A Phase 2a Study to Investigate the Effect of a Single Dose of Migalastat HCl on Active Agalsidase Activity in Fabry Patients Receiving Enzyme Replacement Therapy

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Objectives and Study Design

Fabry disease is an X-linked lysosomal storage disease caused by mutations in *GLA*, the gene encoding α-Galactosidase A (α-Gal A). Migalastat HCl (AT1001; GR181413A) is a pharmacological chaperone that reversibly binds and stabilizes endogenous and exogenous certain forms of α-Gal A. When co-administered with an Enzyme Replacement Therapy (ERT), such as agalsidase alfa or beta, migalastat HCl is intended to bind to the infused α-Gal A enzyme, stabilizing it in its properly folded and active form. AT1001-013 (NCT # 01196871) is an open-label, non-randomized, Phase 2a drug-drug interaction study to evaluate the safety and pharmacokinetic (PK) effects of a single oral dose of migalastat HCl (150 mg or 450 mg) co-administered with intravenous agalsidase alfa or beta in male patients with Fabry disease. Patients received an IV infusion of ERT alone. A single oral dose of migalastat HCl was co-administered 2 hours prior to the next IV infusion of ERT at the same dose and regimen. Patients also received 150 mg migalastat HCl alone 7 days after the next IV infusion of ERT.

Preliminary Results

Patient Disposition and Demographics

Twenty-three patients completed the study. Twelve received 150 mg migalastat HCl and 11 received 450 mg migalastat HCl.

- 150 mg Cohort: Eight patients received agalsidase beta alone and 4 patients received agalsidase alfa alone during Period 1. Migalastat HCl was co-administered two hours prior to their next IV infusion of the same ERT at the same dose and regimen during Period 2. All patients received a single dose of 150 mg migalastat HCl alone 7 days after their next regularly scheduled ERT visit during Period 3 .
- 450 mg Cohort: Seven patient received agalsidase beta alone and 4 patients received agalsidase alfa alone during Period 1. Migalastat HCl was co-administered two hours prior to their next IV infusion of the same ERT at the same dose and regimen during Period 2. 450 mg migalastat HCl was not administered alone.

Alone and when co-administered with migalastat HCl, agalsidase alfa 0.2 mg/kg was infused for ~40 minutes; agalsidase beta 0.5 mg/kg or 1.0 mg/kg was infused for ~2 hrs.
Due to the temporary shortage of agalsidase beta, 6 of 15 patients received half (0.5 mg/kg) of the prescribed 1.0 mg/kg dose.

All patients were males with Fabry disease aged 22-60 years, body mass index (BMI) ranged from 19.4-29.1 kg/m^2 and estimated GFR ranged from 52-140 mL/min.

Table 1. *GLA* Genotypes

Patient ID	Amino Acid Change	Patient ID	Amino Acid Change
FAB1.0+150	N298S	NAB1.0+450	E48Q
AAB0.5+150	Q250X	OAB1.0+450	L120P/A121T
JAB1.0+450	Q250X	PAA0.2+150	A156G
KAB1.0+450	P205T	QAA0.2+150	H125L/G128E
BAB0.5+150	Q221X	RAA0.2+150	H125L/G128E
GAB1.0+150	717DELAA	TAA0.2+450	p.Q99fsX19
CAB0.5+150	W236X	UAA0.2+450	M284T
DAB0.5+150	R227X	HAB1.0+150	C12Ffs*104
IAB0.5+450	Q221X	SAA0.2+150	A348P
LAB1.0+450	R227X	VAA0.2+450	A348P
EAB0.5+150	R227X	WAA0.2+450	L414S
MAB1.0+450	R227X		

Migalastat HCl Increases Active Enzyme Levels in Plasma

Figure 1. Plasma Active Enzyme AUC vs. Treatment with 0.2 mg/kg Agalsidase Alfa

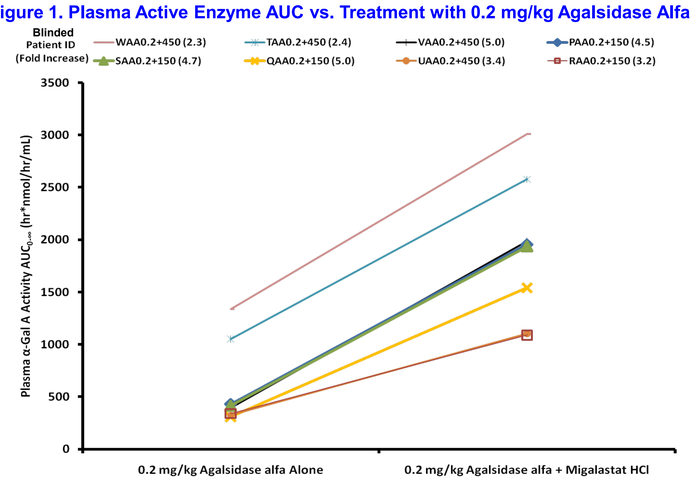


Figure 2. Plasma Active Enzyme AUC vs. Treatment with 0.5 mg/kg Agalsidase Beta

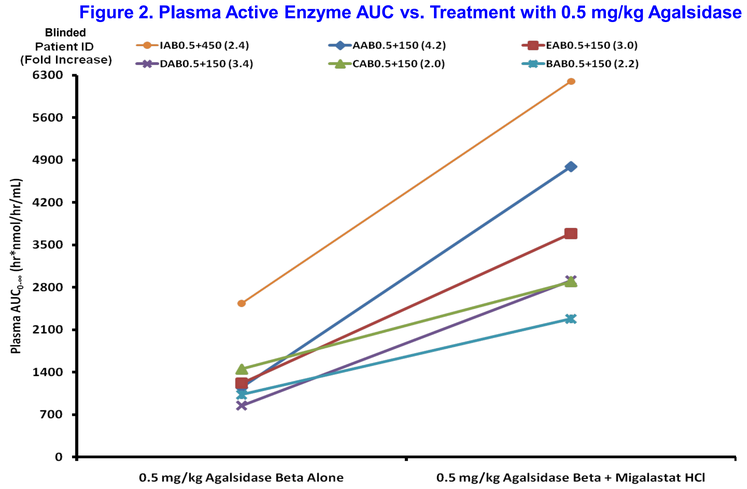


Figure 3. Plasma Active Enzyme AUC vs. Treatment with 1.0 mg/kg Agalsidase Beta

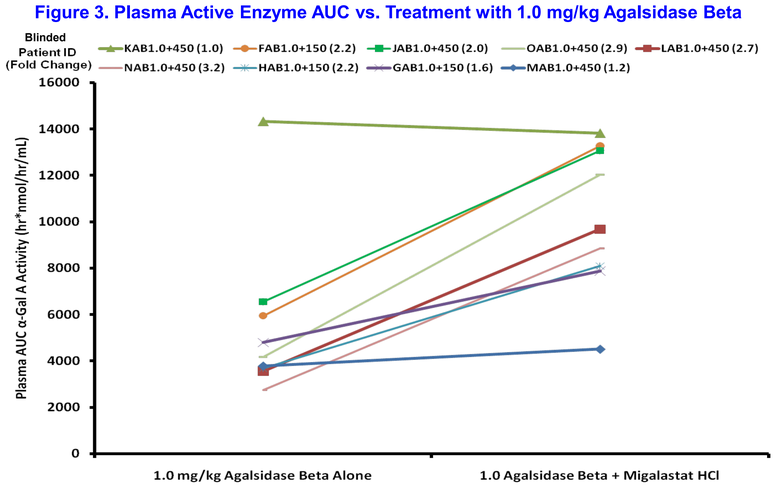


Figure 4. Mean (SD) Plasma Active Enzyme vs. Time for Each Agalsidase Treatment Administered Alone

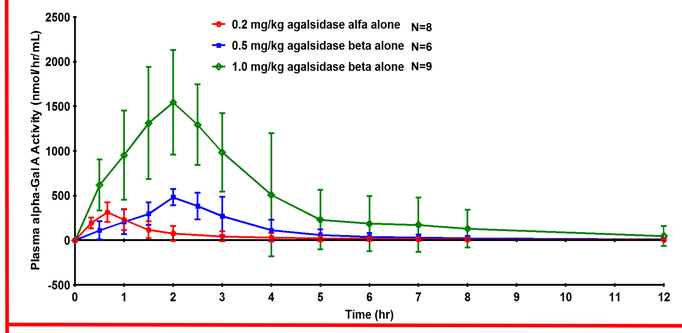
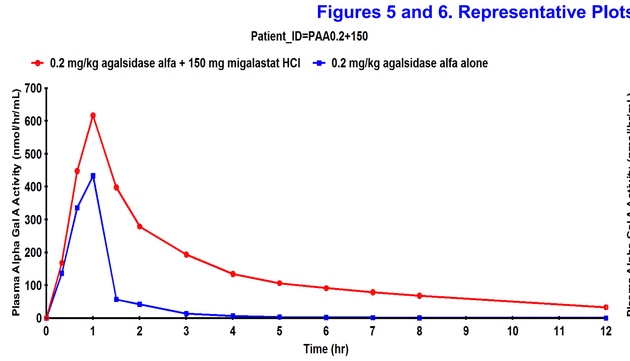


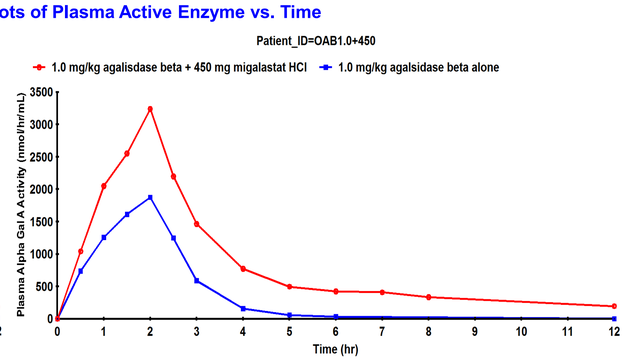
Table 2. Plasma PK Active Enzyme Summary

Treatment	C_{max}[a] (nmol/hr/mL)	T_{max}[b] (hr)	$AUC_{0-\infty}$[a] (hr*nmol/hr/mL)	T½[c] (hr)	AUC Ratio[a]
0.2 mg/kg agalsidase alfa alone (N=4)	300 (29.6)	0.67 (0.67 - 1.0)	370 (15.6)	4.1 (3.4)	-
0.2 mg/kg agalsidase alfa + 150 mg migalastat HCl (N=4)	519 (15.1)	0.67 (0.67 - 1.0)	1588 (25.0)	4.3 (1.5)	4.3 (36.3)
0.2 mg/kg agalsidase alfa alone (N=4)	358 (30.5)	0.67 (0.67 - 1.0)	652 (63.9)	5.5 (4.2)	-
0.2 mg/kg agalsidase alfa + 450 mg migalastat HCl (N=4)	605 (22.8)	0.67 (0.67 - 1.0)	2030 (38.1)	5.2 (2.2)	3.1 (38.6)
0.5 mg/kg agalsidase beta alone (N=5)	509 (17.0)	2.0 (2 - 2.5)	1120 (19.7)	4.2 (1.9)	
0.5 mg/kg agalsidase beta + 150 mg migalastat HCl (N=5)	877 (26.2)	2.0 (2 - 3)	3207 (29.2)	3.5 (1.3)	3.0 (30.1)
1.0 mg/kg agalsidase beta alone (N=3)	1646 (24.2)	2.0 (1.5 - 3)	4712 (23.7)	5.4 (4.0)	
1.0 mg/kg agalsidase beta + 150 mg migalastat HCl (N=3)	2292 (38.7)	2.0 (2 - 3)	9446 (31.1)	4.3 (1.7)	2.0 (16.2)
0.5 mg/kg agalsidase beta alone (N=1)	684	3.0	2536	6.5	-
0.5 mg/kg agalsidase beta + 450 mg migalastat HCl (N=1)	1351	3.0	6198	3.5	2.4
1.0 mg/kg agalsidase beta alone (N=6)	1655 (38.6)	2.3 (2 - 4)	4931 (74.3)	3.1 (1.9)	-
1.0 mg/kg agalsidase beta + 450 mg migalastat HCl (N=6)	2316 (33.1)	2.3 (2 - 4)	9711 (33.3)	4.9 (1.4)	2.0 (43.2)

[a] Geometric mean (CV%)
[b] Median (range)
[c] Arithmetic mean (SD)

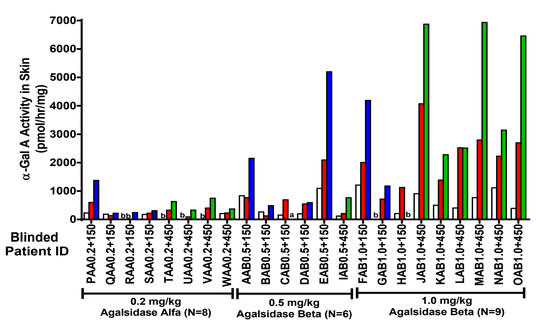
Figures 5 and 6. Representative Plots of Plasma Active Enzyme vs. Time





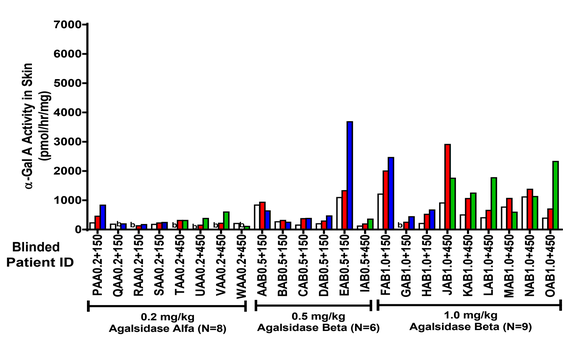
Migalastat HCl Increases Uptake of Active Enzyme into Skin

Figure 7. Day 2 Active Enzyme Levels in Skin



[a] Lost biopsy sample
[b] Insufficient total α-Gal A protein level from skin sample prohibited determination of α-Gal A activity

Figure 8. Day 7 Active Enzyme Levels in Skin



[b] Insufficient total α-Gal A protein level from skin sample prohibited determination of α-Gal A activity

Agalsidase has No Effect on Plasma Migalastat Pharmacokinetics

Figure 9. Mean (SD) Plasma Migalastat Concentration-Time Profiles

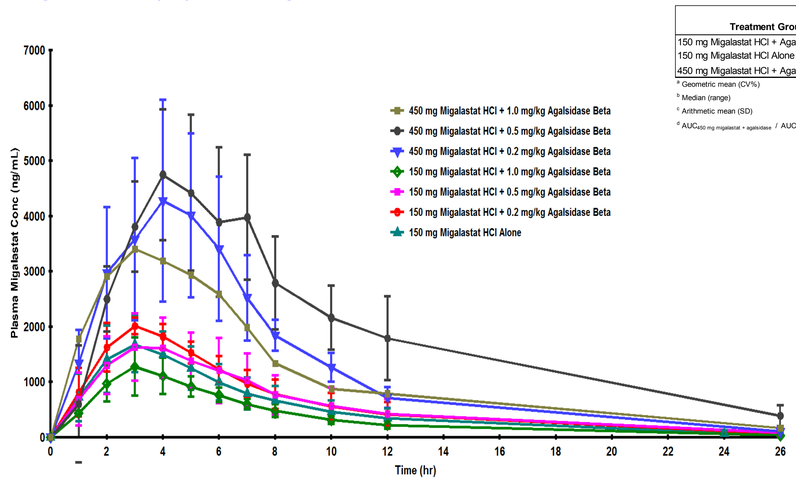


Table 3. Plasma Migalastat PK Summary

Treatment Group	C_{max}[a] (ng/mL)	T_{max}[b] (hr)	AUC_{0-T}[a] (ng·hr/mL)	$AUC_{0-\infty}$[a] (ng·hr/mL)	AUC F_{rel}[a]	T½[c] (hr)
150 mg Migalastat HCl + Agalsidase (N=12)	1626 (32.4)	3.0 (2 - 4)	12459 (42.3)	12877 (44.6)	-	5.1 (0.8)
150 mg Migalastat HCl Alone (N=12)	1630 (30.0)	3.0 (2 - 4)	11936 (35.2)	12419 (36.5)	1.0 (33.4)	5.0 (1.0)
450 mg Migalastat HCl + Agalsidase (N=11)	3935 (32.8)	4.0 (2 - 6)	29869 (33.4)	31115 (34.3)	2.5[d]	4.9 (1.3)

[a] Geometric mean (CV%)
[b] Median (range)
[c] Arithmetic mean (SD)
[d] $AUC_{450\ mg\ migalastat\ +\ agalsidase}$ / $AUC_{150\ mg\ migalastat\ alone}$

Summary of Results and Conclusions

- Preliminary results show single doses of 150 mg and 450 mg migalastat HCl with agalsidase doses of 0.2 mg/kg, 0.5 mg/kg, and 1.0 mg/kg increased active plasma α-Gal A AUC levels by 1.2- to 5.0-fold in 22 out of 23 Fabry patients (95.7%) relative to agalsidase administered alone. For the one exception there was no change.
  - When agalsidase was administered alone, active enzyme exposures following 0.2 mg/kg were 2.4-fold lower than 0.5 mg/kg. Both 0.2 mg/kg and 0.5 mg/kg had much lower active enzyme exposures, 9.6- and 4.0-fold, respectively, than 1.0 mg/kg.
  - Relative increases in active plasma α-Gal A AUC were agalsidase dose-dependent. The largest increases occurred at the lowest dose (0.2 mg/kg) and the smallest increases occurred at the highest dose (1.0 mg/kg).
- Following co-administration with 150 mg or 450 mg migalastat HCl, levels of active α-Gal A enzyme from Day 2 skin biopsies demonstrated consistent increases (19 out of 23, 82.6%) relative to agalsidase alone, verifying proof-of-concept of increased tissue uptake of α-Gal A.
  - Relative to baseline, increases in active α-Gal A levels were generally agalsidase dose-dependent.
  - Relative to agalsidase alone, increases in active α-Gal A levels following co-administration appeared to be migalastat HCl dose-dependent.
- The plasma pharmacokinetics of migalastat were not impacted by co-administration with agalsidase (mean AUC ratio of co-administered 150 migalastat HCl to 150 mg migalastat HCl alone = 1.0).
  - The 450 mg dose was slightly less than dose proportional to the 150 mg dose (mean AUC ratio of 450 mg to 150 mg = 2.5).
  - The single dose pharmacokinetics in these Fabry patients were similar to results from healthy volunteers.
- Co-administration of migalastat HCl at doses of 150 mg and 450 mg with agalsidase was generally well-tolerated.
  - Two serious adverse events (SAEs) occurred in one subject. Both SAEs were deemed unrelated to study drug by the investigator.
    - One of the SAEs was a transient ischemic attack (TIA) at screening. The other was a hospitalization for acute pain and acroparesthesia due to Fabry Disease which occurred approximately 5 months after the most recent dose of study drug.

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