Migalastat and Enzyme Replacement Therapy Have Comparable Effects on Renal Function in Fabry Disease: Phase 3 Study Results

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Introduction

Fabry Disease

Progressive X-linked lysosomal storage disorder with an estimated incidence of 1 in 100,000. Actual incidence maybe higher.
Mutations in the *GLA* gene lead to low or absent α-galactosidase A (α-Gal A) activity.
More than 800 disease-causing mutations in *GLA* have been identified; ~60% of these are missense mutations.
Affects males and females; females have a mosaic of healthy & diseased cells.
Globotriaosylceramide (GL-3) and globotriaosylsphingosine (lyso-Gb_3) accumulate in multiple organs and tissues leading to the symptoms and sequelae of Fabry disease.

Migalastat for Fabry Disease

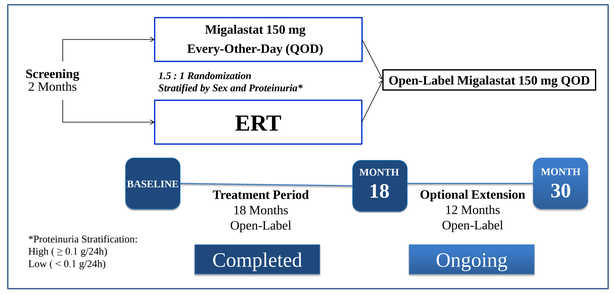
Orally administered investigational pharmacological chaperone for patients with amenable mutations (estimated to be 30-50% of patients with Fabry disease).
Facilitates proper folding and cellular trafficking of specific mutant forms of α-Gal A from the endoplasmic reticulum to lysosomes where the breakdown of GL-3 and related substrates can proceed.
In development for treatment of patients expressing mutant forms of α-Gal A identified as amenable to this chaperone in an validated HEK-293 cell-based assay (GLP HEK assay).

Design of AT1001-012 (NCT01218659) – ATTRACT Study

A Randomized, Open-Label Study to Compare The Efficacy and Safety Of AT1001 and Enzyme Replacement Therapy (ERT) in Patients with Fabry Disease and AT1001-Responsive *GLA* Mutations, Who were Previously Treated with ERT

Key Inclusion and Exclusion Criteria for 012 study

- Male or female, diagnosed with Fabry disease.
- Age between 16 and 74 years inclusive.
- Amenable GLA mutation (identified by HEK cell-based assay).
- Initiated treatment with ERT at least 12 months prior to baseline visit.
- Dose level and regimen of ERT stable for the 3 months prior to baseline visit and ≥ 80% of labeled dose.
- GFR $_{MDRD}$≥ 30 mL/min/1.73 m^2 .
- Subjects taking ACEs or ARBs must be on a stable dose for a minimum of 4 weeks before the screening visit..



Methods

- Patients were randomized 1.5:1 to switch to 18-months open-label migalastat or remain on ERT.
- **The co-primary endpoints were mean annualized change in estimated glomerular filtration rate ($eGFR_{CKD-EPI}$) and measured GFR ($mGFR_{iohexol}$) assessed for migalastat and ERT over 18 months.** Medians, LS means and 95% CIs were calculated using an ANCOVA model. Comparability of migalastat and ERT was pre-specified based on: ≥ 50% overlap of 95% CIs for the annualized change in GFR, and mean changes within 2.2 mL/min/1.73 m2/year.
- Secondary efficacy parameters assessed at month 18: Composite Clinical Outcome (renal, cardiac, cerebrovascular events or death); plasma lyso-Gb_3 (a biomarker of Fabry disease); and left ventricular mass index.

Baseline Characteristics
Intent-To-Treat Population

	ERT n=21	Migalastat n=36	Total n=57
Sex Female n (%) Male n (%)	12 (57) 9 (43)	20 (56) 16 (44)	32 (56) 25 (44)
Age Median (range)	48 (18, 72)	54 (18, 70)	53 (18, 72)
Ethnicity White n (%) Asian n (%)	19 (90) 2 (10)	29 (81) 5 (14)	48 (84) 7 (12)
Years since diagnosis Mean (SD)	13 (12)	10 (12)	11 (12)
24-hour Urine Protein (mg/24 hr) Mean (SD)	417 (735)	260 (532)	339 (665)
mGFR mL/min/1.73 m^2 Mean (SD)	84 (24)	82 (18)	83 (20)
eGFR (CKD-EPI) mL/min/1.73 m^2 Mean (SD)	96 (19)	90 (22)	92 (21)
ACEi/ARB /RI Use: n (%)	11 (52)	16 (44)	27 (47)
GLP HEK Amenable: n (%)	19 (90)	34 (94)	53 (93)

- Patients were randomized based on GLA mutations classified with the clinical trial HEK assay.
- During the conduct of the 012 study, the clinical trial HEK assay was analytically validated in compliance with GLP regulations (GLP HEK assay); 4 of 57 randomized and treated patients were re-categorized as having non-amenable mutations with the GLP HEK assay.
- Analyses presented in this poster were based on the 53 of 57 treated patients with amenable mutations with the GLP HEK assay.
- Safety results were based on all 57 treated patients.

Results at Month 18

Annualized GFR[1] from Baseline to Month 18

	Overlap of 95% CI (means)	Difference between Migalastat and ERT (means)	Mean Values ± SEM		Median Values	
			Migalastat (n=34)	ERT (n = 18)	Migalastat (n=34)	ERT (n = 18)
eGFR CKD-EPI	100%	+0.63	-0.40±0.93	-1.03±1.29	-1.29	-0.87
mGFR iohexol	100%	-1.11	-4.35±1.64	-3.24±2.27	-3.23	-3.57

[1]mL/min/1.73m^2/year.

The annualized changes in GFR were comparable for migalastat and ERT. The 95% confidence intervals for annualized rates of change overlapped 100%, and the difference between groups was less than 2.2 mL/min/1.73 m^2 per year, meeting the pre-specified criteria for comparability between the two treatments.

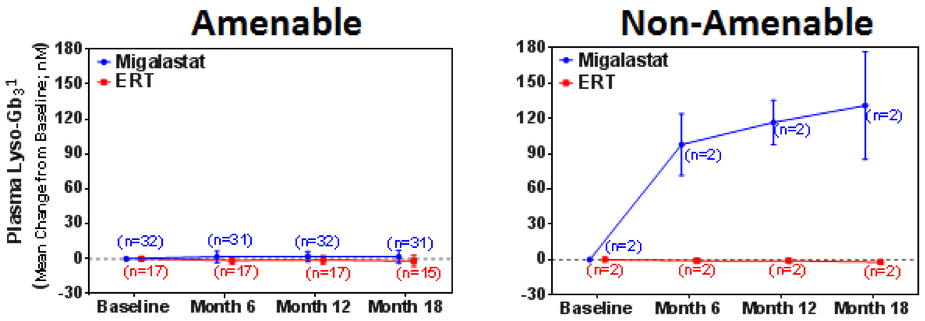
Number (%) of Patients Who Experienced a Composite Clinical Event (18 Months)*

Event	Migalastat (n=34)	
Renal	8 (24%) ↑proteinuria (6), ↓GFR (2)	6 (33%) ↑proteinuria (4), ↓GFR (3)
Cardiac	2 (6%) chest pain, VT/chest pain	3 (17%) cardiac failure, dyspnoea, arrythhmia
Cerebro-vascular	0 (0%)	1 (6%) TIA**
Number of Patients	**10 (29%)**	**8 (44%)**

*2 additional subjects with non-amenable mutations had a renal event (1 in each group);
**Transient ischemic attack.
Proteinuria event defined as >33% increase in 24-hr urine protein and level >300 mg, GFR event defined as >15 ml/min decline in CKD-EPI eGFR and level below 90.

The composite endpoint (renal, cardiac or cerebrovascular events) was observed in 29% of patients on migalastat compared to 44% of patients on ERT. No deaths occurred.

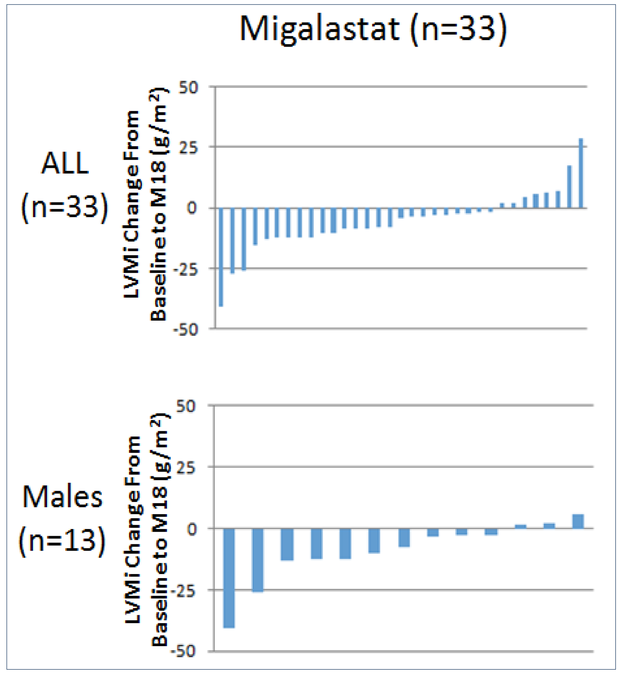
Plasma Lyso-Gb_3 (18 Months)



Plasma lyso-Gb_3 remained low and stable in male and female patients with amenable mutations who continued on ERT, and those who switched from ERT to migalastat.

In two male patients with non-amenable mutations, plasma lyso-Gb_3 increased following switch from ERT to migalastat as compared to two patients (1M, 1F), who remained on ERT.

Left Ventricular Mass Index (18 Months)



Cardiac ECHO Parameter	Migalastat Baseline Mean (% abnormal) n=33	Migalastat Change from Baseline to M18 (mean, 95%CI, n) n=31	ERT Baseline Mean (% abnormal) n=16-17	ERT Change from Baseline to M18 (mean, 95%CI) n=13-15
LV Mass Index (g/m^2)	**95.3 (39%)**	**-6.6** **[-11.0, -2.1]**	**92.9 (38%)**	**-2.0** **[-11.0, +7.0]**

Patients on ERT and switched to migalastat for 18 months demonstrated a reduction in LV Mass Index (95% CI -11.0: -2.1, p < 0.05) (Based on preliminary analysis of the data).

Safety (18 Months)

- Migalastat was generally safe and well tolerated based on adverse event, laboratory and physical exam data.
- There were no treatment related SAEs and no deaths.
- There were 2 withdrawals due to AEs (depression, chest pain) unrelated to migalastat.

CONCLUSIONS

- Changes in GFR were comparable for migalastat and ERT over 18 months in patients with amenable mutations.
- Patients on ERT who switched to migalastat for 18 months demonstrated a reduction in left ventricular mass index.
- Effects of migalastat and ERT on plasma lyso-Gb3 levels were comparable; lyso-Gb3 remained stable in patients with amenable mutations.
- Migalastat was generally safe and well tolerated.

The following is a complete list of the investigators in the AT1001-012 Study: Francois Eyskens, Patrick Deegan, David Dimmock, Ulla Feldt-Rasmussen, David Finegold/ Gerard Vockley, Dominique Germain, Ozlem Goker-Alpan, Eric Hachulla, Derralynn Hughes, Ana Jovanovic, David Koeller, Robin Lachmann, Charles Lourenco, Ichiei Narita, Khan Nedd, Kathy Nicholls, Toya Ohashi, Iacopo Olivotto, Norio Sakai, Suma Shankar, Gere Sunder-Plassmann, Akemi Tanaka, Matt Taylor, Mark Thomas, Bill Wilcox.