Phenotype of Fabry Disease in Patients with Mutations Amenable to Migalastat

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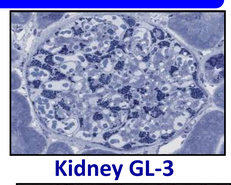
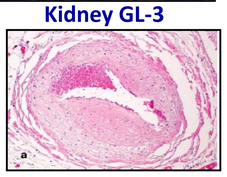
Introduction

Fabry Disease

- A devastating X-linked inherited disorder caused by the functional deficiency of lysosomal α-galactosidase A (α-Gal A), with accumulation of glycosphingolipids, including globotriaosylceramide (GL-3), leading to impairment of kidney, heart, brain, and premature death.
- 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.



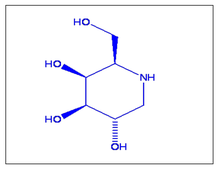
Kidney GL-3



Coronary GL-3

Migalastat for Fabry Disease

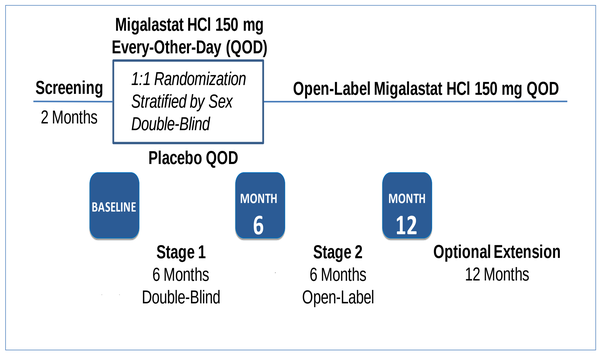
- Binds to α-Gal A, increasing its physical stability, lysosomal trafficking, and cellular activity.
- First-in-class orally administered (QOD) pharmacological chaperone being developed as a targeted medicine for the treatment of Fabry disease in patients with amenable *GLA* mutations.
- Between 30-50% of people with Fabry disease express mutant forms of α-Gal A that are *amenable* to migalastat, based on an *in vitro* GLP-validated Migalastat Amenability Assay.



AT1001; Migalastat HCl; Deoxygalactonojirimycin

DESIGN of AT1001-011 (FACETS, NCT00925301)

Study AT1001-011: 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

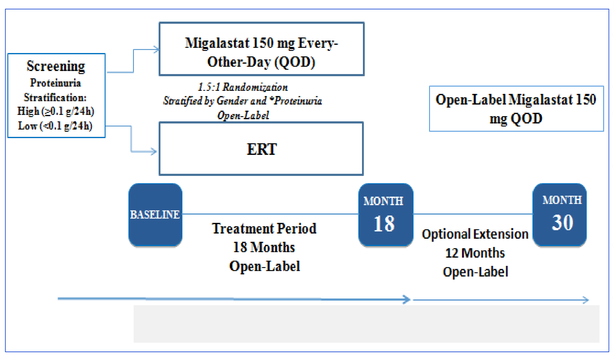


Key Inclusion/Exclusion Criteria:

- 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.
- eGFR (MDRD) 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 ≥4 weeks before screening.

DESIGN of AT1001-012 (ATTRACT, NCT01218659)

Study AT1001-012: A Randomized, Open-Label Study To Compare The Efficacy and Safety Of Migalastat and Enzyme Replacement Therapy (ERT) in Patients With Fabry Disease and Migalastat-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.
- eGFR (MDRD) at screening ≥30 ml/min/1.73 m^2.
- Subjects taking ACE inhibitors, ARBs, or renin inhibitors on a stable dose for ≥4 weeks before screening.

Methods

TESTING OF GENOTYPES FOR AMENABILITY:

- 600 Fabry disease-causing mutations were expressed in transfected HEK-293 cells and α-Gal A activity was measured in the presence and absence of 10 µM migalastat.
- Amenable mutant forms were defined by a ≥1.20-fold relative increase and a ≥3.0% wild-type absolute increase in the presence of 10 µM migalastat.
- 268 amenable mutations were identified.

PHENOTYPE :

- Proportions of patients enrolled in Studies 011 and 012 with disease-related involvement of ≥2 organ systems were determined.
- Patient's phenotypes (classical/non-classical) were assessed based on the medical literature definition of genotypes. The classical Fabry phenotype has been used to described patients with early onset, low residual α-Gal A activity (in male patients), elevated plasma lyso-Gb$_3$, and multiple organ-system disease.

Clinical Phenotypes

- Among mutations characterized in the literature, a majority (64%) of patients in the Phase 3 studies had mutations associated with the classical phenotype.

Study 011: Amenable mutations of patients and the corresponding clinical phenotype, based on the medical literature

Amino Acid Change (number of patients with the mutation)	Literature Phenotype	Amino Acid Change	Literature Phenotype
D33G	Unknown	P259R (n=3)	Classical (Ashley, Shabbeer et al. 2001)
L36W (n=2)	Unknown	G260A	Classical (Okumiya, Ishii et al. 1995)
D55V/Q57L	Unknown	D264Y	Classical (Shabbeer, Yasuda et al. 2006)
G85D	Unknown	I270T	Classical (Ries, Gupta et al. 2005)
R112H	Non-classical (Eng 1994)	G271S D313Y	Classical (Shabbeer[a], Yasuda et al. 2006)
G144V	Classical (Eng 1994)		Both (Eng 1993, Froissart, Guffon et al. 2003)
A156T (n=3)	Classical (Eng 1994)	M284T (n=2)	Classical (Blanch, Meaney et al. 1996)
C174R	Classical (Meng, Zhang et al. 2010)	P293T (n=2)	Classical (Shabbeer, Yasuda et al. 2006)
G183D (n=2)	Classical (Topaloglu, Ashley et al. 1999)	F295C	Unknown
M187I	Unknown	L300P	Unknown
P205T (n=2)	Classical (Blanch, Meaney et al. 1996)	R301Q (n=3)	Both (Sakuraba, Oshima et al. 1990, Ishii 1992, Germain and Poenaru 1999, Germain, Shabbeer et al. 2002)
Y216C (n=3)	Classical (Filoni, Caciotti et al. 2010)	I317T	Classical (Shabbeer, Yasuda et al. 2002)
L243F	Classical (Germain, Shabbeer et al. 2002)	D322E (n=2)	Classical (Lee, Heo et al. 2010)
D244N	Classical (Eng 1994)	G325R (n=2)	Unknown
G258R (n=2)	Unknown	R356W	Classical (Bernstein 1989)
I253T (n=4)	Unknown	G373S	Classical (Okumiya, Ishii et al. 1995)

Abbreviations: ITT=modified intent-to-treat.| [a] A female patient had 2 mutations on different chromosomes; categorised as classical based on G271S. | Number of patients with each mutation is 1 unless indicated otherwise

Study 012: Amenable mutations of patients and the corresponding clinical phenotype, based on the medical literature

Amino Acid Change (number of patients with the mutation)	Literature Phenotype	Amino Acid Change	Literature Phenotype
M96I	Unknown	G260A	Classical (Okumiya, Ishii et al. 1995)
L32P (n=3)	Unknown	Q279E	Non-classical (Ishii 1992)
G35R	Non-classical (Davies, Christomanou et al. 1994)	M284T	Classical (Blanch, Meaney et al. 1996)
D55V/Q57L	Unknown	M296I	Non-classical (Nakao 1995)
G85D (n=4)	Unknown	R301P (n=3)	Classical (Ashley, Shabbeer et al. 2001)
A97V	Non-classical (Eng 1997)	R301Q	Both (Sakuraba, Oshima et al. 1990, Ishii 1992, Germain and Poenaru 1999, Germain, Shabbeer et al. 2002)
R112G	Unknown	G328A	Classical (Eng 1993)
R112H	Non-classical (Eng, Niehaus et al. 1994)	Q312R	Non-classical (Shimotori, Maruyama et al. 2008)
A143T (n=3)	Non-classical (Spada, Pagliardini et al. 2006)	D322E (n=4)	Classical (Lee, Heo et al. 2010)
A156T (n=6)	Classical (Eng 1994)	R356Q	Non-classical (Chien, Olivova et al. 2011)
P205T	Classical (Blanch, Weber et al. 1997)	R363H	Both (Blaydon, Hill et al. 2001, Shabbeer, Yasuda et al. 2002)
N215S (n=10)	Non-classical (Dobrovolny, Dvorakova et al. 2005)	L403S	Classical (Shimotori, Maruyama et al. 2008)
Y216C	Classical (Filoni, Caciotti et al. 2010)	P409T	Unknown
I253S	Unknown		

Abbreviations: mITT =modified intent-to-treat

Patients had Low α-Gal A Activity and Elevated Plasma Lyso-Gb$_3$ Levels

- Low residual α-Gal A activity in male patients and elevated levels of plasma lyso-Gb$_3$ in males and females have been associated with the classical Fabry phenotype (Desnick, Brady et al., 2003; Wilcox, Oliveira et al., 2008; Rombach, Dekker et al., 2010).
- In Study 011, >90% of patients had plasma lyso-Gb$_3$ levels comparable to patients with a classical phenotype (Rombach, Dekker et al., 2010); 91% of males had plasma lyso-Gb$_3$ >51 nM; 94% of females had plasma lyso-Gb$_3$ >1.19 nM.
- 44% of males had baseline α-Gal A Activity <1% of normal, and 87% had baseline activity <3% of normal.
- (Due to previous ERT treatment in patients entering Study 012, enzyme activity and plasma lyso-Gb$_3$ levels were confounded.)

Patients Had Significant Baseline Disease Severity

Sex	Fabry Disease in ≥2 Organ Systems	Angio-keratoma or Corneal Whorling	Cardiac Involvement	CNS Involvement	Neuropathic Pain	Renal Involvement	Gastro-intestinal
Study AT1001-012 (n=57)							
Males n (%)	21/24 (88%)	13/24 (54%)	16/24 (67%)	18/24 (75%)	14/24 (58%)	18/24 (75%)	14/24 (58%)
Females n (%)	29/33 (88%)	16/33 (48%)	25/33 (75%)	12/33 (36%)	22/33 (67%)	25/33 (76%)	20/33 (61%)
Study AT1001-011 (n=50)							
Males n (%)	18/18 (100%)	12/18 (67%)	15/18 (83%)	11/18 (61%)	13/18 (72%)	18/18 (100%)	10/18 (56%)
Females n (%)	29/32 (91%)	13/32 (41%)	11/32 (35%)	16/32 (50%)	25/32 (78%)	27/32 (84%)	18/32 (56%)

Abbreviations: CNS = Central Nervous System; eGFR = estimated glomerular filtration rate; LVH = left ventricular hypertrophy; LVMi = left ventricular mass index; TIA = transient ischaemic attack | Notes: Angiokeratoma or Corneal Whorling based on medical history finding. Cardiac Involvement includes previous cardiac event (based on medical history), LVH, or conduction abnormality (eg, tachycardia, ST-T segment abnormality) based on medical history finding or baseline assessment of LVMi. CNS involvement was based on medical history findings (stroke/TIA, tinnitus/hearing loss). Renal Involvement based on medical history finding or baseline eGFR <90 mL/min/1.73m^2, 24-hr Protein ≥150 mg

- Overall, 91% of patients had Fabry disease involvement in ≥2 organ systems, indicating significant disease burden.
- In Study 011, all patients had clinical manifestations, and 90% of patients had renal involvement, 52% had cardiac involvement, and 54% had CNS involvement.
- In Study 012, all patients had clinical disease manifestations, and 75% of patients had renal involvement, 72% had cardiac involvement, and 53% had CNS involvement.

Patients Enrolled in the Migalastat Phase 3 Studies Are Comparable With Fabry Disease Patients Currently Receiving ERT

Baseline Characteristics in Phase 3 Migalastat Studies Versus ERT Registries

	Male Patients				Female Patients			
	FOS	FR	011	012	FOS	FR	011	012
Age at enrolment	39	40	40	47/44[1)]	44	44	44	50/47[1)]
Body System involvement (%)								
Dermatologic	78	31	67	38	50	12	28	21
Cardiac	69	13	83	67	65	10	35	75
CNS	69[2)]	17[3)]	61	75	74[2)]	16[3)]	50	36
Neuroparesthesias	76	62	72	58	64	41	78	67
Renal	50	17	100	75	50	11	84	76
Gastrointestinal	55	19	56	58	50	13	56	61

Abbreviations: CNS=Central Nervous System; FOS=Fabry Outcomes Survey; FR=Fabry Registry; TIA=transient ischaemic attack | [1)] Second number reflects age at start of ERT which is more relevant comparison to age at enrolment into ERT registry; [2)] Combines auditory and TIA/Stroke; [3)] Combines cerebrovascular and neurological: other |Fabry Outcomes Survey (Mehta, Beck et al. 2009); Fabry Registry (Eng, Fletcher et al. 2007; 2014)

Summary and Conclusions

- The very high proportion of patients with multi-organ system involvement in the Phase 3 studies of migalastat (Studies 011 and 012), associated elevated plasma lyso-Gb$_3$ and low α-Gal A activity in patients not receiving ERT, indicate substantial disease burden in this population.
- A majority of patients in the Phase 3 migalastat studies had a phenotype associated with the classical phenotype.
- Patients enrolled in the migalastat Phase 3 studies are comparable with the current Fabry disease population being treated with ERT, as reflected in both the Fabry Outcome Survey (Mehta, Beck et al., 2009) and the Fabry Registry (Eng, Fletcher et al., 2007; 2014).

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