Oral Migalastat HCl as an Investigational Therapy Evaluated in Females with Fabry Disease

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BACKGROUND

Fabry disease (FD) is an X-linked lysosomal storage disorder characterized by deficiency of alpha galactosidase A (α-Gal A). This results in accumulation of globotriaosylceramide (GL-3) in tissues and body fluids, leading to progressive, multi-organ disease. Heterozygote females may develop significant multi-system pathology, but generally later than males. Many females require supportive and enzyme replacement therapies.

STUDY OBJECTIVES

Primary: To evaluate the safety and tolerability of oral migalastat HCl (AT1001/GR181413A) 50, 100, or 250 mg once every other day) in female patients with FD.

Secondary: To evaluate pharmacokinetics (PK) and pharmacodynamics (PD) of migalastat HCl, including assessing changes in α-Gal A activity and GL-3 .

STUDY DESIGN

FAB-CL-204 (NCT00304512) was a Phase 2, multicenter, open-label trial of migalastat HCl in female patients with FD. The trial included a 12-week treatment phase and an optional 36-week treatment extension.

Eligible patients were females, 18 to 65 years old with Fabry disease and documented end-organ dysfunction, missense *GLA* mutations, and enhanceable α-Gal A activity (mutant and/or wild type) in an ex vivo lymphocyte-based assay. Written informed consent, approved by Institutional Review Board/Ethics Committee, was obtained from all patients prior to any study procedures. Each patient was randomized to receive 50, 100, or 250 mg of migalastat HCl once every other day throughout the study.

This study was conducted according to globally accepted standards of Good Clinical Practice (ICH-GCP) and in agreement with the Declaration of Helsinki.

SAFETY & PD PARAMETERS

Adverse events (AEs), serious AEs, vital signs, clinical laboratory tests (hematology, serum chemistry, and urinalysis), physical examinations, and use of concomitant medications; heart, kidney, and CNS evaluations; α-Gal A activity in peripheral blood mononuclear cells (WBC α-Gal A activity), kidney, and skin; GL-3 in urine (uGL-3), kidney, plasma, and skin.

BIOANALYTICAL METHODS

α-Gal A activity: measured using a fluorometric assay with catalysis to 4-methylumbelliferone (4-MU) as the activity measure.

Urine GL-3 analysis: done using liquid-liquid extraction to extract urinary lipids from whole urine samples. Following chromatography, GL-3 isoforms (C16, C20, C22, C24, and C24.1) were detected by electrospray ionization tandem mass spectrometry in multi-reaction mode. The limit of quantification was approximately 1 ng/mL. GL-3 was normalized to total phosphatidylcholine (PC), measured in the same LC-MS/MS assay.

Histological analyses of kidney GL-3: tissue was fixed, embedded in plastic (epon), cut (1 µm), and stained with methylene blue and Azure II. Slide assessment was blinded. All slides were evaluated by an independent pathologist examining GL-3 in multiple cell types (e.g., interstitial capillaries, podocytes, and distal tubular cells). For each cell type, a GL-3 score was assigned using categorical scoring in which 0 represented no GL-3 and 3 represented the most severe level of GL-3 (0, 1, 2, or 3: none, mild, moderate, or severe, respectively). For interstitial capillaries, a fully quantitative BLISS*-LM (Barisoni Lipid Inclusions Scoring System-Light Microscopy) method was applied. GL-3 inclusions in 50 to 180 interstitial capillaries were counted and the average number of inclusions per capillary was reported. Unlike categorical scoring, this method was able to detect GL-3 inclusions at baseline in all patients.

*Barisoni LMC, Jennette JC, Colvin RB, *et al.* Novel Quantitative Virtual Microscopy-Based method to evaluate GL-3 inclusions in renal peritubular capillaries in patients with Fabry disease. ASN Renal week 2010 Denver, CO, November 16-21, 2010 abstract SA-PO3064

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RESULTS

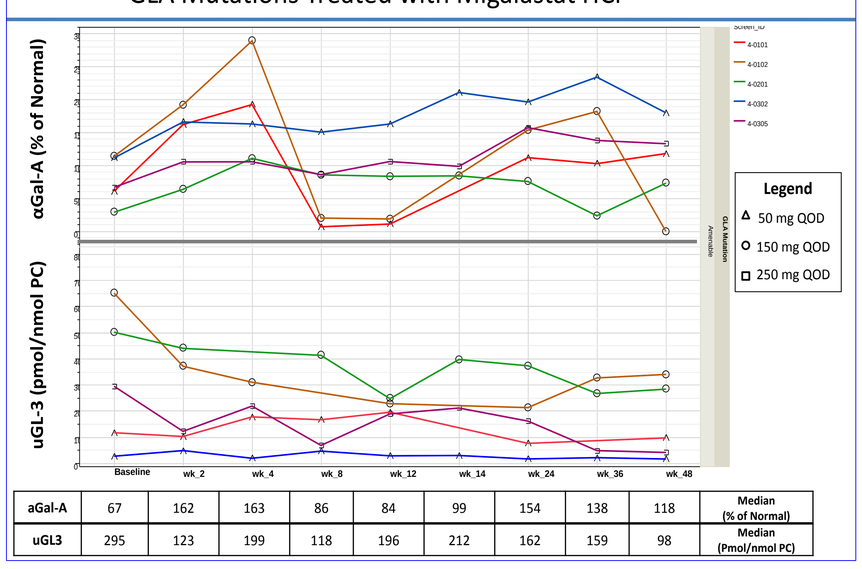
Table 1: Demographic and Baseline Disease Characteristics of Female Patients with Fabry Disease

Subject	Age	Age at diagnosis	*GLA* Genotype	Medical History and/or Baseline Disease Characteristics	eGFR (mL/min 1.73m²)	WBC α-Gal A activity (% of normal[3])	Urine GL-3 (fold X ULN)	Kidney GL-3 Deposition			
								Podocytes	Distal Tubules	Interstitial Capillaries	
								Score	Score	Score	BLISS
Patients with Amenable *GLA* Mutations[1]											
01-01	62	55	P259R	LVH, Bradycardia, 2nd degree AV block	90.1	61	2	3	1.5	0	0.4
01-02	39	33	P259R	Bradycardia, Acroparesthesia, Proteinuria	84.9	114	12	3	0	0	0.2
02-01	59	57	P205T	LVH, Bradycardia, TIA, Acroparesthesia	76.4	29	9	2.5	2.5	0.5	0.3
03-02	36	32	R112H	TIA, Acroparesthesia, Abdominal pain, Angiokeratoma, Depression	100.6	111	normal	1.5	0	0	0.2
03-05	43	43	L32P	Acroparesthesia, Abdominal pain, Depression	116.0	67	5	3	0.5	0	0.2
Patients with Non-Amenable *GLA* Mutations[1]											
02-03	37	32	C52G	LVH, Hearing loss, Proteinuria, Depression	107.8	79	normal	3	0	0	0.2
03-01	42	19	R227X[2]	Acroparesthesia, Angiokeratoma, Abdominal pain, Depression	73.0	15	8	3	0	0	0.1
04-02	44	39	E358K	LVH, Bradycardia, Acroparesthesia, Angiokeratoma, Proteinuria, Hearing loss	79.8	112	5	2	0	0	0.2
06-03	47	44	M1I	LVH, Bradycardia, Short PR, Proteinuria	82.7	60	3	3	3	0	0.1

Footnotes: (1) Per post hoc analysis, *GLA* mutations were considered likely to be amenable or non-amenable to migalastat treatment based on an in vitro HEK-293 cell-based assay; amenable mutant forms showed an increase in α-Gal A activity that was ≥1.2-fold above baseline and an absolute increase that was ≥3% of wild-type after incubation with migalastat HCl 10 µmol/L, (2) R227X is a deletion mutation, (3) Normal α-Gal A activity in healthy male volunteers is 22 ± 5.7 nmol 4-MU/hr/mg protein.
Abbreviations: eGFR = estimated glomerular filtration rate by MDRD equation; WBC= white blood cells; MU = methylumbelliferone; LVH = left ventricular hypertrophy; TIA=transient ischemic attack; ULN=upper limit of normal

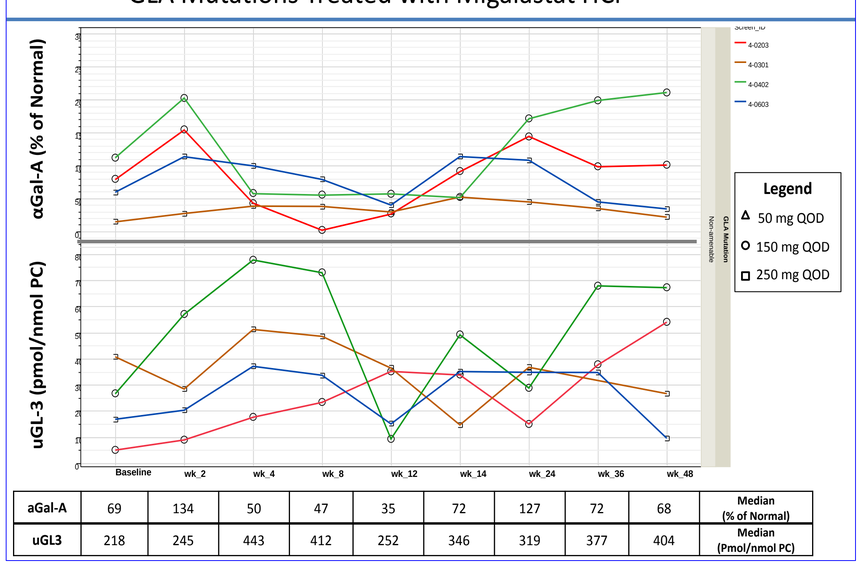
- Baseline disease characteristics were similar between females with amenable and non-amenable *GLA* mutations
- All nine patients had manifestations of FD: Acroparesthesia (6), LVH (5), Bradycardia (5), CKD stage 2 (5)
- Median age at diagnosis was 36 years; only one patient was diagnosed before age of 30
- At baseline, 6 of 9 patients had lower than normal WBC α-Gal A activity and 7 of 9 patients had elevated urine GL-3
- Renal biopsies demonstrated that the most severely affected cells by GL-3 inclusions were podocytes; interstitial capillaries were minimally affected

Figure 1A WBC αGal-A and uGL-3 in Females with Amenable GLA Mutations Treated with Migalastat HCl



aGal-A	67	162	163	86	84	99	154	138	118	Median (% of Normal)
uGL3	295	123	199	118	196	212	162	159	98	Median (Pmol/nmol PC)

Figure 1B WBC αGal-A and uGL-3 in Females with Non-Amenable GLA Mutations Treated with Migalastat HCl



aGal-A	69	134	50	47	35	72	127	72	68	Median (% of Normal)
uGL3	218	245	443	412	252	346	319	377	404	Median (Pmol/nmol PC)

Figure 2A Kidney Interstitial Capillary GL-3 in Females with Amenable GLA Mutations Treated with Migalastat HCl

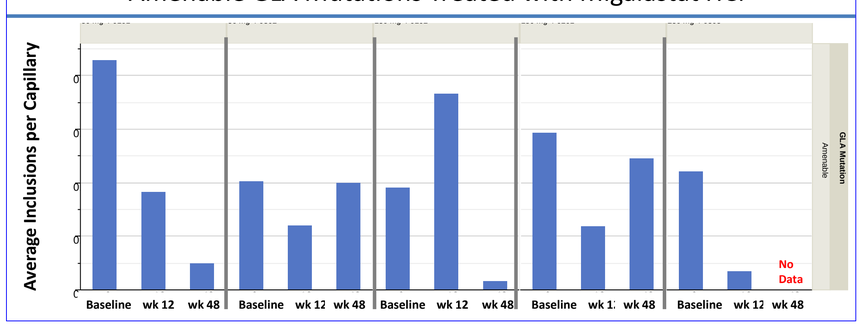
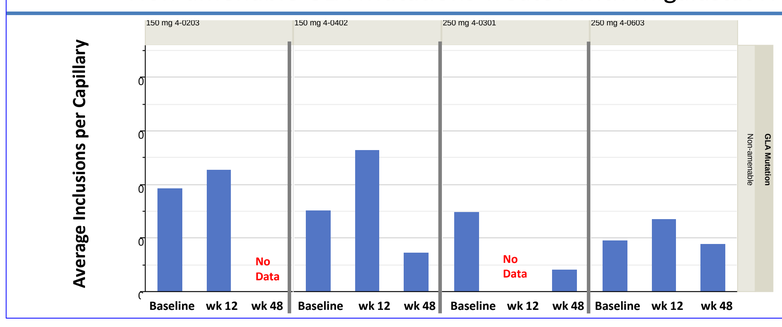


Figure 2B Kidney Interstitial Capillary GL-3 in Females with Non-amenable GLA Mutations Treated with Migalastat HCl



- Females with amenable *GLA* mutations who were on the 150 or 250 mg dose of migalastat HCl demonstrated reduction in urine GL-3 when compared to baseline at each treatment visit [fig. 1A bottom]
- No consistent reduction in urine GL-3 was seen in females with non-amenable mutations, at any dose [fig. 1B bottom]
- Four out of 5 females with amenable mutations demonstrated a decline in GL-3 inclusions in interstitial capillary cells in their last available kidney biopsy [fig. 2A]
- No changes in podocyte GL-3 inclusions were detected after treatment period of 48 weeks

SAFETY SUMMARY

- No serious adverse events (SAEs) related to treatment were reported. Two SAEs unrelated to treatment were reported: 1) cardiac tamponade occurred during the screening period following cardiac biopsy; 2) muscular chest pain occurred after 1 month of study treatment; an ECG and laboratory tests ruled out cardiac etiology
- All patients completed 48 weeks of treatment. No patients interrupted, reduced, or discontinued study drug dosing due to an AE
- All treatment-related AEs (TEAEs) were mild or moderate in severity. Two of those AEs were reported as possibly or probably related to study drug: 1) atrioventricular block was reported at Week 4 and resolved without any intervention while patient continued migalastat HCl treatment; 2) abdominal discomfort. All other TEAEs were reported as unlikely or not related to study drug

SUMMARY AND CONCLUSIONS

- Females in this study had significant manifestations of FD despite relatively high baseline WBC α-Gal A activity.
- Low GL-3 burden in kidney interstitial capillary cells was in contrast to heavily affected podocytes, probably due to different cell turnover rates
- The earliest and most consistent declines in urine GL-3 were seen in three patients with amenable *GLA* mutations, treated with 150 or 250 mg migalastat HCl. These three patients also demonstrated a decrease in GL-3 inclusions in interstitial capillary cells
- Treatment with migalastat HCl 50, 150, or 250 mg QOD for 48 weeks was well tolerated. No treatment-limiting toxicities were identified
- These results suggest that the efficacy and safety of migalastat HCl should be further investigated in females with FD
- Ongoing Phase 3 studies [AT1001-011 (NCT00925301) and AT1001-012 (NCT01218659)] will provide additional information on the treatment effectiveness of migalastat HCl for Fabry disease