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Regular Article

Long-term efficacy and safety of migalastat treatment in Fabry disease: 30-month results from the open-label extension of the randomized, phase 3 ATTRACT study☆

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ABSTRACT

Results from the 18-month randomized treatment period of the phase 3 ATTRACT study demonstrated the efficacy and safety of oral migalastat compared with enzyme replacement therapy (ERT) in patients with Fabry disease who previously received ERT. Here, we report data from the subsequent 12-month, migalastat-only, open-label extension (OLE) period. ATTRACT (Study AT1001–012; NCT01218659) was a randomized, open-label, active-controlled study in patients aged 16–74 years with Fabry disease, an amenable *GLA* variant, and an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2. During the OLE, patients who received migalastat 150 mg every other day (QOD) during the randomized period continued receiving migalastat (Group 1 [MM]); patients who received ERT every other week discontinued ERT and started migalastat treatment (Group 2 [EM]). Outcome measures included eGFR, left ventricular mass index (LVMi), composite clinical outcome (renal, cardiac or cerebrovascular events), and safety. Forty-six patients who completed the randomized treatment period continued into the OLE (Group 1 [MM], n = 31; Group 2 [EM], n = 15). eGFR remained stable in both treatment groups. LVMi decreased from baseline at month 30 in Group 1 (MM) in patients with left ventricular hypertrophy at baseline. Only 10% of patients experienced a new composite clinical event with migalastat treatment during the OLE. No new safety concerns were reported. In conclusion, in patients with Fabry disease and amenable *GLA* variants, migalastat 150 mg QOD was well tolerated and demonstrated durable, long-term stability of renal function and reduction in LVMi.

1. Introduction

Fabry disease is a rare, devastating X-linked lysosomal disorder caused by pathogenic *GLA* variants that result in functional deficiency of α-galactosidase A (α-Gal A) [1,2]. The accumulation of α-Gal A substrate globotriaosylceramide (GL-3) throughout the body leads to chronic inflammation and damage in multiple organs including the heart, kidneys, and central nervous system, and likely premature death [1–3]. To date, more than 1000 disease-causing *GLA* variants have been identified, including single nucleotide changes, duplications and

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deletions [4].

Both males and females are affected by Fabry disease, which is estimated to occur in up to 1:40,000 births [2,5], although newborn screening surveys suggest that this may be an underestimation [6]. Due to the X-linked nature of this disorder, hemizygous males tend to be more α-Gal A deficient, whereas females may harbor cells expressing normal or mutant enzyme, manifesting as a spectrum of phenotypes and disease severity ranging from asymptomatic to severe [2,7]. Until recently, the only treatment option was enzyme replacement therapy (ERT) with one of two recombinant enzymes (agalsidase alfa or agalsidase beta) administered via intravenous infusions every 2 weeks [8]. However, ERT has several potential limitations, including the risk of infusion reactions, development of antibodies against agalsidase and complications of vascular access over time, which may limit its efficacy [7,9,10]. Lifelong ERT infusions also impose considerable psychosocial stress on patients with Fabry disease and their families as well as a substantial impact on health economics and health resources [11,12].

Migalastat is an orally administered, small molecule pharmacological chaperone that binds to and stabilizes *amenable* mutant forms of α-Gal A, facilitating lysosomal trafficking and restoring endogenous enzyme activity [13,14]. Oral migalastat is an important therapeutic option for patients with Fabry disease, and has been approved for its treatment in 39 countries including the United States, Japan and the European Union [15]. Migalastat has broad tissue distribution [16] and has demonstrated efficacy in reducing disease substrates and addressing both renal and cardiac manifestations in patients with Fabry disease [17–19].

The phase 3 ATTRACT study demonstrated the efficacy and safety of oral migalastat versus ERT infusion in an initial 18-month randomized treatment period in males and females with Fabry disease who had previously received ERT [18]. Herein, data are presented from patients who entered the subsequent 12-month, migalastat-only, open-label extension period in the ATTRACT study.

2. Methods

2.1. Study design and participants

ATTRACT (Study AT1001-012; NCT01218659) was a phase 3, randomized, open-label study including an initial 18-month active-controlled treatment period, during which patients received migalastat or ERT, followed by a 12-month optional open-label extension period, during which all patients received migalastat. The study objective was to compare the efficacy and safety of migalastat with ERT in male and female patients with Fabry disease who had been receiving ERT and had migalastat-responsive (amenable) *GLA* variants [18].

Eligible patients were 16–74 years of age with a genetically confirmed diagnosis of Fabry disease; had initiated ERT ≥12 months before the baseline visit (ie, prior to the first dose of study drug in the initial 18-month treatment period); had an amenable *GLA* variant based on a preliminary amenability assay (final determination of amenability was based on the Good Laboratory Practice–validated migalastat amenability assay, which became available during the study [18,20]); and had an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2. Patients taking angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs) had to be on a stable dose for ≥4 weeks before the screening visit.

Participants were enrolled from 25 study centers in 10 countries (Australia, Austria, Belgium, Brazil, Denmark, France, Italy, Japan, the United Kingdom, and the United States). In the initial 18-month period, eligible patients were randomly assigned 1.5:1 to receive migalastat hydrochloride (HCl) (150 mg, every other day) or to continue ERT (either agalsidase alfa 0.2 mg/kg every other week or agalsidase beta 1.0 mg/kg every other week) (Fig. 1). During the 12-month open-label extension period, patients who received migalastat during the 18-month randomized treatment period continued receiving migalastat (Group 1 [MM]); patients who received ERT during the randomized period discontinued ERT and started treatment with migalastat (Group 2 [EM]).

2.2. Ethics

This study was designed and monitored in accordance with the ethical principles of Good Clinical Practice and the Declaration of Helsinki. The clinical study protocol was reviewed and approved by the appropriate Independent Ethics Committee/Institutional Review Board at each study site. All participants provided written informed consent prior to initiation of any study procedures.

2.3. Efficacy variables

Efficacy variables were assessed at baseline, months 1, 3, 6, 9, 12, 15, 18, 19, 21, 24, and 30, unless specified otherwise. Renal function measures included annualized rate of change in eGFR assessed using the Chronic Kidney Disease Epidemiology Collaboration equation ($eGFR_{CKD\text{-}EPI}$) and 24-h urine protein; primary efficacy analyses during the 18-month study period were reported previously [18]. Cardiac function was measured by echocardiogram at baseline and at months 6, 12, 18, 24, and 30. Measurable variables to assess cardiac structure and function included LVMi (left ventricular mass/body surface area), midwall fractional shortening, intraventricular septum wall thickness (IVSWT), left ventricular posterior wall thickness (LVPWT), and left ventricular ejection fraction. Composite clinical outcome was calculated as the number of patients who experienced any prespecified renal, cardiac, or cerebrovascular event or death (Fabry-associated clinical events) during the study. Renal events consisted of a decrease in $eGFR_{CKD\text{-}EPI}$ ≥15 mL/min/1.73 m^2 relative to baseline, with the decreased eGFR < 90 mL/min/1.73 m^2 or an increase in 24-h urine protein ≥33% relative to baseline, with the elevated protein ≥300 mg. Cardiac events comprised myocardial infarction; unstable cardiac angina, as defined by the American College of Cardiology/American Heart Association national practice guidelines; new symptomatic arrhythmia requiring antiarrhythmic medication, direct current cardioversion, pacemaker, or defibrillator implantation; or congestive heart failure, New York Heart Association class III or IV. Cerebrovascular events consisted of stroke or transient ischemic attack [18].

Additional variables included plasma globotriaosylsphingosine (lyso-Gb_3, a diagnostic biomarker) concentrations (measured at baseline, and months 6, 12, 18, and 30) and white blood cell α-Gal A activity (reported for male patients only because white blood cells in females express both mutant and wild-type α-Gal A [21]).

2.4. Safety outcomes

Safety outcomes included treatment-emergent adverse events (AEs), vital signs, body weight, clinical laboratory tests (chemistry, haematology, and urinalysis), 12-lead electrocardiograms (ECGs), physical examinations, and use of concomitant medications. Treatment-emergent AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) v16.1.

2.5. Statistical analyses

Safety data are reported for all patients who completed the 18-month randomized treatment period and took ≥1 dose of migalastat during the open-label extension period. Efficacy data are reported for all patients in the open-label extension who had amenable variants based on the Good Laboratory Practice-validated migalastat amenability assay. Annualized rate of change in eGFR and LVMi were analyzed by treatment group and sex.

All analyses were reported with descriptive statistics. Where appropriate, two-sided 95% confidence intervals (CIs) were calculated.

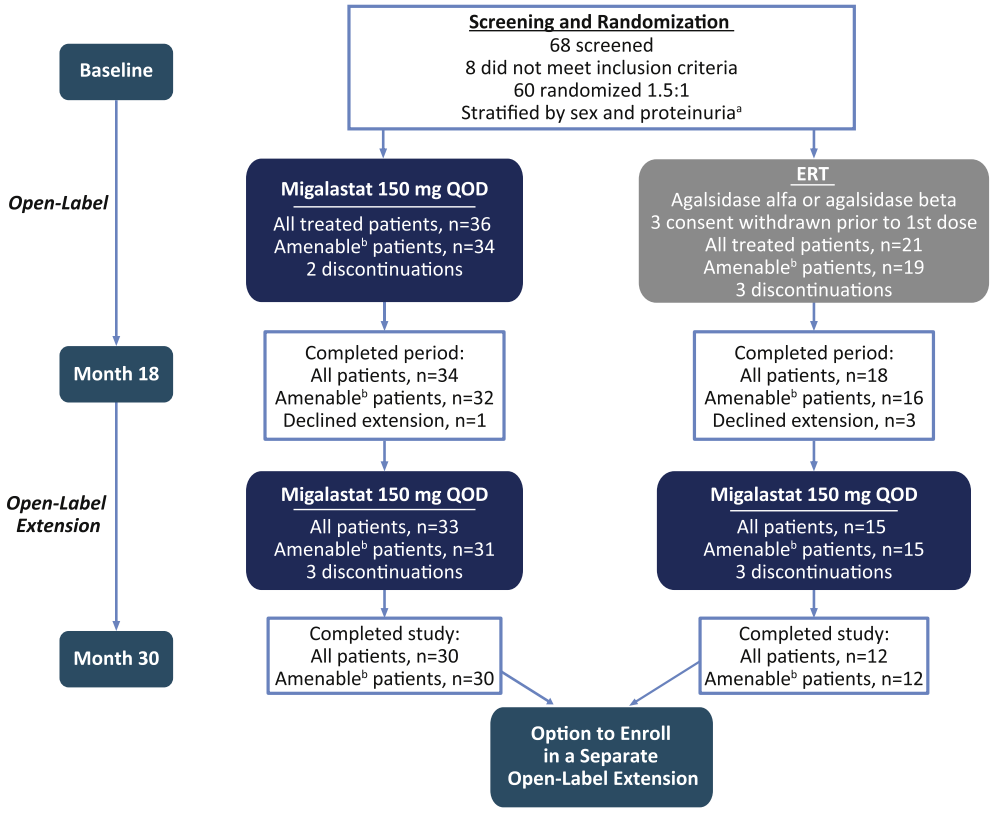

Fig. 1. ATTRACT study design.
ERT, enzyme replacement therapy; QOD, every other day.
[a]Proteinuria stratification: high, ≥0.1 g/24 h; low, < 0.1 g/24 h.
[b]Determination of amenability was based on the Good Laboratory Practice–validated migalastat amenability assay, which became available during the study. Therefore, some enrolled patients were later determined to be not amenable.

Annualized rates of change in GFR were analyzed using an analysis of covariance (ANCOVA) model, as described previously [18]. Statistical analyses and reporting were performed using SAS Version 9.2. Missing efficacy data were not imputed to ensure consistency with the procedure and methodology used previously [18], and no adjustments for multiplicity were performed.

For Group 1 (MM), efficacy and safety outcomes were calculated over the entire 30-month treatment period. For Group 2 (EM), efficacy and safety outcomes were compared between the initial 18-month ERT treatment period and the subsequent 12-month open-label migalastat treatment period (ie, after treatment switch).

3. Results

3.1. Patient disposition and baseline characteristics

Of the 52 patients who completed the 18-month randomized treatment period, 48 continued into the 12-month open-label extension (Group 1 [MM], n = 33 [31 amenable]; Group 2 [EM], n = 15 [all amenable]) (Fig. 1). Overall, 91.3% of patients with amenable *GLA* variants in the open-label extension population completed the 30 months of treatment. Six patients (MM and EM: 3 patients each) discontinued the study. In the MM group, reasons for discontinuation were pregnancy, lack of efficacy, and patient withdrawal due to family planning. In the EM group, reasons for discontinuation were physician's decision, loss to follow-up, and patient withdrawal due to re-initiation of ERT. However, there were no discontinuations due to treatment-emergent AEs during either the randomized or the open-label extension periods; the most common reason for discontinuation at any time during the study was withdrawal by patient.

At baseline (ie, prior to the first dose of study drug in the initial 18-month treatment period), demographic and disease characteristics were comparable between treatment groups in the open-label extension population (Table 1).

3.2. Efficacy

3.2.1. Renal function

Annualized rate of change in $eGFR_{CKD\text{-}EPI}$ is shown in Fig. 2A. In Group 1 (MM), the mean annualized rate of change from baseline to month 30 was −1.7 mL/min/1.73 m^2 (median: −1.9; 95% CI: −2.7, −0.8); the values for male (n = 14) and female (n = 17) patients were −2.1 mL/min/1.73 m^2 (median: −2.2; 95% CI: −3.2, −0.9) and −1.4 mL/min/1.73 m^2 (median: −1.0; 95% CI: −3.0, 0.1), respectively. In Group 2 (EM), the mean annualized rate of change was comparable between the initial 18-month ERT treatment period (−2.0 mL/min/1.73 m^2 [median: −0.8; 95% CI: −5.7, 1.6]; males [n = 5]: −2.1 mL/min/1.73 m^2 [median: −0.9; 95% CI: −8.4, 4.2]; females [n = 10]: −2.0 mL/min/1.73 m^2 [median: −0.01; 95% CI: −7.4, 3.4]), and the subsequent 12-month open-label migalastat treatment period (−2.1 mL/min/1.73 m^2 [median: 1.2; 95% CI: −9.0, 4.8]; males [n = 5]: −5.7 mL/min/1.73 m^2 [median: 1.2; 95% CI: −22.0, 10.6]; females [n = 10]: −0.3 mL/min/1.73 m^2 [median: 1.1; 95% CI: −9.2, 8.5]).

No significant change from baseline in 24-h urine protein was observed in Group 1 (MM) from 0 to 30 months, and in Group 2 (EM) during both the initial 18-month period (ERT) and the subsequent 12-month open-label extension period (migalastat) (Fig. 2B).

3.2.2. Cardiac structure and function

In Group 1 (MM), LVMi was stable from baseline to month 30 overall (mean change: −3.8 g/m^2 [median: −4.6; 95% CI: −8.9, 1.3]) and in male and female patients (Table 2), but decreased in the subgroup of patients with left ventricular hypertrophy at baseline (n = 10; mean change: −10.0 g/m^2 [median: −11.3; 95% CI: −16.6, −3.3]), which was statistically significant based on the 95% CIs (individual patient values are provided in Supplementary Table 1). In Group 2 (EM), the mean change in LVMi during the initial 18-month period (ERT) was −2.8 g/m^2 (median: −7.7 g/m^2; 95% CI: −12.5, 6.9) overall (Table 2) and 3.9 g/m^2 (median: 3.2; 95% CI: −33.6, 41.4) in patients with left ventricular hypertrophy at baseline (n = 4). During

Table 1
Patient demographics and baseline characteristics (Open-label extension population).

Variable	Group 1 (MM)	Group 2 (EM)	Total
No. of patients	33[a]	15	48
Age, years			
Mean (SD)	50.3 (14.4)	45.3 (15.7)	48.7 (14.8)
Median (range)	54.0 (18, 70)	48.0 (18, 70)	52.5 (18, 70)
Age ≤ 65 years, *n* (%)	30 (90.9)	14 (93.3)	44 (91.7)
Sex, *n* (%)			
Male	16 (48.5)	5 (33.3)	21 (43.7)
Female	17 (51.5)	10 (66.7)	27 (56.2)
Race, *n* (%)			
White	26 (78.8)	14 (93.3)	40 (83.3)
Asian	5 (15.2)	1 (6.7)	6 (12.5)
Black or African American	1 (3.0)	0	1 (2.1)
Multiple	1 (3.0)	0	1 (2.1)
Years since Fabry diagnosis, mean (SD)	10.6 (12.2)	16.1 (13.6)	12.3 (12.7)
$eGFR_{CKD\text{-}EPI}$ (mL/min/1.73 m^2)			
Mean (SD)	90.6 (22.9)	96.0 (21.0)	92.3 (22.2)
Median (range)	88.1 (51, 145)	96.8 (45, 130)	92.1 (45, 145)
24-h urine protein at baseline, mg/24 h			
Mean (SD)	276.1 (427.2)	372.6 (800.5)	306.3 (563.2)
Median (range)	128.0 (0, 2282)	108.0 (0, 3154)	123.5 (0, 3154)
ERT at baseline, *n* (%)[b]			
Agalsidase alfa	22 (66.7)	10 (66.7)	32 (66.7)
Agalsidase beta	10 (30.3)	5 (33.3)	15 (31.3)
Use of ACEI/ARB/RI at baseline, *n* (%)	15 (45.5)	7 (46.7)	22 (45.8)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; $eGFR_{CKD\text{-}EPI}$, estimated glomerular filtration rate assessed by the Chronic Kidney Disease Epidemiology Collaboration equation; EM, ERT to migalastat treatment; ERT, enzyme replacement therapy; MM, migalastat to migalastat treatment; RI, renin inhibitor; SD, standard deviation.

[a] Includes 2 patients who were subsequently found to have non-amenable variants by Good Laboratory Practice-validated migalastat amenability assay and who were excluded from the efficacy analyses.

[b] The ERT at baseline was not collected for 1 patient in Group 1 (MM) as this patient transferred to another study site.

the subsequent 12-month open-label extension period (migalastat), mean LVMi in Group 2 overall remained unchanged (−0.3 g/m^2 [95% CI: −8.6, 9.7]). Similarly, mean LVMi in patients with left ventricular hypertrophy remained stable (−3.7 g/m^2 [median: −3.2; 95% CI: −28.7, 21.2]); individual patient values are provided in Supplementary Table 2).

Mid-wall fractional shortening did not change from baseline in either Group 1 (MM) or Group 2 (EM) patients (Table 2). Mean change from baseline to month 30 was −0.3% (median: −0.3%; 95% CI: −1.2, 0.6) in Group 1; in Group 2, mean changes during the initial 18-month ERT treatment period and the subsequent 12-month open-label migalastat treatment period were −0.3% (median change: −0.3%; 95% CI: −1.6, 0.9) and 0% (median change: 0.1%; 95% CI: −1.0, 1.0), respectively.

A similar lack of change was observed for IVSWT, LVPWT, left ventricular ejection fraction (Supplementary Table 3), functional diastolic grade, or functional systolic grade in both treatment groups.

3.2.3. Composite clinical outcome

Overall, 10/31 (32.3%) patients in Group 1 (MM) had renal or cardiac events (35 events total) during the 30-month study (Fig. 3A), averaging 428 events per 1000 patient-years. During the initial 18-month treatment period, the event rate in Group 1 was 370 events per 1000

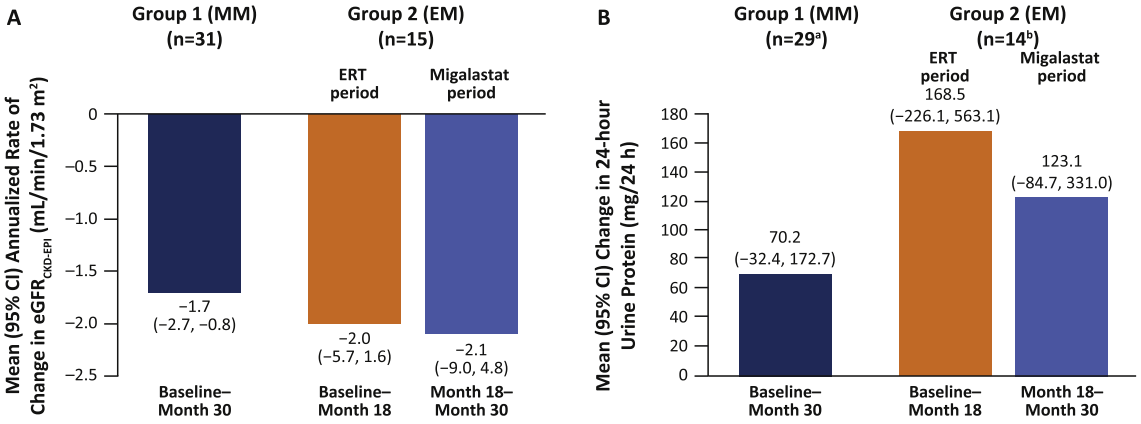

Fig. 2. Change from baseline in renal variables (open-label extension population; patients with amenable variants only); (A) mean annualized rate of change in $eGFR_{CKD\text{-}EPI}$ (mL/min/1.73 m^2) and (B) mean change in 24-h urine protein (mg/24 h).
CI, confidence interval; $eGFR_{CKD\text{-}EPI}$, estimated glomerular filtration rate assessed by the Chronic Kidney Disease Epidemiology Collaboration equation; EM, ERT to migalastat treatment; ERT, enzyme replacement therapy; MM, migalastat to migalastat treatment.
[a]For 24-h urine protein, there were 29 evaluable patients in Group 1 (MM).
[b]For 24-h urine protein, there were 14 evaluable patients in Group 2 (EM).

Table 2
Change from baseline in left ventricular mass index and midwall fractional shortening (Open-label extension population; patients with amenable variants only).

Variable	Group 1 (MM) $n = 31$			Group 2 (EM) $n = 15$		
	Overall $n = 31$	Males $n = 14$	Females $n = 17$	Overall $n = 15$	Males $n = 5$	Females $n = 10$
LVMi, g/m^2, median (95% CI)						
Baseline[a]	89.8 (63.6, 165.7) [$n = 30$]	95.0 (69.9, 165.7) [$n = 13$]	87.8 (63.6, 112.6) [$n = 17$]	80.7 (53.3, 129.1) [$n = 13$]	120.8 (70.7, 129.1) [$n = 5$]	77.8 (53.3, 107.3) [$n = 8$]
Baseline-Month 30	−4.6 (−8.9, 1.3) [$n = 28$]	−4.0 (−12.7, 1.3) [$n = 11$]	−7.3 (−10.2, 5.1) [$n = 17$]	NA	NA	NA
Initial 18 months	NA	NA	NA	−7.7 (−12.5, 6.9) [$n = 12$]	2.7 (−22.1, 29.1) [$n = 5$]	−7.7 (−15.9, 1.5) [$n = 7$]
12-month open-label extension	NA	NA	NA	2.9 (−8.6, 7.9) [$n = 10$]	−1.3 (−30.1, 26.1) [$n = 4$]	2.9 (−6.6, 8.1) [$n = 6$]

Variable	Group 1 (MM) Overall $n = 31$	Group 2 (EM) Overall $n = 15$
LVMi in patients with LVH at baseline, g/m^2, median (95% CI)[b]		
Baseline[a]	109.8 (95.9, 165.7) [$n = 11$]	124.2 (107.3, 129.1) [$n = 4$]
Baseline-Month 30	−11.3 (−16.6, −3.3) [$n = 10$]	NA
Initial 18 months	NA	3.2 (−33.6, 41.4) [$n = 4$]
12-month open-label extension	NA	−3.2 (−28.7, 21.2) [$n = 4$]
MWFS, % (95% CI)		
Baseline[a]	15.7 (11, 21) [$n = 30$]	16.8 (9, 21) [$n = 13$]
Baseline-Month 30	−0.3 (−1.2, 0.6) [$n = 29$]	NA
Initial 18 months	NA	−0.3 (−1.6, 0.9) [$n = 13$]
12-month open-label extension	NA	0.1 (−1.0, 1.0) [$n = 13$]

CI, confidence interval; EM, ERT to migalastat treatment; ERT, enzyme replacement therapy; LVH, left ventricular hypertrophy; LVMi, left ventricular mass index; MM, migalastat to migalastat treatment; MWFS, midwall fractional shortening, NA, not assessed.

[a] Median (range) shown for baseline values.

[b] LVMi in patients with LVH at baseline and MWFS were not calculated for male and female patients separately.

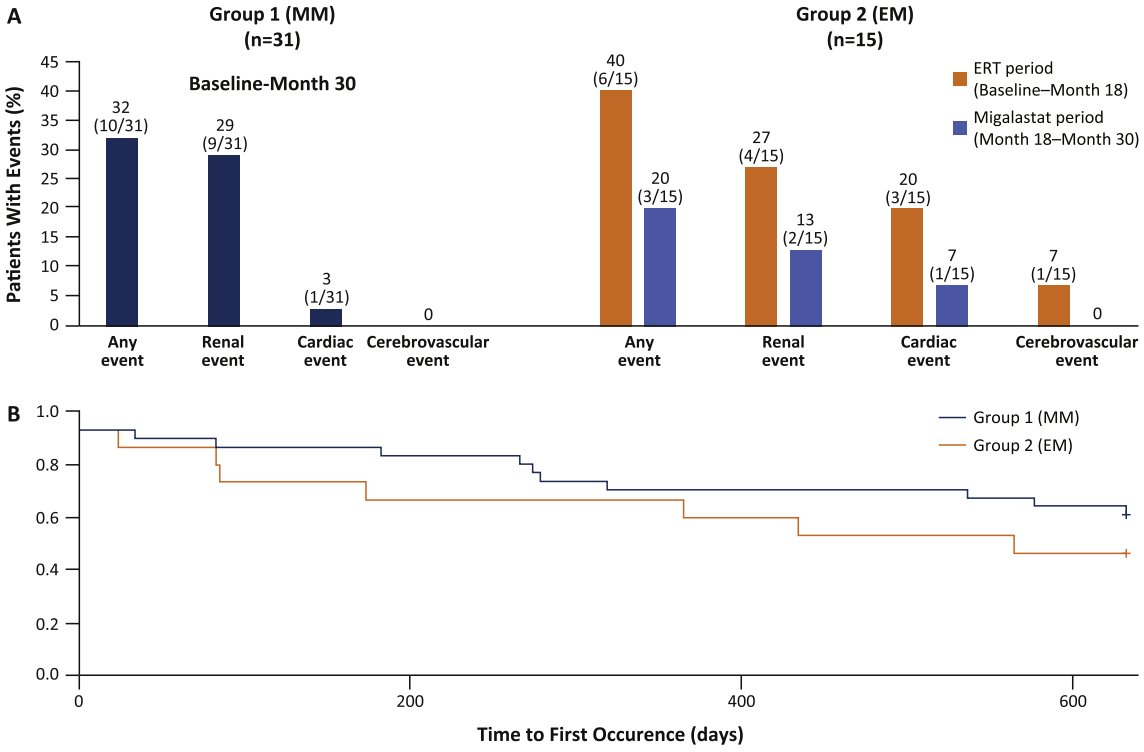

Fig. 3. Composite clinical outcome (open-label extension population; patients with amenable variants only); (A) incidence of composite clinical outcome event and (B) time to first event.

$eGFR_{CKD\text{-}EPI}$, estimated glomerular filtration rate assessed by the Chronic Kidney Disease Epidemiology Collaboration equation; EM, ERT to migalastat treatment; ERT, enzyme replacement therapy; MM, migalastat to migalastat treatment.

[a]Renal event was defined as a decrease in $eGFR_{CKD\text{-}EPI}$ ≥15 mL/min/1.73 m^2 relative to baseline, with the decreased $eGFR_{CKD\text{-}EPI}$ < 90 mL/min/1.73 m^2, or an increase in 24-h urine protein ≥33% relative to baseline, with the increased protein ≥300 mg/24 h. Cardiac events included myocardial infarction; unstable cardiac angina (defined by the American College of Cardiology/American Heart Association national practice guidelines); new symptomatic arrhythmia necessitating anti-arrhythmic medication, direct current cardioversion, pacemaker, or defibrillator implantation; or congestive heart failure, New York Heart Association Class III or IV. Cerebrovascular events included stroke and transient ischemic attack.

[b]A patient may have appeared in more than one event but was counted once in the composite outcome.

[c]For month 18-Month 30, only Group 2 EM patients with new events during the migalastat period are shown.

patient-years; 6/31 (19.4%) patients in Group 1 had renal events and 1/31 (3.2%) had cardiac events. During the subsequent 12-month open-label extension period, 29.0% (9/31) of Group 1 patients had renal events but no cardiac events; only 3 patients experienced a new event relative to the initial 18-month period. No patient in Group 1 had events in 2 or more categories. There were no cerebrovascular events or deaths during the 30-month study period. The mean time to first occurrence of any event in the composite clinical outcome was 318.5 days (Fig. 3B).

During the initial 18-month period, when patients in Group 2 (EM) were receiving ERT, 6/15 (40.0%) had a renal, cardiac, or cerebrovascular event (17 events total) (Fig. 3A), averaging 791 events per 1000 patient-years. Two patients had renal events only, 1 patient had cardiac events only, 2 patients had both renal and cardiac events, and 1 patient had a cerebrovascular event. During the subsequent 12-month

Table 3
Summary of safety (Open-label extension population).

Variable, *n* (%)	Group 1 (MM)	Group 2 (EM)	
	Months 0–30	Months 0–18	Months 18–30
No. of patients	33[a]	15	15
≥1 TEAE	32 (97.0)	15 (100)	15 (100)
≥1 TEAE potentially related to treatment	14 (42.4)	3 (20.0)	4 (26.7)
≥1 serious TEAE	11 (33.3)	7 (46.7)	3 (20.0)
Discontinuation due to TEAE	0	0	0
TEAE leading to death	0	0	0
Maximum severity of TEAE			
Mild	10 (30.3)	4 (26.7)	5 (33.3)
Moderate	16 (48.5)	9 (60.0)	8 (53.3)
Severe	6 (18.2)	2 (13.3)	2 (13.3)

EM, ERT to migalastat treatment; ERT, enzyme replacement therapy; MM, migalastat to migalastat treatment; TEAE, treatment-emergent adverse event.

[a] Includes 2 patients who were subsequently found to have non-amenable variants by Good Laboratory Practice-validated migalastat amenability assay.

open-label extension period, when Group 2 patients received migalastat, 6/15 (40.0%) experienced a composite clinical outcome (27 events total), averaging 1516 events per 1000 patient-years. Five patients had renal events only and 1 patient had both renal and cardiac events. Only 3 of these patients had new events relative to the initial 18-month period: 2 were renal events (including 1 event of a GFR measurement that was considered an outlier in the context of previous and subsequent GFR values in the same patient) and 1 was a cardiac event (Fig. 3A). The mean time to first occurrence of any event in the composite clinical outcome in Group 2 was 246.9 days (Fig. 3B). No patient in Group 2 died during the 30-month study period.

3.2.4. Plasma lyso-Gb_3 level

Plasma lyso-Gb_3 levels remained low in both treatment groups over 30 months. In Group 1 (MM), the mean change from baseline to month 30 was 3.6 nmol/L (median: 0.8; 95% CI: −1.5, 8.7). In Group 2 (EM), there was no significant change from baseline to month 18 when patients were receiving ERT (mean change: −1.3 nmol/L; median: −0.03; 95% CI: −3.8, 1.2) and during the subsequent 12-month open-label migalastat treatment period (mean change: 4.9 nmol/L; median: 1.5; 95% CI: −4.1, 13.9).

3.2.5. White blood cell α-Gal A activity

Male patients in Group 1 (MM; $n = 14$) had a significant increase in white blood cell α-G activity from baseline to month 30 (mean change from baseline: 4.1 nmol/h/mg; median: 3.5; 95% CI: 1.9, 6.3). In males in Group 2 (EM), white blood cell α-Gal A activity remained stable from baseline to month 18 during ERT treatment ($n = 5$; mean: −0.6 nmol/h/mg; median: 0.07; 95% CI: −2.7, 1.5) and after 12 months of open-label migalastat treatment ($n = 4$; mean: 3.4 nmol/h/mg; median: 2.3; 95% CI: −2.7, 9.4).

3.3. Safety

The mean and median durations of migalastat exposure were 31.0 and 29.7 months in Group 1 (MM; $n = 33$) and 14.3 and 15.2 months in Group 2 (EM; $n = 15$). The mean and median durations of exposure during the open-label extension period were comparable between the treatment groups (Group 1: 13.2 and 12.0 months; Group 2: 14.3 and 15.2 months).

A summary of treatment-emergent AEs is shown in Table 3. In Group 1 (MM), 32 patients (97.0%) experienced ≥1 treatment-emergent AE at any time in the study, of which 14 (42.4%) were thought to be potentially treatment related. Most treatment-emergent AEs were mild or moderate in severity; however, 11 patients (33.3%) experienced ≥1 serious AE (SAE). In Group 2 (EM), all 15 patients (100%) experienced ≥1 treatment-emergent AE both during the 18-month randomized treatment period and during the open-label extension period. The frequency of SAEs was greater during months 0–18 compared with months 18–30 (46.7% vs 20.0%). No patients in either treatment group died or discontinued from the study due to a treatment-emergent AE.

In Group 1 (MM), the most frequently reported treatment-emergent AEs (in ≥25% of patients) between baseline and month 30 were nasopharyngitis (42%), headache (36%), and influenza (27%). The most frequently reported treatment-emergent AE potentially related to treatment was headache, which occurred in 6 patients in Group 1 (18%). In Group 2 (EM), nasopharyngitis was the only treatment-emergent AE that occurred in ≥25% of patients (27%) during the initial 18-month ERT treatment period; none was thought to be treatment-related. The most frequent treatment-emergent AEs during the subsequent 12-month open-label extension migalastat treatment period were nasopharyngitis (33%), vomiting (27%), and diarrhea (27%); no treatment-emergent AE potentially related to treatment occurred in more than 1 patient in Group 2. No clinically relevant effect of migalastat and no clinically relevant treatment group differences were noted for any laboratory test, ECG variable, vital sign, or physical finding.

4. Discussion

The aim of the ATTRACT study was to investigate the efficacy and safety of migalastat HCl 150 mg every other day in patients with Fabry disease who had previously been treated with ERT. Data from the 18-month randomized treatment period demonstrated that compared with ERT, migalastat had comparable effects on renal function and a possible superior effect on reducing cardiac mass; moreover, the percentage of patients experiencing Fabry-associated clinical events was numerically lower with migalastat versus ERT. Migalastat was generally safe and well-tolerated over 18 months of treatment [18]. The current analysis of data from the 12-month open-label extension period suggests that migalastat efficacy was maintained over 30 months of treatment, with no new safety concerns.

Assessment of renal function in amenable Group 1 (MM) patients showed durability of the response to migalastat with long-term treatment, further supporting the clinical efficacy of migalastat. Compared with healthy individuals, patients with Fabry disease experience decline in eGFR at an earlier age and more rapidly, particularly in men. Studies of untreated patients with Fabry disease reported annualized changes in eGFR of up to −7 mL/min/1.73 m^2 [22,23]. Long-term (2–7 years) use of ERT has been shown to slow or stabilize the decline in renal function, with annualized rates of change in eGFR of −0.8 to −3.7 mL/min/1.73 m^2 [8,24–28]. Over 30 months of treatment in the ATTRACT study, eGFR remained stable with migalastat in both Group 1 (MM) and Group 2 (EM) patients, with mean annualized rates of change of −1.7 and −2.1 mL/min/1.73 m^2, respectively. A potential study limitation is that data were not analyzed by age subgroups, as the rate of decline in renal function was shown to be associated with age [28], although the mean baseline ages of patients in our study were similar in Group 1 and Group 2 (50.3 and 45.3 years, respectively).

Cardiac disease has replaced renal disease as the most frequent cause of death in patients with Fabry disease in recent years [29]. Left ventricular hypertrophy is the greatest risk factor for cardiac events in Fabry disease [30], and its improvement positively impacts cardiovascular morbidity and mortality in hypertensive heart disease [31,32]. Although ERT has demonstrated effects in stabilizing or even improving cardiac structure based on left ventricular mass or LVMi measurements in some studies [33–36], available data were mostly from observational studies and the effects were markedly variable. Recently, a retrospective Danish nationwide cohort study of patients with Fabry disease showed no significant difference between the ERT-treated and non-ERT groups in the progression of myocardial involvement based on LVMi [37]. Thus, data regarding the benefit of ERT on cardiac involvement in Fabry disease remain equivocal and warrant further research. It was also observed that ERT did not appear to provide notable benefit in the subset of patients with left ventricular hypertrophy [35].

In the current study, migalastat treatment was shown to reduce cardiac mass in ERT-experienced patients (Group 1) with baseline left ventricular hypertrophy. In contrast, cardiac mass remained stable in Group 2 (EM) patients with baseline left ventricular hypertrophy during ERT treatment (months 0–18). These results suggest that switching to migalastat treatment from ERT can lead to sustained improvements in cardiac structure in patients with left ventricular hypertrophy, who are at increased risk of cardiac events [30]. The mean change in LVMi after switching from ERT to migalastat during the open-label extension period in Group 2 (−0.3 g/m^2; 95% CI: −8.6, 7.9) was less pronounced than that of patients who switched from ERT to migalastat treatment at the beginning of the ATTRACT study (ie, during the initial randomized 18-month period: −6.6 g/m^2; 95% CI: −11.0, −2.2) [18]. Given that the duration of migalastat treatment was 12 months for the EM group in this study compared with 18 months for the randomized period, it is possible that the shorter duration of migalastat treatment in this study contributed to the smaller change in LVMi. In addition, the proportion of patients with LVH, who demonstrated greater decreases in LVMi compared with the overall study population, was higher among patients

switched at the beginning of ATTRACT vs patients in the EM group (39.4% [13/33] vs 26.7% [4/15] patients) [18]. The number of patients in the EM group ($n = 15$) was smaller than the number of patients switched at the beginning of ATTRACT ($n = 33$) and results from the latter may be more representative of patients switching from ERT to migalastat.The beneficial long-term effects on cardiac architecture suggest that migalastat has the potential to reduce the risk of cardiac complications associated with Fabry disease. Interpretation of these data is limited by the low number of patients with left ventricular hypertrophy at baseline and the wide range of LVMi values observed in this group.

The effects of migalastat therapy on renal and cardiac diseases in patients with Fabry disease and amenable variants have been reported outside of clinical trials in 2 studies. In a German single-center study of 14 patients (11 males and 3 females) with Fabry disease who received migalastat therapy for 12 months, the mean change in eGFR was −9 and −4 mL/min/1.73 m^2 in male and female patients, respectively [38]. Expanding that study, results from multiple centers in Germany reported a mean change in eGFR of −5 and −7 mL/min/1.73 m^2 for 31 male and 28 female patients (62% ERT-experienced), respectively, following 12 months of migalastat treatment [39]. Both of these studies reported a substantial reduction in LVMi: Müntze et al. reported a mean change in LVMi of −19.0 and −9.0 g/m^2 in male and female patients, respectively [38]; Lenders et al. reported a mean change in LVMi of −13.7 and −7.2 g/m^2 in male and female patients, respectively [39]. Compared with the results from the current report, the 2 German studies demonstrated greater decline in renal function and comparable or better improvement in cardiac mass. The differences in the results may reflect differences in the patient populations studied. For example, patients in the multicenter study may have had greater renal involvement given that renin-angiotensin inhibitor use was substantially higher in these patients compared with those of the current report (72.1% [31/43] vs 45.5% [15/33]). The percentage of patients with LVH was lower in the current study compared with the multicenter study (32.6% [15/46] vs 55.4% [31/56]) and may explain why reductions in LVMi were more pronounced in the latter [39]. In addition, single-center studies, although informative, may not be generalizable as they do not include a variety of practice patterns that are observed in the real-world setting across multiple centers and regions. Future studies assessing the effects of long-term migalastat therapy on cardiac and renal function are warranted.

Composite clinical endpoints have been used in several prospective trials and retrospective analyses in Fabry disease to evaluate outcomes with or without ERT; however, variation of the specific measures across studies limits the ability to draw meaningful comparisons [33]. The incidence of composite clinical outcome in patients who received placebo in one study was reported to be 42% over a study duration of up to 35 months [40], whereas incidence of 16–37% have been reported in cohorts of patients receiving ERT over durations of 24–120 months, suggesting improved composite outcomes following ERT treatment [8,25,33,40–42]. Due to the rarity of events, data on the respective effectiveness of ERT for preventing renal, cardiac, or cerebrovascular events are inconclusive. Because ERT may not effectively penetrate the blood vessel wall beyond the endothelium [43], its impact on cerebrovascular complications and other effects resulting from Fabry vasculopathy is expected to be limited. Interestingly, stroke was the most frequent event (9.6%) during a 10-year follow-up of 52 agalsidase beta-treated patients [42]; in contrast, a randomized controlled study showed that stroke or transient ischemic attack were less frequent (6.5%) than cardiac or renal events in 31 untreated patients [40]. Weidemann et al. reported that 6/40 ERT-treated patients suffered cardiac death over 6 years and overall event rates were not different between the ERT-treated group and an untreated control group from the Fabry Registry [25]. During the initial 18-month period in ATTRACT, the composite clinical outcome incidence with migalastat (23%) appeared to be reduced by around half when compared with the historical placebo cohort [40], whereas incidence in the ERT-treated group (40%) was relatively high compared with published data. During the 12-month migalastat open-label extension, few patients experienced a new event: 3 patients in Group 1 (MM; all renal) and 3 patients in Group 2 (EM; 2 renal, 1 cardiac). Future research needs to evaluate the impact of migalastat on clinical outcomes in larger patient populations.

Consistent with results from the randomized treatment period [18], plasma lyso-Gb_3 levels remained low in both groups throughout the study. Notably, however, lyso-Gb_3 has not been validated as a biomarker for monitoring treatment outcome, and a retrospective study of long-term outcomes with ERT found that neither absolute nor relative changes in lyso-Gb_3 were associated with risk of clinical events during ERT [44]. Multiple factors may impact the magnitude and temporal profile of lyso-Gb_3 changes observed with migalastat and ERT, including disparate penetration into different tissues. ERT preferentially targets the liver (which has large stores of lyso-Gb_3) [45,46]; in contrast, migalastat has broad tissue distribution [16], and thus its impact on lyso-Gb_3 is based on a broad, multi-organ effect. It is also possible that other Gb_3 analogues correlate better with Fabry disease activity than lyso-Gb_3 [47].

One of the strengths of the ATTRACT study was that the baseline characteristics of the patients enrolled and treated were comparable to those of the general Fabry population, as reported in the Fabry Outcomes Survey [48,49] and the Fabry Registry [50], suggesting that the beneficial outcomes reported herein could also be expected in the real-world patient population. Moreover, the current 30-month data add to our knowledge of long-term safety and efficacy of migalastat. Another strength of the ATTRACT study is the large number of patients relative to those included in phase 3 studies of agalsidase beta as well as the inclusion of more female patients [34,51]. Nevertheless, the patient subgroups in the study were limited in size and the findings are descriptive only. Additional limitations include the lack of adjustments for multiplicity in the analyses, lack of patient stratification by phenotype (classic or late-onset), and unknown anti-ERT antibody status of patients. Future studies should explore symptoms of Fabry disease that have not been addressed here, such as pain, hearing, and gastrointestinal findings. In addition, the benefit of being able to take therapy orally rather than intravenously should be investigated, in particular with regard to quality of life, work productivity, and burden of therapy.

5. Conclusions

In ERT-experienced patients with Fabry disease and an amenable *GLA* variant, switching to migalastat HCl 150 mg every other day was safe and well tolerated over 30 months, demonstrating durable, long-term stability of renal function in the overall patient group and reduction in LVMi in patients with left ventricular hypertrophy. Few patients experienced new Fabry-associated clinical events during the 12-month migalastat open-label extension period.

Declaration of competing interest

UFR has served on advisory boards for Amicus Therapeutics, Shire, Freeline, and Sanofi Genzyme, as a speaker for Amicus Therapeutics and Sanofi Genzyme, and has received research funding from Shire, Amicus Therapeutics, and Sanofi Genzyme. DH has received honoraria and research funding from Amicus Therapeutics, Shire, Sanofi Genzyme, Protalix, and Actelion. GSP has served on advisory boards for Amicus Therapeutics and Greenovation, as a speaker for Sanofi Genzyme, and has received research funding from Amicus Therapeutics, Idorsia, and Shire. SS has served as an investigator for Amicus Therapeutics. K Nedd received fees from Sanofi Genzyme and Shire-Takeda. IO has received research funding from and served as a speaker for Shire, Sanofi Genzyme, and MyoKardia. DO has served on advisory boards for Sanofi Genzyme. TH has nothing to disclose. TO has received research funding from DSP, Sanofi Genzyme, and Avrobio. NS,

JY, and JAB are employees of and hold stock in Amicus Therapeutics. K Nicholls has served on advisory boards for Amicus Therapeutics, Sanofi Genzyme, and Shire, as a speaker for Amicus Therapeutics, and has received research funding from Sanofi Genzyme and Shire.

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Author contributions

UFR, DH, TO, NS, JAB participated in study design; UFR, DH, GSP, SS, K Nedd, IO, DO, TO, TH, K Nicholls, JY assisted in the acquisition of data; DH, SS, NS, JY, JAB analyzed and interpreted the data; UFR, DH, K Nicholls, SS, NS drafted the article; all authors critically revised the manuscript; all authors gave final approval of the submitted version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data availability statement

All data relevant to the current analysis of this study are included in the article or uploaded as supplementary information.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2020.07.007.

References

[1] D.P. Germain, Fabry disease, Orphanet J. Rare Dis. 5 (2010) 30.
[2] R.J. Desnick, Y. Ioannou, C.M. Eng, a-Galactosidase A deficiency: Fabry disease, in: D. Valle (Ed.), The Online Metabolic and Molecular Bases of Inherited Disease, McGraw-Hill Companies, Inc., 2016.
[3] P. Rozenfeld, S. Feriozzi, Contribution of inflammatory pathways to Fabry disease pathogenesis, Mol. Genet. Metab. 122 (2017) 19–27.
[4] Amicus Therapeutics, Inc, Galafold® (Migalastat) Amenability Table, http://www.galafoldamenabilitytable.com/hcp.
[5] P.J. Meikle, J.J. Hopwood, A.E. Clague, W.F. Carey, Prevalence of lysosomal storage disorders, JAMA 281 (1999) 249–254.
[6] R. Schiffmann, M. Ries, Fabry disease: a disorder of childhood onset, Pediatr. Neurol. 64 (2016) 10–20.
[7] T. Alegra, F. Vairo, M.V. de Souza, B.C. Krug, I.V. Schwartz, Enzyme replacement therapy for Fabry disease: a systematic review and meta-analysis, Genet. Mol. Biol. 35 (2012) 947–954.
[8] S.M. Sirrs, D.G. Bichet, R. Casey, J.T. Clarke, K. Lemoine, S. Doucette, et al., Outcomes of patients treated through the Canadian Fabry disease initiative, Mol. Genet. Metab. 111 (2014) 499–506.
[9] M. Lenders, J. Stypmann, T. Duning, B. Schmitz, S.M. Brand, E. Brand, Serum-mediated inhibition of enzyme replacement therapy in Fabry disease, J. Am. Soc. Nephrol. 27 (2016) 256–264.
[10] C.J. Hendriksz, P. Harmatz, R. Giugliani, J. Roberts, G.S. Arul, Risks of long-term port use in enzyme replacement therapy for lysosomal storage disorders, Mol. Genet. Metab. Rep. 15 (2018) 71–73.
[11] S. De Portu, A. Pisani, A. Scalzone, B. Cianciaruso, L.G. Mantovani, Economic impacts of the Fabry-Anderson disease treatment, Value Health 11 (2008) A638. Abstract PSY31.
[12] R. Santamaria, J. De Juan-Ribera, F. Martinez-Sanchez, V. Pendon-Ruiz De Mier, C. Gil-Garcia, M.J. Lopez-Ruiz, et al., Burden of disease in patients with Fabry disease-economic burden of health care resources consumption, Nephrol. Dial. Transplant. 34 (Suppl. 1) (2019). Abstract FP136.
[13] G.H. Yam, C. Zuber, J. Roth, A synthetic chaperone corrects the trafficking defect and disease phenotype in a protein misfolding disorder, FASEB J. 19 (2005) 12–18.
[14] S. Ishii, H.H. Chang, K. Kawasaki, K. Yasuda, H.L. Wu, S.C. Garman, et al., Mutant alpha-galactosidase A enzymes identified in Fabry disease patients with residual enzyme activity: biochemical characterization and restoration of normal intracellular processing by 1-deoxygalactonojirimycin, Biochem. J. 406 (2007) 285–295.
[15] Galafold [Prescribing Information], Amicus Therapeutics, Inc., Cranbury, NJ, 2020.
[16] F.K. Johnson, P.N. Mudd Jr., A. Bragat, M. Adera, P. Boudes, Pharmacokinetics and safety of migalastat HCl and effects on agalsidase activity in healthy volunteers, Clin. Pharmacol. Drug Devel. 2 (2013) 120–132.
[17] D.P. Germain, D.A. Hughes, K. Nicholls, D.G. Bichet, R. Giugliani, W.R. Wilcox, et al., Treatment of Fabry's disease with the pharmacologic chaperone migalastat, N. Engl. J. Med. 375 (2016) 545–555.
[18] D.A. Hughes, K. Nicholls, S.P. Shankar, G. Sunder-Plassmann, D. Koeller, K. Nedd, et al., Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study, J. Med. Genet. 54 (2017) 288–296.
[19] G. Sunder-Plassmann, R. Schiffmann, K. Nicholls, Migalastat for the treatment of Fabry disease, Expert Opin. Orphan Drugs. 6 (2018) 301–309.
[20] E.R. Benjamin, M.C. Della Valle, X. Wu, E. Katz, F. Pruthi, S. Bond, et al., The validation of pharmacogenetics for the identification of Fabry patients to be treated with migalastat, Genet. Med. 19 (2017) 430–438.
[21] L. Echevarria, K. Benistan, A. Toussaint, O. Dubourg, A.A. Hagege, D. Eladari, et al., X-chromosome inactivation in female patients with Fabry disease, Clin. Genet. 89 (2016) 44–54.
[22] C. Wanner, J.P. Oliveira, A. Ortiz, M. Mauer, D.P. Germain, G.E. Linthorst, et al., Prognostic indicators of renal disease progression in adults with Fabry disease: natural history data from the Fabry Registry, Clin. J. A. Soc. Nephrol. 5 (2010) 2220–2228.
[23] R. Schiffmann, D.G. Warnock, M. Banikazemi, J. Bultas, G.E. Linthorst, S. Packman, et al., Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy, Nephrol. Dial. Transplant. 24 (2009) 2102–2111.
[24] L.J. Anderson, K.M. Wyatt, W. Henley, V. Nikolaou, S. Waldek, D.A. Hughes, et al., Long-term effectiveness of enzyme replacement therapy in Fabry disease: results from the NCS-LSD cohort study, J. Inherit. Metab. Dis. 37 (2014) 969–978.
[25] F. Weidemann, M. Niemann, S. Stork, F. Breunig, M. Beer, C. Sommer, et al., Long-term outcome of enzyme-replacement therapy in advanced Fabry disease: evidence for disease progression towards serious complications, J. Intern. Med. 274 (2013) 331–341.
[26] O. Goker-Alpan, K. Nedd, S.P. Shankar, Y.H. Lien, N. Weinreb, A. Wijatyk, et al., Effect and tolerability of agalsidase alfa in patients with Fabry disease who were treatment naive or formerly treated with agalsidase beta or agalsidase alfa, JIMD Rep. 23 (2015) 7–15.
[27] M. Lenders, B. Schmitz, J. Stypmann, T. Duning, S.M. Brand, C. Kurschat, et al., Renal function predicts long-term outcome on enzyme replacement therapy in patients with Fabry disease, Nephrol. Dial. Transplant. 32 (2017) 2090–2097.
[28] C.V. Madsen, H. Granqvist, J.H. Petersen, A.K. Rasmussen, A.M. Lund, P. Oturai, et al., Age-related renal function decline in Fabry disease patients on enzyme replacement therapy: a longitudinal cohort study, Nephrol. Dial. Transplant. 34 (2018) 1525–1533.
[29] A. Mehta, J.T. Clarke, R. Giugliani, P. Elliott, A. Linhart, M. Beck, et al., Natural course of Fabry disease: changing pattern of causes of death in FOS - Fabry Outcome Survey, J. Med. Genet. 46 (2009) 548–552.
[30] M.R. Patel, F. Cecchi, M. Cizmarik, I. Kantola, A. Linhart, K. Nicholls, et al., Cardiovascular events in patients with fabry disease natural history data from the fabry registry, J. Am. Coll. Cardiol. 57 (2011) 1093–1099.
[31] R.E. Katholi, D.M. Couri, Left ventricular hypertrophy: major risk factor in patients with hypertension: update and practical clinical applications, Int. J. Hypertens. 2011 (2011) 495349.
[32] S.D. Pierdomenico, F. Cuccurullo, Risk reduction after regression of echocardiographic left ventricular hypertrophy in hypertension: a meta-analysis, Am. J. Hypertens. 23 (2010) 876–881.
[33] M. Beck, D. Hughes, C. Kampmann, S. Larroque, A. Mehta, G. Pintos-Morell, et al., Long-term effectiveness of agalsidase alfa enzyme replacement in Fabry disease: a Fabry Outcome Survey analysis, Mol. Genet. Metab. Rep. 3 (2015) 21–27.
[34] D.A. Hughes, P.M. Elliott, J. Shah, J. Zuckerman, G. Coghlan, J. Brookes, 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 94 (2008) 153–158.
[35] D.P. Germain, F. Weidemann, A. Abiose, M.R. Patel, M. Cizmarik, J.A. Cole, et al., Analysis of left ventricular mass in untreated men and in men treated with agalsidase-beta: data from the Fabry Registry, Genet. Med. 15 (2013) 958–965.
[36] C. Kampmann, A. Perrin, M. Beck, Effectiveness of agalsidase alfa enzyme replacement in Fabry disease: cardiac outcomes after 10 years' treatment, Orphanet J. Rare Dis. 10 (2015) 125.
[37] C.V. Madsen, H. Bundgaard, A.K. Rasmussen, S.S. Sorensen, J.H. Petersen, L. Kober, et al., Echocardiographic and clinical findings in patients with Fabry disease during long-term enzyme replacement therapy: a nationwide Danish cohort study, Scand. Cardiovasc. J. 51 (2017) 207–216.
[38] J. Muntze, D. Gensler, O. Maniuc, D. Liu, T. Cairns, D. Oder, et al., Oral chaperone therapy migalastat for treating Fabry disease: enzymatic response and serum

biomarker changes after 1 year, Clin. Pharmacol. Ther. 105 (2019) 1224–1233.
[39] M. Lenders, P. Nordbeck, C. Kurschat, N. Karabul, J. Kaufeld, J.B. Hennermann, et al., Treatment of Fabry's disease with migalastat: outcome from a prospective observational multicenter study (FAMOUS), Clin. Pharmacol. Ther. 108 (2020) 326–337.
[40] M. Banikazemi, J. Bultas, S. Waldek, W.R. Wilcox, C.B. Whitley, M. McDonald, et al., Agalsidase-beta therapy for advanced Fabry disease: a randomized trial, Ann. Intern. Med. 146 (2007) 77–86.
[41] M. Arends, M. Biegstraaten, C. Wanner, S. Sirrs, A. Mehta, P.M. Elliott, et al., Agalsidase alfa versus agalsidase beta for the treatment of Fabry disease: an international cohort study, J. Med. Genet. 55 (2018) 351–358.
[42] D.P. Germain, J. Charrow, R.J. Desnick, N. Guffon, J. Kempf, R.H. Lachmann, et al., Ten-year outcome of enzyme replacement therapy with agalsidase beta in patients with Fabry disease, J. Med. Genet. 52 (2015) 353–358.
[43] R. Schiffmann, D.F. Moore, Neurological effects of enzyme replacement therapy in Fabry disease, in: A. Mehta (Ed.), Fabry Disease: Perspectives from 5 Years of FOS, Oxford PharmaGenesis, 2006.
[44] M. Arends, M. Biegstraaten, D.A. Hughes, A. Mehta, P.M. Elliott, D. Oder, et al., Retrospective study of long-term outcomes of enzyme replacement therapy in Fabry disease: analysis of prognostic factors, PLoS One 12 (2017) e0182379.
[45] R. Schiffmann, G.J. Murray, D. Treco, P. Daniel, M. Sellos-Moura, M. Myers, et al., Infusion of alpha-galactosidase A reduces tissue globotriaosylceramide storage in patients with Fabry disease, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 365–370.
[46] Replagal [Summary of Product Characteristics], Shire Pharmaceuticals Ireland Limited, Dublin, Ireland, 2016.
[47] M. Boutin, C. Auray-Blais, Multiplex tandem mass spectrometry analysis of novel plasma lyso-Gb(3)-related analogues in Fabry disease, Anal. Chem. 86 (2014) 3476–3483.
[48] A. Mehta, R. Ricci, U. Widmer, F. Dehout, A. Garcia de Lorenzo, C. Kampmann, et al., Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey, Eur. J. Clin. Investig. 34 (2004) 236–242.
[49] M. Beck, Demographics of FOS – the Fabry Outcome Survey, in: A. Mehta (Ed.), Fabry Disease: Perspectives from 5 Years of FOS, Oxford PharmaGenesis, 2006.
[50] C.M. Eng, J. Fletcher, W.R. Wilcox, S. Waldek, C.R. Scott, D.O. Sillence, et al., Fabry disease: baseline medical characteristics of a cohort of 1765 males and females in the Fabry Registry, J. Inherit. Metab. Dis. 30 (2007) 184–192.
[51] R. Schiffmann, J.B. Kopp, H.A. Austin 3rd, S. Sabnis, D.F. Moore, T. Weibel, et al., Enzyme replacement therapy in Fabry disease: a randomized controlled trial, JAMA 285 (2001) 2743–2749.