2667

Improvements in Cardiac Mass With Long-Term Migalastat Treatment in Patients With Fabry Disease: Results From Two Phase 3 Trials (FACETS and ATTRACT)

Jovanovic A[1], Schiffmann R[2], Nicholls K[3], Feldt-Rasmussen U[4], Bichet DG[5], Hughes DA[6], Jain V[7], Yu J[7], Castelli JP[7], Skuban N[7], Barth JA[7], Giugliani R[8]

[1]Salford Royal Hospital and NHS Foundation Trust, Manchester, UK; [2]Baylor Research Institute, Dallas, TX, USA; [3]Royal Melbourne Hospital, Parkville, VIC, Australia; [4]Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [5]Hôpital du Sacré-Coeur, University of Montreal, Montreal, Quebec, Canada; [6]Royal Free NHS Foundation Trust and University College London, London, UK; [7]Amicus Therapeutics, Inc., Cranbury, NJ, USA; [8]Medical Genetics Service, HCPA/UFRGS, Porto Alegre, Brazil

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] and the main risk factor for Fabry disease–related cardiac complications (eg, heart failure, myocardial infarction, sudden cardiac death)[4]
- 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[5]
- 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[6,7]
- While 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[8,9]
- Migalastat, a first-in-class, orally administered small molecule, is a pharmacological chaperone approved in the European Union, Switzerland, Israel, 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 outcomes in patients with Fabry disease and amenable mutations who were enrolled in two randomized phase 3 studies

METHODS

Study Designs

- FACETS (AT1001-011, NCT00925301) was a phase 3, double-blind, randomized, placebo-controlled study to evaluate the efficacy, safety, and pharmacodynamics of migalastat 150 mg every other day in ERT-naive patients with Fabry disease with amenable *GLA* mutations[12]
- ATTRACT (AT1001-012, NCT01218659) was a phase 3, randomized, open-label study to compare the efficacy and safety of migalastat and ERT in patients with Fabry disease with amenable *GLA* mutations who were previously treated with ERT[13]
- Patients completing either FACETS or ATTRACT were eligible to enter an open-label extension (OLE) study examining the long-term efficacy and safety of migalastat (AT1001-041, NCT01458119)

Key Inclusion Criteria for FACETS and ATTRACT

- Male and female patients aged 16-74 years diagnosed with Fabry disease with amenable *GLA* mutations
- Naive to ERT or had not received ERT for ≥6 months before screening (FACETS)
- Initiated treatment with ERT ≥12 months before baseline visit and had a stable ERT dose (at ≥80% labeled dose) for 3 months before baseline visit (ATTRACT)
- $eGFR_{MDRD}$ of ≥30 mL/min/1.73 m^2 at screening
- Urine globotriaosylceramide of ≥4× the upper limit of normal (24-hour collection) at screening (FACETS)
- 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

Analyses

- Cardiac echocardiograms were evaluated (blinded, central review) by a single reader specialized in echocardiography
- Cardiac echocardiographic findings were used to assess changes in LVMi and MWFS with migalastat or ERT over time
- The analyses presented herein were restricted to patients with amenable mutations per the Migalastat Amenability Assay[14]

RESULTS

Patients

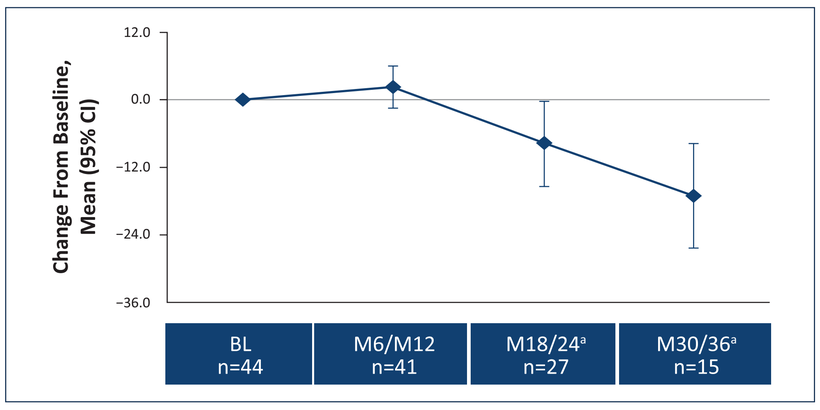
- The FACETS trial randomized 67 patients, 50 of whom had amenable mutations. Forty-one patients with amenable mutations completed the study, 35 of whom continued into the OLE extension
- The ATTRACT trial randomized 60 patients, 56 of whom had amenable mutations

Cardiac Mass

FACETS

- 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 18/24 months of migalastat treatment (–7.7 g/m^2; 95% confidence interval [CI] –15.4, –0.01; n=27; 18 months for patients randomized to placebo and 24 months for patients randomized to migalastat) (**Figure 1**)
- Further reductions in LVMi were observed at months 30/36 in patients from FACETS who entered the OLE study (change from baseline, –17.0 g/m^2; 95% CI –26.2, –7.9; n=15) (**Figure 1**)

Figure 1. Mean Change From Baseline in LVMi (g/m^2) Over Time With Migalastat Treatment (FACETS; patients with amenable mutations)



BL=baseline; CI=confidence interval; LVMi=left ventricular mass index; M=month.
[a]Statistically significant change from baseline based on 95% CI.

- LVH was reported in 11 patients at baseline (mean LVMi, 138.9 g/m^2)
- The majority of patients (9/11) with LVH at baseline had a reduction in LVMi, and 5/11 patients demonstrated normalization of LVMi (**Table 1**)

Table 1. Changes From Baseline in LVMi (g/m^2) With Migalastat Treatment in Patients With Amenable Mutations and LVH at Baseline (FACETS; mean LVMi at baseline, 138.9 g/m^2)

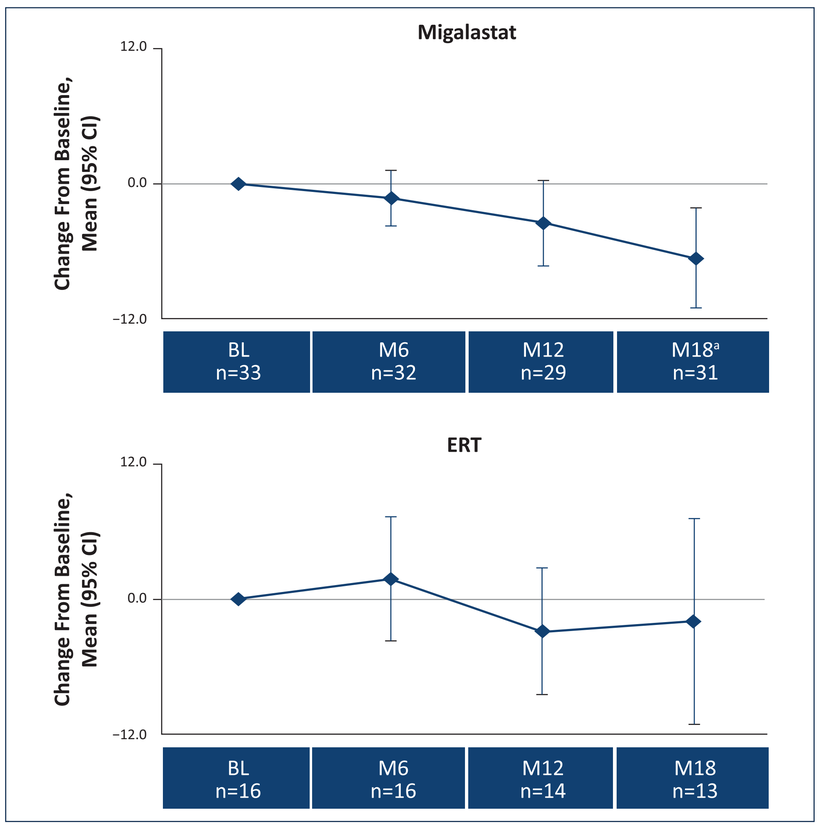
	Timepoint				
	Month 12	Month 24	Month 36	Month 48	LOCF
n	9	9	4	4	11
Mean change from baseline (95% CI)	8.8 (–8.9, 26.6)	–22.5[a] (–41.6, –3.4)	–30.0[a] (–57.9, –2.2)	–33.1[a] (–60.9, –5.4)	–20.8[a] (–37.4, –4.1)
Any reduction	5/9 (56%)	7/9 (78%)	4/4 (100%)	4/4 (100%)	9/11 (82%)
Normalization	0/9 (0%)	3/9 (33%)	2/4 (50%)	3/4 (75%)	5/11 (46%)

Normal LVMi is ≤95 g/m^2 for females and ≤115 g/m^2 for males.
Last observation carried forward (LOCF) analyses are based on last study assessment, including any unscheduled or early termination visits, and data are summarized for all patients with data at that timepoint.
LVH=left ventricular hypertrophy.
[a]Statistically significant based on 95% CI.

ATTRACT

- At baseline, mean LVMi was 95.3 g/m^2 (SD, 22.8; n=33) in patients given migalastat and 92.9 g/m^2 (SD, 25.7; n=16) in patients given ERT
- A statistically significant mean change from baseline in LVMi was observed after 18 months of treatment with migalastat (–6.6 g/m^2; 95% CI –11.0, –2.1; n=31), but not ERT (–2.0 g/m^2; 95% CI –11.0, 7.0; n=13) (**Figure 2**)
- 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=30)

Figure 2. Mean Changes From Baseline in LVMi (g/m^2) With 18 Months of Migalastat or ERT Treatment (ATTRACT; patients with amenable mutations)



ERT=enzyme replacement therapy.
[a]Statistically significant based on 95% CI.

- LVH at baseline was reported in 13 patients randomized to migalastat (mean LVMi, 116.7 g/m^2) and 5 patients randomized to ERT (mean LVMi, 123.3 g/m^2)
- The majority of patients (11/13) with LVH at baseline who were randomly assigned to migalastat had a reduction in LVMi, and 4/13 patients demonstrated normalization of LVMi (**Table 2**)
- Based on a last observation carried forward (LOCF) analysis, the mean change in LVMi from baseline in patients with LVH at baseline who were randomized to ERT was 4.5 g/m^2 (95% CI –20.9, 29.9); 2/5 (40%) patients demonstrated a reduction in LVMi

Table 2. Changes From Baseline in LVMi (g/m^2) With Migalastat Treatment in Patients With Amenable Mutations and LVH at Baseline (ATTRACT; mean LVMi at baseline, 116.7 g/m^2)

	Timepoint				
	Month 12	Month 18	Month 24	Month 30	LOCF
n	12	13	11	10	13
Mean change from baseline, (95% CI)	–5.2 (–11.9, 1.6)	–8.4[a] (–14.9, –2.0)	–14.7[a] (–21.4, –8.0)	–10.0[a] (–16.6, –3.3)	–9.0[a] (–14.5, –3.6)
Any reduction	8/12 (67%)	10/13 (77%)	10/11 (91%)	9/10 (90%)	11/13 (85%)
Normalization	3/12 (25%)	5/13 (39%)	5/11 (46%)	4/10 (40%)	4/13 (31%)

Normal LVMi is ≤95 g/m^2 for females and ≤115 g/m^2 for males.
LOCF analyses are based on last study assessment, including any unscheduled or early termination visits, and data are summarized for all patients with data at that timepoint.
[a]Statistically significant based on 95% CI.

Improvements in MWFS

- At baseline, impaired MWFS (<15% for females and <14% for males) was reported in 9 and 19 (14 migalastat, 5 ERT) patients from the FACETS and ATTRACT trials, respectively
  - Lower mean MWFS was observed in patients with LVH vs those without LVH at baseline in both studies (FACETS, 12.2% vs 17.4%; ATTRACT, 13.4% vs 17.2%)
- In FACETS, the majority of patients with impaired MWFS at baseline demonstrated increases after long-term migalastat treatment (**Table 3**)

Table 3. Changes From Baseline in MWFS (%) With Migalastat Treatment in Patients With Amenable Mutations and Impaired MWFS at Baseline (FACETS; mean MWFS at baseline, 11.3%)

	Timepoint				
	Month 12	Month 24	Month 36	Month 48	LOCF
n	7	8	4	3	8
Mean change from baseline (95% CI)	0.1 (–1.2, 1.4)	1.4 (–1.3, 4.0)	1.4 (–1.5, 4.3)	2.4 (–2.1, 6.9)	1.9 (–0.8, 4.5)
Any increase	2/7 (29%)	5/8 (63%)	3/4 (75%)	3/3 (100%)	6/8 (75%)
Normalization	0	2/8 (25%)	2/4 (50%)	2/3 (67%)	3/8 (38%)

LOCF analyses are based on last study assessment, including any unscheduled or early termination visits.
Abnormal MWFS is <15% for females and <14% for males.
MWFS=midwall fractional shortening.

- In ATTRACT, an LOCF analysis revealed generally stable MWFS in patients with impaired MWFS at baseline over 30 months of treatment with migalastat (–0.2%; 95% CI –1.3, 1.0; n=14) and over 18 months of treatment with ERT (–0.6%; 95% CI –2.6, 1.4; n=5)

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 increases in MWFS, a measure of systolic function, in a majority of patients in FACETS with abnormal MWFS at baseline
- These beneficial long-term effects on LVMi and LVH suggest that migalastat has the potential to reduce the risk of cardiac complications associated with Fabry disease

REFERENCES

1. Waldek S et al. *Genet Med*. 2009;11(11):790-796.
2. Morrissey RP et al. *Cardiovasc J Afr*. 2011;22(1):38-44.
3. Weidemann F et al. *Annu Rev Med*. 2011;62:59-67.
4. Patel MR et al. *J Am Coll Cardiol*. 2011;57(9):1093-1099.
5. Kampmann C et al. *Clin Ther*. 2009;31(9):1966-1976.
6. Kampmann C et al. *Int J Cardiol*. 2008;130(3):367-373.
7. Patel V et al. *Heart*. 2015;101(12):961-966.
8. Mehta A et al. *Lancet*. 2009;374(9706):1986-1996.
9. Weidemann F et al. *Circulation*. 2009;119(4):524-529.
10. Galafold (summary of product characteristics). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004059/WC500208434.pdf. Accessed August 1, 2017.
11. Yam GH-F et al. *FASEB J*. 2005;19(1):12-18.
12. Germain DP et al. *N Engl J Med*. 2016;375(6):545-555.
13. Hughes DA et al. *J Med Genet*. 2017;54(4):288-296.
14. Benjamin ER et al. *Genet Med*. 2017;19(4):430-438.

ACKNOWLEDGMENTS

The authors acknowledge the patients and their families, as well as the FACETS and ATTRACT study investigators. Third-party medical editorial assistance was provided by ApotheCom and was supported by Amicus Therapeutics, Inc.

DISCLOSURES

Conflicts of Interest

AJ has no conflicts of interest to disclose. RS has received research funding from Amicus Therapeutics, Protalix Biotherapeutics, Genzyme, and Shire. KN serves on advisory boards for and has received research funding from Amicus Therapeutics, Genzyme, and Shire. UFR serves on advisory boards for and has received research funding from Amicus Therapeutics, Genzyme, and Shire. DGB serves as a consultant and speaker for Amicus Therapeutics and Genzyme, and has received research funding from Amicus Therapeutics, Genzyme, and Shire. DAH is a consultant for and has received research and travel funding from Amicus Therapeutics, Genzyme, Shire, Actelion, and Protalix. VP, JY, JPC, NS, and JAB are employees of and hold stock in Amicus Therapeutics. RG serves as a speaker for Amicus Therapeutics, BioMarin, Genzyme, and Shire.

Supported by Amicus Therapeutics, Inc.

Presented at the 13th International Congress of Inborn Errors of Metabolism; September 5-8, 2017; Rio de Janeiro, Brazil