LB-18

Cardiac Outcomes With Long-term Migalastat Treatment in Patients With Fabry Disease: Results From Phase 3 Trials

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INTRODUCTION

- Cardiac complications are common in Fabry disease, a rare X-linked disorder of lysosomal α-galactosidase A deficiency, and are the main cause of death in patients with this condition[1,2]
- Left ventricular hypertrophy (LVH) is the hallmark of Fabry cardiomyopathy[2,3]
- A progressive decline in midwall fractional shortening (MWFS) may be observed in earlier stages of Fabry disease and is one of the first signs of systolic impairment[4]
- Studies assessing left ventricular mass (LVM) in untreated patients with Fabry disease reported a progressive increase in LVM index (LVMi) of 1.52-4.07 g/m^2/year; progression occurred regardless of disease phenotype[5-7]
- Although reductions in LVM have been observed in patients with Fabry disease following treatment with enzyme replacement therapy (ERT), the effect of ERT on LVM has been inconsistent, per the published literature[5,8,9]
- Migalastat, a first-in-class, orally administered small molecule, is a pharmacological chaperone approved in the European Union, Switzerland, Israel, Republic of Korea, Canada, and Australia for the treatment of Fabry disease in patients with *amenable GLA* mutations[10]
- Migalastat restores lysosomal trafficking and enzyme activity by binding, inducing proper folding, and stabilizing amenable mutant forms of α-galactosidase A[11]

OBJECTIVE

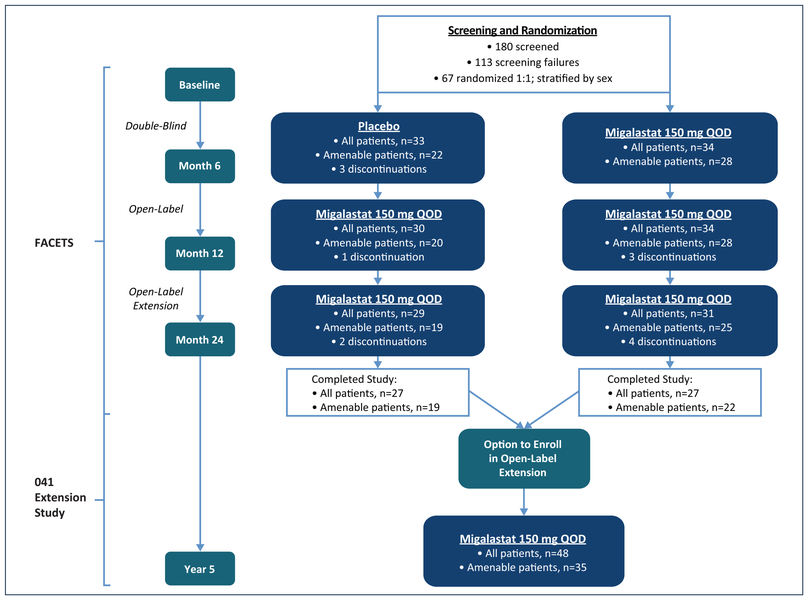
- To summarize the effects of long-term migalastat treatment on cardiac architecture and function in patients with Fabry disease and amenable *GLA* mutations who were enrolled in 2 randomized Phase 3 studies

METHODS

Study Designs

- FACETS (NCT00925301) was a Phase 3, double-blind, randomized, placebo-controlled study to evaluate the efficacy, safety, and pharmacodynamics of 6 months of migalastat 150 mg every other day or placebo, followed by 18 months of migalastat in ERT-naive patients with Fabry disease and amenable mutations[12] (**Figure 1**)
  - Patients completing FACETS were eligible to enter a separate open-label extension (OLE) study (referred to herein as the 041 extension study; NCT01458119)

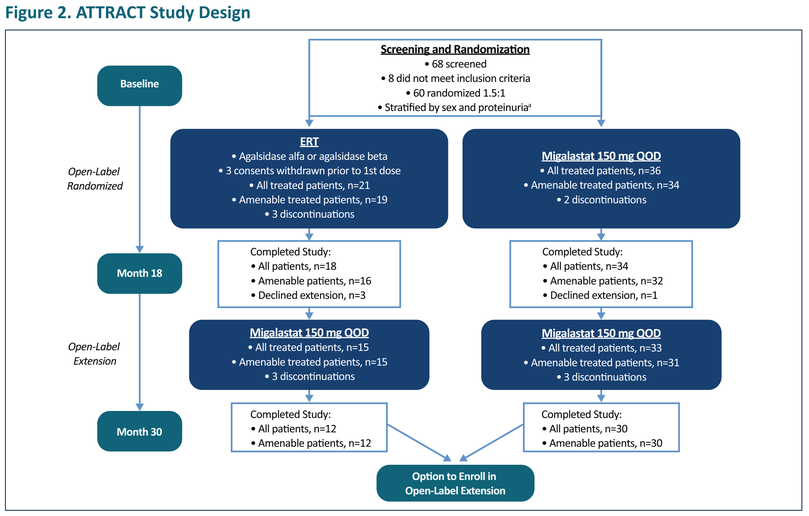
Figure 1. FACETS and 041 Extension Study Designs



QOD=every other day.

- ATTRACT (NCT01218659) was a Phase 3, randomized (1.5:1), open-label study to compare the efficacy and safety of 18 months of migalastat or ERT, followed by a 12-month OLE of migalastat, in patients with Fabry disease with amenable mutations who were previously treated with ERT[13] (**Figure 2**)

Figure 2. ATTRACT Study Design



ERT=enzyme replacement therapy.
[a]Proteinuria stratification: high (≥0.1 g/24 h); low (<0.1 g/24 h).

Key Inclusion Criteria for FACETS and ATTRACT

- Male and female patients aged 16-74 years diagnosed with Fabry disease with amenable *GLA* mutations
- eGFR$_{MDRD}$ of ≥30 mL/min/1.73 m^2 at screening
- Patients taking angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or renin inhibitors had to be on a stable dose for ≥4 weeks before the screening visit
- FACETS only
  - Naive to ERT or had not received ERT for ≥6 months before screening
  - Urine globotriaosylceramide of ≥4× the upper limit of normal (24-hour collection) at screening
- ATTRACT only
  - Initiated treatment with ERT ≥12 months before baseline visit and had a stable ERT dose (≥80% labeled dose) for 3 months before baseline visit

Analyses

- During FACETS, echocardiograms were performed at baseline and at months 6 and 12 and then at baseline and every 12 months during the 041 extension study
- During ATTRACT, echocardiograms were performed at baseline and at months 6, 12, 18, 24, and 30
- Echocardiograms were evaluated (blinded, central review) by a single reader specialized in echocardiography
- Echocardiographic findings were used to assess changes in LVMi and MWFS with migalastat or ERT over time
- Analyses were restricted to patients with amenable *GLA* mutations per the Migalastat Amenability Assay[14]
- The analyses herein were performed for the subgroup of patients who completed FACETS and entered the 041 extension study and for patients enrolled in ATTRACT who entered the OLE of the trial

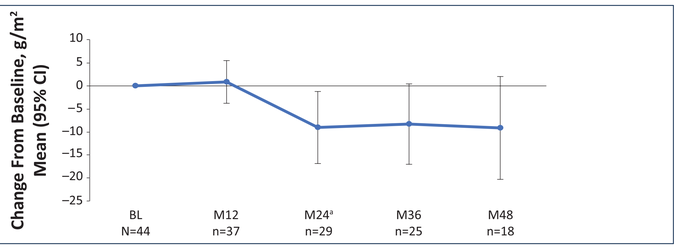
RESULTS

Cardiac Mass

FACETS and 041 Extension Study

- At baseline, mean LVMi was 96.5 g/m^2 (standard deviation [SD], 32.9; n=44)
- A statistically significant mean change from baseline in LVMi was observed after 24 months (or 18 months for patients initially randomized to placebo) of migalastat treatment (**Figure 3**)
- Reductions from baseline were sustained at months 36 and 48 (**Figure 3**)

Figure 3. Change From Baseline in LVMi With Migalastat



BL=baseline; CI=confidence interval; LVMi=left ventricular mass index; M=month.
Baseline was defined as the last available measurement taken prior to the first dose of migalastat; this was the study baseline for patients randomized to migalastat and the value at the Month 6 visit for patients randomized to placebo.
[a]Statistically significant change from baseline based on 95% CI.

- LVH was reported in 11 patients with amenable mutations at baseline (mean LVMi, 138.9 g/m^2)
- The majority of evaluable patients (8/10) with LVH at baseline had a reduction in LVMi, and 5/10 patients demonstrated normalization of LVMi (**Table 1**)

Table 1. Change From Baseline in LVMi in Patients With LVH at Baseline

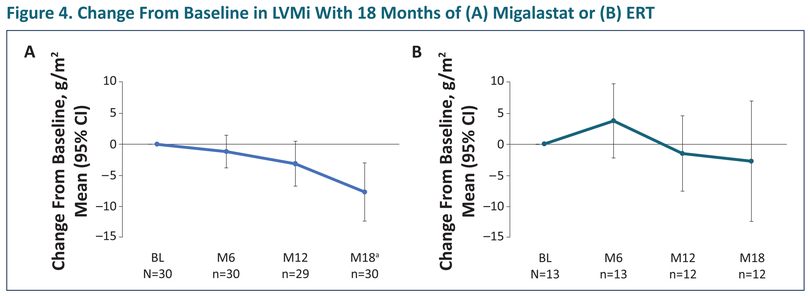
	Baseline	Change From Baseline				
		Month 12	Month 24	Month 36	Month 48	LOCF
n	11	9	9	4	4	10
g/m^2, mean (SD) or (95% CI)	138.9 (37.1)	8.8 (−8.9, 26.6)	−22.5[a] (−41.6, −3.4)	−30.0[a] (−57.9, −2.2)	−33.1[a] (−60.9, −5.4)	−22.8[a] (−40.8, −4.8)
Any Reduction	—	5/9 (56%)	7/9 (78%)	4/4 (100%)	4/4 (100%)	8/10 (80%)
Normalization	—	0/9 (0%)	3/9 (33%)	2/4 (50%)	3/4 (75%)	5/10 (50%)

LOCF=last observation carried forward; LVH=left ventricular hypertrophy.
LVH subgroup: LVMi >95 g/m^2 (females) or >115 g/m^2 (males).[15]
LOCF analyses were based on last study assessment, including any unscheduled or early termination visits.
[a]Statistically significant change from baseline based on 95% CI.

ATTRACT

- At baseline, mean LVMi was 94.6 g/m^2 (SD, 22.4; n=30) in patients randomized to migalastat and 88.5 g/m^2 (SD, 25.6; n=13) in patients randomized to ERT
- A statistically significant mean change from baseline in LVMi was observed after 18 months of treatment with migalastat but not ERT (**Figure 4**)
- During the OLE phase, patients on migalastat continued to demonstrate numerical reductions from baseline in LVMi with another 12 months of treatment (month 30: −3.8 g/m^2 [95% CI, −8.9, 1.3]; n=28)

Figure 4. Change From Baseline in LVMi With 18 Months of (A) Migalastat or (B) ERT



[a]Statistically significant change from baseline based on 95% CI.

- LVH at baseline was reported in 11 patients randomized to migalastat (mean LVMi, 116.4 g/m^2) and 4 patients randomized to ERT (mean LVMi, 121.2 g/m^2)
- Among those with baseline LVH, LVMi was significantly reduced with migalastat but not ERT (**Table 2**)

Table 2. Change From Baseline in LVMi in Patients With LVH at Baseline

	Baseline, g/m^2, Mean (SD)	Change From Baseline, g/m^2, Mean (95% CI)				
		Month 6	Month 12	Month 18	Month 24	Month 30
Migalastat → migalastat (0-30 mo), n=11	116.4 (20.9)	−4.2[a] (−8.2, −0.1)	−3.9 (−10.7, 2.9)	−9.2[a] (−16.5, −1.9)	−14.7[a] (−21.4, −8.0)	−10.0[a,b] (−16.6, −3.3)
ERT (0-18 mo) → migalastat (18-30 mo), n=4	121.2 (9.9)	12.9 (−8.4, 34.2)	3.5 (−18.1, 25.2)	3.9 (−33.6, 41.4)	−4.2[c] (−98.7, 90.4)	0.1 (−13.0, 13.3)

LVH subgroup: LVMi >95 g/m^2 (females) or >115 g/m2 (males).[15]
[a]Statistically significant change from baseline based on 95% CI.
[b]n=10.
[c]n=2.

Cardiac Function

- In FACETS, baseline MWFS for patients with LVH was 12.2% (SD, 2.6; n=10)
- In patients with LVH, numerical increases (ie, improvements) in MWFS were observed with long-term migalastat treatment (**Table 3**)

Table 3. Change From Baseline in MWFS With Migalastat in Patients With LVH at Baseline (FACETS and 041 Extension Study)

	Baseline	Change From Baseline				
		Month 12	Month 24	Month 36	Month 48	LOCF
n	10	9	9	5	4	10
%, mean (SD) or (95% CI)	12.2 (2.6)	0.2 (−0.8, 1.1)	0.9 (−1.6, 3.4)	0.7 (−2.1, 3.4)	0.6 (−5.7, 6.9)	1.0 (−1.5, 3.5)
Any Increase	—	4/9 (44%)	5/9 (56%)	3/5 (60%)	3/4 (75%)	7/10 (70%)
Normalization	—	2/9 (22%)	2/9 (22%)	1/5 (20%)	0	2/10 (20%)

MWFS=midwall fractional shortening.
LVH subgroup: LVMi >95 g/m^2 (females) or >115 g/m^2 (males).[15]
LOCF analyses are based on last study assessment, including any unscheduled or early termination visits.

CONCLUSIONS

- In both FACETS and ATTRACT, long-term treatment with migalastat was associated with sustained reductions in LVMi and evidence of LVH regression
- Migalastat treatment resulted in numerical increases (ie, improvements) in MWFS, a measure of systolic function, in a majority of patients in FACETS with LVH at baseline
- These beneficial long-term effects on cardiac architecture and function suggest that migalastat has the potential to reduce the risk of cardiac complications associated with Fabry disease

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DISCLOSURES

Conflicts of Interest

DPG has received honoraria and research funding from Amicus, Sanofi Genzyme, and Shire. RS has received research funding from Amicus Therapeutics, Protalix Biotherapeutics, Sanofi Genzyme, and Shire. AJ has received advisory fees, sponsorship for attendance at professional meetings, and honoraria from BioMarin, Shire, Sanofi Genzyme, and Amicus Therapeutics. UFR has served on advisory boards for and has received speaker honoraria from Amicus Therapeutics, Sanofi Genzyme, and Shire and has received research funding from Genzyme and Shire. DGB has served as a consultant and speaker for Amicus Therapeutics and Sanofi Genzyme and has received research funding from Amicus Therapeutics, Genzyme, and Shire. DAH has served as a consultant for and has received research and travel funding from Amicus Therapeutics, Sanofi Genzyme, Shire, Actelion, and Protalix. JPC, NS, and JAB are employees of and hold stock in Amicus Therapeutics. KN has served on advisory boards for and has received research funding from Amicus Therapeutics, Sanofi Genzyme, and Shire.

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