Persistence of Positive Renal and Cardiac Effects of Migalastat in Fabry Patients with Amenable Mutations Following 30 Months of Treatment in the ATTRACT Study

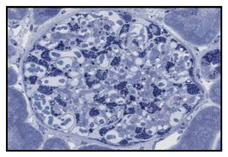
Bichet DG[1], Germain DP[2], Giugliani R[3], Hughes D[4], Schiffmann R[5], Wilcox W[6], Castelli J[7], Cantor E[7], Kirk J[7], Skuban N[7], and Barth J[7] on behalf of the ATTRACT investigators

[1]Hôpital du Sacré-Coeur, University of Montreal, Canada; [2]Hôpital Raymond Poincaré (AP-HP), University of Versailles – St. Quentin en Yvelines (UVSQ), Garches, France; [3]Medical Genetics Service, HCPA/UFRGS Porto Alegre, Brazil; [4]Royal Free Campus, University College London, London, UK; [5]Baylor Research Institute, Dallas, TX; [6]Department of Human Genetics, Emory University, Georgia; [7]Amicus Therapeutics, 1 Cedar Brook Drive, Cranbury, NJ, USA

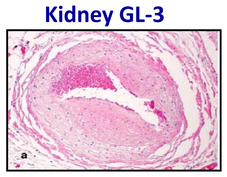
Introduction

Fabry Disease

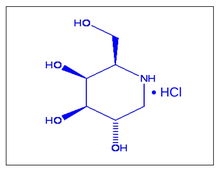
- A devastating X-linked inherited disorder caused by the functional deficiency of lysosomal α-galactosidase A, with accumulation of glycosphingolipids, including globotriaosylceramide (GL-3), leading to impairment of kidney, heart, brain, and premature death.
- More than 800 disease-causing mutations in *GLA* have been identified (~60% missense).
- Affects males and females; females have mosaic of healthy and diseased cells.
- The stabilization or slowing of renal dysfunction and reduction of cardiac complications remain critical medical needs for individuals living with Fabry disease.



Kidney GL-3



Coronary GL-3



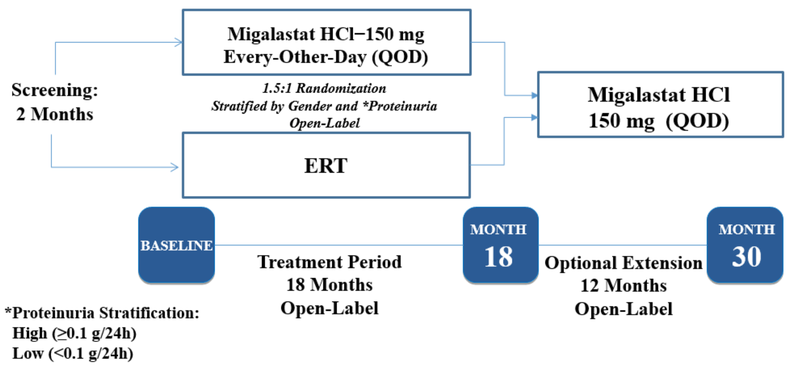
AT1001; Migalastat HCl; Deoxygalactonojirimycin

Migalastat for Fabry Disease

- 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-galactosidase A that are *amenable* to migalastat, based on an *in vitro* GLP-validated Migalastat Amenability Assay.
- In patients with Fabry disease, migalastat binds and stabilizes the amenable mutant forms of the enzyme in the endoplasmic reticulum throughout the body and restores trafficking to lysosomes where the enzyme can catabolize accumulated glycosphingolipids.
- As an oral small molecule treatment, migalastat therapy is unlikely to exhibit the limitations of ERT, which include infusion-associated reactions, formation of antibodies to the exogenous protein, and the significant burden that biweekly infusions place on patients and their families.

DESIGN of AT1001-012 (ATTRACT, NCT01218659)

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



Randomized patients were 16-74 years of age and had:

- A genetically confirmed diagnosis of Fabry disease.
- Initiated ERT ≥12 months before the baseline visit and a stable dose (>80% of the labeled does) for 3 months prior to the baseline visit.
- A responsive *GLA* mutation based on a preliminary cell-based assay.
- Estimated glomerular filtration rate ($eGFR_{MDRD}$) ≥30ml/min/1.73m^2.
- Patients taking angiotensin converting enzyme inhibitors, angiotensin receptor blockers had to be on a stable dose for ≥4-weeks before the screening visit.

Methods

RENAL

- $eGFR_{CKD-Epi}$ was assessed at intervals of 2-3 weeks until month 24 and again at month 30.
- $mGFR_{Iohexol}$ was assessed at baseline and months 6, 12, 18, and 30.
- The long-term effect was assessed by calculating the annualized rates of change for each patient using the slope of the linear regression between the observed values and the assessment times.

ECHOCARDIOLOGY

- Left ventricular mass index (LVMi) collected by Echo using 2D or M-mode every 6-12 months through blinded, centralized evaluation (Cardiocore, Rockville, MD).
- The long-term effect was assessed by calculating the change from baseline to the last available timepoint and the 95% confidence interval for each patient.

Baseline Characteristics

Intent-to-Treat Population	Migalastat Arm (n=36)	ERT Arm (n=21)
Sex Female n (%) Male n (%)	 20 (56) 16 (44)	 12 (57) 9 (43)
Median Age (range)	54 (18, 70)	48 (18, 72)
Years since diagnosis Mean (SD)	10 (12)	13 (12)
$eGFR_{CKD-EPI}$, (mL/min/1.73 m^2) Mean (SD)	89.6 (22)	95.8 (19)
$mGFR_{iohexol}$ (mL/min/1.73 m^2) Mean (SD)	82.4 (18)	83.6 (24)
24-hr Urine Protein (mg) Mean (SD)	260 (532)	417 (735)
ACEi/ARB /RI Use: n (%)	16 (44)	11 (52)
Amenable based on Migalastat Amenability Assay: n (%)	34 (94)	19 (90)

Baseline Disease Severity

Sex	Fabry Disease in ≥2 Organ Systems	Angio-keratoma or Corneal Whorling	Cardiac	CNS	Neuro-pathic Pain	Renal	Gastro-intestinal
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%)

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. |

- All Study 012 patients with amenable mutations had clinical manifestations of Fabry and were eligible for treatment based on current guidelines.
- The age at enrollment/start of ERT treatment and the percentages of patients with involvement of different organ systems in Study 012 were comparable with those for patients reported in the Fabry Outcomes Survey (Mehta, Ricci et al. 2004) and the Fabry Registry (Eng, Fletcher et al. 2007).
- These findings indicate that Study 012 patients are comparable with the current Fabry population being treated with ERT, as reflected in the ERT registries.

30-Month Renal Results

		Parameter	
Parameter	Statistic	$eGFR_{CKD-EPI}$	$mGFR_{iohexol}$
Annualized Rate of Change (mL/min/1.73 m^2)			
Baseline – Month 30	n	31	30
	Mean	-1.718	-2.746
	SD	2.5501	5.5318
	95% CI	(-2.653, -0.782)	(-4.812, -0.681)
	Median	-1.934	-3.190

- The 30-month analyses include patients with amenable mutations (based on the Migalastat Amenability Assay) and baseline/post-baseline measures of eGFR and mGFR (renal analyses) or LVMi (ECHO analyses).

30-Month LVMi Results

		Group	
Parameter	Statistic	Overall	LVH at Baseline
LVMi (g/m^2)			
Baseline	n	30	11
	Median	89.780	109.780
	Mean	94.649	116.440
	SD	22.4222	20.9471
OLE Period Month 30			
Actual	n	29	10
	Median	87.140	101.075
	Mean	89.266	105.583
	SD	20.2636	18.5857
Change from Baseline	n	28	10
	Median	-4.580	-11.335
	Mean	-3.772	-9.959
	SD	13.1540	9.3260
	95% CI	(-8.873, 1.328)	(-16.630, -3.288)

Summary of 30-Month Study Renal and LVMi Findings

- 31 male/female patients with amenable mutations who were randomized to the migalastat group completed the 18-month randomized period and entered the 12-month open-label extension . 49 patients with amenable mutations received ≥1 dose of migalastat during the combined 30 months.
- The annualized rates of change in $eGFR_{CKD-EPI}$ and $mGFR_{iohexol}$ for migalastat (see Table above) are comparable to those previously reported in patients receiving ERT for 18 months: -1.0 (-3.6, 1.6) and -3.2 (-7.8, 1.3), respectively.
- For patients receiving ERT, previously reported 18-month changes in LVMi were -2.0 (-11.0, 7.0) for all patients and +4.5 (-20.9, 29.9) for patients with baseline LVH.
- For renal function, in patients switched from ERT, the effect of migalastat is persistent, with similar results observed over 18 and 30 months of treatment.
- For LVMi, the reduction in patients switched from ERT to migalastat is also persistent with similar results observed over 18 and 30 months of migalastat treatment.
- In patients with LVH at baseline, the reduction to month 30 for migalastat was statistically significant based on the 95% CIs.

Safety (ITT Patients)

- The 51 patients in the safety population – amenable/non-amenable mutations– had a mean duration of migalastat exposure of 896 days.
- Only 1 SAE was assessed as possibly related to migalastat by the investigator: proteinuria. This occurred during pregnancy in a patient with history of proteinuria during pregnancy.
- Migalastat was generally safe and well tolerated based on adverse event, laboratory, and physical exam data.

Conclusions

- The GFR stabilization and reduction in LVMi demonstrated with migalastat treatment are clinically relevant.
- Based on the literature, annualized rates of decline in GFR in ERT-treated Fabry patients are -2.2 to -2.9 ml/min/m^2.
- In patients switched from ERT to migalastat, the annualized rates of change (95% CI) in $eGFR_{CKD-EPI}$ and $mGFR_{iohexol}$ at month 30 were: -1.0 (-3.6, 1.6) and -3.2 (-7.8, 1.3), respectively.
- LVH is the greatest risk factor for cardiac events in Fabry disease (Patel, Cecchi et al. 2011), and any reduction in LVH has been shown to have a positive impact on cardiovascular morbidity and mortality in hypertensive heart disease (Pokharel and Bella 2013).
- Migalastat reduced cardiac mass in all 012 patients following 30-month treatment and, most importantly, in patients with LVH (cardiac hypertrophy), the reduction was statistically significant.
- The effects of migalastat on GFR and LVMi observed following 18 months persist over 30 months.
- The results suggest that migalastat is a promising first-in-class oral chaperone treatment for male and female patients with amenable mutations.

Acknowledgments

Patients and their families
Study 012 PIs:

- Patrick Deegan (UK)
- David Dimmock (US)
- Francois Eyskens (France)
- David Feingold (US)
- Ulla Feldt-Rasmussen (Denmark)
- Dominique Germain (France)
- Ozlem Goker-Alpan (US)
- Tashaski Hamazaki (Japan)
- Eric Hachulla (France)
- Derralynn Hughes (UK)
- Ana Javanovic (UK)
- David Koehler (US)
- Robin Lachmann (UK)
- Charles Lourenco (Brazil)
- Ichiei Narita (Japan)
- Khan Nedd (US)
- Kathy Nicholls (Australia)
- Toya Ohashi (Japan)
- Iacopo Olivotto (Italy)
- Norio Sakai (Japan)
- Suma Shankar (US)
- Gere Sunder-Plassmann (Austria)
- Akemi Tanaka (Japan)
- Mark Thomas (Australia)
- Roser Torra (Spain)
- Ahmad Tuffaha (US)
- Gerald Vockley (US)