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Response of Patients With Fabry Disease With the Amenable GLA Mutation p.N215S to Treatment With Migalastat (ATTRACT Study)

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INTRODUCTION

- Fabry disease is a devastating, rare, and progressive X-linked lysosomal storage disorder caused by mutations in the *GLA* gene, resulting in the deficient activity of α-galactosidase A (α-Gal A)[1,2]
- Accumulation of α-Gal A substrates can lead to functional impairments in the kidney, heart, and brain and premature death[1,2]
- Renal dysfunction progresses over time in a majority of male patients with Fabry disease, and can lead to end-stage renal disease. However, cardiac disease is currently the main cause of death in patients with Fabry disease[2]
- Migalastat, a first-in-class, orally administered small molecule, is a pharmacological chaperone approved in the European Union for the treatment of Fabry disease in adults and adolescents aged >16 years with *amenable GLA* mutations[3-5]
- Migalastat restores lysosomal trafficking and enzyme activity by binding, inducing proper folding, and stabilizing amenable mutant forms of α-Gal A[1,6]
- As an orally administered small molecule, migalastat may obviate the need for lifelong biweekly agalsidase infusions or enzyme replacement therapy (ERT) in patients with amenable mutations[3-5,7]
- p.N215S, often referred to as a "cardiac genetic variant",[8] is a common *GLA* mutation observed in Fabry disease. In general, the p.N215S phenotype is associated with higher plasma enzyme activity, older age of symptom onset, and significant cardiac disease. It is also less associated with expression of the early symptoms typically seen with severe classical disease. However, more research is needed to better understand p.N215S phenotypic expression[9,10]

OBJECTIVE

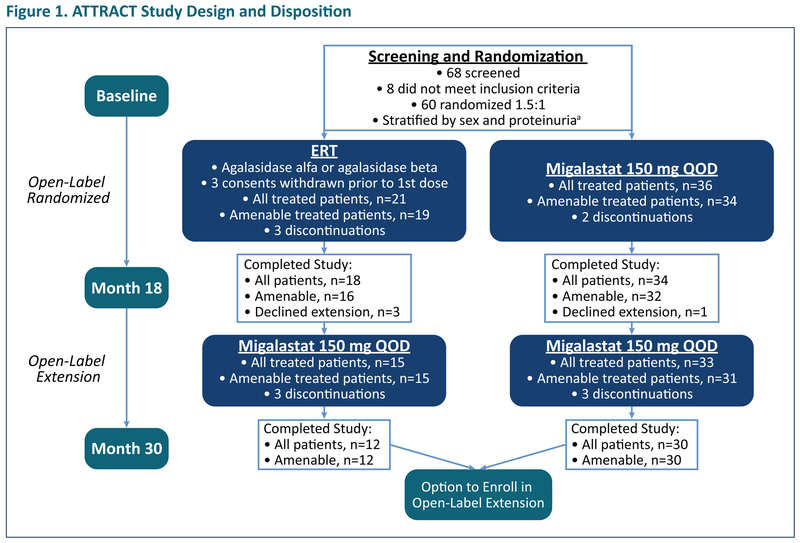
- To assess the efficacy of migalastat in a subset of patients with Fabry disease with the amenable p.N215S mutation relative to all patients with Fabry disease with amenable mutations during the first 18 months of the phase 3 ATTRACT study

METHODS

Study Design

- ATTRACT (AT1001-012, NCT01218659) is a phase 3, randomized, open-label, 30-month study comparing the efficacy and safety of migalastat and ERT in patients with Fabry disease with amenable *GLA* mutations who were previously treated with ERT (**Figure 1**)
- The intention-to-treat (ITT) amenable population consisted of patients with amenable mutations based on the Good Laboratory Practice Human Embryonic Kidney 293 cells (GLP-HEK) assay[11]
- Patients completing ATTRACT were eligible to enter open-label extensions (OLE) examining the long-term safety and efficacy of migalastat (NCT01458119 and NCT02194985)

Figure 1. ATTRACT Study Design and Disposition



ERT=enzyme replacement therapy; QOD=every other day.
[a]Proteinuria stratification: high (≥0.1 g/24 h); low (<0.1 g/24 h).

Key Inclusion Criteria

- Male and female patients aged 16-74 years diagnosed with Fabry disease with responsive *GLA* mutations based on a preliminary GLP-HEK 293 cell assay
- Treatment initiation with ERT ≥12 months before baseline visit and stable ERT dose (at ≥80% labeled dose) for 3 months before baseline visit
- $eGFR_{MDRD}$ at screening ≥30 mL/min/1.73 m^2
- Patients taking angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or renin inhibitors had to be on a stable dose for ≥4 weeks before the screening visit

Amenability of Mutant α-Gal A Forms

- Amenability was determined using a GLP-validated assay, which became available after study initiation[11]
- Testing was completed before unblinding of the data

Renal Assessments

- $eGFR_{CKD-EPI}$ was assessed at baseline and at months 1, 3, 6, 9, 12, 15, and 18
- $mGFR_{iohexol}$ was assessed at baseline and at months 6, 12, and 18
- The long-term effect of migalastat on renal activity 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

Cardiac Assessments

- Left ventricular mass index (LVMi) was measured by echocardiography using 2D or M-mode every 6 months through blinded, centralized evaluation (Cardiocore, Rockville, MD, USA)
- The long-term effect of migalastat on LVMi was assessed by calculating the change from baseline to the last available time point and the 95% confidence interval for each patient

RESULTS

- Patient disposition is summarized in **Figure 1**
- The intention-to-treat (ITT) amenable population consisted of 53/57 (34 migalastat; 19 ERT) patients
- 10 patients in the ITT amenable population had the p.N215S mutation; 7 were randomized to migalastat, while 3 remained on ERT

Baseline Disease Severity and Characteristics

- Age, plasma globotriaosylsphingosine (lyso-Gb_3), and eGFR at baseline were similar between patients in the p.N215S population and all patients in the ITT-amenable population. However, consistent with the literature, patients with the p.N215S mutation had higher median LVMi and had lower median 24-hour protein urine at baseline compared with all patients in the ITT-amenable population (**Tables 1** and **2**)
- 5/7 migalastat-treated patients and 1/3 ERT-treated patients with the p.N215S mutation had left ventricular hypertrophy at baseline
- A greater proportion of patients with the p.N215S mutation had cardiac disease at baseline than all patients (80% vs 52%). Patients with the p.N215S mutation had disease involvement in multiple organs/systems, including renal, central nervous system, and gastrointestinal but not angiokeratoma or corneal whorling (**Figure 2**)

Table 1. Individual Baseline Characteristics of Patients With the p.N215S Mutation

Patient p.N215S ID	Treatment	Age (years)	Years Since Diagnosis	Years Since Start of ERT	Plasma Lyso-Gb_3[a] (nmol/L)	LVMi (g/m^2)	24-hr Urine Protein (mg)	$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)
Males								
1	Migalastat	60	2	2	8.61	125	0	78
2	Migalastat	59	5	N/A	7.19	N/A	119	83
3	Migalastat	64	7	5	5.18	95	99	88
4	Migalastat	64	4	4	6.23	138	130	78
5	ERT	57	6	6	8.89	121	0	97
Females								
6	ERT	39	9	9	1.47	70	619	103
7	ERT	23	6	5	1.73	55	45	113
8	Migalastat	70	6	4	4.64	105	0	72
9	Migalastat	63	4	2	2.31	100	0	78
10	Migalastat	59	4	2	3.47	98	265	89

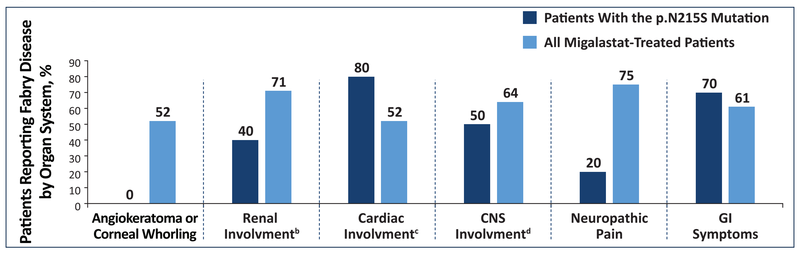
$eGFR_{CKD-EPI}$=estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration; LVMi=left ventricular mass index; lyso-Gb_3=globotriaosylsphingosine; N/A=not available; WBC α-Gal A=white blood cell α-galactosidase A;
[a]Confounded by ERT.

Table 2. Group Baseline Characteristics of Patients With the p.N215S Mutation and All Patients Randomized to Migalastat at Baseline

Characteristic	p.N215S Patients (n=10)	All Patients (n=36)
Age	59.50 (23, 70)	54 (18,70)
Years since diagnosis	5.50 (2, 9)	4.50 (1, 43)
Plasma lyso-Gb_3[a] (nmol/L)	4.91 (1.47, 8.89)	6.345 (0.80, 59.07)[b]
LVMi (g/m^2)	100.0 (55, 138)	90.14 (63.56, 165.73)[c]
24-hr urine protein (mg)	72.00 (0, 619)	129 (0, 2282)
$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)	85.50 (72, 113)	85.914 (51.33, 145.12)

Data are represented as median (min, max).
[a]Confounded by ERT.
[b]n=32.
[c]n=33.

Figure 2. Organ System Involvement at Baseline[a]

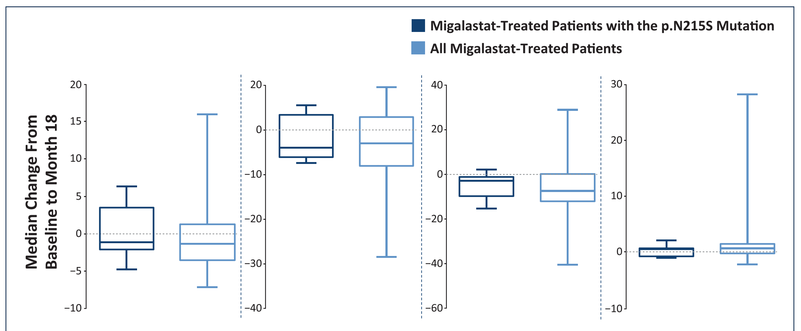


CNS=central nervous system; GI=gastrointestinal.
[a]Angiokeratoma, corneal whorling, neuropathic pain, and GI symptoms were based on medical history findings.
[b]Renal involvement was based on medical history or baseline eGFR <90 mL/min/1.73 m^2 and 24-hour protein ≥150 mg.
[c]Cardiac involvement included previous cardiac event (based on medical history), left ventricular hypertrophy, or conduction abnormality (eg, tachycardia, ST-segment abnormality) based on medical history finding or baseline assessment of LVMi.
[d]CNS involvement was based on medical history (stroke/transient ischemic attack, tinnitus/hearing loss).

Change from Baseline to Month 18

- The median change from baseline to month 18 for $eGFR_{CKD-EPI}$, $mGFR_{iohexol}$, LVMi, and plasma lyso-Gb_3 was similar between migalastat-treated patients with the p.N215S mutation and all migalastat-treated patients in the ITT-amenable population (**Figure 3**)
- In patients with the p.N215S mutation, 5/7 migalastat-treated patients and 1/3 ERT-treated patients achieved a decrease in LVMi
- There was a reduction in median GFR and stabilization of plasma lyso-Gb_3 in migalastat-treated patients with and without the p.N215S mutation; there was a small range across measured outcomes in patients with the p.N215S mutation
- Patients with the p.N215S mutation had a response to treatment similar to that of all migalastat-treated patients in ATTRACT

Figure 3. Change from Baseline to Month 18 in Patients With the p.N215S Mutation and All Patients Randomized to Migalastat at Baseline



	$eGFR_{CKD-EPI}$ Annualized Rate of Change From Baseline to Month 18		$mGFR_{iohexol}$ Annualized Rate of Change From Baseline to Month 18		LVMi Change From Baseline to Month 18		Plasma Lyso-Gb_3 Change From Baseline to Month 18	
	p.N215S Treated with Migalastat (n=7)	All Migalastat-Treated Patients (n=34)	p.N215S Treated with Migalastat (n=7)	All Migalastat-Treated Patients (n=34)	p.N215S Treated with Migalastat (n=6)	All Migalastat-Treated Patients (n=31)	p.N215S Treated with Migalastat (n=7)	All Migalastat-Treated Patients (n=30)
Mean ± SEM (95% CI)	0.05 ± 1.42 (−3.42, 3.52)	−0.40 ± 0.93 (−2.27, 1.48)	−1.92 ± 1.86 (−6.48, 2.64)	−4.35 ± 1.64 (−7.65, −1.06)	−5.10 ± 2.44 (−11.38, 1.18)	−6.58 ± 2.17 (−11.01, −2.15)	0.23 ± 0.42 (−0.80, 1.25)	−1.68 ± 1.03 (−0.42, −3.77)
Median (min, max)	−1.13 (−4.73, 6.38)	−1.29 (−6.97, 15.82)	−4.11 (−7.57, 5.27)	−3.23 (−28.77, 9.45)	−3.08 (−15.6, 1.67)	−7.74 (−40.72, 28.43)	0.52 (−1.10, 2.07)	0.54 (−2.27, 28.30)

Data are graphed as median (center line), first/third quartiles (box perimeter), and min/max (error bars).
CI=confidence interval; $mGFR_{iohexol}$=measured GFR using iohexol clearance; SEM=standard error of the mean.

- Individual treatment outcomes for the 3 patients with the p.N215S mutation treated with ERT are listed in **Table 3**

Table 3. Individual Change From Baseline to Month 18 in Renal Function, Cardiac Mass, and Substrate Level in p.N215S Patients Treated With ERT

Patient p.N215S ID	$eGFR_{CKD-EPI}$ Annualized Rate of Change From Baseline to Month 18	$mGFR_{iohexol}$ Annualized Rate of Change From Baseline to Month 18	LVMi Change From Baseline to Month 18	Plasma Lyso-Gb_3 Change From Baseline to Month 18
5	0.4	−1.7	22.7	2
6	−0.8	−7.9	−7.7	0
7	−1.9	−3.8	−7.6	−0.1

CONCLUSIONS

- Following 18 months of treatment with migalastat in the phase 3 ATTRACT study, a majority of patients with Fabry disease with the p.N215S mutation had a response similar to that of all migalastat-treated patients and demonstrated a decrease in LVMi.
  - The small reduction in eGFR in this ERT-experienced population is noteworthy based on data in the literature demonstrating a worsening of renal function over 12-15 months after stopping ERT treatment[12] or reducing ERT dose[13]
- Migalastat may offer promise as an oral treatment alternative for patients with Fabry disease with amenable mutations, including those with the p.N215S mutation and female patients with Fabry disease with amenable mutations

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DISCLOSURES

Conflicts of Interest

DAH is a consultant/advisor and speaker for and has received research funding and travel support from Shire, Sanofi, and Biomarin. KN has received research funding from Genzyme/Sanofi. SPS has received honoraria and travel support from Amicus Therapeutics, Biomarin, Genzyme/Sanofi, Protalix Biotherapeutics, Pfizer, and Shire. GS-P has received fees from Amicus Therapeutics, Genzyme/Sanofi, and Shire HGT. DGB is an investigator for and has received research funding from Amicus Therapeutics, Genzyme, and Shire. RS is a consultant for and has received research funding from Protalix Biotherapeutics and Amicus Therapeutics. CV is an employee of and owns stock in Amicus Therapeutics. NS, JY, JPC, and JAB are employees of Amicus Therapeutics. UF-R is an advisor for and has received research funding from Amicus Therapeutics, Genzyme/Sanofi, and Shire.

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