Patients with Fabry Disease and Amenable Mutations Treated with Migalastat Show Reduced Left Ventricular Mass Index and Continue to Demonstrate Stable Renal Function over Three Years in a Phase 3 Extension Study

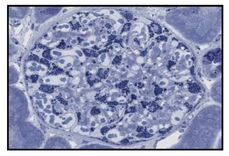
Germain DP[1], Bichet DG[2], Giugliani R[3], Hughes D[4], Schiffmann R[5], Wilcox W[6], Castelli J[7], Benjamin ER[7], Yu J[7], Kirk J[7], Skuban N[7], and Barth J[7] on behalf of the FACETS investigators

[1]Hôpital Raymond Poincaré (AP-HP), University of Versailles – St. Quentin en Yvelines (UVSQ), Garches, France; [2]Hôpital du Sacré-Coeur, University of Montreal, Canada; [3]Medical Genetics Service, HCPA/UFRGS Porto Alegre, Brazil; [4]Royal Free Campus, University College London, London, UK; [5]Baylor Research Institute, Dallas, TX; [6]Department of Human Genetics, Emory University, Georgia; [7]Amicus Therapeutics, 1 Cedar Brook Drive, Cranbury, NJ, USA;

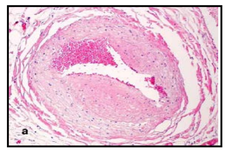
Introduction

Fabry Disease

- Progressive X-linked lysosomal storage disorder with an estimated incidence of 1 in 100,000. Actual incidence is thought to be higher.
- Mutations in the *GLA* gene lead to a paucity or absence of α-galactosidase A (α-Gal A) activity and accumulation of substrates in multiple organs.
- More than 800 disease-causing mutations in *GLA* have been identified (~60% missense).
- Affects males and females; females have mosaic of healthy & diseased cells.
- Globotriaosylceramide (GL-3), plasma globotriaosylsphingosine (lyso-Gb_3), and other substrates of α-Gal A accumulate in multiple tissues including the kidney, heart, brain, GI, skin leading to the symptoms and sequelae of Fabry disease and early mortality.



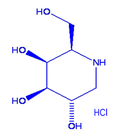
Kidney GL-3



Coronary GL-3

Migalastat for Fabry Disease

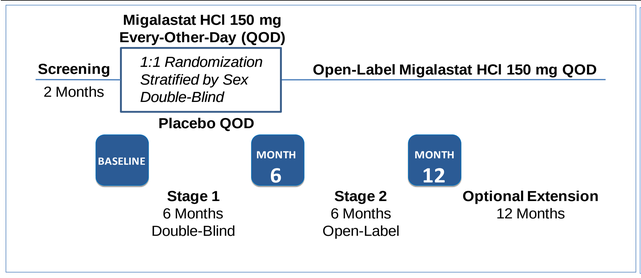
- Orally administered investigational pharmacological chaperone in development as an alternative monotherapy to enzyme replacement therapy.
- By reversibly binding to the active site of α-Gal A, migalastat stabilizes specific mutant forms of the enzyme to facilitate their proper folding and cellular trafficking from the endoplasmic reticulum to lysosomes where dissociation of migalastat allows α-Gal A to breakdown accumulated substrate.
- In development for treatment of patients with Fabry disease expressing mutant forms of α-Gal A categorized as 'amenable' in an *in vitro* GLP-validated cell-based assay.



Deoxygalactonojirimycin (DGJ)
AT1001

Overview: AT1001-011 (FACETS, NCT00925301) & AT1001-041 (NCT01458119)

Study 011: A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy, Safety and Pharmacodynamics of Migalastat HCl in Patients With Fabry Disease and Amenable *GLA* Mutations	Study 041: Open-label Extension to Evaluate the Long-term Safety of Migalastat



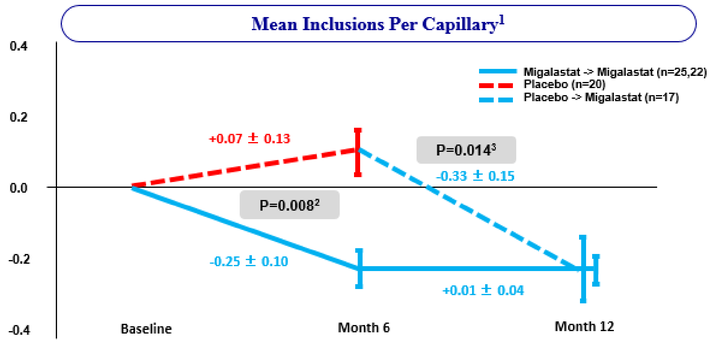
1. Eligible male and female patients were 16-74 years old and had a genetically confirmed diagnosis of Fabry disease; initiated ERT ≥12 months before the baseline visit; a responsive *GLA* mutation based on the preliminary human embryonic kidney-293 (HEK) assay; and estimated glomerular filtration rate (eGFR) ≥30ml/min/1.73m^2.
2. Patients taking angiotensin converting enzyme inhibitors or angiotensin receptor blockers had to be on a stable dose for ≥4-weeks before the screening visit.
3. Enrolled patients were required to have responsive mutant α-Gal A forms based on a preliminary HEK assay. Determination of amenability of the mutant α-Gal A forms was based on testing with the GLP-validated HEK assay, which became available during the study. Amenable mutant α-Gal A forms had to meet the following criteria in the GLP HEK assay: relative increase in α-Gal A activity ≥ 1.2-fold above baseline and absolute increase in α-Gal A activity ≥ 3% of wild-type in HEK cells after incubation with 10 uM migalastat.
4. Estimated GFR was assessed in Studies 011 and 041.
5. Echocardiography (ECHO) parameters were assessed in Studies 011 and 041 through blinded, centralized evaluation (Cardiocore, Rockville, MD).
6. Patient-reported gastrointestinal symptoms were assessed in Study 011 using the Gastrointestinal Symptoms Rating Scale. The GSRS was not assessed in Study 041.

Baseline Characteristics of the Intent-to-treat Population

	Placebo n=33	Migalastat n=34	Total n=67
Gender Female n (%) Male n (%)	21 (64) 12 (36)	22 (65) 12 (35)	43 (64) 24 (36)
Age Median (range)	37 (24, 64)	46 (16, 68)	45 (16, 68)
24-hour Urine Protein (mg/24 hr) Mean (SD)	452.4 (626.3)	342.1 (452.4)	396.5 (546.5)
mGFR mL/min/1.73 m^2 Mean (SD)	85 (21)	88 (24)	87 (23)
eGFR (CKD-Epi) mL/min/1.73 m^2 Mean (SD)	91 (21)	94 (26)	92 (24)
ACEi/ARB /RI Use: n (%)	13 (39)	6 (18)	19 (28)
Previously on ERT: n (%)	12 (36)	5 (15)	17 (25)
GLP HEK Amenable: n (%)	22 (67)	28 (82)	50 (75)

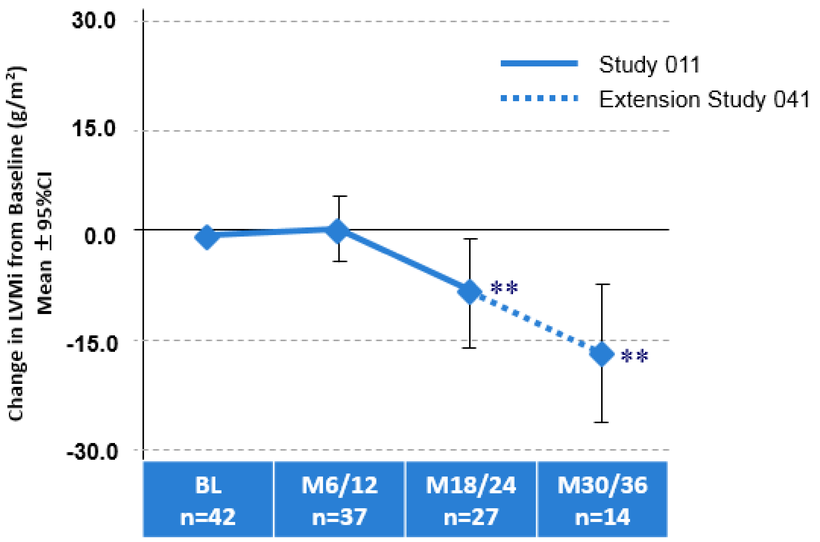
- 17 of 67 randomized patients were categorized as having non-amenable mutations based on the GLP HEK assay.
- Renal and left ventricular mass index (LVMi) findings presented in this poster are based on patients with amenable mutations completing Study 011 and baseline and post-baseline values.
- Safety results are based on all randomized patients.

Statistically Significant Reduction in Kidney Interstitial Capillary GL-3 at Months 6 and 12 Following Treatment with Migalastat (Study 011)



*All patients with evaluable paired biopsies and amenable GLA mutations in the GLP HEK assay – post hoc at month 6 and pre-specified at month 12; [1]Data points are baseline corrected; represent mean ± standard error (SEM) change from baseline in the mean number of GL-3 inclusions per capillary after 6 months of treatment with Migalastat or placebo. [2]Analysis of covariance (ANCOVA) model with covariate adjustment for baseline value and factors for treatment group and treatment by baseline interaction. P-value corresponding to least-square mean difference between Migalastat and placebo is displayed. [3]MMRM Pbo change M6 to M12.

Statistically Significant Change in LVMi from Baseline up to Month 36 after Migalastat Treatment (Studies 011 + 041)



*Mean change in patients with amenable mutations with baseline + post-baseline values. **Statistically significant (95% CI does not overlap zero). Sample size differences due to some patients not yet reaching a given time point or due to missing ECHOs

eGFR Remained Stable Over an Average of 32 Months on Migalastat (Studies 011 and 041) versus Natural History

Annualized eGFR (ml/min/m^2/yr) BL (Migalastat-Migalastat) or M6 (Placebo-Migalastat) to Last Available		Male			Female			All		
Migalastat	**Baseline 24 Hr Urine Protein (mg)**	**N**	**Mean**	**(SEM)**	**N**	**Mean**	**(SEM)**	**N**	**Mean**	**(SEM)**
$eGFR_{CKD-EPI}$	<100	–	–	–	7	0.5	(0.6)	7	0.5	(0.6)
	100-1000	12	0.4	(0.7)	18	-0.2	(1.2)	30	0.0	(0.8)
	>1000	2	-4.1	(0.1)	2	-2.0	(2.1)	4	-3.1	(1.1)
	ALL	14	-0.3	(0.6)	27	-0.2	(0.8)	41	-0.2	(0.6)
$eGFR_{MDRD}$	<100	–	–	–	7	0.6	(0.5)	7	0.6	(0.5)
	100-1000	12	1.4	(0.2)	18	0.9	(1.7)	30	1.1	(1.1)
	>1000	2	-3.6	(1.1)	2	-1.5	(1.9)	4	-2.6	(1.0)
	ALL	14	0.6	(1.0)	27	0.7	(1.1)	41	0.6	(0.8)
Untreated (Literature)	**24 Hr Urine Protein (mg)**	**N**	**Mean**	**(SEM)**	**N**	**Mean**	**(SEM)**	**N**	**Mean**	**(SEM)**
$eGFR_{MDRD}$ (Schiffmann et al., 2009)[1]	<100	18	-1.6	(1.5)	7	-0.6	(2.6)	Not reported		
	100-1000	21	-3.3	(1.8)	17	-2.2	(2.2)			
	>1000	22	-6.9	(1.5)	5	-4.6	(2.3)			
	All	128[2] 17[3]	-2.9[2] -3.8[3]		51[2] 4[3]	-1.0[2] -3.1[3]				

[1]Schiffmann et al., Nephrol Dial Transplant (2009) | [2]For patients not developing ESRD | [3]For patients developing ESRD

- Renal function remained stable in patients with amenable mutations over an average of 32 months in Studies 011 and 041, with mean annualized eGFR changes (mL/min/ 1.73m^2/ yr) of -0.20±0.60 ($eGFR_{CKD-Epi}$) and +0.63±0.08 ($eGFR_{MDRD}$).

Patient-reported Gastrointestinal Symptoms (Study 011)

- From baseline to month 6 (double-blind treatment), improvements (decrease in scores) were seen in migalastat-treated patients with amenable mutations (-0.3, n=28) versus placebo-treated patients (+0.2, n=19), in the diarrhoea domain of the GSRS ($p< 0.05$).
- For patients with symptoms at baseline (post-hoc analysis, n=10 in the migalastat group and n=6 in the placebo group), a significant improvement in the reflux domain was found at month 6, favouring migalastat over placebo ($p < 0.05$).
- After long-term open-label migalastat treatment (month 24 of Study 011), statistically significant improvements were observed at month 18/24 in the diarrhea, reflux, and indigestion domains of the GSRS, and a positive trend in the constipation domain (n=40).
- The GSRS was not assessed in Study 041.

Safety (All Randomized Patients) in Studies 011 and 041 To-Date

- In Studies 011 and 041, no patient met the mandatory stopping criteria: 30% decrease from baseline in serum creatinine, 25% decrease from baseline in cardiac ejection fraction, or cerebrovascular event with significant sequelae. There were no withdrawals due to treatment-related AEs or SAEs.
- In Study 011, two SAEs, fatigue and paresthesia (reported in the same patient) were deemed possibly related to migalastat by the Principal Investigator. These SAEs resolved, the patient completed Study 011 and enrolled in the extension Study 041.
- In Study 041, there were no treatment related SAEs.
- In Study 041, two deaths, both unrelated to migalastat, were reported: One (cause of death unknown) was reported in a 63-year old male, whose medical history included obesity, hypertension, type 2 diabetes mellitus and coronary artery disease (myocardial infarction, stent, and triple bypass surgery). The second death (metastatic breast cancer) was reported in a 64-year old female.

Conclusions

- LVMi decreased over 18-24 months in Study 011, and up to 36 months in Studies 011+041.
- Kidney function (eGFR) remained stable over 18-24 months in Study 011, and up to 36 months in Studies 011 and 041.
- Observed rates of change in eGFR compare favorably to natural history when matched for gender and baseline proteinuria.
- Improvement in the diarrhea domain of GSRS observed at month 6 versus placebo; improvements in diarrhea, reflux and indigestion over 24 months in Study 011.
- Migalastat, an oral pharmacological chaperone, offers promise as a first-in-class treatment option for male and female Fabry patients with amenable mutations.