Migalastat Exposure in Japanese Healthy Volunteers and Non-Japanese Subjects Provides Evidence That These Populations Are Similar to Japanese Patients With Fabry Disease

Johnson FK[1], Ohashi T[2], Yang L[1], Yu J[1], Skuban N[1], Castelli JP[1], Barth JA[1]

[1]Amicus Therapeutics, Inc., Cranbury, NJ, USA; [2]The Jikei University School of Medicine, Tokyo, Japan

INTRODUCTION

- Fabry disease is a devastating, rare, and progressive X-linked disorder caused by mutations in the *GLA* gene, resulting in the functional deficiency of the lysosomal enzyme α-galactosidase A (α-Gal A)[1]
- Accumulation of α-Gal A substrate, such as globotriaosylceramide (GL-3), can cause functional impairments in the kidney, heart, and brain and may result in premature death[1]
- 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[2,3]
- Migalastat is a low-molecular-weight iminosugar and is an analogue of the terminal galactose of GL-3 that binds to the active site of α Gal-A[1,4]
- Migalastat selectively and reversibly binds, with high affinity, to the active site of both wild-type and specific mutant forms of α-Gal A, referred to as amenable mutations. Binding stabilizes these mutant forms of α-Gal A in the endoplasmic reticulum and facilitates trafficking to lysosomes, where dissociation of migalastat allows α-Gal A to reduce GL-3 storage material[1,4]

Dose Proportionality in Migalastat Studies

- In phase 1 studies in non-Japanese healthy volunteers, dose proportionality was observed for migalastat between 75 mg and 1250 mg, based on single-dose administration[5]
- In the phase 1 MGM115806 study in Japanese healthy volunteers, dose proportionality was observed across all doses tested for migalastat (50-450 mg) after single-dose administration[6]
  - The maximum plasma concentration (C_{max}) of migalastat was dose proportional between 25 mg and 75 mg and area under the curve (AUC) was slightly greater than dose proportional, most likely due to the difficulty in accurately evaluating the elimination phase at low doses
  - In the phase 1 FAB-CL-104 study, the 1250-mg and 2000-mg exposures were not different, perhaps due to a saturation effect

OBJECTIVE

- To evaluate the pharmacokinetic (PK) properties of a single administration of migalastat in Japanese healthy volunteers, non-Japanese healthy volunteers, and non-Japanese patients with Fabry disease
  - The PK properties in these patients can be used to predict the PK properties of migalastat in Japanese patients with Fabry disease, as there are currently no PK data available for this patient population

METHODS

Study Design

- This study was a pooled analysis that combined PK exposure data (AUC and C_{max}) from migalastat studies performed in different patient populations
- The phase 1 clinical trials included in this pooled analysis were MGM115806, AT1001-010, AT1001-015, AT1001-016, AT1001-018, FAB-CL-101, FAB-CL-102, and FAB-CL-104; the analysis also included the phase 3 clinical trial FACETS (AT1001-011, NCT00925301)[2,5-9]

PK Analysis

- Plasma migalastat determinations were performed with a liquid chromatography-mass spectrometry assay; noncompartmental PK analyses were performed with WinNonlin version 5.2 or higher
- Graphical presentations were performed in SAS and GraphPad Prism, version 6.05
- Migalastat exposure data were graphically compared using 2 methods
  - Weight-normalized comparisons for 2 single-ascending dose studies in Japanese healthy volunteers (MGM115806) and non-Japanese healthy volunteers (FAB-CL-101)
  - Unnormalized and weight-normalized comparisons for the marketed dose (150 mg) in Japanese healthy volunteers, non-Japanese healthy volunteers, and non-Japanese patients with Fabry disease

RESULTS

Subjects

- A total of 13 healthy Japanese volunteers and 118 healthy non-Japanese volunteers from single-dose phase 1 studies, as well as 62 patients with Fabry disease from phase 3 FACETS, were included in the PK analysis (**Tables 1-3**)

Table 1. PK Parameters at Multiple Doses of Migalastat in Japanese and Non-Japanese Healthy Volunteers

	Japanese Healthy Volunteers (MGM115806)			Non-Japanese Healthy Volunteers (FAB-CL-101)			
	50 mg (n=14)[a]	150 mg (n=13)	450 mg (n=13)	25 mg (n=6)	75 mg (n=6)	225 mg (n=6)	675 mg (n=6)
C_{max}, ng/mL, geometric mean (SD)	695 (19.3)	2124 (58.5)	5695 (141)	210 (71)	693 (113)	2200 (921)	6645 (1527)
t_{max}, hr, median (range)	3.0 (1.5-5.0)	3.5 (2.0-5.0)	3.5 (2.5-5.0)	3.0 (2.0-4.0)	3.0 (1.5-5.0)	3.0 (2.0-4.0)	2.5 (2.0-4.0)
$AUC_{0-\infty}$, hr*ng/mL, geometric mean (SD)	3962 (115)	11,519 (420)	30,722 (901)	1178 (359)	4744 (415)	12,637 (5579)	36,419 (8228)
CL/F, L/hr, arithmetic mean (SD)	13.33 (4.89)	13.47 (3.74)	15.42 (5.24)	18.95 (6.54)	13.00 (1.08)	18.63 (12.13)	15.78 (3.46)
$t_{1/2}$, hr, geometric mean (SD)	3.25 (0.71)	3.82 (0.25)	4.02 (0.23)	3.04 (0.48)	4.05 (0.67)	4.62 (0.71)	4.19 (0.30)
CLr, L/hr, arithmetic mean (SD)	6.43 (1.31)	6.21 (1.08)	6.08 (0.96)	5.90 (0.09)	5.73 (1.71)	7.54 (1.31)	7.66 (1.60)

$AUC_{0-\infty}$=area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time; CL/F=apparent total clearance; CLr=renal clearance; C_{max}=maximum plasma concentration; hr=hours; PK=pharmacokinetic; SD=standard deviation; $t_{1/2}$=terminal phase half-life; t_{max}=time of occurrence of C_{max}.
[a]One healthy volunteer discontinued after the first dose.

Table 2. PK Parameters of Migalastat 150 mg in Japanese and Non-Japanese Healthy Volunteers

	Japanese Healthy Volunteers	Non-Japanese Healthy Volunteers				
	MGM115806 (n=13)	AT1001-016 (n=19)	AT1001-018 (n=10)	AT1001-015 (n=8)	AT1001-010 (n=51)	FAB-CL-102 (n=6)
Formulation	Capsule	Capsule	Capsule	Capsule	Solution	Solution
BW, kg, mean (SD)	63.5 (8.46)	76.7 (9.54)	76.4 (8.2)	77.8 (12.6)	72.0 (14.3)[a]	79.7 (5.0)
C_{max}, ng/mL, geometric mean (CV%)	2124 (36.3)	1561 (33.8)	1786 (25.9)	2100 (26.0)	1635 (27.3)	1723 (46.6)
C_{max} corr. BW[b], ng/mL, mean	1928	1709	1949	2334	1682	1960
$AUC_{0-\infty}$, hr*ng/mL, geometric mean (CV%)	11,519 (27.4)	9805 (26.8)	9881 (25.6)	12,397 (27.7)	10,449 (24.7)	9482 (40.2)
AUC corr. BW[b], hr*ng/mL, mean	10,456	10,737	10,784	13,778	10,748	10,789
$t_{½}$, hr, geometric mean (CV%)	3.82 (6.6)	3.9 (11.3)	6.28 (60.4)	6.42 (1.93)[c]	3.82 (10.2)	2.43 (5.37)
t_{max}, hr, median (range)	3.50 (2.0-5.0)	3.00 (1.50-6.00)	2.75 (1.50-4.00)	2.50 (1.50-3.00)	3.00 (1.00-6.00)	3.50 (1.50-4.00)

BW=body weight; CV=coefficient of variation.
[a]n=52.
[b]Estimated body weight is 70 kg.
[c]Data are arithmetic mean (SD).

Table 3. Summary of Plasma Migalastat PK Parameters for Phase 1 Single-Dose Studies in Healthy Volunteers and Phase 3 Population PK Results in Patients With Fabry Disease

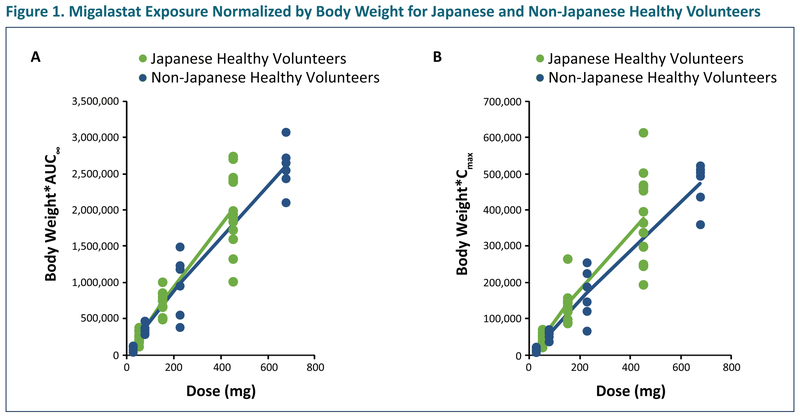
Study	Study Description (N)	Dose (mg)/ Formulation/ Condition	Geometric Mean C_{max} (ng/mL)	Median t_{max} (hr)	Geometric Mean AUC_{0-t} (hr*ng/mL)	Geometric Mean $AUC_{0-\infty}$ (hr*ng/mL)	Geometric Mean $t_{½}$ (hr)[a]
MGM115806	Japanese HV (14)	50/soln[b]	695	3.0	3905	3961	3.2/24/24
MGM115806	Japanese HV (13)	150/soln	2124	3.5	11,431	11,519	3.8/24/24
MGM115806	Japanese HV (13)	450/soln	5695	3.5	30,454	30,722	4.0/24/24
FAB-CL-101	SAD/FIH (6)	25/soln	210	3.0	1141	1178	3.0/24/16
FAB-CL-101	SAD/FIH (6)	75/soln	693	3.0	4677	4744	4.0/24/24
FAB-CL-101	SAD/FIH (6)	225/soln	2200	3.0	12,462	12,637	4.6/24/24
FAB-CL-101	SAD/FIH (6)	675/soln	6645	2.5	35,999	36,419	4.2/24/24
AT1001-010	TQT (51)	150/soln	1635	3.0	10,306	10,449	3.8/22.5/22.5
AT1001-010	TQT (52)	1250/soln	12,579	3.0	71,200	72,165	4.0/22.5/22.5
AT1001-014	C^{14} mass-balance (6)	150/cap[b]/ plasma	1516	4.0	10,957	11,029	6.3/240/48
AT1001-015	Renal impairment (8)	150/cap/HV	2100	2.5	12,306	12,397	6.4/120/48
AT1001-016	Food effect (19)	150/cap/ fasted	1561	3.0	9696	9805	3.9/24/24
AT1001-018	Absolute BA (10)	150/cap	1786	2.8	9777	9881	7.3/48/48
AT1001-011	Pop PK (62)	150/cap/ Fabry	1180	3.0	9515	NA	NA

BA=bioavailability; cap=capsule; FIH=first in human; HV=healthy volunteers; NA=not available; Pop PK=population pharmacokinetics; SAD=single ascending dose; soln=solution; TQT=thorough QT.
[a]Mean/time of last blood sample/time of last quantifiable concentration for any subject.
[b]Powder reconstituted to an oral solution; capsule is 100% bioavailable to the oral solution.

PK Properties of Migalastat in Japanese and Non-Japanese Healthy Volunteers

- The PK data obtained in single-dose administration studies revealed that exposure to migalastat was similar between Japanese and non-Japanese healthy volunteers (**Table 1**)
- After normalizing C_{max} and AUC by body weight, exposures between Japanese and non-Japanese healthy volunteers were not different (**Figure 1**)
  - The mean difference between Japanese and non-Japanese healthy volunteers was much smaller than the interindividual variability of the PK parameters within each race

Figure 1. Migalastat Exposure Normalized by Body Weight for Japanese and Non-Japanese Healthy Volunteers



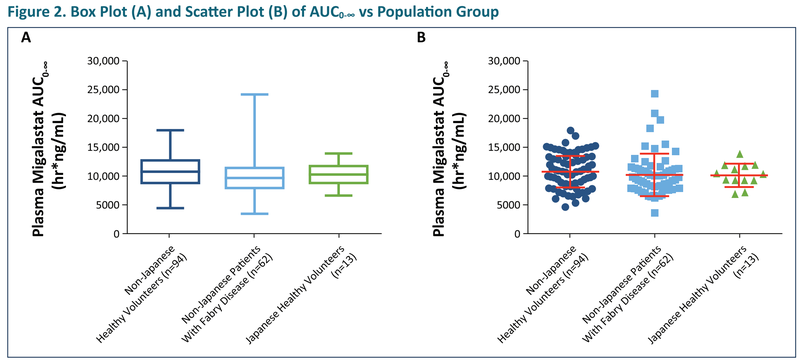
Solid circles indicate individual body weight normalized by (A) $AUC_{0-\infty}$ and (B) C_{max} in Japanese healthy volunteers (green) and non-Japanese healthy volunteers (blue) from phase 1 clinical trials with migalastat. Solid lines indicate the mean body weight normalized by (A) $AUC_{0-\infty}$ and (B) C_{max} in Japanese healthy volunteers (green) and non-Japanese healthy volunteers (blue) from phase 1 clinical trials with migalastat.

- The PK parameters for migalastat 150 mg observed in Japanese healthy volunteers were within the ranges observed in non-Japanese healthy volunteers; this is more apparent when normalized by body weight (**Table 2**)

PK Properties for 150-mg Migalastat Solution in Non-Japanese Healthy Volunteers vs Patients With Fabry Disease

- The estimated individual PK exposures (AUC, C_{max}, and C_{48h}) and phase 2 PK data were consistent with the historical plasma PK data in healthy volunteers[10]
- The predicted exposures in the population PK analysis, which included data from Japanese healthy volunteers, were similar for patients with Fabry disease and healthy volunteers; differences between groups of 16% and 27% for CL_T/F and V2/F, respectively, were not clinically relevant (**Table 3**)
- After pooling data from studies in which Japanese and non-Japanese healthy volunteers received a single dose of migalastat 150 mg and non-Japanese patients with Fabry disease received multiple doses of migalastat 150 mg, no appreciable differences in PK parameters were observed (**Figure 2**)
  - The mean difference between Japanese and non-Japanese subjects was much smaller than the interindividual variability of the PK parameters within each race

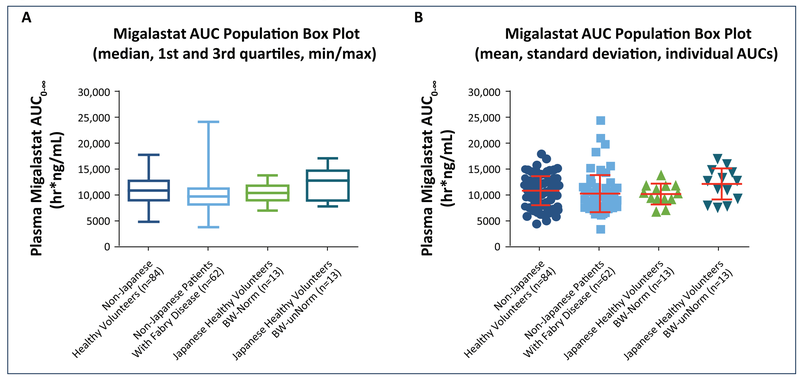
Figure 2. Box Plot (A) and Scatter Plot (B) of $AUC_{0-\infty}$ vs Population Group



Box plot includes median, 25th and 75th quartile, minimum, and maximum values; scatter plot includes mean, standard deviation bars, and individual values.

- Characterization of PK in Japanese healthy volunteers is similar to non-Japanese subjects, and is more apparent when Japanese healthy volunteers are normalized to Caucasian body weight (**Tables 2** and **3** and **Figure 3**)

Figure 3. Median (A) and Mean (B) Plasma Migalastat Values for AUC vs Population Box Plot



BW-Norm=body weight normalized; BW-unNorm=body weight unnormalized.

CONCLUSIONS

- Consistent with previous reports, data from phase 1 clinical trials demonstrate dose proportionality from 50-450 mg after single-dose administration of migalastat in Japanese and non-Japanese healthy volunteers
- Plasma migalastat exposures obtained in single-dose administration studies revealed that exposure to migalastat was similar between Japanese healthy volunteers, non-Japanese healthy volunteers, and non-Japanese patients with Fabry disease; when normalizing for body weight, the similarity between Japanese and non-Japanese healthy volunteers and non-Japanese patients with Fabry disease is more apparent
- Based on these evaluations and the totality of the data, the PK properties of migalastat in Japanese patients with Fabry disease should therefore not be different from Japanese and non-Japanese healthy volunteers and non-Japanese patients with Fabry disease

REFERENCES

1. Ishii S et al. *Biochem J.* 2007;406(2):285-295.
2. Germain DP et al. *N Engl J Med.* 2016;375(6):545-555.
3. Galafold (summary of product characteristics). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004059/WC500208434.pdf. Accessed October 14, 2016.
4. Yam GH-F et al. *FASEB J.* 2005;19(1):12-18.
5. Johnson FK et al. *Clin Pharmacol Drug Dev.* 2013;2(2):120-132.
6. Ino H et al. *J Drug Assess.* 2013;2(1):87-93.
7. Johnson FK et al. *Clin Pharmacol Drug Dev.* 2015;4(4):256-261.
8. Johnson FK et al. *Clin Pharmacol Drug Dev.* 2015;4(3):193-202.
9. Germain DP et al. *Orphanet J Rare Dis.* 2012;7:91.
10. Data on file. Amicus Therapeutics, Inc.

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DISCLOSURES

Conflicts of Interest

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