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Long-term multisystemic efficacy of migalastat on Fabry-associated clinical events, including renal, cardiac and cerebrovascular outcomes

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ABSTRACT

Background Fabry disease is a rare, multisystemic disorder caused by *GLA* gene variants that lead to alpha galactosidase A deficiency, resulting in accumulation of glycosphingolipids and cellular dysfunction. Fabry-associated clinical events (FACEs) cause significant morbidity and mortality, yet the long-term effect of Fabry therapies on FACE incidence remains unclear.

Methods This *posthoc* analysis evaluated incidence of FACEs (as a composite outcome and separately for renal, cardiac and cerebrovascular events) in 97 enzyme replacement therapy (ERT)-naïve and ERT-experienced adults with Fabry disease and amenable *GLA* variants who were treated with migalastat for up to 8.6 years (median: 5 years) in Phase III clinical trials of migalastat. Associations between baseline characteristics and incidence of FACEs were also evaluated.

Results During long-term migalastat treatment, 17 patients (17.5%) experienced 22 FACEs and there were no deaths. The incidence rate of FACEs was 48.3 events per 1000 patient-years overall. Numerically higher incidence rates were observed in men versus women, patients aged >40 years versus younger patients, ERT-naïve versus ERT-experienced patients and men with the classic phenotype versus men and women with all other phenotypes. There was no statistically significant difference in time to first FACE when analysed by patient sex, phenotype, prior treatment status or age. Lower baseline estimated glomerular filtration rate (eGFR) was associated with an increased risk of FACEs across patient populations.

Conclusions The overall incidence of FACEs for patients during long-term treatment with migalastat compared favourably with historic reports involving ERT. Lower baseline eGFR was a significant predictor of FACEs.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Fabry disease is a rare, inherited disorder that can cause multisystem organ dysfunction and can lead to serious renal and cardiac events, such as myocardial infarction, arrhythmia, renal insufficiency and stroke. Typically, Fabry disease clinical trials include a relatively small number of patients due to the rarity of the condition.

WHAT THIS STUDY ADDS

⇒ Using pooled data from clinical trials of migalastat, this *posthoc* study assessed the multisystemic efficacy and safety profile of migalastat in a large group of patients with Fabry disease over a prolonged duration. Incidence rates of Fabry-associated clinical events in migalastat-treated patients were low overall (48.3 per 1000 patient-years, n=97) and for renal, cardiac and cerebrovascular events individually (4.4, 30.7 and 13.2 per 1000 patient-years, respectively) and were comparable to those from previous trials with enzyme replacement therapy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Data from this study suggest that migalastat is an effective long-term treatment option for patients with Fabry disease.

INTRODUCTION

Fabry disease is a multisystemic lysosomal disorder caused by *GLA* variants that result in functional deficiency of alpha galactosidase A (α-Gal A). This deficiency leads to progressive accumulation of glycosphingolipids, predominantly globotriaosylceramide (Gb3), throughout the body,[1 2] and to irreversible tissue injury via promotion of chronic inflammation and fibrosis.[2] This cascade can ultimately cause damage to multiple tissues and organs, including the heart, kidneys, vasculature and peripheral and central nervous systems.

Fabry disease affects both men and women, encompassing a wide spectrum of clinical presentations with regard to age of onset, disease severity and organ involvement.[1] While there is no single accepted definition of the 'classic' phenotype, patients with the early-onset 'classic' presentation of Fabry disease, who are mostly male, have absent or extremely low α-Gal A activity, resulting in onset of symptoms in childhood or adolescence followed by progressive multiorgan failure and eventually premature death if untreated.[3] Patients with late-onset presentation of Fabry disease comprised a larger group of patients (both male and female)

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with higher levels of residual α-Gal A activity and variable clinical symptoms.[3–5]

Fabry-associated clinical events (FACEs; renal, cardiac, cerebrovascular events) are associated with high morbidity and mortality in patients with Fabry disease.[6] Before Fabry-specific treatment was available, the most common causes of death among patients with Fabry disease were complications of renal failure in men and cerebrovascular events (stroke or transient ischaemic attack) and heart disease in women.[7] Later data from the Fabry Registry (2001–2008) showed that cardiovascular disease was the most common cause of death among both sexes, followed by cerebrovascular disease and renal disease.[6] In a retrospective multicentre study of 499 adults with Fabry disease, the rates of cardiac, cerebral and renal events were significantly higher in men with 'classic' disease than in men with late-onset disease.[8]

Currently approved therapies for Fabry disease include the oral pharmacological chaperone migalastat and infused enzyme replacement therapy (ERT) with agalsidase alfa and agalsidase beta. Clinical trial data have demonstrated the benefit of migalastat therapy in patients with Fabry disease and amenable *GLA* variants. In the randomised, 18-month ERT-controlled treatment period of the Phase III ATTRACT study (NCT01218659), patients who received migalastat had significant reductions in cardiac (left ventricular) mass and comparable changes in renal function compared with patients who received ERT; furthermore, the percentage of patients who experienced renal, cardiac and cerebrovascular events was numerically lower with migalastat compared with ERT.[9] Similar results were seen in the Phase III, randomised, placebo-controlled, double-blind FACETS trial (NCT00925301) in ERT-naïve patients. Specifically, in the subset of male patients with the classic phenotype and amenable *GLA* variants, there was a reduction in cardiac (left ventricular) mass and stabilisation of renal function up to 24 months with migalastat.[10] Integrated clinical trial data indicated that migalastat-treated patients (including men with the classic phenotype) maintained generally stable renal function for up to 8.6 years.[11]

FACEs are often life threatening and are associated with significant morbidity and mortality.[6 7] The long-term effects of migalastat therapy on the occurrence of FACEs have not yet been fully investigated. In this *posthoc* analysis, we used integrated data from clinical trials to assess the incidence of FACEs in ERT-naïve and ERT-experienced patients with Fabry disease and amenable *GLA* variants who were treated with migalastat for up to 8.6 years. The incidence of FACEs was assessed as a measure of the multisystemic efficacy of migalastat.

METHODS

Ethics statement

FACETS, ATTRACT, AT1001-041 and AT1001-042 were designed and monitored in accordance with the ethical principles of Good Clinical Practice and the Declaration of Helsinki. Clinical study protocols and the informed consent form were reviewed and approved by the appropriate Independent Ethics Committee/Institutional Review Board at each study site. All participants provided written informed consent prior to study initiation.

Study design and patients

This *posthoc* analysis included integrated data from ERT-naïve and ERT-experienced adult patients (aged 16–74 years) who had received migalastat treatment in Phase III clinical trials of migalastat, including the randomised, double-blind, placebo-controlled FACETS (NCT00925301) study,[12] the randomised, open-label, active-controlled ATTRACT study (NCT01218659)[9] and the open-label extension (OLE) studies (AT1001-041 (NCT01458119) and AT1001-042 (NCT02194985)) in which migalastat efficacy and safety were assessed for up to 5 additional years beyond the original studies (online supplemental figure S1). Study design and patient eligibility criteria of FACETS and ATTRACT have been previously published.[9 12] Briefly, eligible patients from FACETS had never received ERT or had not received ERT for at least 6 months,[12] and eligible patients from ATTRACT must have initiated ERT >12 months prior to the study.[9] All patients had genetically confirmed Fabry disease and had an amenable *GLA* variant based on the Good Laboratory Practice validated human embryonic kidney assay.[9 13] Patients had estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m^2 and had not undergone (or been scheduled to undergo) kidney transplantation or received dialysis. FACETS patients had urinary Gb3 levels at least four times the upper limit of the normal range.[12] Patients were excluded if they had clinically significant unstable cardiac disease (eg, symptomatic arrhythmia or New York Heart Association class III/IV congestive heart failure requiring active management) or have had a transient ischaemic attack, stroke, unstable angina or myocardial infarction within 3 months of the baseline visit of ATTRACT or AT1001-042, or within 12 months of the baseline visit of AT1001-041. Patients with clinically significant abnormal laboratory findings and clinically significant ECG findings at baseline were also ineligible. Patients with elevated troponin were not excluded as troponin was not evaluated in this study.

Assessment of FACEs

The following events were defined as FACEs and their occurrences were recorded: (1) renal events, which included doubling of serum creatinine levels from the start of baseline (where levels remained double or greater between two consecutive values) or end-stage renal disease requiring long-term dialysis or transplantation; (2) cardiac events, which included myocardial infarction; new symptomatic arrhythmia requiring medication, direct current cardioversion or an interventional procedure (eg, ablation, pacemaker or defibrillator implantation); unstable angina defined by national practice guidelines and accompanied by electrocardiographic changes; congestive heart failure requiring hospitalisation; any major cardiac medical procedure (eg, valve replacement, stent implantation, transplant or persistent atrial fibrillation) and (3) cerebrovascular events, including stroke or transient ischaemic attack as documented by a physician. Any death due to FACEs was recorded based on the FACE category. The baseline for all FACEs was defined as the start of migalastat treatment.

Statistical analysis

The data lock date for the AT1001-042 study was 9 March 2020, after which data were integrated across the entire Phase III+OLE programme. Analyses were performed on all patients with amenable variants treated with migalastat. Analyses were stratified by patient sex, prior treatment status (ERT naïve or ERT experienced) and age (≤40 and >40 years). ERT-naïve patients were stratified by phenotype: male patients were classified as having the classic phenotype if they had residual white blood cell (WBC) α-Gal A activity <3% of normal and multiorgan involvement, which was defined as involvement of ≥2 of the following organ systems: renal, cardiac, central nervous system, peripheral nervous system and gastrointestinal system.[10] The classification of

'other' included ERT-naïve male patients who did not meet the above criteria and all ERT-naïve female patients.[10] ERT-experienced male patients were not evaluated by phenotype because their baseline WBC α-Gal A activity may have been confounded by previous ERT. Instead, we analysed a subset of ERT-experienced male patients who had multiorgan involvement at baseline.

Incidence rate of FACEs was calculated as events per 1000 patient-years as a method of standardisation and to facilitate indirect comparisons across studies, as well as to account for the rarity of clinically significant events, differences in individual patient exposure of migalastat and the length of the study period. Time to first FACE (as composite events and separately for each event category) was assessed via Kaplan–Meier analysis and significance was tested using log-rank test. Descriptive statistics, including mean, median and standard deviation (SD), are also presented.

The association between baseline characteristics and the rate of FACEs was assessed using a Cox proportional hazards model. The model was based on the subset of patients with all covariates present and treated time to the first FACE (either a composite FACE or each event category) as a dependent variable. The following baseline variables were used in the model as covariates: age, time since Fabry diagnosis, previous clinical events (see online supplemental methods), urine protein at baseline, left ventricular mass index (LVMI) at baseline and eGFR based on the Chronic Kidney Disease Epidemiology Collaboration equation ($eGFR_{CKD\text{-}EPI}$) at baseline. The impact of each covariate on the time to the first FACE was evaluated individually. The impact of each covariate was evaluated for three sets of data (ERT naïve, ERT experienced and all data). Patients who discontinued from the studies or had not experienced any events at data cut-off were right censored. Further details are provided in the online supplemental methods.

A literature search was performed to identify historical Fabry studies reporting FACE incidence; details of the search are included in the online supplemental methods.

RESULTS

Baseline characteristics

A total of 97 patients (48 ERT naïve; 49 ERT experienced) with amenable *GLA* variants were included in this analysis. Overall, 61.9% of patients were female and mean (SD) age was 46.4 (13.2) years; ERT-experienced patients were older than ERT-naïve patients (mean (SD) age 49.5 (14.2) vs 43.1 (11.3) years, respectively; table 1). ERT-naïve patients were more recently diagnosed compared with ERT-experienced patients (median (Q1, Q3) 5.0 (2.0, 9.0) vs 6.0 (5.0, 18.0) years, respectively) at migalastat initiation. Female patients had longer median (Q1, Q3) times between Fabry diagnosis and migalastat treatment than male patients (6.0 (3.0, 16.0) vs 5.0 (3.0, 9.0) years). Male patients with the classic phenotype comprised 29.2% of the ERT-naïve group and male patients with multiorgan involvement comprised 32.7% of the ERT-experienced group. Genotypes of patients with the classic phenotype and multiorgan involvement are shown in online supplemental table 1. Many patients showed renal involvement, with 48% of patients having eGFR≤90 mL/min/m^2 and 41% of patients taking inhibitors of the renin–angiotensin system. Due in part to the FACETS inclusion criterion that subjects had urine Gb3 four times the upper limit of normal, the percentage of patients with eGFR<60 mL/min/m^2 was higher in ERT-naïve patients vs ERT-experienced patients (10% vs 6%). It was also higher in men versus women (16% vs 3%). Median (Q1, Q3) duration of migalastat exposure was 5.1 (2.3, 6.8) years (ERT naïve: 6.5 (2.0, 7.5); ERT experienced: 4.9 (3.0, 5.7)). Individual patient exposure of migalastat ranged from 0.1 to 8.6 years.

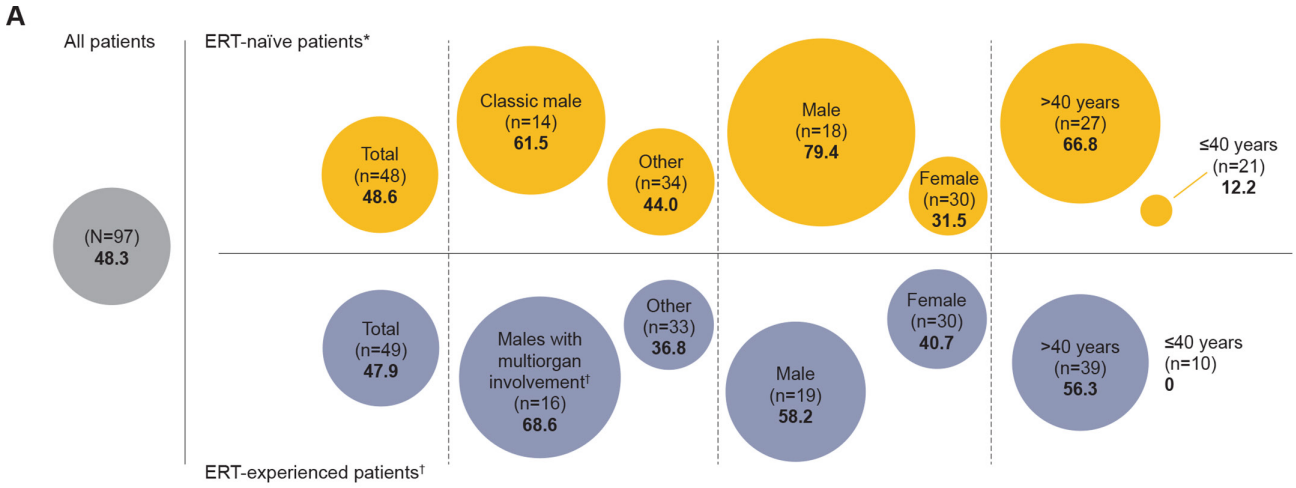
Incidence of FACEs

The overall incidence rate of FACEs was 48.3 per 1000 patient-years with long-term treatment with migalastat (median (Q1, Q3) follow-up of 5.1 (2.3, 6.8) years). The majority of ERT-naïve (n=37, 77.1%) and ERT-experienced (n=43; 87.8%) patients experienced no FACEs on migalastat. Overall, 17 patients (17.5%) experienced 22 on-migalastat FACEs. One patient (1.0%) had consecutive measurements of elevated serum

Table 1 Patient demographics and baseline characteristics from the beginning of migalastat treatment

	Overall n=97	ERT-naïve patients n=48	ERT-experienced patients n=49
Sex, n (%)			
Male	37 (38.1)	18 (37.5)	19 (38.8)
Female	60 (61.9)	30 (62.5)	30 (61.2)
Age, years			
Mean (SD)	46.4 (13.15)	43.1 (11.27)	49.5 (14.17)
Median (Q1, Q3)	47.0 (36.0, 57.0)	45.0 (35.0, 49.5)	53.0 (43.0, 59.0)
Time since Fabry diagnosis, years			
Mean (SD)	9.84 (10.38)	7.13 (7.69)	12.45 (11.93)
Median (Q1, Q3)	5.5 (3.0, 11.0)	5.0 (2.0, 9.0)	6.0 (5.0, 18.0)
$eGFR_{CKD\text{-}EPI}$, mean (SD), mL/min/1.73 m^2	90.83 (22.35)	92.75 (24.26)	88.96 (20.39)
$eGFR_{CKD\text{-}EPI}$ category, n (%)			
>90 mL/min/1.73 m^2	50 (51.5)	26 (54.2)	24 (49.0)
60–90 mL/min/1.73 m^2	39 (40.2)	17 (35.4)	22 (44.9)
>30–<60 mL/min/1.73 m^2	8 (8.2)	5 (10.4)	3 (6.1)
Urinary protein, median (Q1, Q3), mg/24 hours	198.0 (82.0, 353.0)	245.0 (121.5, 399.5)	116.0 (0.0, 265.0)
LVMI, mean (SD), g/m^2	93.88 (29.59)	96.50 (32.90)	91.48 (26.32)
Patients taking ACEI/ARB/RI, n (%)	40 (41.2)	14 (29.2)	26 (53.1)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; $eGFR_{CKD\text{-}EPI}$, estimated glomerular filtration rate using the chronic kidney disease epidemiology collaboration equation; ERT, enzyme replacement therapy; LVMI, left ventricular mass index; RI, renin inhibitor.



B

Per 1000 patient-years	Overall total N=97	ERT naïve			ERT experienced			Males n=37	Females n=60	Patients aged ≤40 years n=31	Patients aged >40 years n=66
		Overall n=48	Classic males n=14	Others n=34	Overall n=49	Males with multiorgan involvement n=16	Others n=33				
Renal event	4.4	4.1	15.4	0	4.8	13.7	0	11.5	0	0	5.8
Cardiac event	30.7	32.4	15.4	38.5	28.7	41.2	22.1	40.2	24.9	0	40.9
Cerebrovascular event	13.2	12.2	30.8	5.5	14.4	13.7	14.7	17.2	10.7	8.8	14.6

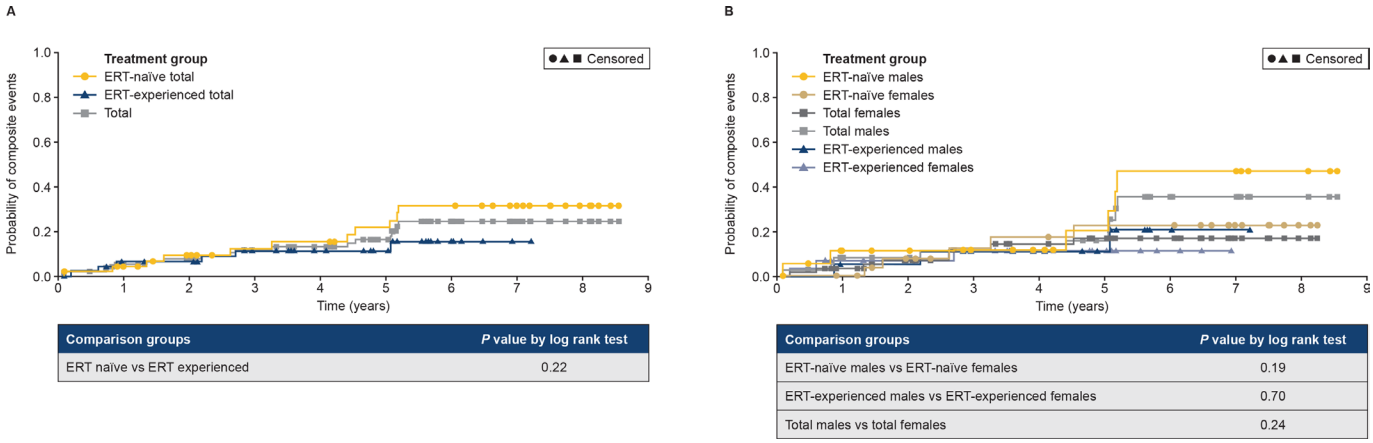
Figure 1 FACE incidence per 1000 patient-years by ERT status and baseline characteristics while receiving migalastat, (A) overall and (B) by event category. Incidence rates of FACEs while receiving migalastat. (A) For overall FACEs, shown as events per 1000 patient-years for all patients and for ERT-naïve patients* or ERT-experienced patients,† both further analysed by sex and age (≤40 or >40 years) and by phenotype (classic man or other) in ERT-naïve patients or by multiorgan involvement or other in ERT-experienced patients. Circle size correlates with number of events. Overall FACEs included all cardiac, cerebrovascular and renal events (as previously defined) and death due to FACE. (B) For individual renal, cardiac and cerebrovascular events, shown as events per 1000 patient-years, for all patients, sex, age (≤40 years or >40 years) and by ERT status, which were further analysed by phenotype (classic man or other) for ERT-naïve patients* or by men with multiorgan involvement or other in ERT-experienced patients.† Classic men are defined as men with multiorgan involvement (ie, at least two organs of the renal system, cardiac system, central nervous system, peripheral nervous system and gastrointestinal system are affected) and baseline white blood cell α-Gal A<3% of wild type. 'Other' patients include non-classic men and all women. *ERT naïve is defined as never having received ERT or not having received ERT for >6 months. †ERT experienced is defined as having initiated ERT>12 months prior to study. ERT, enzyme replacement therapy; FACE, Fabry-associated clinical event.

creatinine at least twice the baseline value. Twelve patients (12.4%) had 14 cardiac events: 7 patients had atrial fibrillation (1 of whom had 2 instances of atrial fibrillation), 1 had complete atrioventricular block, 1 had sinus bradycardia, 1 had chest pain, 1 had chest pain and ventricular tachycardia and 1 had atrial flutter. Five patients (5.2%) had six cerebrovascular events: one cerebral haemorrhage, one embolic stroke and four transient ischaemic attacks. There were no deaths during the follow-up.

FACE incidence varied by phenotype, level of organ involvement, sex and age (figure 1A). In ERT-naïve and ERT-experienced patients, incidence rates were 48.6 and 47.9 events per 1000 patient-years, respectively. Numerically higher incidence rates were observed in men versus women, men with the classic phenotype vs all others and patients aged >40 years versus younger patients (figure 1A). ERT-naïve classic men (n=14) had an incidence rate of 61.5 FACEs per 1000 patient-years and ERT-experienced men with multiorgan involvement (n=16) had a rate of 68.6 events per 1000 patient-years. Overall incidence rates for cardiac, renal and cerebrovascular events were 30.7, 4.4 and 13.2 per 1000 patient-years, respectively (figure 1B). Three patients experienced multiple FACEs: one female patient experienced two transient ischaemic attacks; one male patient experienced ventricular tachycardia and chest pain and one male patient experienced two occurrences of atrial fibrillation.

Incidence of FACEs in patients treated with migalastat or ERT over 18 months

A side-by-side comparison of patients treated with migalastat or ERT over 18 months showed that migalastat was associated with a lower incidence of FACEs versus continued ERT. At baseline, patients in the migalastat-treated group (n=49) were older and more clinically affected than patients in the ERT-treated group (n=15; online supplemental table 2). Following 18 months of treatment, in the overall migalastat population versus the continued ERT population, incidence rates were 60.6 vs 326.6 per 1000 person-years, respectively. In men with multiorgan involvement receiving migalastat (n=16) versus those receiving ERT (n=5), incidence rates were 89.6 vs 138.5, respectively. For men with non-multiorgan involvement and all women receiving migalastat (n=33) versus those receiving ERT (n=10), incidence rates were 45.7 vs 422.2 per 1000 patient-years, respectively.



Comparison groups	*P* value by log rank test
ERT naïve vs ERT experienced	0.22

Comparison groups	*P* value by log rank test
ERT-naïve males vs ERT-naïve females	0.19
ERT-experienced males vs ERT-experienced females	0.70
Total males vs total females	0.24

Figure 2 Kaplan–Meier analysis of time to first composite event by (A) prior treatment status and (B) sex. Time to first composite event by (A) ERT-naïve and ERT-experienced patients and (B) sex, which was further analysed according to ERT status. Composite event included cardiac, cerebrovascular and renal events (as previously defined) and death due to FACE. Number of subjects with events at time 0 is 0. ERT, enzyme replacement therapy.

Time to first FACE

Kaplan–Meier analysis of time to first composite event showed that there was no statistically significant difference in the time-to-composite-event Kaplan–Meier curves between ERT-naïve and ERT-experienced patients (p=0.22; figure 2A) or between male and female patients (p=0.24; figure 2B). There was a trend of decreased time to composite event in patients aged>40 years relative to those aged ≤40 years, but this did not reach statistical significance (online supplemental figure S2A; p=0.06). Among ERT-naïve patients, 71% of male patients with the classic phenotype and 79% of all others remained event-free on migalastat treatment; there was no statistically significant difference in time-to-composite-event curves between classic men and all others (p=0.60; online supplemental figure S2B). Similarly, there was no statistically significant difference in time-to-composite-event curves between ERT-experienced men with multiorgan involvement and other ERT-experienced patients (p=0.46; online supplemental figure S2C). Overall, 91 patients with non-missing covariates were included in the Cox model, 15 of whom experienced at least one FACE. In this group, median time to first FACE was 2.6 years from start of migalastat therapy (ERT naïve: 3.8 years, ERT experienced: 0.9 years).

Association between baseline variables and rate of FACEs

A Cox proportional hazards regression model was used to identify factors associated with rate of composite FACEs. For most baseline variables assessed individually in the Cox regression model in this study (patient age, time from diagnosis, prior clinical events, baseline proteinuria and baseline LVMI), the 95% confidence intervals (CIs) of hazard ratios (HRs) included one (figure 3; online supplemental table 3), suggesting these variables are not associated with FACEs in this relatively small population. The only baseline variable associated with rate of FACEs was eGFR; higher baseline eGFR (per 10 mL/min/1.73 m^2) was associated with lower rate of composite FACEs in the overall population (HR: 0.68; 95% CI=0.55, 0.85; figure 3).

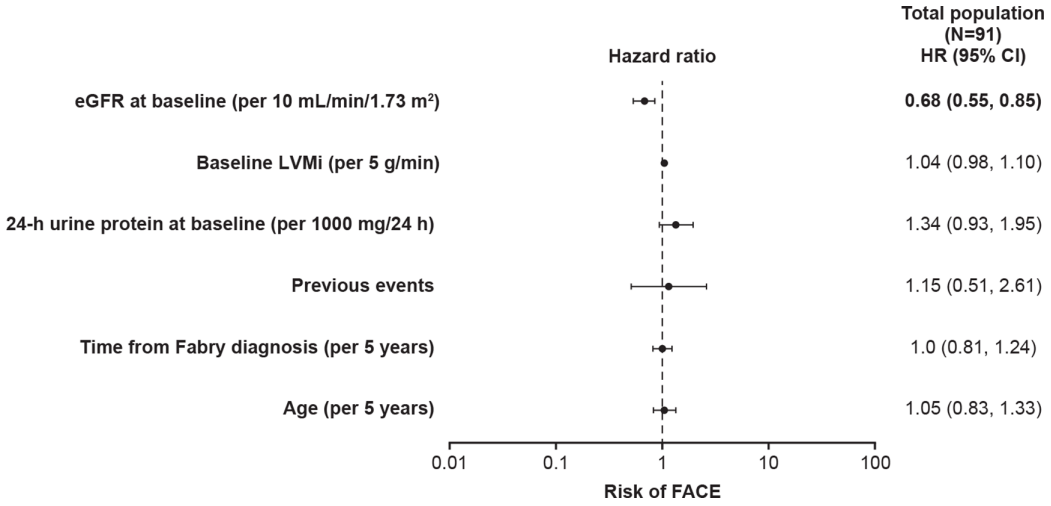


Figure 3 Influence of baseline variables on the risk of FACE occurrence (time to first FACE) during migalastat treatment. This analysis included only patients with non-missing covariates (n=91). HR for each baseline factor (left side of the graph) is assessed for its influence on time to first FACE during migalastat treatment using Cox regression. HR>1 indicates increased risk of FACE and HR<1 indicates decreased risk of FACE. FACE included renal, cardiac or cerebrovascular events (as previously defined) or death due to FACE. See online supplemental table 3 for associations between baseline variables and the risk of FACEs (composite events). eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; FACE, Fabry-associated clinical event; LVMI, left ventricular mass index.

Summary of FACE definitions and outcomes across Fabry studies

Summaries of definitions of FACEs used in the current analysis and in relevant literature are included in table 2 and online supplemental file 1. While cross-trial comparisons should only be made with caution due to disparate patient populations and procedures, the incidence of FACEs with migalastat treatment appears to be comparable to that observed in similar datasets of ERTs. Definitions of FACEs varied between studies, highlighting the need for a standardised definition of FACEs.

DISCUSSION

In this study, we used integrated data from clinical trials to assess the long-term treatment effects of migalastat on the occurrence of severe clinical complications of Fabry disease or FACEs and identified the risk factors associated with FACEs in patients with amenable *GLA* variants.

This analysis measured clinically meaningful events that indicate serious renal, cardiac and cerebrovascular outcomes in patients and assessed the incidence of FACEs as a measure of both long-term efficacy and safety of migalastat. FACEs are disease-related symptoms; typically, the natural course of Fabry disease is associated with an increase in FACEs as patients age and the extent of organ involvement increases.[1] Effective disease management may reduce the incidence of FACEs. The fact that, in our analysis, FACE incidence was low both overall and in each individual FACE category during long-term migalastat treatment may support long-term multisystemic efficacy with migalastat (figure 4).

The incidence of renal, cardiac and cerebrovascular events during migalastat treatment has been reported in the randomised, ERT-controlled Phase III ATTRACT study, using definitions consistent with short-term clinical monitoring goals.[9 14] During the 18-month randomised treatment period of ATTRACT, despite the small sample size and heterogeneity, the percentage of patients who experienced renal, cardiac or cerebrovascular events (according to the definition in the previous analysis) was numerically lower with migalastat compared with ERT (29% vs 44%).[9] These results were maintained over the 30-month open-label migalastat extension, with few patients experiencing FACEs during the extension period.[14] In contrast, the definition of FACEs in the current analysis was chosen with the aim of evaluating long-term clinical outcomes of patients receiving migalastat treatment and comparison with the body of historical data on ERT. At baseline, the migalastat and ERT groups were similar overall, with the migalastat cohort having lower eGFR, higher age and higher LVMI at the beginning of migalastat treatment compared with the ERT cohort. When we reanalysed the ATTRACT data using the current definition of FACEs, migalastat was associated with lower incidence of FACEs per 1000 patient-years compared with continuing ERT up to 18 months of treatment (61 vs 327 per 1000 patient-years, respectively), although it should be noted that the number of patients on ERT was relatively small (15 ERT vs 49 migalastat).

It is important to consider our findings, in which we report the first long-term FACE outcomes for migalastat in an amenable population in the context of data from other studies, although direct comparisons cannot be made. Two independent studies showed that 27% of patients receiving agalsidase beta or agalsidase alfa over a median follow-up of 5 years experienced FACEs.[15 16] In a study of clinical events in agalsidase-beta-treated patients, Ortiz *et al* reported 111 first-time FACEs per 1000 patient-years during the first 6 months; the incidence rate subsequently decreased and remained stable at 40–58 FACEs per 1000 patient-years.[17] The overall incidence rate over the entire 5-year follow-up was 61 events per 1000 patient-years[17] (vs 48.3 per 1000 patient-years in the current study), with higher incidence rates in male patients and patients aged ≥40 years at ERT initiation. Overall, 17% of patients experienced first-time FACEs within 5 years of treatment initiation.[17] The current analysis demonstrates that 17.5% of migalastat-treated patients experienced FACEs with a median 5-year follow-up (online supplemental file 1). Direct comparisons are flawed due to differences in baseline characteristics, participants' *GLA* variants, varying FACE definitions, statistical analyses (eg, Ortiz *et al* only counted first event in any predefined categories, whereas the current study counted all events including recurrent ones) and study settings.[17] The different methods for data collection in these studies should also be noted. The current analysis used prospectively collected clinical trial data. In contrast, Arends *et al* was a retrospective study and its data were not collected through a uniform protocol; Ortiz *et al* was based on the Fabry Registry, which was limited by missing data and a lack of standard timing of assessments.[17 18] Various composite clinical outcomes with different definitions of clinical events and different methods of analyses have been used in various studies of patients with Fabry disease.[9 14 16–22] This highlights the clear need for standardising the definitions of FACEs to allow for better evaluation of treatment outcomes across studies,[23] as well as the need for data sharing across multiple industry and academic partners.

Similar to previous reports on ERT-treated patients,[17] our analysis observed higher incidence of FACEs principally among men overall and ERT-naïve men with the classic phenotype, in men with multiorgan involvement at baseline and in patients who were older at treatment initiation. We observed similar FACE incidence among ERT-naïve and ERT-experienced patients. It should be noted that ERT-naïve patients had to have urine Gb3 levels at least four times the upper limit of normal at screening to be enrolled in FACETS; thus, the FACETS population was enriched for patients with renal involvement.[12] This is reflected by the higher median urinary protein level and higher percentage of ERT-naïve patients versus ERT-experienced patients with eGFR <60 mL/min/1.73 m^2 in our analysis. Additionally, 29.2% of ERT-naïve patients were being treated with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or renin inhibitors, compared with 53.1% of ERT-experienced patients, highlighting a difference in the management of their renal disease at baseline. This suggests that these patients had more advanced renal involvement at baseline, so they were more likely to experience renal events and all FACEs.[3 24]

There is an unmet need for predictors of treatment outcomes with migalastat as well as biomarkers used for clinical monitoring. For example, the incidence of cardiac events observed in migalastat-treated patients in this study points to the need for more robust prognostic cardiac biomarkers that may be able to predict incidence of cardiac FACEs in this patient population. Additionally, Bichet *et al* showed that, despite its wide use, plasma lyso-Gb3 is not a predictor of FACEs in patients receiving migalastat for Fabry disease.[24] Interestingly, both that study and the current analysis also showed that only baseline eGFR was able to predict the incidence of FACEs during long-term migalastat treatment, highlighting the importance of managing renal disease.[24] Alternatively, lower eGFR at baseline may be reflective of Fabry disease that is further along the clinical continuum. Furthermore, there is evidence to suggest that significant cardiac involvement impacts renal function and

Table 2 Summary of FACE definitions across various Fabry studies

Treatment	Migalastat N=97	Agalsidase beta N=52	Agalsidase beta N=40	Agalsidase alfa or beta N=178	Agalsidase alfa or beta N=387	Agalsidase beta N=1411	Migalastat N=31	Agalsidase beta N=51	Migalastat, N=36	Agalsidase beta N=1044
Author, year	Current analysis	Germain, 2015	Weidemann, 2013	Sirrs, 2014	Arends, 2018	Hopkin, 2016	Feldt-Rasmussen, 2020	Banikazemi, 2007	Hughes, 2017	Ortiz, 2016
Patient population	Pts with amenable mutations (37 M; 60 F)	Adult pts with classic FD (50 M; 2 F)	Adult pts with advanced FD (31 M; 9 F)	Pts with FD meeting Canadian ERT criteria (100 M; 78 F)	Pts with FD (195 M; 192 F)	Pts in the Fabry Registry (969 M; 442 F)	ERT-experienced pts with amenable mutations (16 M; 17 F)*	Adult pts with advanced FD (45 M; 6 F)	ERT-experienced pts with amenable mutations (16 M; 20 F)	Pts in the Fabry Registry (641 M; 403 F)
Length of follow-up, median	5 y	10 y	6 y	5 y	5 y	M: 4 y F: 3 y	2.5 y	1.5 y	1.5 y	NR†
Events overall, % of patients	18%	19%	33%	27%	27%	M: 21%; F: 13%	32%	28%	29%	17%
Renal events, % of patients	2%	7.7%	10%	3%‡	3%‡	M: 7%; F: 2%	29%	20%	24%	6%
Cardiac events, % of patients	12%	4%	15%	17%	14%	M: 9%; F: 7%	3%	6%	6%	7%
Cerebrovascular events, % of patients	5%	10%	10%	8%	7%	M: 5%; F: 3%	0%	0%	0%	3%
Death, % of patients	0%		18%	5%	3%	M: 4%; F: 1%	0%	2%	0%	1%
Death due to	Fabry disease		Any cause	Any cause	Any cause	Any cause§	Fabry disease	Any cause	Any cause	Any cause

Studies in the table are ordered by longest to shortest median follow-up time. Definitions of renal events include various combinations of: end-stage renal disease; dialysis; transplant; serum creatinine (predefined increase); increased urinary protein (predefined) and GFR decrease (predefined rate). Definitions of cardiac events included various combinations of: cardiac-related death; myocardial infarction; chronic heart failure; atrial fibrillation; ventricular tachyarrhythmia; symptomatic arrhythmia requiring medication or intervention; heart disease progressive enough to require a pacemaker; bypass surgery (CABG); coronary artery dilation; implantation of cardioverter or defibrillator; direct cardioversion; unstable angina; percutaneous transluminal coronary angioplasty; valve replacement surgery; stent; acute coronary syndrome; heart block; cardiac arrest and cardiac ablation. Definitions of cerebrovascular events included various combinations of: stroke; transient ischaemic attack and acute hearing loss. Full details of definitions of each event type are included in online supplemental file 1.

*33 patients were originally included in the open-label population; 2 patients were subsequently found to have non-amenable variants by Good Laboratory Practice validated migalastat amenability assay and were excluded from the efficacy analyses.

†Median follow-up duration was not reported. Maximum follow-up was 5 years.

‡Patients needing renal replacement therapy; excludes patients who had end-stage renal disease at study entry.

§Non-cardiac death.

CABG, coronary artery bypass grafting; ERT, enzyme replacement therapy; F, female; GFR, glomerular filtration rate; M, male; NR, not reported; y, years.

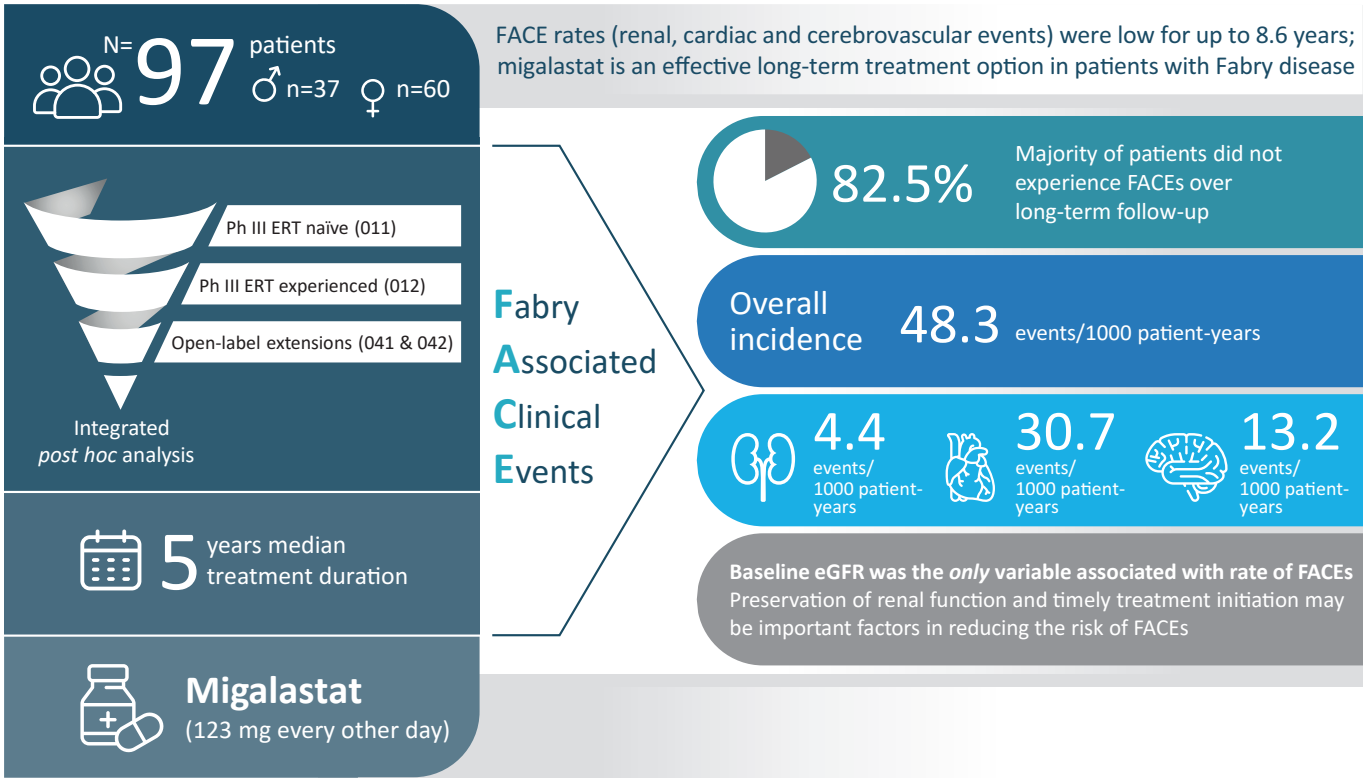


Figure 4 Graphical abstract.

vice versa and patients with secondary cardiorenal syndrome are at higher risk of clinical events.[25] Migalastat demonstrated long-term stabilisation of renal measures regardless of sex or phenotype in both ERT-naïve and ERT-experienced patients with Fabry disease and amenable *GLA* variants who were treated with migalastat for at least 2 years and up to 8.6 years.[11] Timely treatment initiation may be necessary to stabilise or slow the decline in renal function in Fabry disease,[26] given that renal podocytes are terminally differentiated cells and their potentially irreversible injury occurs in early childhood.[20 27 28] However, further investigation is needed to determine the impact and optimal time of treatment initiation of Fabry therapies, including migalastat.

This study has several limitations. Although the data were prospectively collected, this is a *posthoc* analysis, which may be biased in its statistical methods and selection of outcomes. The study was not powered to show differences in patient subgroups and the patient numbers in some subgroups were small. Assessment of prior clinical events was based on medical history collected during screening and may be incomplete, so could not be determined in the same quantitative way as the prospective analysis. Events were reported at the treating physician's discretion and according to local treatment norms. As such, cardiac biomarkers and ECG may not have been recorded at the time of events. Interpretation of the findings is limited by a lack of an appropriate parallel untreated control group. Additionally, a change in serum creatinine levels, which were used as a FACE outcome in this study, may not be secondary to treatment effect and could instead be in response to other factors, including dehydration or use of non-steroidal anti-inflammatory drugs.

The impact of migalastat on renal, cardiac and cerebrovascular events shown in the current study may be partly attributed to its broad distribution in the body, particularly in Fabry-disease-relevant tissues such as the kidneys, heart, brain and gastrointestinal tract, some of which may be difficult for ERT to penetrate.[9 29–31] All patients, regardless of ERT-naïve and ERT-experienced status, had amenable variants in this study and similar characteristics at baseline; therefore, the low incidence of events cannot be attributed to a selective difference arising from the difference in migalastat action. Overall, the incidence rate of FACEs observed in this study is likely to be an accurate estimate of the event rate experienced by a migalastat-treated amenable patient population within a clinical setting. Additionally, migalastat, which is an orally delivered, non-immunogenic iminosugar with a high volume of distribution,[32 33] has the effect of stabilising and chaperoning endogenously produced enzymes, thereby increasing enzyme activity without any potential to generate anti-enzyme antibodies.[32 33] These properties may have influence on the long-term clinical outcomes reported herein. Further assessment of the benefit of migalastat treatment on FACEs and other clinical measures relative to no treatment and ERT will be investigated in the ongoing followME registry (ENCEPP registration: EUPAS20599).

CONCLUSION

In this *posthoc* analysis of data from 97 patients with amenable *GLA* variants who were enrolled in Phase III clinical trials of Fabry disease, the incidence rate of FACEs remained low for ERT-naïve and ERT-experienced patients receiving migalastat treatment for up to 8.6 years. Baseline eGFR was found to be a significant predictor of composite FACEs. Preservation of renal function and timely treatment initiation may be important factors in reducing the risk of FACEs.

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