Migalastat Reduces Left Ventricular Mass Index in Fabry Patients Naïve to ERT and Previously Treated With ERT

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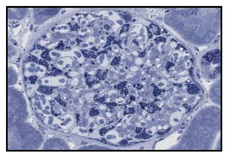
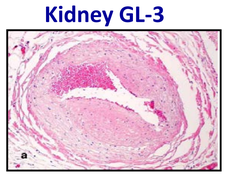
Introduction

Fabry Disease

- Progressive X-linked lysosomal storage disorder with an estimated frequency of 1 in 100,000. Actual prevalence is thought to be higher.
- Mutations in the GLA gene lead to a deficiency of α-galactosidase A (α-Gal A) activity.
- More than 800 disease-causing mutations in GLA have been identified (~60% missense).
- Affects males and females; females have mosaic of healthy and diseased cells.
- Globotriaosylceramide (GL-3) and other substrates of α-Gal A accumulate in multiple tissues including the kidney, heart, brain, GI, and skin leading to the symptoms and sequelae of Fabry disease.
- Cardiac complications are common in Fabry disease, and are the main causes of death.



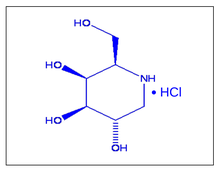
Kidney GL-3



Coronary GL-3

Migalastat HCl for Fabry Disease

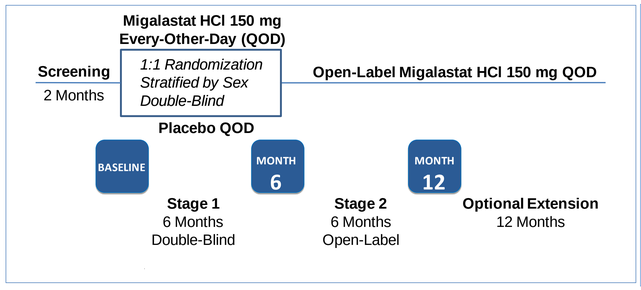
- Orally administered investigational pharmacological chaperone.
- In development for treatment of patients that express mutant forms of α-Gal A identified as amenable to this chaperone, based on an in vitro GLP-validated HEK-293 cell-based assay (estimated 30-50% of patients with Fabry disease).
- Designed to selectively and reversibly bind and stabilize endogenous α-Gal A.
- 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.

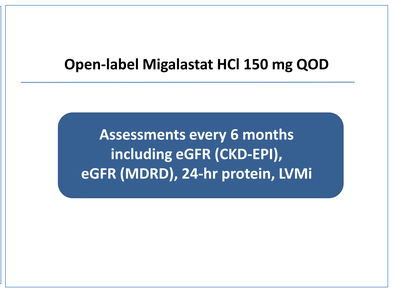


Migalastat HCl
Deoxygalactonojirimycin
AT1001

DESIGNS of AT1001-011 (FACETS, NCT00925301) and 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



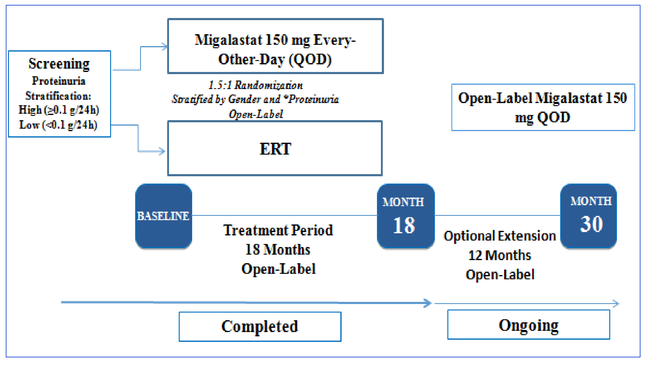


Key Inclusion/Exclusion Criteria:

- Males and females, 16 to 74 years, diagnosed with Fabry disease.
- Amenable *GLA* mutation.
- Naïve to ERT or have not received ERT for ≥6 months before screening,
- Estimated GFR (MDRD) (eGFR) at screening ≥30 ml/min/1.73 m^2.
- Urine GL-3 at screening ≥4 times the upper limit of normal (24-hour collection),
- Subjects taking ACE inhibitors , ARBs, or renin inhibitors on a stable dose for at least 4 weeks before screening.

DESIGN of AT1001-012 (ATTRACT, NCT01218659)

Study 012: 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/Exclusion Criteria:

- Males and females, 16 to 74 years, diagnosed with Fabry disease.
- Amenable GLA mutation
- Initiated treatment with ERT at least 12 months prior to baseline visit.
- Stable ERT dose for 3 months prior to baseline visit and ≥ 80% of labeled dose.
- Estimated GFR (MDRD) (eGFR) at screening ≥30 ml/min/1.73 m^2.
- Subjects taking ACE inhibitors , ARBs, or renin inhibitors on a stable dose for at least 4 weeks before screening.

Methods

- Left ventricular mass index (LVMi), LV posterior wall thickness diastolic (LVPWT), and intraventricular septum thickness diastolic (IVSTD) collected in Study 011, 012 and 041 by Echo using 2D or M-mode every 6-12 months
- Data collected through blinded, centralized evaluation (Cardiocore, Rockville, MD)
- Assessment of the long-term effect of migalastat on LVMi performed using 95% confidence intervals of the change from baseline to the last available timepoint for each subject
- Data are reported for all subjects treated with migalastat with amenable mutations and a baseline and post-baseline measure of LVMi (011-041, n=38; 012, n=33). Data are also reported for subjects on ERT (012, n=18)
- Month 6 used as baseline for 011+041 placebo arm subjects switching from placebo to migalastat at month 6
- Safety results are based on all patients in the intent to treat population (011, n=67; 012 n=57)

Baseline Characteristics of Study 011 and 012 (ITT)

	Study 011: Placebo Arm Switched to Migalastat at M6 (n=33)	Study 011: Migalastat Arm (n=34)	Study 012: Migalastat Arm (n=36)	Study 012: ERT Arm (n=21)
Sex Female n (%) Male n (%)	 21 (64) 12 (36)	 22 (65) 12 (35)	 20 (56) 16 (44)	 12 (57) 9 (43)
Age Median (range)	37 (24, 64)	46 (16, 68)	54 (18, 70)	48 (18, 72)
Years since diagnosis Mean (SD)	7.1 (7.8)	5.7 (6.8)	10 (12)	13 (12)
eGFR (CKD-EPI) mL/min/1.73 m^2 Mean (SD)	94 (21)	95 (29)	90 (22)	96 (19)
24-hr Urine Protein (mg) Mean (SD)	452 (626)	342 (459)	260 (532)	417 (735)
ACEi/ARB /RI Use: n (%)	13 (39)	6 (18)	16 (44)	11 (52)
GLP HEK Amenable: n (%)	22 (67)	28 (82)	34 (94)	19 (90)
Previously on ERT	ERT naïve or off >6 months	ERT naïve or off >6 months	Switched from ERT	Switched from ERT

- During the conduct of Study 011 and 012, the clinical trial HEK assay was analytically validated in compliance with GLP regulations (GLP HEK assay).
- 17 of 67 study 011 patients and 4 of 57 study 012 patients were re-categorized as having non-amenable mutations based on the GLP HEK assay.
- Results below are for patients with amenable mutations in each study.

AT1001-011+041 (ERT Naïve): Change From Baseline in LVMi After Avg of 22 Months Treatment With Migalastat

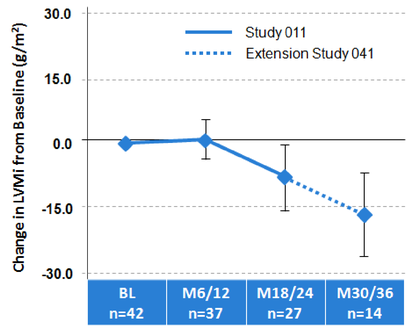
011+041 Patients With Amenable Mutations	Baseline Mean g/m^2 (% Abnormal)	Change From Baseline To Last Timepoint Mean ± 95% CI	Annualized Change From Baseline To Last Timepoint Mean ± 95% CI
All (n=42)	*97.5 (26%)*	-8.0 ± 5.5*	-4.5± 3.1*
Male (n=17)	*121.4 (32%)*	-14.8 ± 9.5*	-6.4± 5.2*
Female (n=25)	*81.3 (18%)*	-3.5 ± 6.6	-3.2 ± 4.1
Abnormal BL LVMi (n=3F, 8M)	*138.9 (100%)*	-17.2 ± 16.5*	-8.5 ± 8.3*

AT1001-012 (ERT switch): Change From Baseline in LVMi After 18 Months Treatment With Migalastat

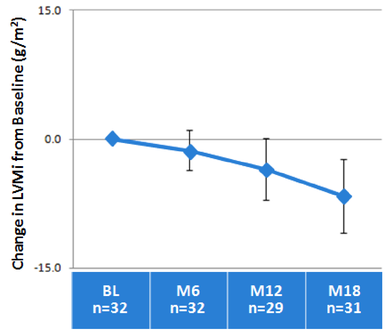
012 Patients With Amenable Mutations	Baseline Mean g/m^2 (% Abnormal)	Change From Baseline To Month 18 Mean ± 95% CI	Annualized Change From Baseline To Month 18 Mean ± 95% CI
All (n=33)	*95.6 (39%)*	-5.7 ± 4.3*	-3.2± 3.2*
Male (n=13)	*103.1 (31%)*	-9.4 ± 6.9*	-6.3± 4.6*
Female (n=20)	*90.2 (45%)*	-3.3 ± 5.3	-1.2 ± 4.1
Abnormal BL LVMi (n=9F, 4M)	*116.7 (100%)*	-8.4 ± 5.8*	-4.8 ± 4.6*

- NOTE: LV Mass Index (g/m2): Normal range: 43-95 (female), 49-115 (male); *Statistically significantly ($p<0.05$) difference based on 95% CIs

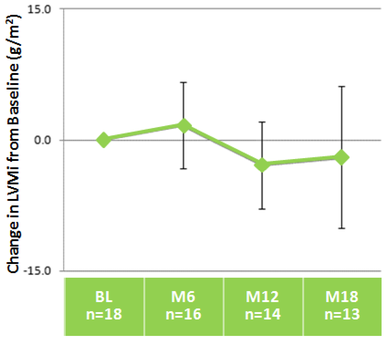
AT1001-011+041 (ERT Naïve): LVMi CFB on Migalastat



AT1001-012 (ERT Switch): LVMi CFB on Migalastat



AT1001-012 (ERT): LVMi CFB on ERT



LVMi Results

- Significant reduction in LVMi observed in 42 ERT-naïve patients treated with migalastat for average of 22 months in Studies 011+041 (-8.0 ± 5.5 g/m^2)
- Significant reduction in LVMi observed in 33 ERT-treated patients who switched to migalastat for 18 months in Study 012 (-5.7 ± 4.3 g/m^2)
- Larger reductions in LVMi observed in subjects with abnormal LVMi at baseline: 011 (-17.2 ± 16.5 g/m^2), 012 (-8.4 ± 5.8 g/m^2),
- Annualized changes in LVMi were correlated (Pearson) with annualized changes in LVPWT (011+041; R^2=0.28, p=0.0005); (012; R^2=0.38, p=0.03) and IVSTD (011+041; R^2=0.33, p=0.0001); (012; R^2=0.64, p<0.0001)
- 54 of 75 (72%) Ph3 011+041 and 012 subjects with amenable mutations treated with migalastat demonstrated a reduction in LVMi.

Safety (All Randomized Patients)

- Migalastat was generally safe and well tolerated based on adverse event, laboratory, and physical exam data.
- In Study 011, there were two SAEs, fatigue and paresthesia (reported in the same patient), considered possibly related to migalastat. These SAEs resolved and the patient completed Study 011. There were no deaths.
- In Study 012 during the 18-month controlled treatment period there were no treatment related SAEs and no deaths.
- In Study 041, during this period there were no treatment related SAEs; one death 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).

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Conclusions

- Left ventricular hypertrophy is an important risk factor for predicting cardiac events in Fabry disease (Patel et al., 2011)
- Reduction of LVMi has been shown to improve outcomes in Fabry and in other cardiac diseases (Rombach et al., 2014, Pokharel and Bella, 2013)
- In Fabry patients with amenable mutations, treatment with migalastat reduces LVMi in both ERT naïve and ERT treated patients who switched to migalastat.