Long-term multisystemic efficacy with migalastat in ERT-naïve and ERT-experienced patients with amenable *GLA* variants

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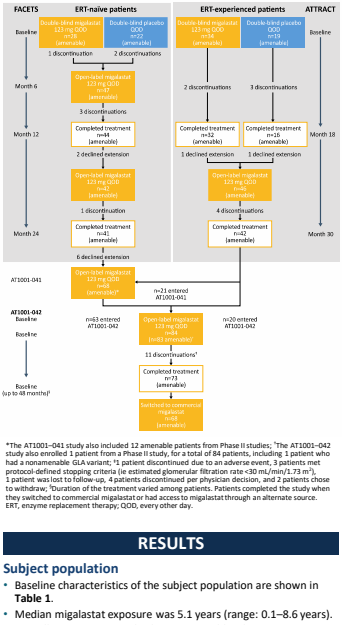
INTRODUCTION

- Fabry disease is a progressive, multisystemic, X-linked disorder caused by variants in the *GLA* gene that result in deficient or absent lysosomal alpha galactosidase A (α-Gal A) activity.[1]
- α-Gal A dysfunction results in accumulation of glycosphingolipids, including Gb3, within lysosomes and subsequent spread to other cellular compartments[2]
  - This leads to multisystem organ dysfunction and can result in sensory abnormalities and pain, myocardial infarction, arrhythmia, renal insufficiency and stroke.[3–5]
- Continuous exposure to glycosphingolipids can trigger multiple inflammatory pathways[6]
  - The accumulation of Gb3 in kidney cells triggers pathological inflammatory and profibrotic process that leads to glomerular injury.[7]
- Approved therapies for Fabry disease include enzyme replacement therapy (ERT) and migalastat – a small molecule chaperone that stabilises α-Gal A.
- This study prospectively examined the multisystemic efficacy of migalastat in both ERT-experienced and ERT-naïve subjects over an 8.6-year period.

METHODS

- This *post-hoc* analysis integrated data from the double-blind, randomised, placebo-controlled FACETS trial; the randomised, open-label, active-controlled ATTRACT study; and the open-label extension studies AT1001-041 and AT1001-042 (**Figure 1**). Full inclusion and exclusion criteria for the studies and definitions of the subject subgroups (ERT-naïve vs ERT-experienced; ERT-naïve classic males vs males with multisystemic involvement) are detailed in supplementary materials Table S1 and Section S1, respectively.
- The percentage of subjects with any Fabry-associated clinical event (FACE) and the incidence of FACEs per 1000 patient years were assessed. Further details of the statistical analysis can be found in Section S2 of the supplementary materials.
- FACEs were defined as follows:
  - Renal events: doubling of serum creatinine levels from the start of baseline (two consecutive values) or end-stage kidney disease requiring long-term dialysis or transplantation
  - Cardiac events: myocardial infarction; new symptomatic arrhythmia requiring medication, direct current cardioversion, or 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; or any major cardiac medical procedure (eg valve replacement, stent implantation, transplant, or persistent atrial fibrillation)
  - Cerebrovascular events: stroke or transient ischemic attack as documented by a physician.
- The percentage of subjects with FACEs was compared to other historical published data of ERT in subjects with Fabry disease.
- Serum creatinine levels recorded at baseline and every 6 months were used to assess the estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration equation. Annualised rate of change in eGFR was then calculated using simple linear regression. Further details of the statistical analysis can be found in Section S2 of the supplementary materials.
- An additional interrogation was carried out to investigate the proportion of patients in the FACETS and ATTRACT data who would be eligible for reimbursement of migalastat treatment. Subjects were classified based on criteria used in the Australian Life Saving Drugs Programme (LSDP).[8]

Figure 1. Study design



*The AT1001–041 study also included 12 amenable patients from Phase II studies; †The AT1001–042 study also enrolled 1 patient from a Phase II study, for a total of 84 patients, including 1 patient who had a nonamenable GLA variant; ‡1 patient discontinued due to an adverse event, 3 patients met protocol-defined stopping criteria (ie estimated glomerular filtration rate <30 mL/min/1.73 m^2), 1 patient was lost to follow-up, 4 patients discontinued per physician decision, and 2 patients chose to withdraw; §Duration of the treatment varied among patients. Patients completed the study when they switched to commercial migalastat or had access to migalastat through an alternate source. ERT, enzyme replacement therapy; QOD, every other day.

RESULTS

Subject population

- Baseline characteristics of the subject population are shown in **Table 1**.
- Median migalastat exposure was 5.1 years (range: 0.1–8.6 years).
- Overall, ERT-experienced subjects were older than ERT-naïve subjects (mean [SD] 49.5 [14.2] years vs 43.1 [11.3] years).
- In the ERT-naïve group, males with the classic phenotype were of similar age to the overall population (mean [SD] 42.5 [14.5] years vs 46.4 [13.2] years).
- Many subjects showed renal involvement, with 48% of patients having an eGFR ≤90 mL/min/1.73 m^2.
- Overall, approximately one-third of male subjects had multiorgan involvement
  - Male subjects with the classic phenotype (defined as ≥2 body organs affected and baseline white blood cell α-Gal A <3% of wild type) comprised 29.2% of the ERT-naïve group and male patients with multiorgan involvement made up 32.7% of the ERT-experienced subjects.

Table 1. Patient characteristics

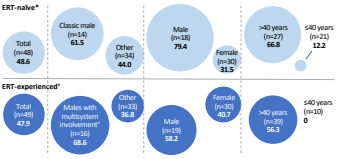
	Overall N=97	ERT-naïve* subjects n=48	ERT-experienced† subjects n=49
Sex, n (%)			
Male	37 (38.1)	18 (37.5)	19 (38.8)
Female	60 (61.9)	30 (62.5)	30 (61.2)
Age			
≤40 years	31 (32.0)	21 (43.8)	10 (20.4)
>40 years	66 (68.0)	27 (56.3)	39 (79.6)
eGFR$_{CKD-EPI}$ category, n (%)			
>90 mL/min/1.73 m^2	50 (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 h	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)

*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. eGFR$_{CKD-EPI}$, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; ERT, enzyme replacement therapy; LVMi, left ventricular mass index; SD, standard deviation.

FACE outcomes by baseline ERT and baseline characteristics

- There was a low number of FACEs over 5.1-years' median follow-up: 17 subjects (17.5%) experienced 22 on-treatment FACEs
  - The majority of both ERT-naïve (n=37, 77.1%) and ERT-experienced (n=43, 87.8%) subjects experienced no FACEs on migalastat.
- Considering all FACEs, events were more common in:
  - Classic males/males with multiorgan involvement compared with others (n=7/30 [23.3%] vs n=10/67 [14.9%])
  - Males compared with females (n=9/37 [24.3%] vs 8/60 [13.3%])
  - Those aged >40 years compared with those aged ≤40 years (n=16/66 [24.2%] vs n=1/31 [3.2%]).
- The incidence rate of on-migalastat FACEs was higher in classic males compared with all others among ERT-naïve subjects (61.5 vs 44.0 per 1000 patient years), and in males with multiorgan involvement compared with all others among ERT-experienced subjects (68.6 vs 36.8 per 1000 patient years). Incidence rate also increased with age (**Figure 2**).
- A side-by-side comparison of subjects treated with migalastat or ERT over 18 months showed that migalastat was associated with a lower incidence of FACEs per 1000 patient years versus continued ERT
  - Males with multiorgan involvement receiving migalastat versus those receiving ERT (90 vs 138; n=16 vs n=5, respectively)
  - Non-multiorgan involvement males and all females receiving migalastat versus those receiving ERT (46 vs 422; n=33 vs n=10, respectively)
  - It should be noted that this analysis was limited by small subject number and shorter exposure to ERT.

Figure 2. Overall FACE incidence per 1000 patient years by ERT status and baseline characteristics

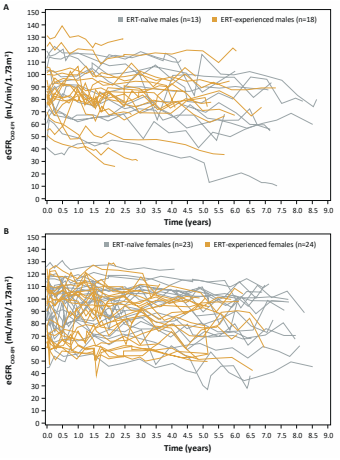


Numbers indicate incidence rate per 1000 patient years.
Rates of FACEs in the overall population over 18 months while on ERT: 326/1000 patient years vs that on migalastat: 61 per 1000 patient years.
Incidence rate of FACE incidence per 1000 patient years. Overall FACEs included all cardiac, cerebrovascular and renal events (as previously defined), and death due to FACEs. Classic males are defined as males with multiorgan involvement (ie ≥2 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 is <3% of wild type. 'Other' subjects include non-classic males and all females. *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.

Renal outcomes with migalastat by ERT experience

- The long-term renal analysis population included 78 patients with ≥2 years' migalastat experience. Of these, 36 were ERT-naïve (23 females) and 42 were ERT-experienced (24 females)
  - 78% of patients had multiorgan involvement (81% of ERT-naïve patients and 76% of ERT-experienced patients with ≥2 organs affected) at baseline
  - Median (range) migalastat exposure was 7.0 (2.0–8.6) and 5.1 (2.1–7.2) years in the ERT-naïve and ERT-experienced patients, respectively.
- eGFR remained stable in ERT-naïve and ERT-experienced subjects (mean [SD] annualised eGFR change: −1.6 [3.1] and −1.6 [3.6] mL/min/1.73 m^2, respectively **[Figure 3]**).

Figure 3. eGFR$_{CKD-EPI}$ over time in subjects with Fabry disease and ≥2 years' migalastat experience[7]



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*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; eGFR$_{CKD-EPI}$, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation.

- The annualised rate of eGFR change was higher among ERT-experienced males with multiorgan involvement compared with all other ERT-experienced patients (mean [SD] −2.5 [5.1] and −1.1 [2.3] mL/min/1.73m^2), but similar among ERT-naïve classic males and all other ERT-naïve patients (mean [SD] −1.7 [3.0] and −1.5 [-3.2] mL/min/1.73m^2).
- Baseline eGFR is a predictor of FACEs in migalastat-treated subjects,[9] highlighting the importance of preserving renal function.

FACE outcomes with migalastat compared with similar trials of ERT

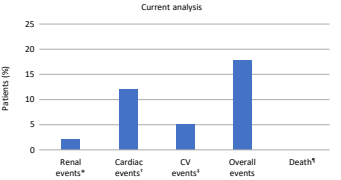
- The incidence of FACEs was generally low among the 97 subjects who received migalastat in the current analysis (**Table 2; Figure 4**).
- Comparisons with similar datasets of ERTs showed that the incidence of FACEs with migalastat were broadly comparable with those seen in subjects treated with ERT (see Supplement Table S2, Supplement Figure S1 and Supplement Section 3).[10–13]

Table 2. Summary of subject characteristics and FACE definitions

Characteristic	Value
Patient population	Subjects with amenable variants (37 M and 60 F)
eGFR$_{CKD-EPI}$, mean (SD), mL/min/1.73 m^2	90.83 (22.35)
LVMi, mean (SD), g/m^2	93.88 (29.59)
Length of follow-up, median (years)	5
FACE outcomes	
Overall events, % of subjects	17.5
Renal events*, % of subjects	2.1
Cardiac events†, % of subjects	12.4
Cerebrovascular events‡, % of subjects	5.2
Death¶, % of subjects	0

*Defined as end-stage renal disease, dialysis, transplant, increase in serum creatine; †Defined as myocardial infarction, chronic heart failure, atrial fibrillation, symptomatic arrhythmia requiring medication or intervention, heart disease progressive enough to require pacemaker, implantation of cardioverter or defibrillator, direct cardioversion, unstable angina, valve replacement surgery, stent, cardiac ablation; ‡Defined as stroke, transient ischemic attack; ¶Due to Fabry disease. eGFR$_{CKD-EPI}$, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; FACE, Fabry-associated clinical event; F, females; M, males; LVMi, left ventricular mass index; SD, standard deviation.

Figure 4. Percentage of migalastat-treated subjects with any FACE outcome



*Defined as end-stage renal disease, dialysis, transplant, increase in serum creatine; †Defined as myocardial infarction, chronic heart failure, atrial fibrillation, symptomatic arrhythmia requiring medication or intervention, heart disease progressive enough to require pacemaker, implantation of cardioverter or defibrillator, direct cardioversion, unstable angina, valve replacement surgery, stent, cardiac ablation; ‡Defined as stroke, transient ischemic attack; ¶Due to Fabry disease. CV, cerebrovascular.

Eligibility for migalastat reimbursement among study participants

- In Australia, patients must demonstrate substantial Fabry-related organ damage to be eligible for reimbursed treatment.[8]
- Among the 97 subjects enrolled in the ATTRACT and FACETs trials and their open-label extensions, including 53 ERT-naïve subjects, 81% met clinical criteria (based on LSDP) for reimbursement for migalastat in Australia.

CONCLUSIONS

- FACE incidence was low in migalastat-treated subjects and compared favourably with historical reports of ERT,[10–13] supporting long-term multisystemic efficacy with migalastat treatment.
- eGFR remained stable in ERT-naïve and ERT-experienced subjects and the eGFR slope with migalastat compared favourably with historical reports of ERT.[7]
- Overall, the patient population in the current analysis is representative of the Fabry disease patient population in Australasia and the majority met the clinical criteria for migalastat reimbursement.

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