SP002

# Clinical Outcomes With Migalastat in Patients With Fabry Disease Based on Degree of Renal Impairment: Results From Phase 3 Trials


**Torra R,[1] Feldt-Rasmussen U,[2] Germain DP,[3] Hughes DA,[4] Bichet DG,[5] Schiffmann R,[6] Yu J,[7] Castelli JP,[7] Skuban N,[7] Barth JA[7]**

[1]Inherited Kidney Diseases, Fundacio Puigvert, Universitat Autonoma de Barcelona, Barcelona, Spain; [2]Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [3]Division of Medical Genetics, University of Versailles–St. Quentin en Yvelines (UVSQ), University Paris-Saclay, Montigny, France; [4]Royal Free NHS Foundation Trust and University College London, London, UK; [5]Hôpital du Sacré-Coeur, University of Montreal, Montreal, Quebec, Canada; [6]Baylor Research Institute, Dallas, TX, USA; [7]Amicus Therapeutics, Inc., Cranbury, NJ, USA


## INTRODUCTION

- Fabry disease is a progressive, X-linked disorder caused by functional deficiency of α-galactosidase A (α-Gal A) that leads to accumulation of globotriaosylceramide (GL-3) in multiple cell types and organs, often culminating in multiorgan disorders and early death[1]
- Migalastat, a first-in-class, orally administered small molecule, is a pharmacological chaperone approved in the European Union, Switzerland, Australia, Israel, Republic of Korea, and Japan for long-term treatment of adults and adolescents aged 16 years and older with a confirmed diagnosis of Fabry disease (α-Gal A deficiency) and who have an migalastat-amenable *GLA* mutation[2,3]
- Migalastat is also approved in Canada for adults (aged 18 years and older)
- Migalastat binds to and stabilizes amenable mutant forms of α-Gal A in the endoplasmic reticulum and facilitates cellular trafficking to lysosomes, whereupon dissociation of migalastat leads to the breakdown of target substrates[4,5]
- In the phase 3 FACETS (NCT00925301) and ATTRACT (NCT01218659) trials, migalastat reduced disease substrates, maintained renal function, and decreased cardiac mass in enzyme replacement therapy (ERT)-naive and ERT-experienced patients[6,7]

## OBJECTIVE

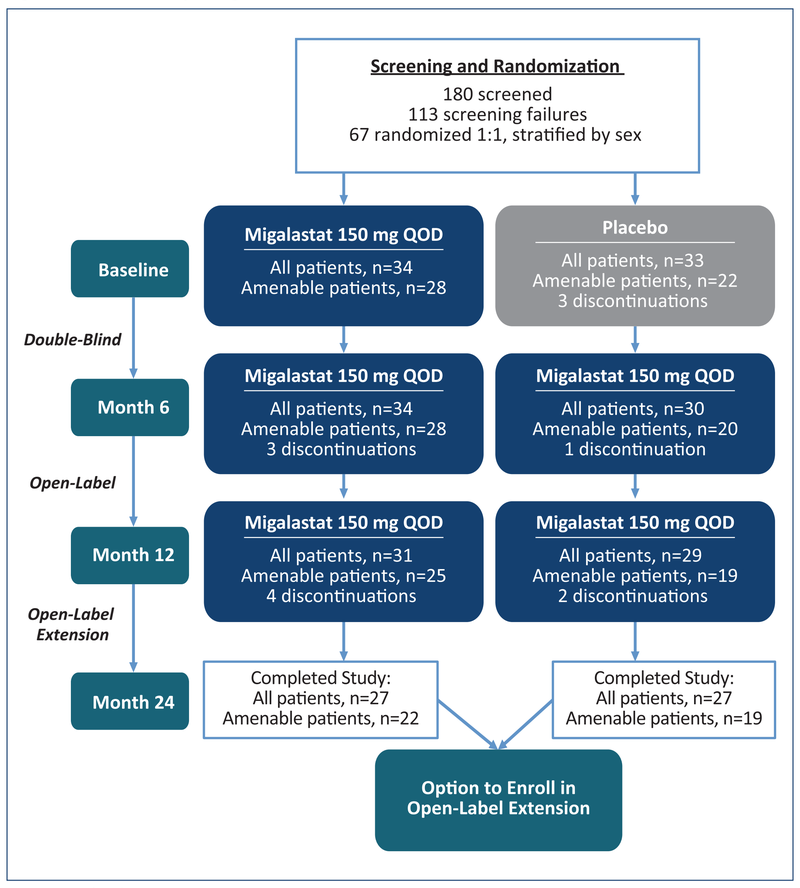
- To assess clinical outcomes by degree of renal impairment at baseline in patients with Fabry disease and amenable *GLA* mutations who received migalastat in the FACETS and ATTRACT studies

## METHODS

### Study Design

- FACETS (NCT00925301) was a phase 3, double-blind, randomized, placebo-controlled study designed to evaluate the efficacy, safety, and pharmacodynamics of 6 months of migalastat 150 mg every other day or placebo, followed by an additional 18 months of open-label migalastat in ERT-naive patients with Fabry disease with amenable mutations[6] (**Figure 1**)

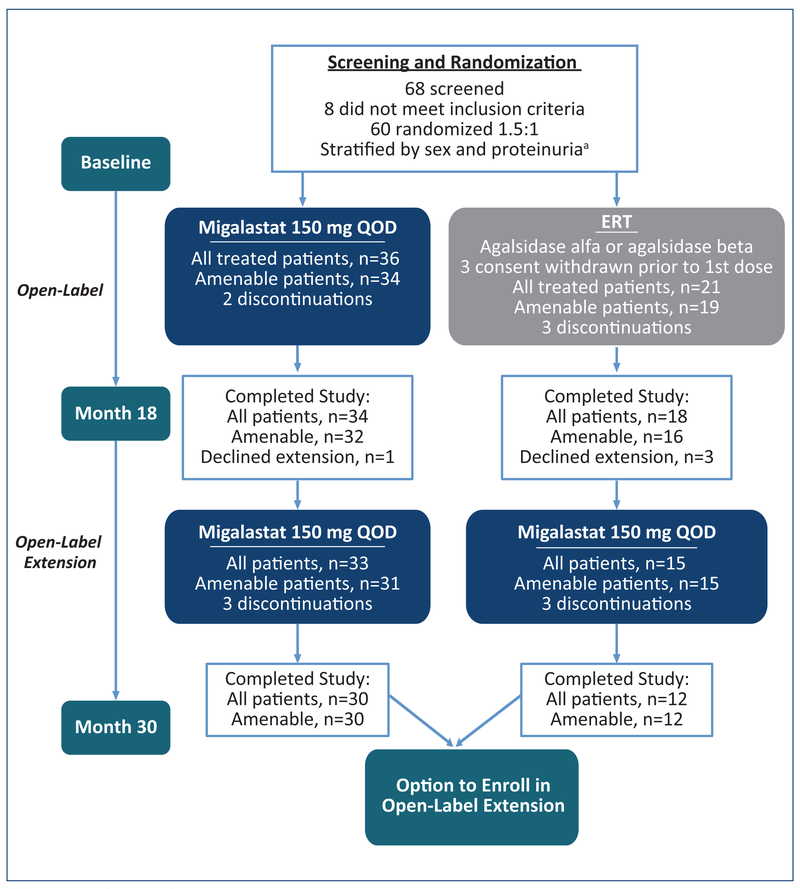
**Figure 1. FACETS Study Design**




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 150 mg every other day or ERT, followed by a 12-month open-label extension of migalastat, in patients with Fabry disease with amenable mutations who were previously treated with ERT[7] (**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 achieved a stable ERT dose (≥80% labeled dose) for 3 months before baseline visit

### Analyses

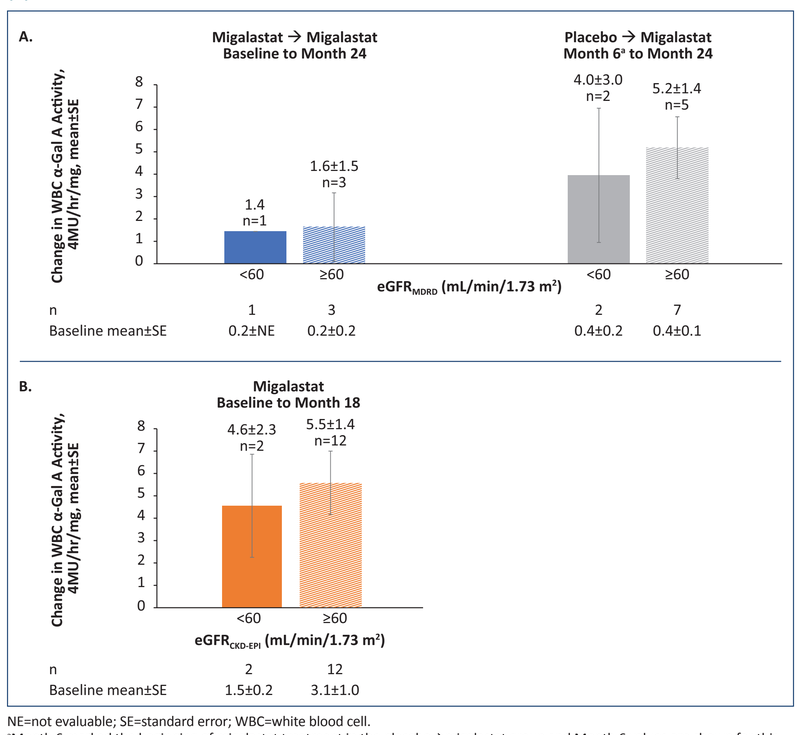
- During the FACETS study, kidney GL-3 was assessed by histologic scoring of the number of inclusions in kidney peritubular capillary (PTC) biopsies
- GFR was estimated using $eGFR_{MDRD}$ and $eGFR_{CKD\text{-}EPI}$
- Echocardiograms were assessed through blinded, centralized evaluation by a single reader specialized in echocardiography and were used to calculate changes in left ventricular mass index (LVMi)
- Analyses were restricted to patients with amenable *GLA* mutations per the Migalastat Amenability Assay[3] and stratified by eGFR at baseline (<60 mL/min/1.73 $m^2$ and ≥60 mL/min/1.73 $m^2$)
- In the FACETS study, patients randomized to receive migalastat at enrollment are referred to as the migalastat→migalastat group; patients initially randomized to receive placebo and switched to migalastat at Month 6 are referred to as the placebo→migalastat group
- Analyses for ATTRACT include data from baseline to Month 18, during which time the patients in the ERT arm did not receive migalastat treatment; therefore, data from the ERT arm are not reported here

## RESULTS

### White Blood Cell α-Gal A Activity

- In FACETS and ATTRACT, white blood cell (WBC) α-Gal A activity (males only) increased with migalastat treatment regardless of baseline renal function (**Figure 3**)

**Figure 3. Change in WBC α-Gal A Activity by Baseline Renal Function During (A) FACETS and (B) ATTRACT**

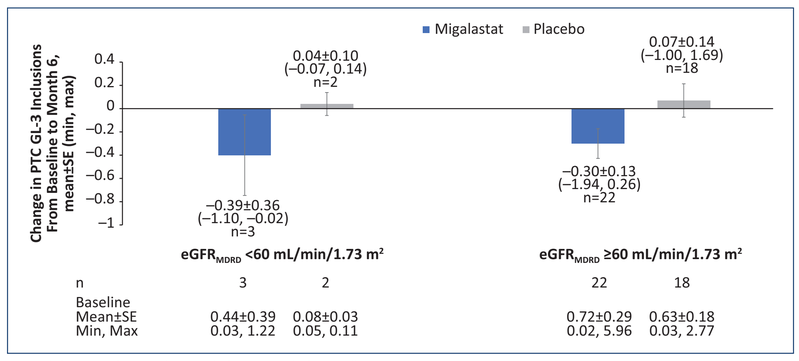



NE=not evaluable; SE=standard error; WBC=white blood cell.
[a]Month 6 marked the beginning of migalastat treatment in the placebo→migalastat group and Month 6 values are shown for this group in the baseline table.
Only male patients were included in this analysis.

### Kidney Peritubular Capillary GL-3 Inclusions

- In FACETS, a reduction in PTC GL-3 inclusions was observed from baseline to Month 6 in patients who began migalastat treatment at randomization but not in placebo→migalastat patients, irrespective of baseline kidney function (**Figure 4**)

**Figure 4. Change in Kidney Peritubular Capillary GL-3 Inclusions From Baseline to Month 6 by Baseline Renal Function During FACETS**




GL-3=globotriaosylceramide; PTC=kidney peritubular capillary.

### Renal Function

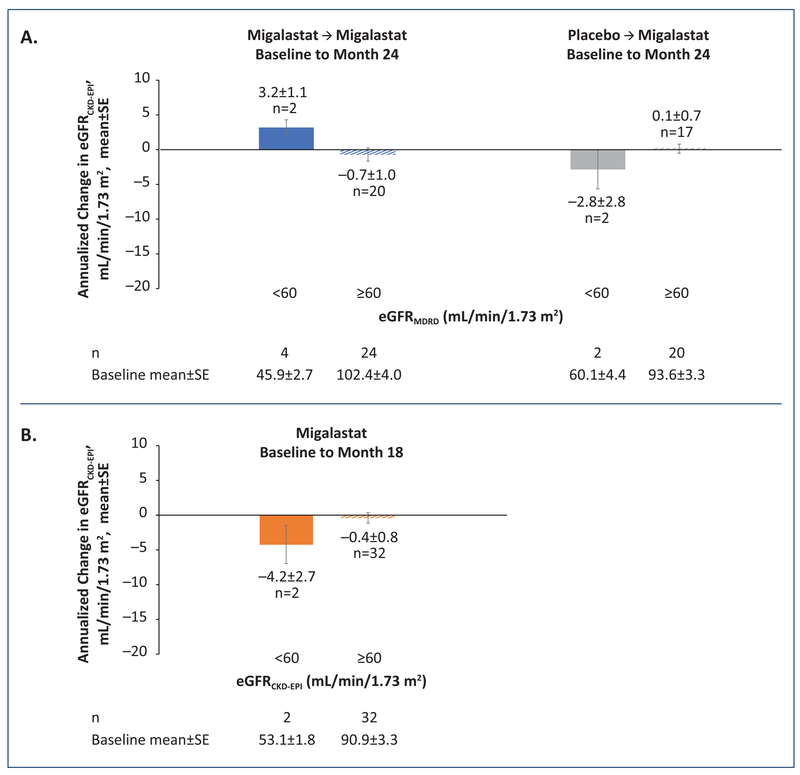
#### FACETS

- In patients with baseline $eGFR_{MDRD}$ ≥60 mL/min/1.73 $m^2$, $eGFR_{CKD\text{-}EPI}$ was stable after 18 or 24 months of migalastat treatment **(Figure 5A)**
  - Among patients with baseline $eGFR_{MDRD}$ <60 mL/min/1.73 $m^2$, those in the migalastat→migalastat group had a slight increase in $eGFR_{CKD\text{-}EPI}$, whereas patients in the placebo→migalastat group had a small reduction in $eGFR_{CKD\text{-}EPI}$

#### ATTRACT

- In patients with baseline $eGFR_{CKD\text{-}EPI}$ ≥60 mL/min/1.73 $m^2$, $eGFR_{CKD\text{-}EPI}$ was stable after 18 months of migalastat treatment **(Figure 5B)**
  - A small reduction in $eGFR_{CKD\text{-}EPI}$ was observed in the 2 migalastat-treated patients with baseline $eGFR_{CKD\text{-}EPI}$ <60 mL/min/1.73 $m^2$

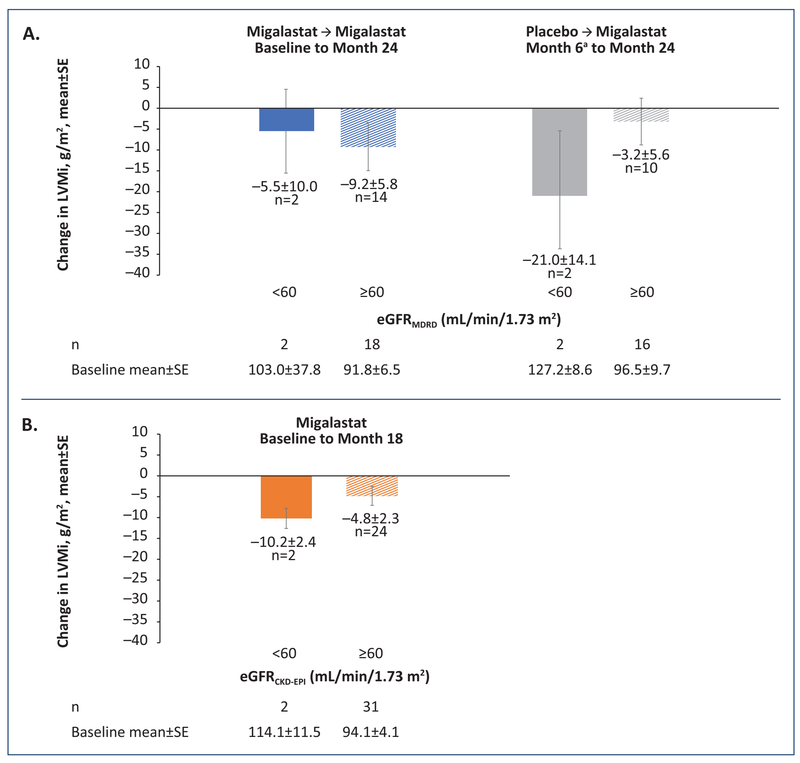
**Figure 5. Annualized Change in $eGFR_{CKD\text{-}EPI}$ Based on Baseline Renal Function in (A) FACETS and (B) ATTRACT**




### Cardiac Mass

- In FACETS and ATTRACT, reductions from baseline in LVMi were observed after 24 and 18 months of treatment with migalastat, respectively (**Figure 6**)

**Figure 6. Change in LVMi Based on Baseline Renal Function During (A) FACETS and (B) ATTRACT**




LVMi=left ventricular mass index; NE=not evaluable.
[a]Month 6 marked the beginning of migalastat treatment in the placebo→migalastat group and Month 6 values are shown for this group in the baseline table.

## CONCLUSIONS

- In both phase 3 trials, patients with Fabry disease and amenable mutations treated with migalastat had similar clinical outcomes regardless of baseline renal function
- The small number of patients with eGFR <60 mL/min/1.73 $m^2$ at baseline should be considered when interpreting these data

## REFERENCES


1. Germain DP. *Orphanet J Rare Dis*. 2010;5:30.
2. Galafold (summary of product characteristics). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004059/WC500208434.pdf. Accessed April 9, 2018.
3. Benjamin ER et al. *Genet Med*. 2017;19(4):430-438.
4. Ishii S et al. *Biochem J*. 2007;406(2):285-295.
5. Yam GH-F et al. *FASEB J*. 2005;19(1):12-18.
6. Germain DP et al. *N Engl J Med*. 2016;375(6):545-555.
7. Hughes DA et al. *J Med Genet*. 2017;54(4):288-296.


## ACKNOWLEDGMENTS


The authors thank the patients, their families, and the FACETS and ATTRACT study investigators. Medical writing assistance was provided by ApotheCom (Yardley, PA) and was supported by Amicus Therapeutics, Inc.


## DISCLOSURES

### Conflicts of Interest

RT has received honoraria from Amicus, Otsuka, Sanofi Genzyme, Orphan Recordatti, Shire, and Novartis. 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 Sanofi Genzyme and Shire. DPG has received honoraria and research grants from Amicus, Sanofi Genzyme, and Shire. DAH has served as a consultant for and has received research and travel funding from Amicus, Sanofi Genzyme, Shire, Actelion, and Protalix. DGB has served as a consultant and speaker for Amicus and Sanofi Genzyme, and has received research funding from Amicus, Sanofi Genzyme, and Shire. RS has received research funding from Amicus, Protalix Biotherapeutics, Sanofi Genzyme, and Shire. JY, JPC, NS, and JAB are employees of and hold stock in Amicus.

http://bit.ly/2GTtZIk


**Supported by Amicus Therapeutics, Inc.**

**Torra R et al. Clinical outcomes with migalastat in patients with Fabry disease based on degree of renal impairment: results from phase 3 trials. Presented at the 55th ERA-EDTA Congress; May 24-27, 2018; Copenhagen, Denmark. Poster SP002**