Improvement in Gastrointestinal Symptoms Observed in the Phase 3 FACETS (AT1001-011) Study of Migalastat in Fabry Patients

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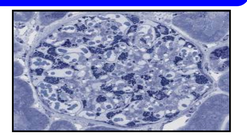
Introduction

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.
- Gastrointestinal symptoms, especially diarrhea and abdominal pain, as well as nausea, vomiting, and constipation, are common to Fabry disease.

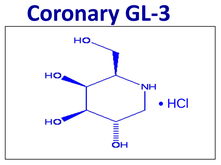
Migalastat HCl for Fabry Disease

- 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.



Kidney GL-3

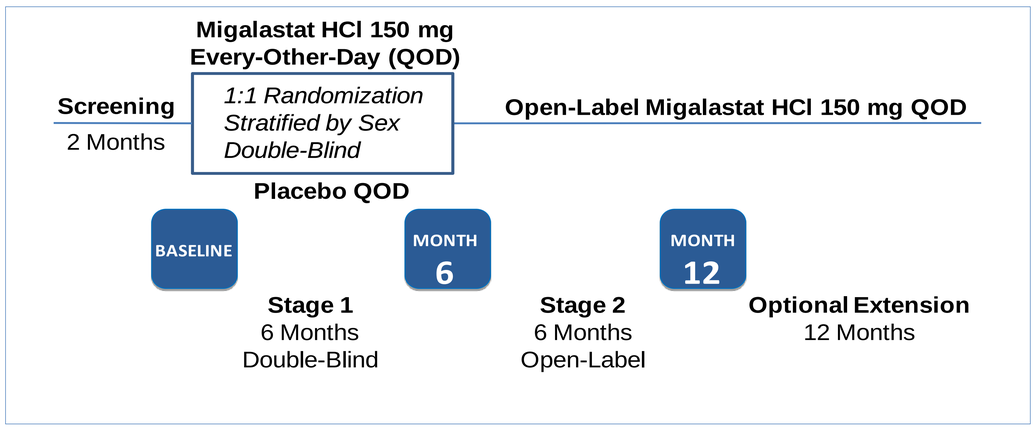
Coronary GL-3



Migalastat HCl, AT1001
Deoxygalactonojirimycin

DESIGN of AT1001-011 (FACETS, NCT00925301)

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



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.

Methods

- Gastrointestinal symptoms were assessed using the Gastrointestinal Symptom Rating Scale (GSRS), a disease-specific instrument of 15 items combined into five domains depicting Diarrhea, Reflux, Indigestion, Constipation and Abdominal pain,
- The GSRS has a seven-point graded scale where 1 represents absence of troublesome symptoms and 7 represents very troublesome symptoms.
- The GSRS has been validated for irritable bowel syndrome which has many similarities to the GI symptoms in Fabry.
- GSRS was assessed for 50 subjects (28 migalastat, 22 placebo) with amenable mutations.
- Statistical comparisons between migalastat and placebo during Stage 1 were performed using an analysis of covariance including treatment, baseline, and the treatment by baseline interaction.
- Assessments of the long-term effect of migalastat in Stage 2/OLE were performed using 95% confidence intervals (95% CI) of the change from baseline (for the migalastat arm) or from month 6 (for the placebo arm) to month 24.
- Analyses were conducted for all subjects as well as for the subset of subjects with symptoms at baseline
- All p-values and 95% CIs are unadjusted for multiple comparisons.

Baseline Characteristics of Study 011 (ITT)

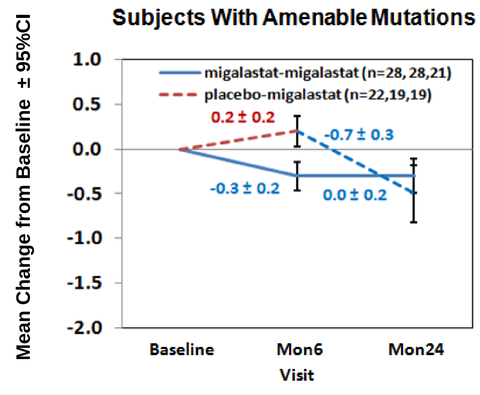
	Placebo (n=33)	Migalastat (n=34)
Female n (%) Male n (%)	21 (64) 12 (36)	22 (65) 12 (35)
Age Median (range)	37 (24, 64)	46 (16, 68)
Years since diagnosis Mean (SD)	7.1 (7.8)	5.7 (6.8)
eGFR (CKD-EPI) mL/min/1.73 m^2 Mean (SD)	94 (21)	95 (29)
24-hr Urine Protein (mg) Mean (SD)	452 (626)	342 (459)
GLP HEK Amenable: n (%)	22 (67)	28 (82)

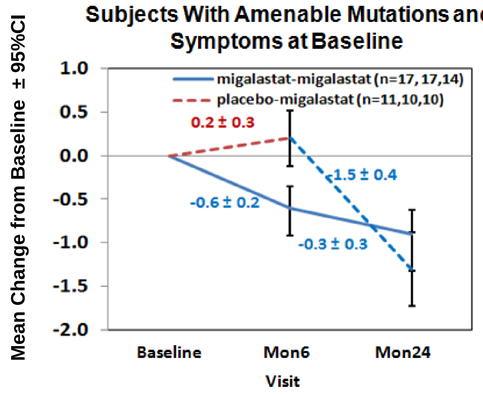
GSRS: Mean Change From Baseline to Month 6 and to Month 24

GSRS Domain	Diarrhea		Reflux		Indigestion		Constipation		Abdominal Pain	
Treatment Group	Migalastat	Placebo	Migalastat	Placebo	Migalastat	Placebo	Migalastat	Placebo	Migalastat	Placebo
Baseline Values : Mean (n)										
All Patients	2.3 (28)	2.1 (22)	1.4 (28)	1.4 (22)	2.5 (28)	2.4 (22)	1.9 (28)	2.0 (22)	2.1 (28)	2.3 (22)
Pts With BL Symptoms	3.2 (17)	3.1 (11)	2.1 (10)	2.6 (6)	2.8 (23)	2.7 (19)	2.5 (17)	2.4 (15)	2.4 (22)	2.9 (15)
Change From Baseline to Month 6 (Stage 1, Double Blind)										
All Patients	-0.3*	+0.2	-0.1	+0.2	-0.1	-0.1	+0.1	+0.2	0.0	0.0
Pts With BL Symptoms	-0.6	+0.2	-0.5*	+0.3	-0.2	-0.2	+0.2	+0.1	-0.1	-0.1
Change from Baseline (Migalastat) or Month 6 (Placebo) to Month 24 (Open-Label Extension Migalastat Treatment)										
All Patients	-0.5 (-0.9, -0.1)**		-0.2 (-0.5, 0.2)		-0.4 (-0.7, -0.04)**		-0.4 (-0.7, 0.0)		-0.2 (-0.4, +0.1)	
Pts With BL Symptoms	-1.0 (-1.5, -0.4)**		-0.6 (-1.5, 0.2)		-0.5 (-0.8, -0.06)**		-0.5 (-1.1, 0.0)		-0.2 (-0.6, 0.1)	

Notes: LS Means shown for change from baseline; *p≤0.05based on ANCOVA, ** Statistically significant based on 95% CIs <0

GSRS – Diarrhea Syndrome: Plot of Change From Baseline to Month 6 and to Month 24





GSRS Results

- During the Stage1 double-blind phase, improvements were observed in:
  - The diarrhea domain of GSRS for migalastat versus placebo for all subjects (mean decrease 0.3 migalastat versus increase 0.2 placebo, p=0.03)
  - The reflux domain of GSRS for subjects with symptoms at baseline (mean decrease 0.5 migalastat versus increase 0.3 placebo, p=0.05)
- During the Stage 2/OLE open-label phase, improvements were observed at month 24 in:
  - The diarrhea domain of GSRS for all subjects (mean decrease 0.5; 95% CI -0.9, -0.1) and for subjects with symptoms at baseline (mean decrease -1.0; 95% CI -1.5, -0.4)
  - The indigestion domain of GSRS for all subjects (mean decrease 0.4; 95% CI -0.8, -0.0) and for subjects with symptoms at baseline (mean decrease 0.5; 95% CI -0.8, -0.1)
  - The reflux domain of GSRS for subjects with symptoms at baseline (mean decrease 0.6; 95% CI -1.480, 0.213)
  - Trend in the constipation domain of GSRS for all subjects (mean decrease 0.4; 95% CI -0.7, +0.0) and for subjects with symptoms at baseline (mean decrease 0.5; 95% CI -0.8, +0.0)

Safety (All Randomized Patients)

- Migalastat was generally safe and well tolerated based on adverse event, laboratory and physical exam data.
- 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.

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Conclusions

- Six months migalastat treatment was associated with a statistically significant (p<0.05) improvement in the diarrhea domain of the GSRS compared to placebo.
- To our knowledge, this is the first report of an improvement in Fabry-associated GI symptoms in a placebo-controlled study.
- Treatment with migalastat for 18-24 months demonstrated a durable improvement in the diarrhea domain
- The improvements found in the reflux, indigestion, and constipation domains of the GSRS over 18-24 months treatment further reinforce the positive effects of migalastat on GI symptoms.