Efficacy of Migalastat in a Cohort of Male Patients With the Classic Fabry Phenotype in the FACETS Phase 3 Study

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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]
- More than 800 disease-causing mutations in *GLA* have been identified (≈60% missense) that are associated with multiorgan impairment and premature death[1,2]
- Migalastat, a first-in-class, orally administered small molecule, is a pharmacologic chaperone approved in the European Union for the treatment of Fabry disease in patients with *amenable GLA* mutations[3,4]
- Migalastat binds and induces proper folding of amenable mutant forms of α-Gal A, restoring lysosomal trafficking and enzyme activity[3,4]

OBJECTIVE

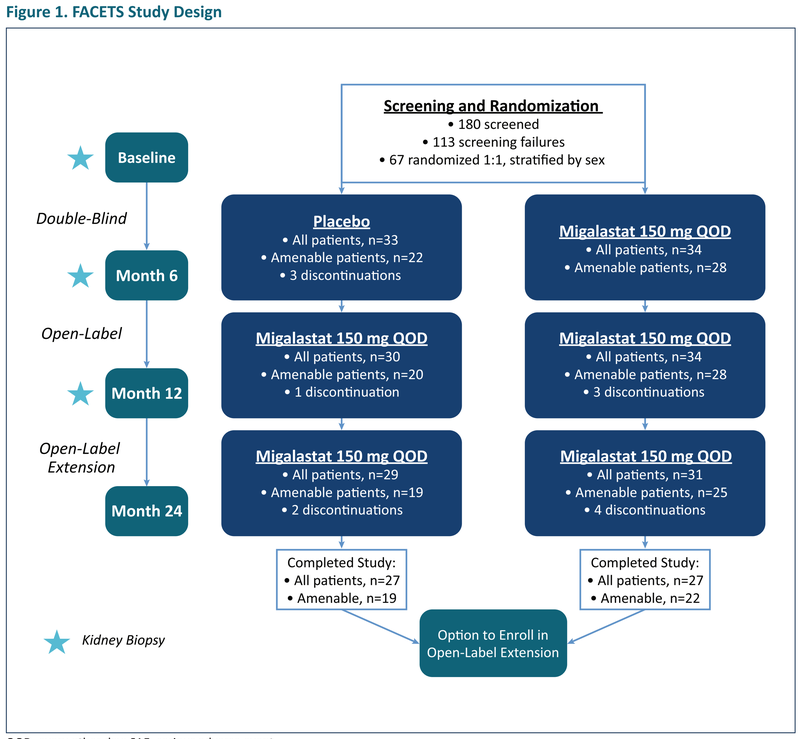
- To evaluate the efficacy of migalastat in male patients presenting with the classic phenotype compared with the efficacy of migalastat in male patients with the non-classic phenotype and in female patients, using data from the phase 3 FACETS study in patients with Fabry disease with amenable *GLA* mutations

METHODS

Study Design

- FACETS (AT1001-011, NCT00985301) is a phase 3, randomized, placebo-controlled study to evaluate the efficacy, safety, and pharmacodynamics of migalastat in patients with Fabry disease and amenable mutations. The study consisted of 6 months of double-blind treatment with migalastat or placebo and 6 months of open-label migalastat, followed by a 12-month open-label extension (AT1001-041, NCT01458119) (**Figure 1**)

Figure 1. FACETS Study Design



QOD=every other day; SAE=serious adverse event.

Summary of Analyses

- Post hoc analyses compared male patients with the classic phenotype to an "Other" group, which consisted of male patients with the non-classic phenotype and female patients
  - The classic phenotype was defined as multiorgan system involvement and white blood cell α-Gal A activity <3%
- Results were compared with those of untreated male patients described in the literature
- Left ventricular mass index (LVMi; calculated from blinded centralized reads of echocardiograms) was assessed at baseline and months 6, 12, and 24
- Renal function was assessed at baseline and months 1, 3, 6, 7, 9, 12, 18, and 24 with $eGFR_{CKD\text{-}EPI}$; $mGFR_{iohexol}$ was assessed at baseline and months 6, 12, 18, and 24
- Plasma globotriaosylsphingosine (lyso-Gb_3) was measured using the retained iohexol plasma samples taken at baseline and months 6 and 12
- The Gastrointestinal Symptoms Rating Scale (GSRS) was used to assess diarrhea (GSRS-D), a common and debilitating gastrointestinal sign in patients with Fabry disease,[5,6] with assessments at baseline and months 6, 12, 18, and 24

RESULTS

Baseline Measurements

- Male patients enrolled in the FACETS study with the classic phenotype had more severe manifestations of Fabry disease compared with the cohort of male patients with the non-classic phenotype and female patients (**Table 1**)
- At baseline, 7 of the 14 male patients with the classic phenotype had left ventricular hypertrophy >115 g/m²

Table 1. Baseline Characteristics

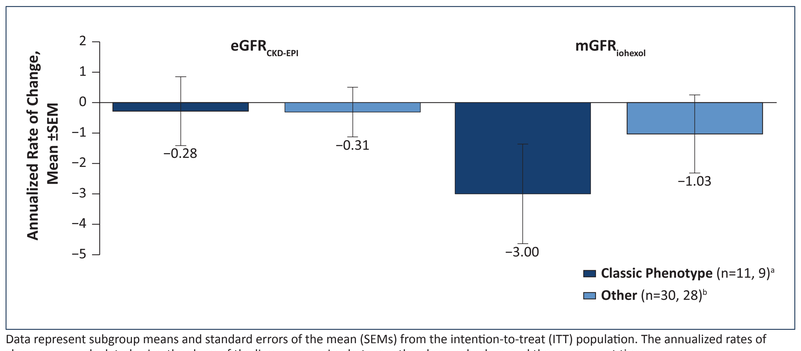
Phenotype	$eGFR_{CKD\text{-}EPI}$	$mGFR_{iohexol}$	LVMi	Lyso-Gb_3
Classic phenotype[a]				
n	14	11	14	7
Mean (SD)	87.80 (33.59)	78.59 (22.89)	114.33 (27.34)	99.83 (35.28)
Other[b]				
n	34	31	30	24
Mean (SD)	95.33 (19.64)	88.17 (21.99)	88.18 (32.32)	29.31 (48.32)

$eGFR_{CKD\text{-}EPI}$=estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; mL/min/1.73 m²); lyso-Gb_3=globotriaosylsphingosine; LVMi=left ventricular mass index (g/m²); $mGFR_{iohexol}$=measured glomerular filtration rate using iohexol clearance; mL/min/1.73 m²); SD=standard deviation.
[a]Classic phenotype: male patients with multiorgan system involvement and white blood cell α-Gal A activity <3%.
[b]Other: male patients with the non-classic phenotype and female patients.

Renal Assessments

- The beneficial effects of migalastat on $eGFR_{CKD\text{-}EPI}$ were found in male patients with the classic phenotype and the subgroup consisting of male patients with the non-classic phenotype and female patients (**Figure 2**)
  - Migalastat treatment reduced or stabilized GFR in all patients (male, female, classic, and non-classic)

Figure 2. Annualized Rate of Change From Baseline/Month 6 to Month 24

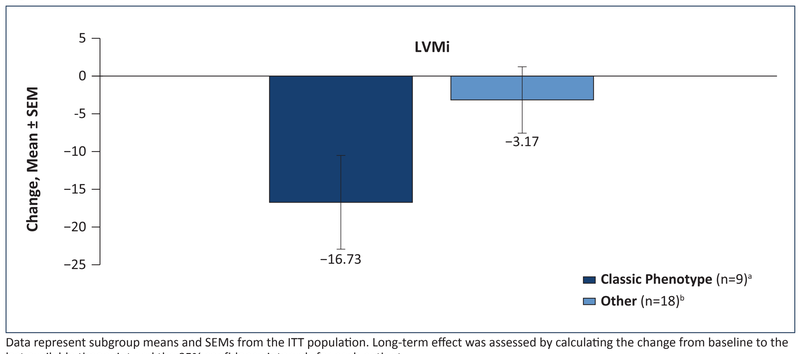


Data represent subgroup means and standard errors of the mean (SEMs) from the intention-to-treat (ITT) population. The annualized rates of change were calculated using the slope of the linear regression between the observed values and the assessment times.
[a]Classic phenotype: male patients with multiorgan system involvement and white blood cell α-Gal A activity <3%.
[b]Other: male patients with the non-classic phenotype and female patients.

Echocardiology: LVMi

- The benefits of migalastat on LVMi were observed in male patients with the classic phenotype and the subgroup consisting of male patients with the non-classic phenotype and female patients (**Figure 3**)
- Larger effects in the classic male patients were associated with higher baseline values

Figure 3. Change in LVMi From Baseline/Month 6 to Month 18/24

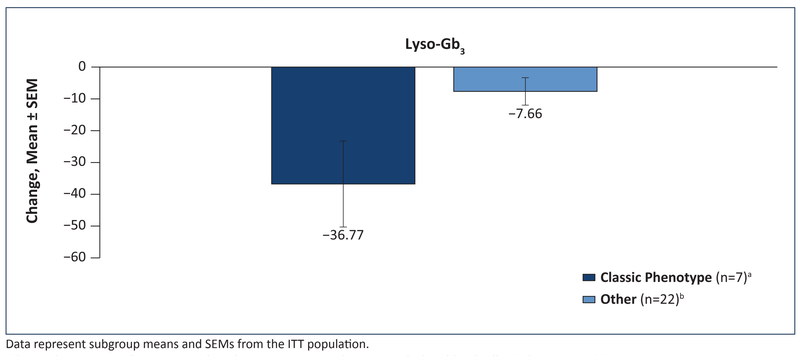


Data represent subgroup means and SEMs from the ITT population. Long-term effect was assessed by calculating the change from baseline to the last available timepoint and the 95% confidence intervals for each patient.
[a]Classic phenotype: male patients with multiorgan system involvement and white blood cell α-Gal A activity <3%.
[b]Other: Non-classic male patients and female patients.

Plasma Lyso-Gb_3

- The benefits of migalastat in reducing lyso-Gb_3 were observed in male patients with the classic phenotype and the subgroup consisting of non-classic male patients and female patients (**Figure 4**)

Figure 4. Change in Plasma Lyso-Gb_3 From Baseline/Month 6 to Month 18/24

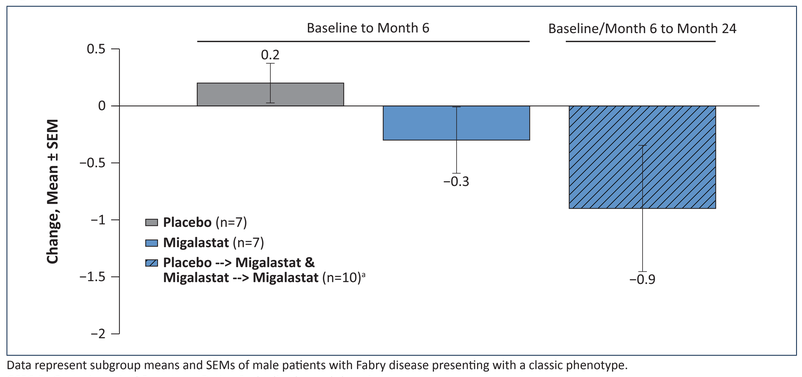


Data represent subgroup means and SEMs from the ITT population.
[a]Classic phenotype: male patients with multiorgan system involvement and white blood cell α-Gal A activity <3%.
[b]Other: male patients with the non-classic phenotype and female patients.

Gastrointestinal Signs and Symptoms-Diarrhea

- Six months of treatment with migalastat improved scores in GSRS-D in male patients presenting with a classic phenotype, whereas treatment with placebo did not (**Figure 5**)
- These results provide additional evidence for the beneficial effects of migalastat in the most severely affected patients in the FACETS study

Figure 5. Change in GSRS-D in Classic Males



Data represent subgroup means and SEMs of male patients with Fabry disease presenting with a classic phenotype.
GSRS-D=Gastrointestinal Symptoms Rating Scale diarrhea subdomain.
[a]Combined results include patients randomized to migalastat at baseline and patients switched to migalastat at month 6.

Comparison of Results With Untreated Male Patients Described in the Literature

- In male patients with the classic phenotype, treatment with migalastat resulted in better outcomes in renal function and LVMi than no treatment
- For GFR, studies with untreated (primarily classic) males reported an annualized change from baseline of −7.0 ± 32.9 for mGFR[7] and an annualized change from baseline ranging from −2.6 to −12.7 for $eGFR_{CKD\text{-}EPI}$[8-11], compared with −3.0 ± 6.0 for mGFR and −0.3 ± 3.8 for $eGFR_{CKD\text{-}EPI}$ for migalastat-treated males with the classic phenotype in FACETS
- For LVMi, studies with untreated males reported an annualized change from baseline ranging from 4.07[12] to 8.0,[13] compared with −10.4 ± 11.8 for migalastat-treated males with the classic phenotype in FACETS

CONCLUSIONS

- The post hoc analyses demonstrated the beneficial effects of migalastat on $eGFR_{CKD\text{-}EPI}$, $mGFR_{iohexol}$, LVMi, lyso-Gb_3, and GSRS-D in both males with the classic phenotype, who constitute the population with the most sensitive and severe form of Fabry disease, and the "Other" subgroup consisting of male patients with the non-classic phenotype and female patients
- Migalastat treatment produced better outcomes in male patients with the classic phenotype compared with untreated male patients with Fabry disease, based on the literature
- All patients (male, female, classic, and non-classic) with amenable mutations could be expected to benefit from treatment with migalastat

REFERENCES

1. Ishii S et al. *Biochem J*. 2007;406(2):285-295.
2. HGMD® Human Gene Mutation Database. http://www.biobase-international.com/product/hgmd. Accessed June 30, 2016.
3. Galafold (summary of product characteristics). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004059/WC500208434.pdf. Accessed January 17, 2017.
4. Yam GH-F et al. *FASEB J*. 2005;19(1):12-18.
5. Hoffmann B et al. *Clin Gastroenterol Hepatol*. 2007;5(12):1447-1453.
6. Svedlund J et al. *Dig Dis Sci*. 1988;33(2):129-134.
7. West M et al. *J Am Soc Nephrol*. 2009:20(5):1132-1139.
8. Wanner C et al. *Clin J Am Soc Nephrol*. 2010;5(12):2220-2228.
9. Schiffmann R et al. *Nephrol Dial Transplant*. 2009;24(7):2102-2111.
10. Schwarting A et al. *Clin Nephrol*. 2006;66(2):77-84.
11. Branton MH et al. *J Am Soc Nephrol*. 2002;13(suppl 2):S139-S143.
12. Kampmann C et al. *Int J Cardiol*. 2008;130(3):367-373.
13. Germain DP et al. *Genet Med*. 2013;15(12):958-965.

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DISCLOSURES

Conflicts of Interest

DPG has no conflicts of interest to disclose. RG is a consultant and an investigator for Amicus Therapeutics, Biomarin, Genzyme, and Shire; has received educational grants from Alexion and Ultragenyx; is a speaker for and has received honoraria from Amicus Therapeutics, Actelion, Biomarin, Genzyme, and Shire; and has received travel grants from Alexion. DGB is an investigator for and has received research funding from Amicus Therapeutics, Genzyme, and Shire. WRW is a consultant for Genzyme; is an investigator for Amicus Therapeutics and Genzyme; has received research funding from Shire; and is a member of the Fabry Registry Board of Advisors. DAH is a consultant/advisor for Shire, Sanofi, Biomarin, Amicus Therapeutics, Actelion, and Protalix; has received research funding from Shire and Sanofi; and is a speaker for and has received travel support from Shire, Sanofi, Biomarin, Amicus Therapeutics, and Protalix. HMA is a consultant and speaker for Shire and Biomarin and has received research funding from Shire, Amicus Therapeutics, and BlueBirdBio. RS has served as a consultant for and received research funding from Protalix Biotherapeutics and Amicus Therapeutics. CV, NS, JPC, and JAB are employees of Amicus Therapeutics.

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