636

Efficacy and Safety of Migalastat, an Oral Pharmacological Chaperone for Fabry Disease: Renal Findings From Two Randomized Phase 3 Studies (FACETS and ATTRACT)

Jovanovic A[1], Schiffmann R[2], Nicholls K[3], Feldt-Rasmussen U[4], Giugliani R[5], Bichet DG[6], Hughes DA[7], Jain V[8], Yu J[8], Castelli JP[8], Skuban N[8], Barth JA[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]Medical Genetics Service, HCPA/UFRGS, Porto Alegre, Brazil; [6]Hôpital du Sacré-Coeur, University of Montreal, Montreal, Quebec, Canada; [7]Royal Free NHS Foundation Trust and University College London, London, UK; [8]Amicus Therapeutics, Inc., Cranbury, NJ, USA

INTRODUCTION

- Fabry disease is a devastating, rare, and progressive X-linked lysosomal storage disorder caused by a mutation in the *GLA* gene, resulting in the functional deficiency of α-galactosidase A (α-Gal A)[1]
- Accumulation of α-Gal A substrates, including glycosphingolipids such as globotriaosylceramide (GL-3) and globotriaosylsphingosine (lyso-Gb_3), can lead to multisystem disease and premature death[1]
- Migalastat, a first-in-class, orally administered small molecule, is a pharmacologic chaperone approved in the European Union, Switzerland, and Israel for the treatment of Fabry disease in patients with *amenable GLA* mutations[2]
- Migalastat restores lysosomal trafficking and enzyme activity by binding and inducing proper folding of amenable mutant forms of α-Gal A[1,3]
- As an orally administered small molecule, migalastat may obviate the need for lifelong biweekly agalsidase infusions or enzyme replacement therapy (ERT)[4,5]

OBJECTIVE

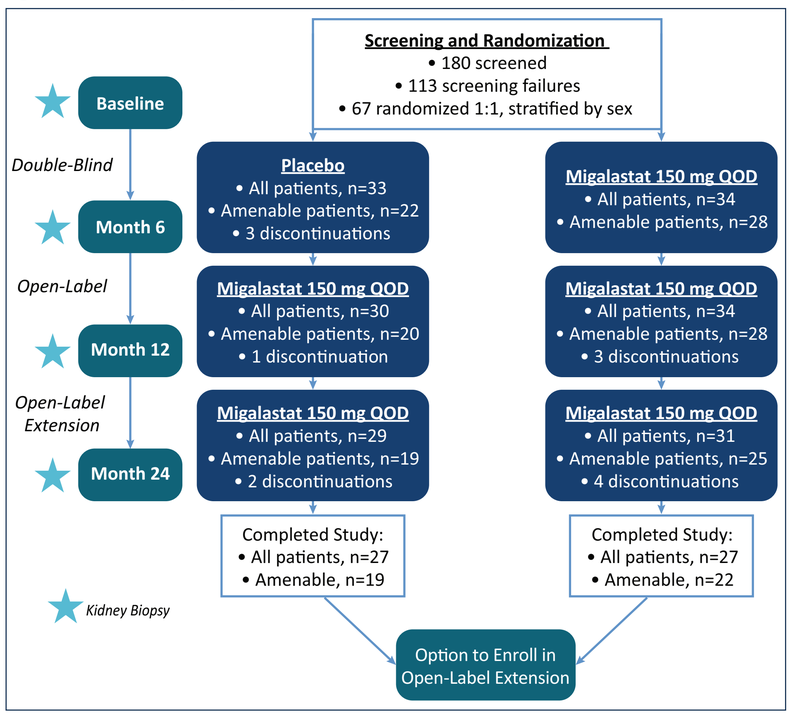
- To summarize renal findings from 2 randomized phase 3 studies of migalastat in patients with Fabry disease

METHODS

Study Designs

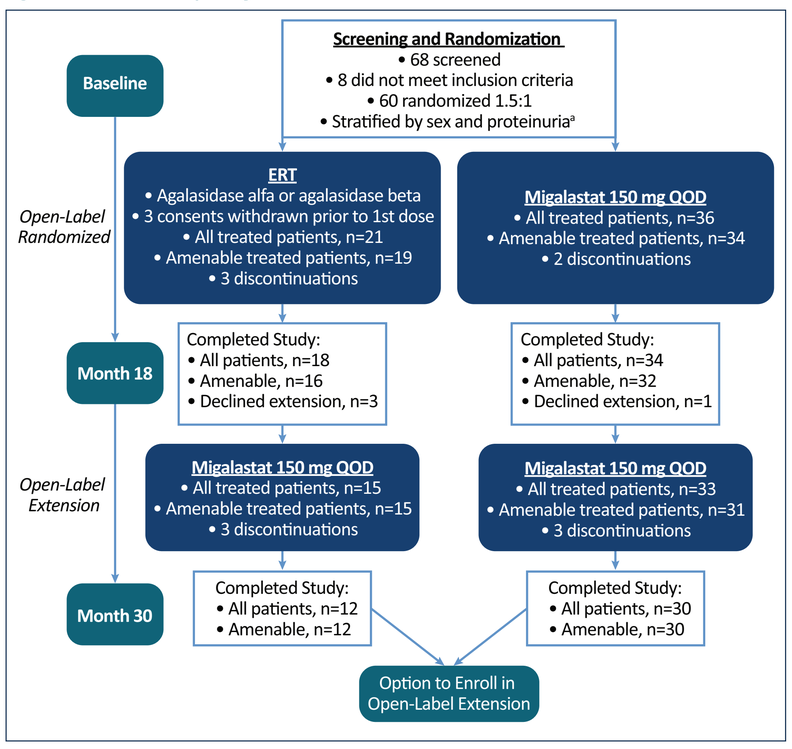
- FACETS (AT1001-011, NCT00925301) was a phase 3, double-blind, randomized, placebo-controlled study to evaluate the efficacy, safety, and pharmacodynamics of migalastat in patients with Fabry disease with amenable *GLA* mutations (**Figure 1**)
- ATTRACT (AT1001-012, NCT01218659) was a phase 3, randomized, 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 (**Figure 2**)

Figure 1. FACETS Study Design



QOD=every other day.

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
- 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)
- $eGFR_{MDRD}$ at screening ≥30 mL/min/1.73 m^2
- Urine GL-3 at screening ≥4× the upper limit of normal (24-hour collection) (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

RESULTS

- The FACETS and ATTRACT studies randomized 67 and 60 patients, respectively, of which 50 and 56 patients, respectively, had amenable mutations
- Patients in both studies had significant baseline disease severity
  - 94% and 88% of patients in the FACETS and ATTRACT studies, respectively, had Fabry disease in ≥2 organ systems[4,6]
  - 90% and 75% of patients in the FACETS and ATTRACT studies, respectively, had renal involvement[4,6]

Disease Substrate

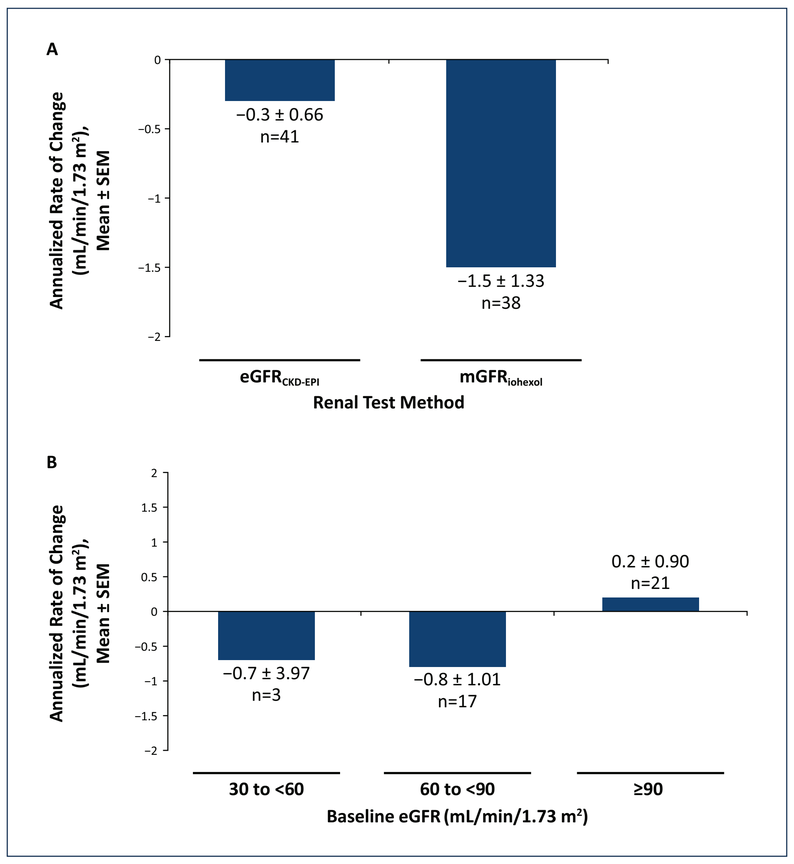
- In FACETS, migalastat treatment significantly reduced interstitial capillary GL-3 inclusions and lyso-Gb_3 levels in patients with Fabry disease with amenable mutations[6]
- In ATTRACT, plasma lyso-Gb_3 levels remained low and stable following the switch from ERT to migalastat in patients with amenable mutations. Plasma lyso-Gb_3 levels increased in 2 patients with non-amenable mutations following the switch from ERT to migalastat, but did not change in 2 patients with non-amenable mutations who remained on ERT[4]

Renal Function

FACETS

- From baseline to month 24, renal function was stable in patients with amenable mutations treated with migalastat in the FACETS study (**Figure 3**)
- Stabilization of renal function was observed regardless of baseline eGFR

Figure 3. Annualized Mean Change From Baseline to Month 24 in (A) $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$ in All Patients and (B) $eGFR_{CKD\text{-}EPI}$ by Baseline eGFR (FACETS; patients with amenable mutations)

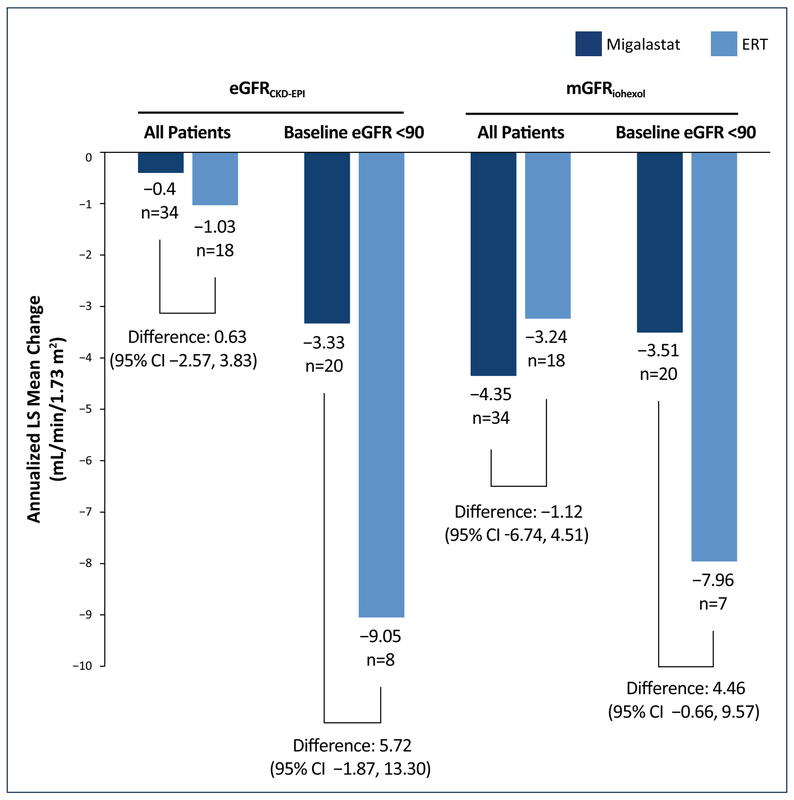


Annualized rates based on the subset of patients who received at least 17 months of treatment with migalastat.
$eGFR_{CKD\text{-}EPI}$=estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; $mGFR_{iohexol}$=measured glomerular filtration rate using iohexol clearance; SEM=standard error of the mean.

ATTRACT

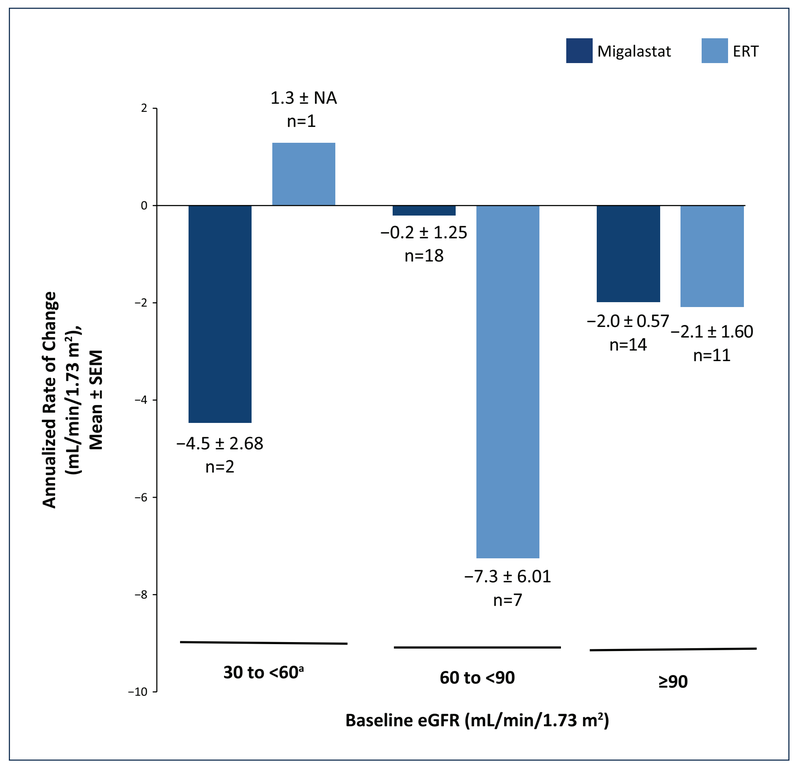
- In the ATTRACT study, migalastat and ERT had comparable favorable effects on renal function at month 18 using both GFR methods (**Figure 4**)
- Migalastat stabilized renal function at 18 months regardless of baseline eGFR (**Figure 5**)

Figure 4. Annualized LS Mean Change in GFR From Baseline to Month 18 (ATTRACT; patients with amenable mutations)



LS means and 95% confidence intervals (CIs) based on analysis of covariance that includes treatment, baseline GFR, sex, age, and 24-hour urine protein.
eGFR=estimated glomerular filtration rate; GFR, glomerular filtration rate; LS=least squares.

Figure 5. Annualized Rate of Change in $eGFR_{CKD\text{-}EPI}$ at Month 18 by Baseline eGFR (ATTRACT; patients with amenable mutations)



NA=not applicable.
[a]Inconclusive due to low n number.

- In ATTRACT, renal function remained stable in patients with amenable mutations following 30 months of migalastat treatment using both GFR methods
  - The mean annualized change from baseline to month 30 in $eGFR_{CKD\text{-}EPI}$ was −1.7 mL/min/1.73 m^2 (95% CI, −2.7 to 0.8) (n=31) and in $mGFR_{iohexol}$ was −2.7 mL/min/1.73 m^2 (95% CI, −4.8 to 0.7) (n=31)

Summary of Safety Findings From FACETS and ATTRACT

- Treatment with migalastat was generally safe and well tolerated, with no adverse event (AE) trends attributable to migalastat
- Most treatment-emergent AEs (TEAEs) reported with migalastat use were mild or moderate, and required no intervention or were readily managed in standard clinical practice
- The profile of TEAEs was similar between migalastat and placebo treatment, with headache the most commonly reported TEAE
- There were few serious AEs considered related to migalastat and no deaths during either study
- There were few discontinuations due to TEAEs, and most were related to underlying Fabry disease comorbidities
- Predefined renal AEs during the 18-month comparison stage of ATTRACT occurred in 24% and 33% of patients receiving migalastat and ERT, respectively
  - No patients progressed to end-stage renal disease

CONCLUSIONS

- Migalastat was generally well tolerated and effective in patients with amenable mutations in FACETS and ATTRACT
- In both FACETS and ATTRACT, treatment with migalastat stabilized renal function
  - In ATTRACT, migalastat and ERT were shown to have comparable effects on renal function
- Approved in the European Union, Switzerland, and Israel, migalastat offers promise as a first-in-class oral treatment for male and female patients aged ≥16 years with Fabry disease with amenable mutations

REFERENCES

1. Ishii S et al. *Biochem J*. 2007;406(2):285-295.
2. 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.
3. Yam GH-F et al. *FASEB J.* 2005;19(1):12-18.
4. Hughes DA et al. *J Med Genet*. 2017;54(4):288-296.
5. Linthorst GE et al. *Kidney Int.* 2004;66(4):1589-1595.
6. Germain DP et al. *N Engl J Med*. 2016;375(6):545-555.

ACKNOWLEDGMENTS

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

DISCLOSURE

Conflicts of Interest

AJ has no conflicts of interest to disclose. RS has received research funding from Amicus Therapeutics, Protalix Biotherapeutics, Shire, and Genzyme. 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. RG has received honoraria from Amicus Therapeutics, BioMarin, Sanofi-Genzyme, and Shire. DGB serves as a consultant and speaker for and has received funding from Amicus Therapeutics and Genzyme, and has received research funding from Shire. DAH is a consultant for and has received research and travel funding from Amicus Therapeutics, Shire, Genzyme, Actelion, and Protalix. VJ, JY, JPC, NS, and JAB are employees of and own stock in Amicus Therapeutics.

Supported by Amicus Therapeutics, Inc.

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