# 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**

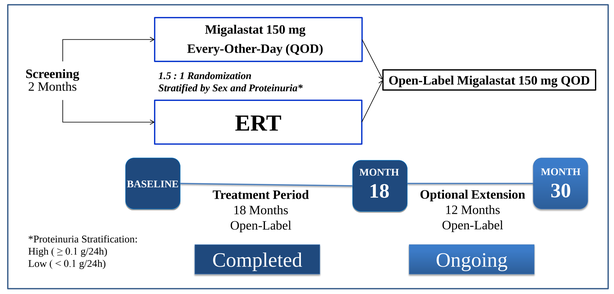
Orally administered investigational pharmacological chaperone for patients with amenable mutations (estimated to be 30-50% of patients with Fabry disease).
Facilitates proper folding and cellular trafficking of specific mutant forms of α-Gal A from the endoplasmic reticulum to lysosomes where the breakdown 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**<br>Female n (%)<br>Male n (%) | 12 (57)<br>9 (43) | 20 (56)<br>16 (44) | 32 (56)<br>25 (44) |
| **Age**<br>Median (range) | 48<br>(18, 72) | 54<br>(18, 70) | 53<br>(18, 72) |
| **Ethnicity**<br>White n (%)<br>Asian n (%) | 19 (90)<br>2 (10) | 29 (81)<br>5 (14) | 48 (84)<br>7 (12) |
| **Years since diagnosis**<br>Mean (SD) | 13 (12) | 10 (12) | 11 (12) |
| **24-hour Urine Protein (mg/24 hr)**<br>Mean (SD) | 417 (735) | 260 (532) | 339 (665) |
| **mGFR mL/min/1.73 $m^2$**<br>Mean (SD) | 84 (24) | 82 (18) | 83 (20) |
| **eGFR (CKD-EPI) mL/min/1.73 $m^2$**<br>Mean (SD) | 96 (19) | 90 (22) | 92 (21) |
| **ACEi/ARB /RI Use:**<br>n (%) | 11 (52) | 16 (44) | 27 (47) |
| **GLP HEK Amenable:**<br>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/1.73$m^2$/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.

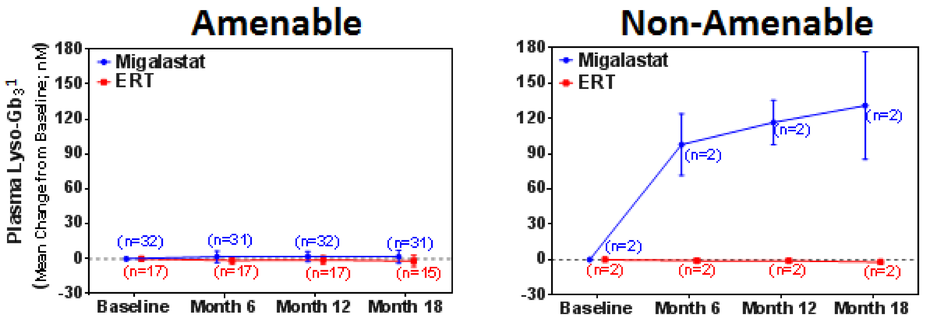
### Number (%) of Patients Who Experienced a Composite Clinical Event (18 Months)*

| Event | Migalastat (n=34) | ERT (n=18) |
|---|---|---|
| **Renal** | 8 (24%)<br>↑proteinuria (6), ↓GFR (2) | 6 (33%)<br>↑proteinuria (4), ↓GFR (3) |
| **Cardiac** | 2 (6%)<br>chest pain, VT/chest pain | 3 (17%)<br>cardiac failure, dyspnoea, arrythhmia |
| **Cerebro-vascular** | 0 (0%) | 1 (6%)<br>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.

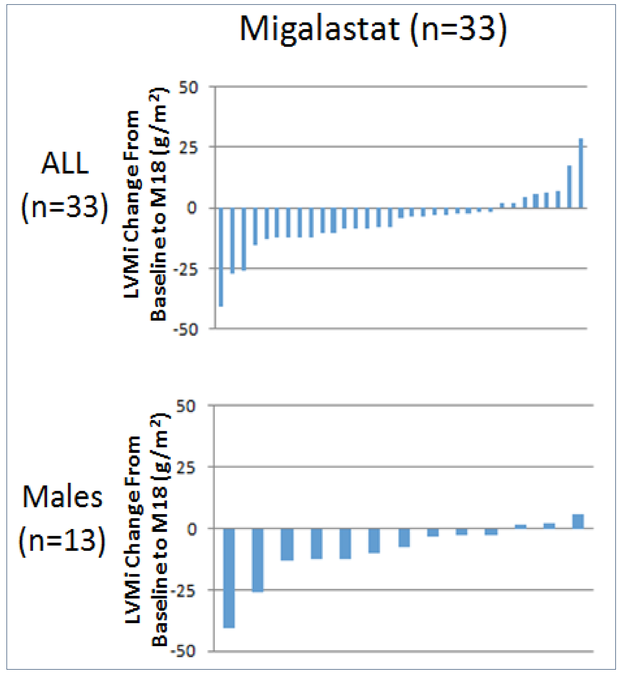
## Plasma Lyso-$Gb_3$ (18 Months)




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**<br>**[-11.0, -2.1]** | **92.9 (38%)** | **-2.0**<br>**[-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).

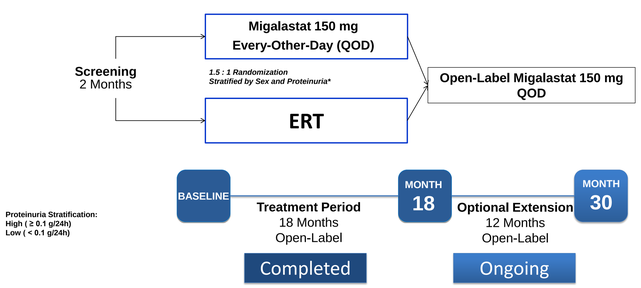
## Safety (18 Months)

- 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.
- Patient-reported outcome measures remained stable in both groups
  - Brief Pain Inventory (BPI) short form and the Short Form 36 (SF36)
- 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.


Migalastat 150 mg
Every-Other-Day (QOD)
Screening
2 Months
1.5 : 1 Randomization
Stratified by Sex and Proteinuria*
ERT
Open-Label Migalastat 150 mg
QOD
BASELINE
Treatment Period
18 Months
Open-Label
MONTH
18
Optional Extension
12 Months
Open-Label
MONTH
30
Completed
Ongoing
Proteinuria Stratification:
High ( ≥ 0.1 g/24h)
Low ( < 0.1 g/24h)