>n</i> (%)	NAb <i>n</i> (%)
Naïve (<i>n</i> = 28) ^a								
Ab negative	28 (96.6)	28 (96.6)	27 (93.1)	27 (93.1)	25 (86.2)	26 (89.7)	9 (31.0)	9 (31.0)
Ab positive	0	0	0	0	2 (6.9)	1 (3.4)	0	0
Switch (<i>n</i> = 71)								
Ab negative	46 (64.8)	55 (77.5)	44 (62.0)	59 (83.1)	45 (63.4)	54 (76.1)	25 (35.2)	35 (49.3)
Ab positive	25 (35.2)	16 (22.5)	25 (35.2)	10 (14.1)	21 (29.6)	12 (16.9)	15 (21.1)	5 (7.0)
Safety population (<i>n</i> = 132)								
Ab negative	98 (74.2)	112 (84.8)	92 (69.7)	115 (87.1)	91 (68.9)	108 (81.8)	36 (27.3)	49 (37.1)
Ab positive	33 (25.0)	19 (14.4)	36 (27.3)	13 (9.8)	32 (24.2)	15 (11.4)	20 (15.2)	7 (5.3)

The assays were performed by a central laboratory. Samples were analyzed using an enzyme-linked immunosorbent assay

^aAntibody data were not available for one naïve patient. *Ab* antibody, *agal α* agalsidase alfa, *NAb* antibody with enzyme-neutralizing activity, *naïve* treatment naïve prior to baseline, *switch* patients formerly treated with agalsidase beta

per internal validation). For naïve patients, mean $\pm$ SE baseline creatinine-normalized urine Gb₃ levels (nmol/mg) were 3.78 ± 0.83 for male patients and 2.48 ± 1.82 for female patients. For switch patients, mean $\pm$ SE baseline creatinine-normalized urine Gb₃ levels (nmol/mg) were 2.74 ± 0.51 for male patients and 0.16 ± 0.049 for female patients. The only significant change from baseline over time was a reduction at month 12 in male switch patients (Fig. 2b).

For naïve patients, mean $\pm$ SE baseline plasma lyso-Gb₃ levels (nM) were 102.67 ± 19.09 for male patients and 27.59 ± 15.40 for female patients. For switch patients, mean $\pm$ SE baseline plasma lyso-Gb₃ levels (nM) were 57.94 ± 5.11 for male patients and 13.82 ± 1.16 for female patients. Naïve male patients demonstrated a significant reduction from baseline in mean plasma lyso-Gb₃ levels (nM) at months 12, 18, and 24; a similar pattern was observed for naïve female patients at month 18 (*n* = 11) and 24 (*n* = 3). Other changes over time were not significant (Fig. 2c).

Discussion

The primary objective of this FD study, the largest agal α clinical trial to date, was to evaluate the safety and tolerability of agal α in an open-label scenario in both naïve and previously treated male and female patients lacking access to a therapeutic alternative. The findings are consistent with the previously reported safety profile of agal α (European Medicines Agency 2014). No new or unexpected safety concerns emerged during the 24 months of treatment. In FD, chronic protean signs and symptoms usually predate initiation of treatment and may persist or

even progress despite ERT. Thus, it is not surprising that most patients experienced one or more treatment-emergent AEs, the majority of which were mild or moderate in intensity, consistent with events observed during disease progression, consistent with events documented during agalsidase alfa clinical trials, and consistent with events recorded in post-marketing safety surveillance.

Also consistent with past experience, IRAEs occurred in approximately one third of patients. The SAEs and deaths mostly encompassed renal, cardiac, and cerebrovascular etiologies in males with classical phenotypes and preexisting advanced heart and kidney disease. These were judged to be natural morbidity of FD rather than drug-related and support the hypothesis that initiating ERT before end-organ damage occurs is key to attaining favorable long-term outcomes.

There was little measurable change in renal function or proteinuria during this 24-month study. Naïve and switch patients had an annualized mean eGFR (ml/min/1.73 m²/year) change of -1.68 and -2.40 , respectively. Given the substantial heterogeneity in our patient population and lack of pre-enrollment renal history, it is difficult to compare these outcomes with those reported in previous clinical trials and observational studies of either agal α or agal β . However, our results are generally similar to those from previous studies with agal α or agal β , which have shown positive effects of ERT to slow down the decline of eGFR (Banikazemi et al. 2007; Germain et al. 2007; Mehta et al. 2009; West et al. 2009; Rombach et al. 2013; Weidemann et al. 2013; Anderson et al. 2014).

Cardiac structure and function remained relatively stable in patients with or without LVH for both switch and naïve patients. Like stabilization of renal function, maintenance of cardiac structure and function is critical with respect to

Fig. 2 Mean $\pm$ SE change over time by sex and by treatment group in (a) plasma Gb₃, (b) creatinine-normalized urinary Gb₃, and (c) plasma lyso-Gb₃. Both plasma and urine Gb₃ and plasma lyso-Gb₃ levels were measured using a liquid chromatography–tandem mass spectrometry assay. *agal* agalsidase alfa, *Gb*₃ globotriaosylceramide,

*lyso-Gb*₃ globotriaosylsphingosine, *naïve* treatment naïve prior to baseline, *SE* standard error, *switch* patients formerly treated with agalsidase beta. *Mean values significantly different from baseline based on 95% confidence intervals

long-term outcomes and is relevant to both groups in this study, given that the annual mean increase in cardiac mass for untreated Fabry patients is $4.07 \text{ g/m}^{2.7}$ in males and $2.31 \text{ g/m}^{2.7}$ in females and even higher ($6.59 \text{ g/m}^{2.7}$ in males and $3.77 \text{ g/m}^{2.7}$ in females) in those with LVH at baseline (Kampmann et al. 2008).

The infrequency of seroconversion in naïve (7.1%) and switch (19.6%) patients is consistent with previous agal α clinical trial experience (Keating 2012). More than half of the switch patients had agal β Abs at baseline, whereas only 35% had agal α Abs, showing that although cross-reactivity is common, it is not inevitable as previously postulated (Linthorst et al. 2004). Antibody status, including presence of neutralizing Abs (found in 15–20% of switch patients), may have affected the glycosphingolipid biomarker response and could, therefore, possibly be clinically relevant.

Baseline plasma Gb₃ and lyso-Gb₃ levels were lower in switch patients versus naïve patients. Although we have no record of biomarker levels when previous agal β treatment was terminated in the switch patients or during treatment lapses, it was similarly reported that even after agal β interruptions or dose reductions of 1.0–1.5 years, plasma lyso-Gb₃ does not return to pretreatment values (Smid et al. 2011). In general with initiation of agal α , there were significant reductions in mean plasma lyso-Gb₃ levels only in naïve male patients; other changes in plasma and urinary biomarkers in switch and naïve patients were inconsistent and generally not significant. These results may be in part attributable to the relative refractoriness of agal α -Ab-positive patients (30–35% of the total at all assessment time points), as reviewed and reported by Rombach and colleagues (Rombach et al. 2012), but results in previously treated patients should be interpreted with caution as the prior treatment may have caused a reduction in “baseline” levels.

The aims and scientific design of this study are limited by its primary purpose as a vehicle to ensure continuity of treatment for a large, varied, at-risk patient population who unexpectedly lacked a therapeutic alternative. Liberal inclusion and exclusion criteria created a clinically heterogeneous population regarding gender, genotype, duration and severity of symptoms, end-organ damage, and comorbidities. There was no control group and no reliable access to clinical or treatment history prior to enrollment, and patient numbers were insufficient for matching analyses. Some patients did not complete 24 months of therapy before the study was terminated, and only half had a formal end-of-study visit. However, over 80% of patients were enrolled at the time of termination, and ~60% received all expected infusions. For a chronic disorder such as FD,

a 2-year study without even more extended follow-up is somewhat limited in its ability to ascertain long-term key renal, cardiac, neurologic, and patient-reported outcomes such as health-related quality of life.

Our results show that for up to 24 months of treatment, agal α was well tolerated in a heterogeneous population of treatment-naïve and switch patients, no new or unexpected safety or immunogenicity concerns emerged, mean surrogate plasma and urine biomarkers (Gb₃ and lyso-Gb₃) showed consistent and significant reductions only in plasma lyso-Gb₃ levels in naïve male patients, and renal and cardiac functions generally remained stable.

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Synopsis

In this cohort of patients with Fabry disease who were treatment naïve or switched from agal β , agal α was generally well tolerated and stabilized renal and cardiac parameters.

Compliance with Ethics Guidelines

Conflicts of Interest

Ozlem Goker-Alpan has received research support from Actelion, Shire, Genzyme Corp, Amicus, and Pfizer-Protalix Biotherapeutics, as well as payments for consultancy from Actelion, Shire, and Pfizer-Protalix Biotherapeutics and payments for speaker bureaus from Actelion, Genzyme Corp, and Shire.

Suma P. Shankar has been site primary investigator in clinical trials and received research support and educational grants from Genzyme, Shire, Protalix, Actelion, and Amicus and has served on speakers bureaus for Genzyme and Shire.

Yeong-Hau H. Lien has received research support from Shire.

Neal Weinreb has received research support and honoraria from Genzyme-Sanofi and Shire and has served on advisory boards for Genzyme-Sanofi, Shire, and Pfizer-Protalix Biotherapeutics and served on speakers bureaus for Genzyme-Sanofi, Actelion, Shire, and Pfizer.

Anna Wijatyk, Peter Chang, and Rick Martin are employees of and hold stock options in Shire.

Khan Nedd declares no potential competing interests.

Patient Consent Statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

Details of the Contributions of Individual Authors

Anna Wijatyk, Peter Chang, and Rick Martin were involved in the study planning. Ozlem Goker-Alpan was the Principal Investigator and signed off on the protocol. Ozlem Goker-Alpan, Khan Nedd, Suma P. Shankar, Yeong-Hau Lien, and Neal Weinreb were involved in the study conduct. Peter Chang conducted the statistical analyses. All authors contributed to the first draft of the manuscript, were involved in the critical review and revision of subsequent drafts, and approved the final draft for submission.

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