UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT PURSUANT TO
SECTION 13 OR 15(D) OF THE
SECURITIES EXCHANGE ACT OF 1934

Date of Report (Date of earliest event reported): **September 6, 2017**

AMICUS THERAPEUTICS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware (State or Other Jurisdiction of Incorporation)	
001-33497 (Commission File Number)	**71-0869350** (IRS Employer Identification No.)
1 Cedar Brook Drive, Cranbury, NJ (Address of Principal Executive Offices)	**08512** (Zip Code)

Registrant's telephone number, including area code: **(609) 662-2000**

(Former Name or Former Address, if Changed Since Last Report.)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

o Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

o Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

o Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

o Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company o

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. o

Item 8.01. Other Events.

On September 6, 2017, Amicus Therapeutics, Inc. (the "Company") presented data related to its Fabry program at the 13th International Congress of Inborn Errors of Metabolism in Rio de Janeiro, Brazil. The posters presented are attached hereto as Exhibit 99.1.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits: The Exhibit Index annexed hereto is incorporated herein by reference.

Exhibit No.	Description
99.1	Amicus Therapeutics, Inc. Fabry program data posters presented at the 13th International Congress of Inborn Errors of Metabolism in Rio de Janeiro, Brazil

EXHIBIT INDEX

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99.1	Amicus Therapeutics, Inc. Fabry program data posters presented at the 13th International Congress of Inborn Errors of Metabolism in Rio de Janeiro, Brazil

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Amicus Therapeutics, Inc.

Date: September 6, 2017

By: /s/ ELLEN S. ROSENBERG
Ellen S. Rosenberg
General Counsel and Corporate Secretary

638

Long-Term Migalastat Treatment Stabilizes Renal Function in Pat With Fabry Disease: Results From a Phase 3 Clinical Study (AT100

Lourenço C[1], Schiffmann R[2], Nicholls K[3], Bichet DG[4], Feldt-Rasmussen U[5], Hughes DA[6], Yu J[7], Castelli JP[7], Skuban N[7], Barth JA
on behalf of the Study 041 Investigators

[1]Ribeirão Preto Medical School, University of São Paulo, São Paulo, Brazil; [2]Baylor Research Institute, Dallas, TX, USA; [3]Royal Melbourne Hospital, Parkville, VIC, Austral
[4]Hôpital du Sacré-Coeur, University of Montreal, Montreal, Quebec, Canada; [5]Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [6]Royal Free NHS Foundation
University College London, London, UK; [7]Amicus Therapeutics, Inc., Cranbury, NJ, USA

INTRODUCTION

- Fabry disease is a devastating, rare, and progressive X-linked lysosomal storage disorder caused by a mutation in the *GLA* gene, resulting in the functional deficiency of α-galactosidase A (α-Gal A)[1]
- Accumulation of α-Gal A substrates, including glycosphingolipids such as globotriaosylceramide (GL-3) and globotriaosylsphingosine, can lead to multiorgan disease and progressive decline in renal function[1]
  - Accumulation of GL-3 in the kidney is a known consequence of Fabry disease[2]
- Progressive impairment of renal function has been shown to be a major risk factor for cardiac events and premature death[3]; thus, stabilizing or slowing renal decline is an important treatment goal in Fabry disease
- Migalastat, a first-in-class, orally administered small molecule, is a pharmacological chaperone approved in the European Union, Switzerland, and Israel for the treatment of Fabry disease in patients with *amenable GLA* mutations[4]
  - Amenability is determined via the Migalastat Amenability Assay by measuring migalastat-induced changes in HEK cells that are transfected with cDNA from Fabry disease–associated *GLA* mutations. Criteria include a relative increase in α-Gal A activity ≥1.2-fold above baseline and an absolute increase in α-Gal A ≥3.0% of wild type after incubation with 10 μM of migalastat[5]
  - Patients do not have to be individually tested for amenability; the http://galafoldamenabilitytable.com website can be used to identify whether a specific mutation has been found to be amenable or non-amenable in the assay
- Migalastat restores lysosomal trafficking and enzyme activity by binding and inducing proper folding of amenable mutant forms of α-Gal A[6,7]
- FACETS (AT1001-011, NCT00925301) was a phase 3, double-blind, randomized, placebo-controlled study to evaluate the efficacy, safety, and pharmacodynamics of migalastat in enzyme replacement therapy (ERT)–naïve patients with Fabry disease with amenable *GLA* mutations[8]
- Patients completing FACETS were eligible for enrollment in the phase 3, open-label, long-term extension AT1001-041 study (NCT01458119; referred to as the 041 extension study herein)

OBJECTIVE

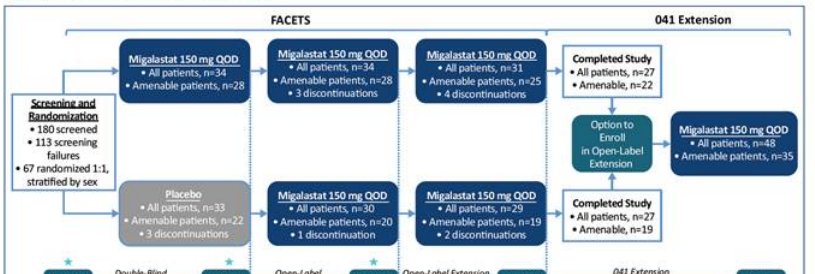
- To evaluate the long-term effects of migalastat on renal function in patients with Fabry disease completing the FACETS study who enrolled in the 041 extension study

METHODS

Study Design

- In FACETS, eligible patients were randomly assigned 1:1 to receive migalastat 150 mg or placebo every other day for 6 months (**Figure 1**)
- After completing the 6-month double-blind period, patients had the option to receive open-label migalastat for an additional 6 months (months 6-12) and for an additional year after that (months 12-24)
- Patients who completed 24 months of treatment in FACETS had the option to enroll in the 041 extension study and receive open-label migalastat for up to 5 years (**Figure 1**)
- The effect of migalastat on renal function was a secondary objective of both FACETS and the 041 extension study

Figure 1. FACETS and 041 Extension Study Designs



QOD=every other day.

Key Inclusion Criteria

- Male and female patients aged 16-74 years diagnosed with Fabry disease with amenable *GLA* mutations
- Naïve to ERT or had 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× the upper limit of normal (24-hour collection)
- 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

Analyses

- In FACETS, eGFR was calculated using $eGFR_{CKD-EPI}$ and $eGFR_{MDRD}$
  - A post hoc analysis examined $eGFR_{CKD-EPI}$ annualized rate of change in subgroups based on eGFR at baseline (30 to <60 mL/min/1.73 m^2, 60 to <90 mL/min/1.73 m^2, and ≥90 mL/min/1.73 m^2)
- mGFR was assessed based on plasma clearance of unlabeled iohexol ($mGFR_{iohexol}$)
- The long-term effect of migalastat on renal function was assessed by calculating the annualized rate of change in $eGFR_{CKD-EPI}$ in patients who received at least 17 months of treatment with migalastat (n=41)
- Annualized change rates were calculated using simple linear regression
- The analyses presented herein were restricted to patients with amenable mutations per the Migalastat Amenability Assay

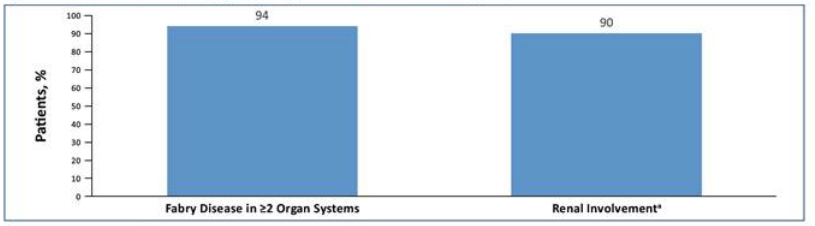
RESULTS

- Of 67 patients (50 of whom had amenable mutations) randomly assigned in the phase 3 FACETS trial, 54 patients (41 of whom had amenable mutations) completed the study, and 48 patients (35 of whom had amenable mutations) entered the 041 extension study
- At the time of these analyses, patients with amenable mutations had received treatment for a median of 3.5 years (range, 1.5-4.9)

Baseline Disease Severity

- Disease severity at baseline was significant among the 50 randomized patients who had amenable mutations (**Figure 2**)

Figure 2. Baseline Disease Severity Per Organ System (patients with amenable mutations; n=50)

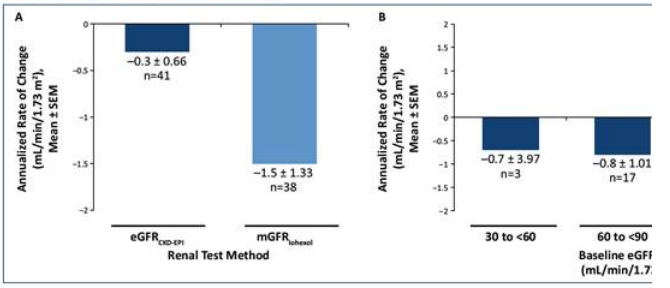


[a]Based on baseline eGFR <90 mL/min/1.73 m^2, 24-hr urine protein ≥150 mg, or renal impairment in medical history.

Renal Function (FACETS study)

- Based on GFR assessments, renal function remained stable over 18 and 24 months of migalastat treatment in patients with amenable mutations

Figure 3. Annualized Mean Change From Baseline to Month 24 in (A) $eGFR_{CKD-EPI}$ and $mGFR_{iohexol}$ in All Patients and (B) $eGFR_{C}$ eGFR Subgroup (patients with amenable mutations)

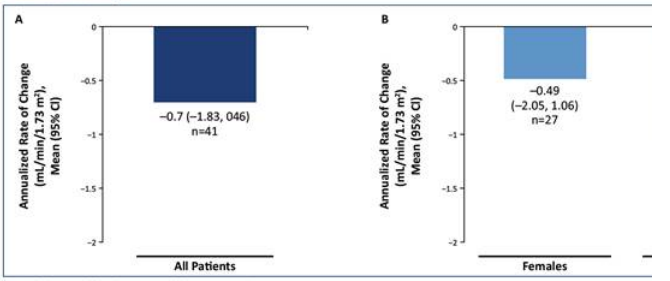


$eGFR_{CKD-EPI}$=estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; $mGFR_{iohexol}$=measured using iohexol clearance; SEM=standard error of the mean.

Renal Function (041 extension study)

- Among patients with amenable mutations, renal function remained stable for up to approximately 5 years of treatme (min, 1.5 years; max, 4.9 years) (**Figure 4A**)
- Long-term stabilization of renal function with migalastat was observed regardless of sex (**Figure 4B**)
  - The mean annualized rate of change in $eGFR_{CKD-EPI}$ from baseline to month 48 was −0.49 mL/min/1.73 m^2 (95% co −2.05, 1.06) in female patients and −1.06 mL/min/1.73 m^2 (95% CI −2.82, 0.70) in male patients
  - The long-term effect of migalastat on renal function compares favorably with the decline reported in untreated p Average annualized declines in eGFR of −3.0 mL/min/1.73 m^2 and −2.6 mL/min/1.73 m^2 have been reported for female and male patients with Fabry disease[9,10]

Figure 4. Annualized Mean Change in $eGFR_{CKD-EPI}$ From Baseline to Month 48 in (A) All Patients and (B) Patients By Sex (pa amenable mutations)



Rate of change calculated using simple linear regression.
CI=confidence interval.

Summary of Safety Findings From FACETS and the 041 Extension Study

- In FACETS and the 041 extension study, migalastat was generally safe and well tolerated over 48 months of treatment
- During the double-blind period of FACETS, the profile of treatment-emergent adverse events (TEAEs) was similar betw
  - Headache was the most common TEAE (migalastat, 35%; placebo, 21%) followed by nasopharyngitis (migalastat,
- Most TEAEs reported with migalastat were mild or moderate, and required no intervention or were readily managed i clinical practice
- During FACETS, 1 patient experienced 2 serious adverse events (AEs; fatigue and paresthesia) considered possibly rela both events resolved
- In FACETS and the 041 extension study, there were no discontinuations due to migalastat-related AEs, including seriou
- Two deaths were reported during the extension study; neither was considered related to migalastat treatment

Renal-Specific Safety

- Between months 12 and 24 in the FACETS study, 4 of 50 (8%) patients with amenable mutations experienced treatme
  - For 1 of these patients, proteinuria was considered possibly related to migalastat
- No patient in FACETS or the 041 extension study progressed to end-stage renal disease

CONCLUSIONS

- In both FACETS and the 041 extension study, treatment with migalastat stabilized renal function regardless of baseline
- In FACETS, migalastat was generally well tolerated and effective in patients with amenable mutations
- Approved in the European Union, Switzerland, and Israel, migalastat offers promise as a first-in-class oral treatment fo tients aged ≥16 years with Fabry disease with amenable mutations

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ACKNOWLEDGMENTS

The authors thank the patients and their families, as well as the FACETS and AT1001-041 investigators. Third-party medical ed by ApotheCom and was supported by Amicus Therapeutics, Inc.

DISCLOSURES

Conflicts of Interest

CL has no conflicts of interest to disclose. RS has received research funding from Amicus Therapeutics, Protalix Biotherapeutic Genzyme, and Shire. KN serves on advisory boards for and has received research funding from Amicus Therapeutics, Genzym and Shire. DGB serves as a consultant and speaker for Amicus Therapeutics and Genzyme, and has received research funding from Amicus Therapeutics, Genzyme, and Shire. UFR serves on advisory boards for and has received research funding from Amicus Therapeutics, Genzyme, and Shire. DAH is a consultant for and has

- treated with placebo and migalastat, respectively, during the double-blind period (**Figure 3A**)
- Stabilization of renal function with migalastat treatment was observed regardless of baseline eGFR (**Figure 3B**)

Protalix. JY, JPC, NS, and JAB are employees of and own stock in Amicus Therapeutics.

Supported by Amicus Therapeutics, Inc.

Presented at the 13th International Congress of Inborn Errors of Metabolism; September 5-8, 2017;

636

Efficacy and Safety of Migalastat, an Oral Pharmacological Chaperone for F Disease: Renal Findings From Two Randomized Phase 3 Studies (FACETS and A

Jovanovic A[1], Schiffmann R[2], Nicholls K[3], Feldt-Rasmussen U[4], Giugliani R[5], Bichet DG[6], Hughes DA[7], Jain V[8], Yu J[8], Castelli JP[8], Skuban N

[1]Salford Royal Hospital and NHS Foundation Trust, Manchester, UK; [2]Baylor Research Institute, Dallas, TX, USA; [3]Royal Melbourne Hospital, Parkville, VIC, Australia; [4]Rigshospitalet Copenhagen, Copenhagen, Denmark; [5]Medical Genetics Service, HCPA/UFRGS, Porto Alegre, Brazil; [6]Hôpital du Sacré-Coeur, University of Montreal, Montreal, Quebec, Canada; [7] Foundation Trust and University College London, London, UK; [8]Amicus Therapeutics, Inc., Cranbury, NJ, USA

INTRODUCTION

- Fabry disease is a devastating, rare, and progressive X-linked lysosomal storage disorder caused by a mutation in the *GLA* gene, resulting in the functional deficiency of α-galactosidase A (α-Gal A)[1]
- Accumulation of α-Gal A substrates, including glycosphingolipids such as globotriaosylceramide (GL-3) and globotriaosylsphingosine (lyso-Gb_3), can lead to multisystem disease and premature death[1]
- Migalastat, a first-in-class, orally administered small molecule, is a pharmacologic chaperone approved in the European Union, Switzerland, and Israel for the treatment of Fabry disease in patients with *amenable GLA* mutations[2]
- Migalastat restores lysosomal trafficking and enzyme activity by binding and inducing proper folding of amenable mutant forms of α-Gal A[1,3]
- As an orally administered small molecule, migalastat may obviate the need for lifelong biweekly agalsidase infusions or enzyme replacement therapy (ERT)[4,5]

OBJECTIVE

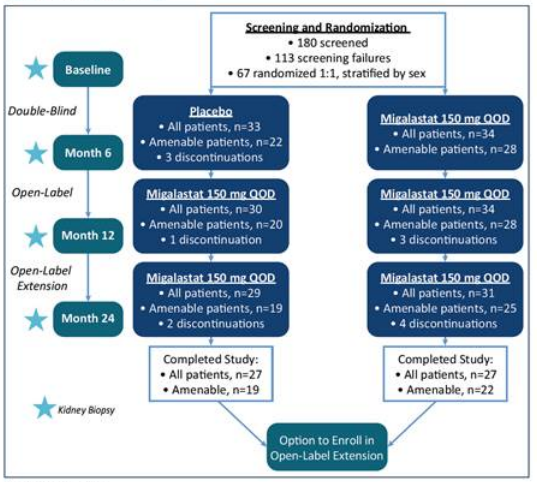
- To summarize renal findings from 2 randomized phase 3 studies of migalastat in patients with Fabry disease

METHODS

Study Designs

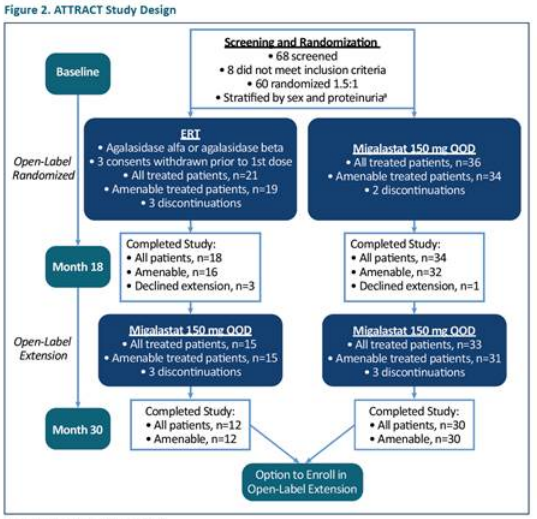
- FACETS (AT1001-011, NCT00925301) was a phase 3, double-blind, randomized, placebo-controlled study to evaluate the efficacy, safety, and pharmacodynamics of migalastat in patients with Fabry disease with amenable *GLA* mutations (**Figure 1**)
- ATTRACT (AT1001-012, NCT01218659) was a phase 3, randomized, open-label study to compare the efficacy and safety of migalastat and ERT in patients with Fabry disease with amenable *GLA* mutations who were previously treated with ERT (**Figure 2**)

Figure 1. FACETS Study Design



QOD=every other day.

Figure 2. ATTRACT Study Design



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

Key Inclusion Criteria for FACETS and ATTRACT

RESULTS

- The FACETS and ATTRACT studies randomized 67 and 60 patients, respectively, of which 50 and 56 patients, respectively, had amenable mutations
- Patients in both studies had significant baseline disease severity
  - 94% and 88% of patients in the FACETS and ATTRACT studies, respectively, had Fabry disease in ≥2 organ systems[4,6]
  - 90% and 75% of patients in the FACETS and ATTRACT studies, respectively, had renal involvement[4,6]

Disease Substrate

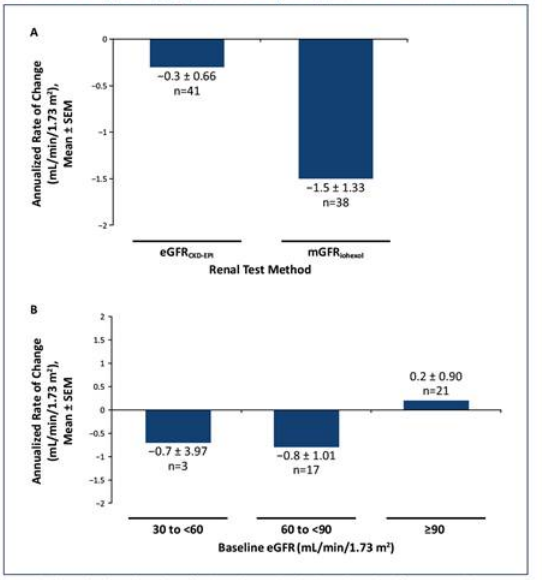
- In FACETS, migalastat treatment significantly reduced interstitial capillary GL-3 inclusions and lyso-Gb_3 levels in patients with Fabry disease with amenable mutations[6]
- In ATTRACT, plasma lyso-Gb_3 levels remained low and stable following the switch from ERT to migalastat in patients with amenable mutations. Plasma lyso-Gb_3 levels increased in 2 patients with non-amenable mutations following the switch from ERT to migalastat, but did not change in 2 patients with non-amenable mutations who remained on ERT[4]

Renal Function

FACETS

- From baseline to month 24, renal function was stable in patients with amenable mutations treated with migalastat in the FACETS study (**Figure 3**)
- Stabilization of renal function was observed regardless of baseline eGFR

Figure 3. Annualized Mean Change From Baseline to Month 24 in (A) $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$ in All Patients and (B) $eGFR_{CKD\text{-}EPI}$ by Baseline eGFR (FACETS; patients with amenable mutations)



Annualized rates based on the subset of patients who received at least 17 months of treatment with migalastat.
$eGFR_{CKD\text{-}EPI}$=estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; $mGFR_{iohexol}$=measured glomerular filtration rate using iohexol clearance; SEM=standard error of the mean.

ATTRACT

- In the ATTRACT study, migalastat and ERT had comparable favorable effects on renal function at month 18 using both GFR methods (**Figure 4**)
- Migalastat stabilized renal function at 18 months regardless of baseline eGFR (**Figure 5**)

Figure 4. Annualized LS Mean Change in GFR From Baseline to Month 18 (ATTRACT; patients with amenable mutations)

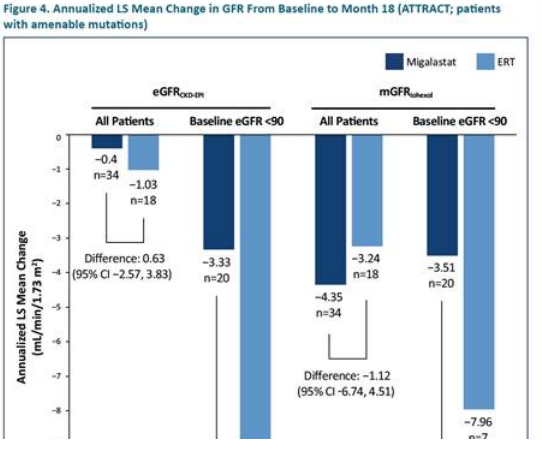
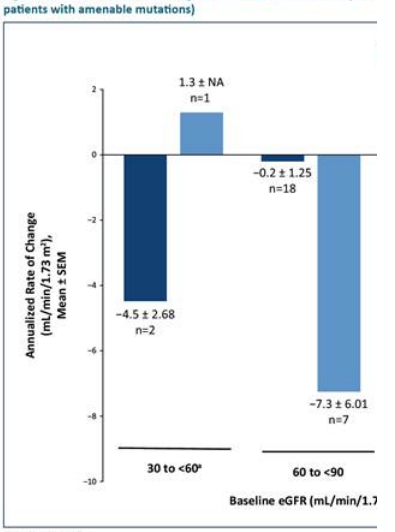


Figure 5. Annualized Rate of Change in $eGFR_{CKD\text{-}EPI}$ at Month 18 by Bas patients with amenable mutations)



NA=not applicable.
[a]Inconclusive due to low n number.

- In ATTRACT, renal function remained stable in patients with am 30 months of migalastat treatment using both GFR methods
  - The mean annualized change from baseline to month 30 i −1.7 mL/min/1.73 m² (95% CI, −2.7 to 0.8) (n=31) and in m −2.7 mL/min/1.73 m² (95% CI, −4.8 to 0.7) (n=31)

Summary of Safety Findings From FACETS an

- Treatment with migalastat was generally safe and well tolerate (AE) trends attributable to migalastat
- Most treatment-emergent AEs (TEAEs) reported with migalasta moderate, and required no intervention or were readily manag practice
- The profile of TEAEs was similar between migalastat and placeb headache the most commonly reported TEAE
- There were few serious AEs considered related to migalastat ar either study
- There were few discontinuations due to TEAEs, and most were Fabry disease comorbidities
- Predefined renal AEs during the 18-month comparison stage of and 33% of patients receiving migalastat and ERT, respectively
  - No patients progressed to end-stage renal disease

CONCLUSIONS

- Migalastat was generally well tolerated and effective in patient in FACETS and ATTRACT
- In both FACETS and ATTRACT, treatment with migalastat stabili
  - In ATTRACT, migalastat and ERT were shown to have comp function
- Approved in the European Union, Switzerland, and Israel, miga first-in-class oral treatment for male and female patients aged with amenable mutations

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3. Yam GH-F et al. *FASEB J.* 2005;19(1):12-18.
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6. Germain DP et al. *N Engl J Med.* 2016;375(6):545-555.

ACKNOWLEDGMENTS

The authors acknowledge the patients and their families, as well as the investigators. Third-party medical editorial assistance was provided by supported by Amicus Therapeutics, Inc.

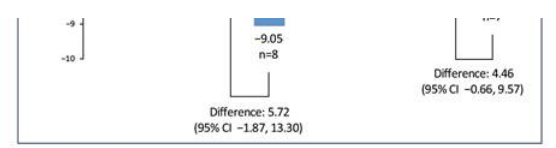
DISCLOSURE

Conflicts of Interest

AJ has no conflicts of interest to disclose. RS has received research fun Therapeutics, Protalix Biotherapeutics, Shire, and Genzyme. KN serves and has received research funding from Amicus Therapeutics, Genzym advisory boards for and has received research funding from Amicus Th Shire. RG has received honoraria from Amicus Therapeutics, BioMarin, DGB serves as a consultant and speaker for and has received funding f and Genzyme, and has received research funding from Shire. DAH is a received research and travel funding from Amicus Therapeutics, Shire, Protalix. VJ, JY, JPC, NS, and JAB are employees of and own stock in Am

Key Inclusion Criteria for FACETS and ATTRACT

- Male and female patients aged 16-74 years diagnosed with Fabry disease with amenable *GLA* mutations
- Naive to ERT or had not received ERT for ≥6 months before screening (FACETS)
- Initiated treatment with ERT ≥12 months before baseline visit and had a stable ERT dose (at ≥80% labeled dose) for 3 months before baseline visit (ATTRACT)
- $eGFR_{MDRD}$ at screening ≥30 mL/min/1.73 m^2
- Urine GL-3 at screening ≥4× the upper limit of normal (24-hour collection) (FACETS)
- 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



LS means and 95% confidence intervals (CIs) based on analysis of covariance that includes treatment, baseline GFR, sex, age, and 24-hour urine protein.
eGFR=estimated glomerular filtration rate; GFR, glomerular filtration rate; LS=least squares.

Supported by Amicus Therapeutics, Inc.

Presented at the 13th International Congress of Inborn Errors of Metabolism; September 5-8, 2017;

2667

Improvements in Cardiac Mass With Long-Term Migalastat Treatment in P With Fabry Disease: Results From Two Phase 3 Trials (FACETS and ATTR

Jovanovic A[1], Schiffmann R[2], Nicholls K[3], Feldt-Rasmussen U[4], Bichet DG[5], Hughes DA[6], Jain V[7], Yu J[7], Castelli JP[7], Skuban N[7], Barth JA

[1]Salford Royal Hospital and NHS Foundation Trust, Manchester, UK; [2]Baylor Research Institute, Dallas, TX, USA; [3]Royal Melbourne Hospital, Parkville, VIC, Australia; University of Copenhagen, Copenhagen, Denmark; [5]Hôpital du Sacré-Coeur, University of Montreal, Montreal, Quebec, Canada; [6]Royal Free NHS Foundation University College London, London, UK; [7]Amicus Therapeutics, Inc., Cranbury, NJ, USA; [8]Medical Genetics Service, HCPA/UFRGS, Porto Alegre, Brazil

INTRODUCTION

- Cardiac complications are common in Fabry disease, a rare X-linked disorder of lysosomal α-galactosidase A deficiency, and are the main cause of death in patients with this condition[1,2]
- Left ventricular hypertrophy (LVH) is the hallmark of Fabry cardiomyopathy[2,3] and the main risk factor for Fabry disease–related cardiac complications (eg, heart failure, myocardial infarction, sudden cardiac death)[4]
- A progressive decline in midwall fractional shortening (MWFS) may be observed in earlier stages of Fabry disease and is one of the first signs of systolic impairment[5]
- Studies assessing left ventricular mass (LVM) in untreated patients with Fabry disease reported a progressive increase in LVM index (LVMi) of 1.52–4.07 g/m^2/year; progression occurred regardless of disease phenotype[6,7]
- While reductions in LVM have been observed in patients with Fabry disease following treatment with enzyme replacement therapy (ERT), the effect of ERT on LVM has been inconsistent, per the published literature[8,9]
- Migalastat, a first-in-class, orally administered small molecule, is a pharmacological chaperone approved in the European Union, Switzerland, Israel, and Australia for the treatment of Fabry disease in patients with *amenable GLA* mutations[10]
- Migalastat restores lysosomal trafficking and enzyme activity by binding, inducing proper folding, and stabilizing amenable mutant forms of α-galactosidase A[11]

OBJECTIVE

- To summarize the effects of long-term migalastat treatment on cardiac outcomes in patients with Fabry disease and amenable mutations who were enrolled in two randomized phase 3 studies

METHODS

Study Designs

- FACETS (AT1001-011, NCT00925301) was a phase 3, double-blind, randomized, placebo-controlled study to evaluate the efficacy, safety, and pharmacodynamics of migalastat 150 mg every other day in ERT-naive patients with Fabry disease with amenable *GLA* mutations[12]
- ATTRACT (AT1001-012, NCT01218659) was a phase 3, randomized, open-label study to compare the efficacy and safety of migalastat and ERT in patients with Fabry disease with amenable *GLA* mutations who were previously treated with ERT[13]
- Patients completing either FACETS or ATTRACT were eligible to enter an open-label extension (OLE) study examining the long-term efficacy and safety of migalastat (AT1001-041, NCT01458119)

Key Inclusion Criteria for FACETS and ATTRACT

- Male and female patients aged 16-74 years diagnosed with Fabry disease with amenable *GLA* mutations
- Naive to ERT or had not received ERT for ≥6 months before screening (FACETS)
- Initiated treatment with ERT ≥12 months before baseline visit and had a stable ERT dose (at ≥80% labeled dose) for 3 months before baseline visit (ATTRACT)
- $eGFR_{MDRD}$ of ≥30 mL/min/1.73 m^2 at screening
- Urine globotriaosylceramide of ≥4× the upper limit of normal (24-hour collection) at screening (FACETS)
- 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

Analyses

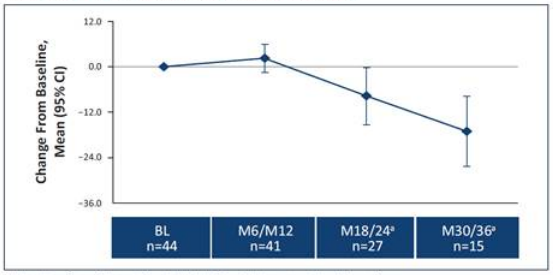
- Cardiac echocardiograms were evaluated (blinded, central review) by a single reader specialized in echocardiography
- Cardiac echocardiographic findings were used to assess changes in LVMi and MWFS with migalastat or ERT over time
- The analyses presented herein were restricted to patients with amenable mutations per the Migalastat Amenability Assay[14]

RESULTS

Patients

- The FACETS trial randomized 67 patients, 50 of whom had amenable

Figure 1. Mean Change From Baseline in LVMi (g/m^2) Over Time With Migalastat Treatment (FACETS; patients with amenable mutations)



BL=baseline; CI=confidence interval; LVMi=left ventricular mass index; M=month.
[a]Statistically significant change from baseline based on 95% CI.

- LVH was reported in 11 patients at baseline (mean LVMi, 138.9 g/m^2)
- The majority of patients (9/11) with LVH at baseline had a reduction in LVMi, and 5/11 patients demonstrated normalization of LVMi (**Table 1**)

Table 1. Changes From Baseline in LVMi (g/m^2) With Migalastat Treatment in Patients With Amenable Mutations and LVH at Baseline (FACETS; mean LVMi at baseline, 138.9 g/m^2)

	Timepoint				
	Month 12	Month 24	Month 36	Month 48	LOCF
n	9	9	4	4	11
Mean change from baseline (95% CI)	8.8 (−8.9, 26.6)	−22.5[a] (−41.6, −3.4)	−30.0[a] (−57.9, −2.2)	−33.1[a] (−60.9, −5.4)	−20.8[a] (−37.4, −4.1)
Any reduction	5/9 (56%)	7/9 (78%)	4/4 (100%)	4/4 (100%)	9/11 (82%)
Normalization	0/9 (0%)	3/9 (33%)	2/4 (50%)	3/4 (75%)	5/11 (46%)

Normal LVMi is ≤95 g/m^2 for females and ≤115 g/m^2 for males.
Last observation carried forward (LOCF) analyses are based on last study assessment, including any unscheduled or early termination visits, and data are summarized for all patients with data at that timepoint.
LVH=left ventricular hypertrophy.
[a]Statistically significant based on 95% CI.

ATTRACT

- At baseline, mean LVMi was 95.3 g/m^2 (SD, 22.8; n=33) in patients given migalastat and 92.9 g/m^2 (SD, 25.7; n=16) in patients given ERT
- A statistically significant mean change from baseline in LVMi was observed after 18 months of treatment with migalastat (−6.6 g/m^2; 95% CI −11.0, −2.1; n=31), but not ERT (−2.0 g/m^2; 95% CI −11.0, 7.0; n=13) (**Figure 2**)
- Patients on migalastat continued to demonstrate numerical reductions from baseline in LVMi with another 12 months of treatment (month 30; −3.8 g/m^2; 95% CI −8.9, 1.3; n=30)

Figure 2. Mean Changes From Baseline in LVMi (g/m^2) With 18 Months of Migalastat or ERT Treatment (ATTRACT; patients with amenable mutations)

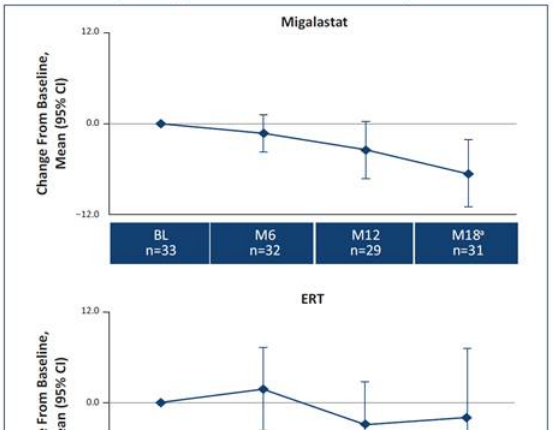


Table 2. Changes From Baseline in LVMi (g/m^2) With Migalasta With Amenable Mutations and LVH at Baseline (ATTRACT; mea 116.7 g/m^2)

	Timepoint			
	Month 12	Month 18	Month 24	M
n	12	13	11	
Mean change from baseline, (95% CI)	−5.2 (−11.9, 1.6)	−8.4[a] (−14.9, −2.0)	−14.7[a] (−21.4, −8.0)	(−1
Any reduction	8/12 (67%)	10/13 (77%)	10/11 (91%)	
Normalization	3/12 (25%)	5/13 (39%)	5/11 (46%)	

Normal LVMi is ≤95 g/m^2 for females and ≤115 g/m^2 for males.
LOCF analyses are based on last study assessment, including any unscheduled or ea are summarized for all patients with data at that timepoint.
[a]Statistically significant based on 95% CI.

Improvements in MWFS

- At baseline, impaired MWFS (<15% for females and <14% reported in 9 and 19 (14 migalastat, 5 ERT) patients from ATTRACT trials, respectively
  - Lower mean MWFS was observed in patients with LVH baseline in both studies (FACETS, 12.2% vs 17.4%; ATT
- In FACETS, the majority of patients with impaired MWFS demonstrated increases after long-term migalastat treatr

Table 3. Changes From Baseline in MWFS (%) With Migalastat With Amenable Mutations and Impaired MWFS at Baseline (FA at baseline, 11.3%)

	Timepoint			
	Month 12	Month 24	Month 36	M
n	7	8	4	
Mean change from baseline (95% CI)	0.1 (−1.2, 1.4)	1.4 (−1.3, 4.0)	1.4 (−1.5, 4.3)	(−2
Any increase	2/7 (29%)	5/8 (63%)	3/4 (75%)	(
Normalization	0	2/8 (25%)	2/4 (50%)	(

LOCF analyses are based on last study assessment, including any unscheduled or ea
Abnormal MWFS is <15% for females and <14% for males.
MWFS=midwall fractional shortening.

- In ATTRACT, an LOCF analysis revealed generally stable M impaired MWFS at baseline over 30 months of treatment 95% CI −1.3, 1.0; n=14) and over 18 months of treatment 95% CI −2.6, 1.4; n=5)

CONCLUSIONS

- In both FACETS and ATTRACT, long-term treatment with m associated with sustained reductions in LVMi and evidence
- Migalastat treatment resulted in increases in MWFS, a mea function, in a majority of patients in FACETS with abnorma
- These beneficial long-term effects on LVMi and LVH sugges the potential to reduce the risk of cardiac complications as disease

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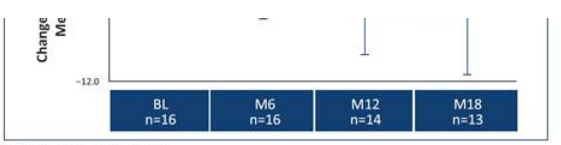
mutations. Forty-one patients with amenable mutations completed the study, 35 of whom continued into the OLE extension

- The ATTRACT trial randomized 60 patients, 56 of whom had amenable mutations

Cardiac Mass

FACETS

- At baseline, mean LVMi was 96.5 g/m² (standard deviation [SD], 32.9; n=44)
- A statistically significant mean change from baseline in LVMi was observed after 18/24 months of migalastat treatment (−7.7 g/m²; 95% confidence interval [CI] −15.4, −0.01; n=27; 18 months for patients randomized to placebo and 24 months for patients randomized to migalastat) (**Figure 1**)
- Further reductions in LVMi were observed at months 30/36 in patients from FACETS who entered the OLE study (change from baseline, −17.0 g/m²; 95% CI −26.2, −7.9; n=15) (**Figure 1**)



ERT=enzyme replacement therapy.
[a]Statistically significant based on 95% CI.

- LVH at baseline was reported in 13 patients randomized to migalastat (mean LVMi, 116.7 g/m²) and 5 patients randomized to ERT (mean LVMi, 123.3 g/m²)
- The majority of patients (11/13) with LVH at baseline who were randomly assigned to migalastat had a reduction in LVMi, and 4/13 patients demonstrated normalization of LVMi (**Table 2**)
- Based on a last observation carried forward (LOCF) analysis, the mean change in LVMi from baseline in patients with LVH at baseline who were randomized to ERT was 4.5 g/m² (95% CI −20.9, 29.9); 2/5 (40%) patients demonstrated a reduction in LVMi

DISCLOSURES

Conflicts of Interest

AJ has no conflicts of interest to disclose. RS has received research f
Therapeutics, Protalix Biotherapeutics, Genzyme, and Shire. KN serv
for and has received research funding from Amicus Therapeutics, G
serves on advisory boards for and has received research funding fro
Genzyme, and Shire. DGB serves as a consultant and speaker for An
Genzyme, and has received research funding from Amicus Therapeu
DAH is a consultant for and has received research and travel funding
Amicus Therapeutics, Genzyme, Shire, Actelion, and Protalix. VP, JY,
NS, and JAB are employees of and hold stock in Amicus Therapeutic
serves as a speaker for Amicus Therapeutics,
BioMarin, Genzyme, and Shire.

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645

Effects of Treatment With Migalastat on the Combined Endpoint of Kidney Globotriaosylceramide Accumulation and Diarrhea in Patie With Fabry Disease: Results From the Phase 3 FACETS Study

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INTRODUCTION

- Fabry disease is a devastating, rare, and progressive X-linked lysosomal storage disorder caused by the functional deficiency of α-galactosidase A (α-Gal A) as a result of mutation in the *GLA* gene[1]
- More than 50% of patients with Fabry disease report or show gastrointestinal (GI) signs and symptoms, including abdominal pain, diarrhea, constipation, nausea, and vomiting[2]
- Migalastat, a first-in-class, orally administered small molecule, is a pharmacological chaperone approved in the European Union, Switzerland, and Israel for the treatment of Fabry disease in patients with *amenable GLA* mutations[3-5]
- The binding of migalastat to the active site of α-Gal A stabilizes certain mutant enzymes (referred to as amenable), thus facilitating proper trafficking to lysosomes, where dissociation of migalastat allows α-Gal A to catabolize accumulated substrates[6-11]
- 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[5,12]

OBJECTIVE

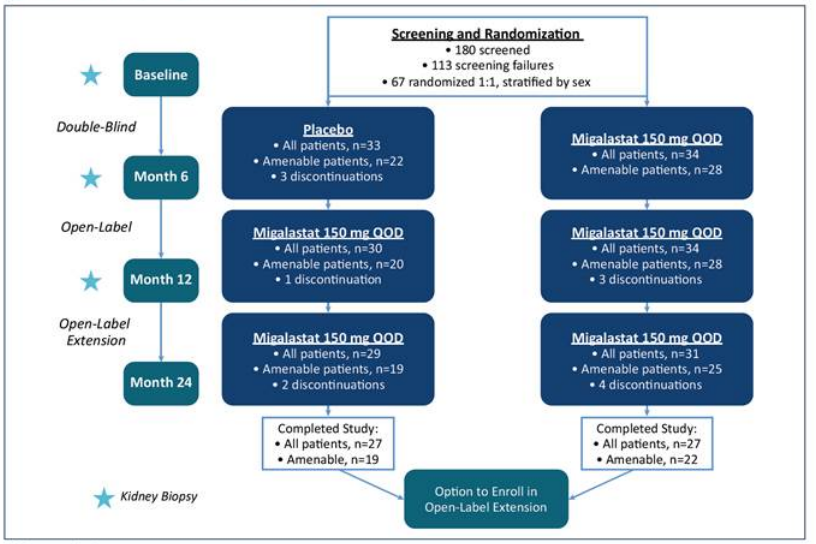
- To assess the effects of migalastat relative to placebo on kidney interstitial capillary globotriaosylceramide (KIC GL-3) content, changes in diarrhea, and the combined endpoint of changes in KIC GL-3 and diarrhea in patients in the phase 3 FACETS study

METHODS

Study Design

- FACETS (AT1001-011, NCT00925301) is a phase 3, randomized, placebo-controlled study to evaluate the efficacy, safety, and pharmacodynamics of migalastat in patients with Fabry disease with amenable mutations (**Figure 1**)

Figure 1. FACETS Study Design and Disposition



QOD=every other day.

Key Inclusion Criteria

- Male and female patients aged 16-74 years with a diagnosis of Fabry disease with responsive *GLA* mutations based on a preliminary human embryonic kidney 293 cell assay
- Naive to ERT or had not received ERT for ≥6 months before screening
- $eGFR_{MDRD}$ ≥30 mL/min/1.73 m² at screening
- Urine GL-3 at screening ≥4× the upper limit of normal (24-hour collection)
- 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[7]

RESULTS

Summary of Baseline and Change from Baseline for KIC GL-3 and GSRS-D in FA

- Sixty-seven patients were randomized in FACETS; 50 treated patients had amenable mutations
- After 6 months, in all patients with amenable mutations, migalastat treatment reduced KIC GL-3 in scores, while placebo did not (**Table 1**)
- Eighty-three percent (15/18) of migalastat-treated patients with amenable mutations demonstrate and/or MCID in GSRS-D when either or both were elevated at baseline, compared with 33% (5/15) with placebo

Table 1. Change From Baseline to Month 6: GSRS-D and KIC GL-3 Inclusions (ITT-Amenable Population)[a]

	Migalastat	
Baseline GSRS-D, mean ± SD (n) Mean change from baseline	2.3 ± 1.61 (28) −0.3	2
Difference (migalastat-placebo)	−0.5 (*P*=0.03)[a]	
Baseline KIC GL-3 inclusions, mean ± SD (n) Change from baseline, mean ± SD	0.649 ± 1.23 (25) −0.25 ± 0.51	0.4
Difference (migalastat-placebo)	−0.3 (*P*=0.008)[a]	

GL-3=globotriaosylceramide; GSRS-D=Gastrointestinal Symptoms Rating Scale-Diarrhea; ITT, intention-to-treat; KIC=kidney interstitial capi
[a]*P* value/least squares (LS) mean from analysis of covariance, comparing the difference in LS means. The model includes treatment, baseli
baseline interaction.

Xu's Statistic and Logistic Regression for KIC GL-3 and GSRS-D

- Xu's statistic revealed a significant difference between treatments from baseline to month 6 for the of KIC GL-3 and GSRS-D (*P*=0.009; 1-sided) (**Table 2**)

Table 2. Xu's Statistic on Combined Changes in KIC GL-3 and GSRS-D in FACETS

Population	1-sided *P*-Value	1-sided *P*-Value	*Bona Fi*
	KIC GL-3	GSRS-D	KIC GL-3 a
ITT-amenable	0.021	0.029	

- Patients with a reduction in KIC GL-3 were 4.3 to 5.6 times more likely to show improvement in GS who did not have a reduction in KIC GL-3 (**Table 3**)

Table 3. Logistic Regression Between Reductions in KIC GL-3 and Improvement in GSRS-D in the ITT and Populations

Population	Parameter and Criteria	Odds Ratio[a]	95% C
ITT	GSRS-D CFBL ≤ −0.33 (n=67) KIC GL-3 CFBL < −0.1	4.298	1
ITT-amenable	GSRS-D CFBL ≤ −0.33 (n=50) KIC GL-3 CFBL < −0.1	5.550	1

CFBL=change from baseline; CI=confidence interval.
[a]Odds ratios and 95% CIs are based on logistic regression that includes the KIC GL-3 and treatment groups.

CONCLUSIONS

- Migalastat simultaneously reduces the disease substrate and improves GI symptoms in patients wi with amenable mutations
- Reductions in KIC GL-3 are associated with improvements in diarrhea
- The significant correlation between KIC GL-3 and the GSRS-D supports the use of KIC GL-3 as a bio predictor of clinical benefit

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- Testing was completed before unblinding of the data

Gastrointestinal Assessments

- The gastrointestinal symptoms rating scale (GSRS) contains 15 items to assess the severity of 5 domains: abdominal pain, reflux, diarrhea, indigestion, and constipation[13]
- Each domain consists of 2-4 questions, scored on a 7-point Likert scale (ranging from 1-absence of burden to 7-severe discomfort)
- The score for the diarrhea domain of the GSRS (GSRS-D) was the mean of the 3 related questions (diarrhea, reflux, indigestion)
- A response in the GSRS-D was defined as a reduction >0.33 (estimated minimal clinical important difference; MCID), which was derived using distribution-based methods and/or anchor-based methodologies from liver transplant patients with GI symptoms (MCID=0.33),[14] patients with autoimmune disease with and without GI symptoms (MCID=0.33),[15] and renal transplant patients with and without GI symptoms (MCID=0.40)[16]
- GSRS scores were collected at baseline and months 6, 12, 18, and 24

KIC GL-3 Inclusion Assessments

- Renal biopsies were collected at baseline and months 6 and 12. The number of KIC GL-3 inclusions was quantitatively measured using digital images[17]
- Response to migalastat was defined as a reduction of >0.1 inclusions per capillary (above background staining)

Statistical Analysis

- The number of patients demonstrating a response in KIC GL-3 and/or GSRS-D from baseline to month 6 was compared between the migalastat and placebo groups
- A retrospective analysis using Xu's statistic, evaluated if treatment had an effect on changes in KIC GL-3 and GSRS-D simultaneously from baseline to month 6 in the intention-to-treat (ITT) amenable population
- Logistic regression assessed the correlation between changes in KIC GL-3 and GSRS-D

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DISCLOSURES

Conflicts of Interest

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644

Response of Patients With Fabry Disease With the Amenable Mutation p.N215S to Treatment With Migalastat

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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[3,6]
- 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

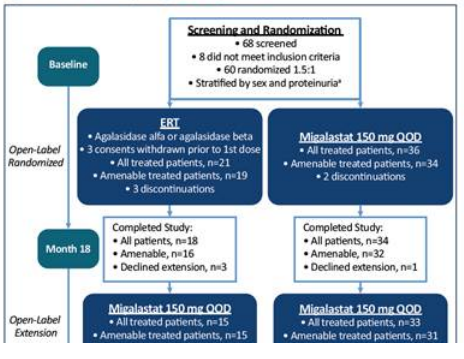
- To assess the efficacy of migalastat in a subset of patients with Fabry disease with the amenable p.N215S mutation relative to all patients with Fabry disease with amenable mutations during the first 18 months of the phase 3 ATTRACT study

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



RESULTS

- Patient disposition is summarized in **Figure 1**
- The 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

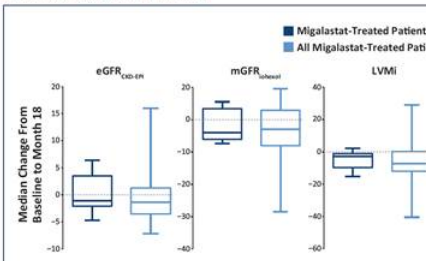
$eGFR_{CKD-EPI}$=estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration; LVMi=left ventricular mass index; lyso-Gb_3=globotriaosylsphingosine; N/A=not available.
[a]Confounded by ERT.

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)	85.91 (51.33, 145.12)

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

Figure 3. Change from Baseline to Month 18 in Patients With the p.N215S Mut 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	
	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 Migalas Treated Patients (n=31)
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 ± 2.1 (−11.01, −2
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

Data are graphed as median (center line), first/third quartiles (box perimeter), and min/m
CI=confidence interval; $mGFR_{Iohexol}$=measured GFR using iohexol clearance; SEM=standard

- Individual treatment outcomes for the 3 patients with the p.N215S muta listed in **Table 3**

Table 3. Individual Change From Baseline to Month 18 in Renal Function, Cardi 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 Chang Baseli Month
5	0.4	−1.7	22.7
6	−0.8	−7.9	−7.7
7	−1.9	−3.8	−7.6

CONCLUSIONS

- Following 18 months of treatment with migalastat in the phase 3 ATTRA of patients with Fabry disease with the p.N215S mutation had a respons migalastat-treated patients and demonstrated a decrease in LVMi
- The small reduction in eGFR in this ERT-experienced population is notew the literature demonstrating a worsening of renal function over 12-15 m ERT treatment[12] or reducing ERT dose[13]
- Migalastat may offer promise as an oral treatment alternative for male a Fabry disease with amenable mutations, including those with the p.N21

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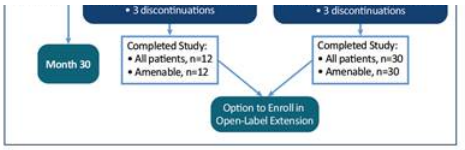


ERT=enzyme replacement therapy; QOD=every other day.
[a]Proteinuria stratification: high (≥0.1 g/24 h); low (<0.1 g/24 h).

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

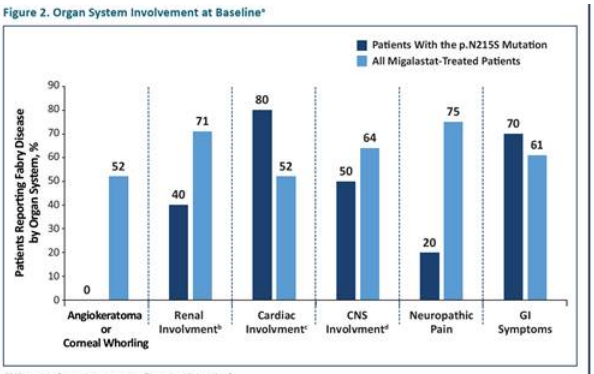
Renal Assessments

- $eGFR_{CKD-EPI}$ 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

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

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Conflicts of Interest

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2576

A Next-Generation Enzyme Replacement Therapy for Fabry Disease: Co-formulation of a Proprietary Recombinant Human α-Galactosidase A W Pharmacological Chaperone Demonstrates Greater Substrate Reductio Than Agalsidase Beta in Mice

Xu S, Schilling A, Gomez N, Frascella M, Garcia A, Hamler R, Ellsworth D, Soska R, Nair A, Della Valle MC, Feng J, Manger H, Valenzano KJ, Do H, Gotschall R, Khanna R

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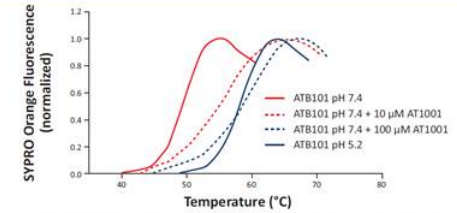
INTRODUCTION

- Fabry disease is an X-linked lysosomal storage disorder caused by a deficiency in α-galactosidase A (α-Gal A) activity, leading to progressive accumulation of lysosomal globotriaosylceramide (GL-3) in multiple tissues
- While enzyme replacement therapy (ERT) with manufactured human α-Gal A, namely agalsidase beta and agalsidase alfa, has brought many therapeutic benefits to patients, the infused enzymes have potential limitations, including low physical stability, short circulating half-lives in blood, and variable uptake into different disease-relevant tissues, that may impact efficacy and tolerability
- Previously, we demonstrated that the pharmacological chaperone AT1001 (migalastat) improves the pharmacological properties of the manufactured enzymes via binding and stabilization
- A proprietary recombinant human α-Gal A (rhα-Gal A), ATB101, has recently been developed and is co-formulated with AT1001 (designated as ATB101/AT1001). The co-formulated ATB101/AT1001 as a single intravenously administered product is aimed to improve the pharmacological properties of the enzyme and result in improved substrate clearance compared with the standard of care. This concept was tested in preclinical studies using a Fabry mouse model (*Gla* knockout [KO])

RESULTS

AT1001 Stabilizes ATB101 In Vitro

Figure 1.



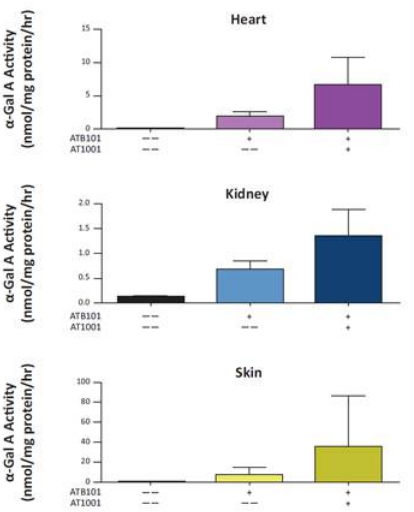
The thermal stability of ATB101 was assessed using a fluorescence-based thermal denaturation assay as described previously.[1,2] The thermal stability scans were performed in the absence and presence of 10 and 100 μM AT1001 at pH 7.4 and in the absence of AT1001 at pH 5.2. Data were normalized to the minimum and maximum fluorescence in each sample. As expected for any lysosomal enzyme at neutral pH, ATB101 was also significantly less stable (melting temperature [T_m]=48.9°C) than at acidic pH (T_m=57.8°C). Co-incubation with AT1001 at neutral pH resulted in a concentration-dependent stabilization of ATB101, with 10 μM AT1001 shifting the T_m to 54.6°C, and 100 μM AT1001 shifting the T_m to 58.4°C. The latter was similar to the T_m observed for ATB101 alone at acidic pH.

AT1001 Co-Formulation Increases the Circulating Levels of ATB101 in *Gla* KO Mice

Figure 2.

ATB101/AT1001 Co-Formulation Increases α-Gal A Activities in Tissues of *Gla* KO Mice

Figure 3.



α-Gal A Activity (nmol/mg protein/hr) (standard deviation)	Heart	Kidney	Skin
ATB101 alone	1.9 (0.7)	0.7 (0.2)	7.2 (7.3)
ATB101/AT1001	6.7 (4.1)	1.4 (0.5)	30.1 (50.5)
Fold increase compared with enzyme alone	3.6	2.0	4.2

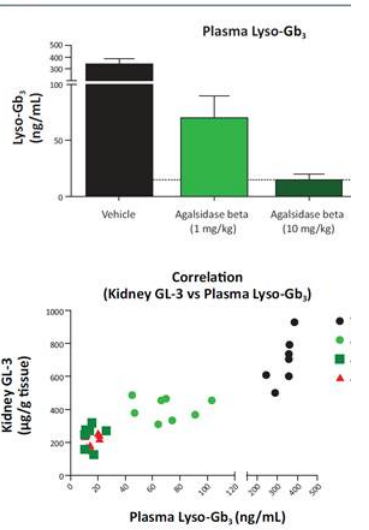
Approximately 16-week-old male *Gla* KO mice (n=8/group) were given 2 biweekly IV bolus administrations of either ATB101 alone (<10 mg/kg) or ATB101/AT1001. Seven days after the final drug administration, the α-Gal A activity in disease-relevant tissues was measured using an enzymatic method with 4MU-Gal as the substrate. Co-formulation with AT1001 substantially increased α-Gal A activity in all tissues measured compared with enzyme alone.

ATB101/AT1001 Co-Formulation Improves the Tissue GL-3 Reduction in *Gla* KO Mice Over Standard of Care

Figure 4.

ATB101/AT1001 Co-Formulation Improves Pl Reduction in *Gla* KO Mice Over Standard of C

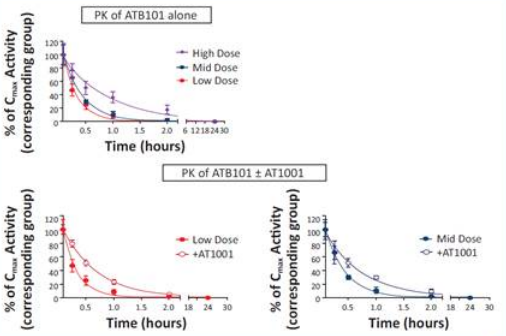
Figure 5.



In the same study described in **Figure 4**, plasma samples w after the last administration, and levels of globotriaosylsph an important biomarker for Fabry disease severity, were de MS/MS. ATB101/AT1001 co-formulation achieved plasma l that was significantly better (p<0.05) than agalsidase beta to the effects seen with agalsidase beta 10 mg/kg, once ag substantially superior efficacy compared with the current s Plasma lyso-Gb_3 levels were correlated with kidney GL-3 (t affected tissue in Fabry disease) using GraphPad version 6. previously for patients with Fabry disease,[3] a strong correla between plasma lyso-Gb_3 and kidney GL-3 was observed, i and reliability of testing plasma lyso-Gb_3 in preclinical studi

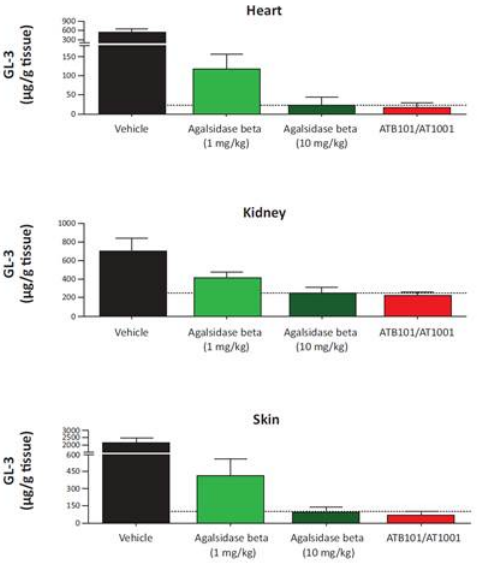
CONCLUSIONS

- AT1001 increased the physical stability of a proprietar currently in nonclinical development
- In mice, following IV administration, ATB101 showed



Half Life, Hours	Low Dose	Mid Dose	High Dose
ATB101 alone	0.19	0.26	0.61
ATB101/AT1001	0.44	0.49	N/A
Fold increase compared with enzyme alone	2.3	1.9	N/A

Approximately 6-month-old male *Gla* KO mice (n=5/group) were given a single intravenous (IV) bolus administration of low-, mid-, or high-dose (up to 10 mg/kg) ATB101 alone or ATB101 co-formulated with AT1001 (ATB101/AT1001) at low or mid enzyme dose. Blood samples were collected from each mouse using serial mandibular bleeds at 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, and 24 hours after IV administration, and α-Gal A activity in plasma was determined using an enzymatic method with 4-MU-galactopyranoside (4MU-Gal) as the substrate. The plasma activity was used to determine pharmacokinetic parameters using GraphPad version 6. For each group, the averaged activity of each timepoint was normalized to the averaged peak plasma α-gal A activity (C_{max}) of the corresponding group, and a plot was made using the normalized activity and the nominal time. The half-life of ATB101 activity following each dosing regimen was calculated using a one-phase decay model. The fitted curves are shown in the graphs, and the calculated half-lives are summarized in the table. When administered alone, ATB101 showed dose-dependent, nonlinear pharmacokinetics, as the half-lives increased with increasing doses. Co-formulation with AT1001 increased circulating α-Gal A activity levels, with an up to 2.3-fold increase in ATB101 half-life. N/A=not applicable; PK=pharmacokinetics.



Approximately 16-week-old male *Gla* KO mice (n=8/group) were given 2 biweekly IV bolus administrations of either 1 or 10 mg/kg of agalsidase beta or co-formulation of AT1001 with <10 mg/kg ATB101 (ATB101/AT1001). Disease-relevant tissues were collected 7 days after the last administration and GL-3 levels were determined by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). In all tissues tested, ATB101/AT1001 co-formulation achieved GL-3 reduction that was significantly greater ($p<0.05$) than agalsidase beta 1 mg/kg (standard of care). Importantly, the GL-3 reduction with ATB101/AT1001 co-formulation reached or exceeded the reduction seen with agalsidase beta 10 mg/kg, demonstrating substantially superior substrate clearance compared with the current standard of care.

nonlinear pharmacokinetics, as the half-lives increase doses. Upon co-formulation with AT1001, the half-life in plasma increased up to 2.3-fold compared with enz

- In *Gla* KO mice, co-formulated ATB101/AT1001 led to increased α-Gal A activity in disease-relevant tissues enzyme alone
- Importantly, under a repeat IV administration regimen ATB101/AT1001 achieved robust GL-3 reduction in kid tissues, reaching or even exceeding the levels achieve agalsidase beta (i.e. 10× the standard-of-care dose)
  - In plasma, a similar effect on the lyso-Gb_3 levels w and levels correlated well with kidney GL-3
- Collectively, these results indicate that ATB101/AT100 increases the stability of the enzyme, resulting in subs substrate reduction in preclinical models compared w standard therapy. Therefore, ATB101/AT1001 co-form a promising next-generation treatment for Fabry disea further investigation

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DISCLOSURES

Conflicts of Interest

All of the authors are employees of and hold stock in Amicus

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