



# Preliminary Results from an Ongoing Phase 2a Study to Investigate the Effect of a Single Dose of Migalastat HCl on Active Agalsidase Levels 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  $\alpha$ -Galactosidase A ( $\alpha$ -Gal A). Migalastat HCl (AT1001; GR181413A) is a pharmacological chaperone that binds and stabilizes mutant forms of  $\alpha$ -Gal A. When co-administered with an Enzyme Replacement Therapy (ERT), such as agalsidase alpha or beta, migalastat HCl is intended to bind to and stabilize the enzyme in the circulation. AT1001-013 (NCT # 01196871) is an ongoing open-label, non-randomized, 2-dose cohort, Phase 2a drug-drug interaction study to evaluate the safety and pharmacokinetic (PK) effects of the co-administration of oral migalastat HCl with intravenous agalsidase in male patients with Fabry disease. Patients received an IV infusion of ERT alone, followed by co-administration of either 150 mg or 450 mg migalastat HCl 2 hours prior to IV infusion of ERT, and 150 mg migalastat HCl alone 7 days after the next IV infusion of ERT.

## Preliminary Results

### Patient Disposition and Demographics

To date, 12 patients with plasma and skin active enzyme levels with and without 150 mg migalastat HCl, and plasma migalastat PK with and without agalsidase have been evaluated.

- Eight patients received agalsidase beta alone and 4 patients received agalsidase alpha alone following by co-administration with 150 mg migalastat HCl 2 hours prior to initiation of agalsidase; all patients received a single dose of 150 mg migalastat HCl 7 days after their next regularly scheduled ERT visit.
- Four patients (identified as Patients A, B, C, and D) received IV infusions of agalsidase alpha 0.2 mg/kg for ~40 minutes.
- Five patients (identified as Patients E, F, G, H, and I) received IV infusions of agalsidase beta 0.5 mg/kg for ~2-hrs with 1 exception: Subject G was infused 40 minutes longer during co-administration, than during agalsidase beta alone.
- Three patients (identified as Patients J, K, and L) received IV infusions of agalsidase beta 1.0 mg/kg for ~2-hr durations.
- All patients were males with Fabry Disease aged 37-60 years, body mass index (BMI) ranged from 16.5-26.0 kg/m<sup>2</sup> and estimated GFR ranged from 52-88 mL/min.

Table 1. *GLA* Genotypes

SubjID	Genotype
A	A15E
B	H125L/G128E
C	H125L/G128E
D	A348P
E	Q250K
F	Q221X
G	W236K
H	R227X
I	R227X
J	N298S
K	L243G/SK4
L	C12F/SK104

### Active Enzyme Levels in Plasma

Figure 1. Plasma active enzyme AUC vs. Treatment with 0.2 mg/kg agalsidase alfa

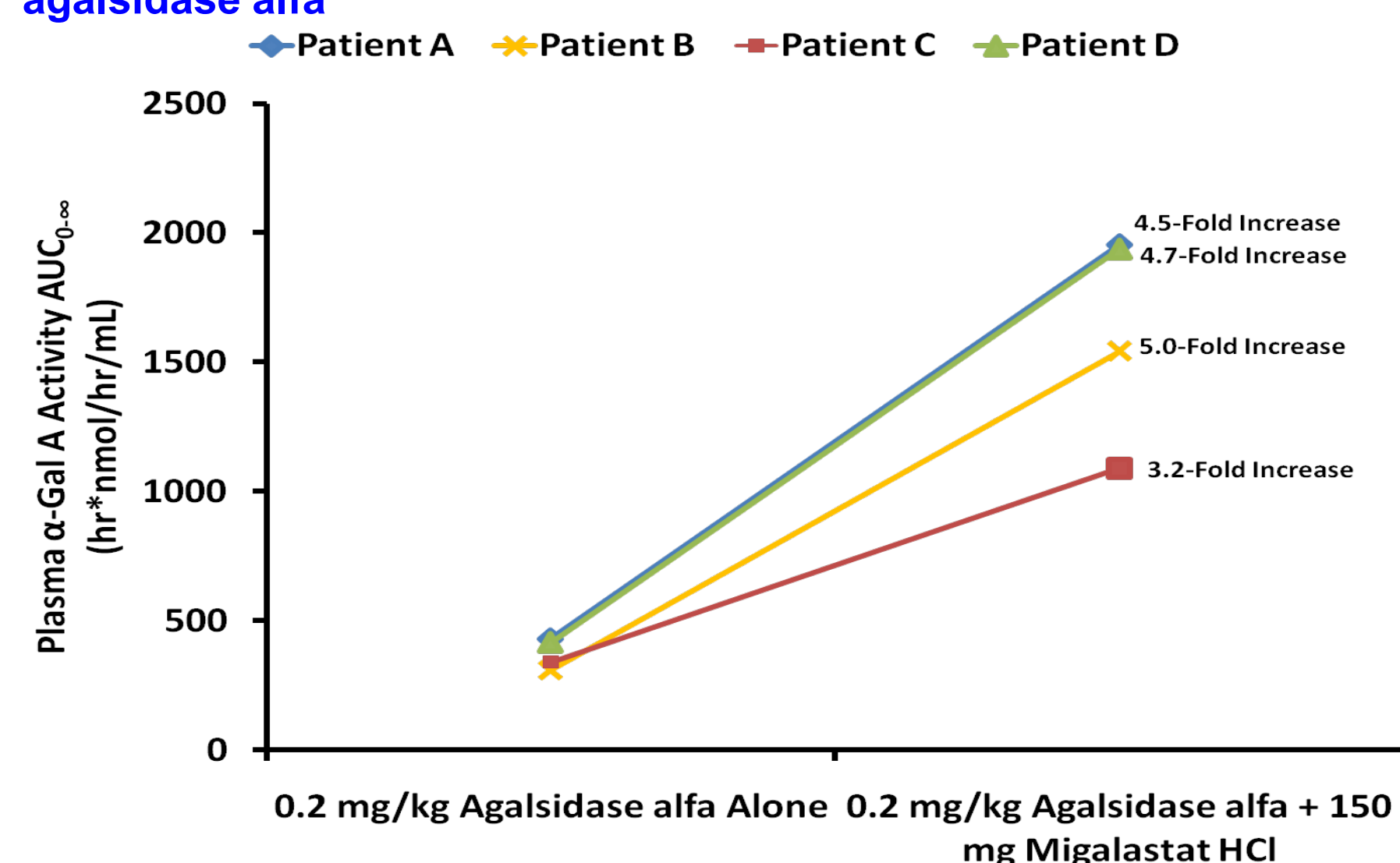


Figure 2. Plasma active enzyme AUC vs. Treatment with 0.5 mg/kg agalsidase beta

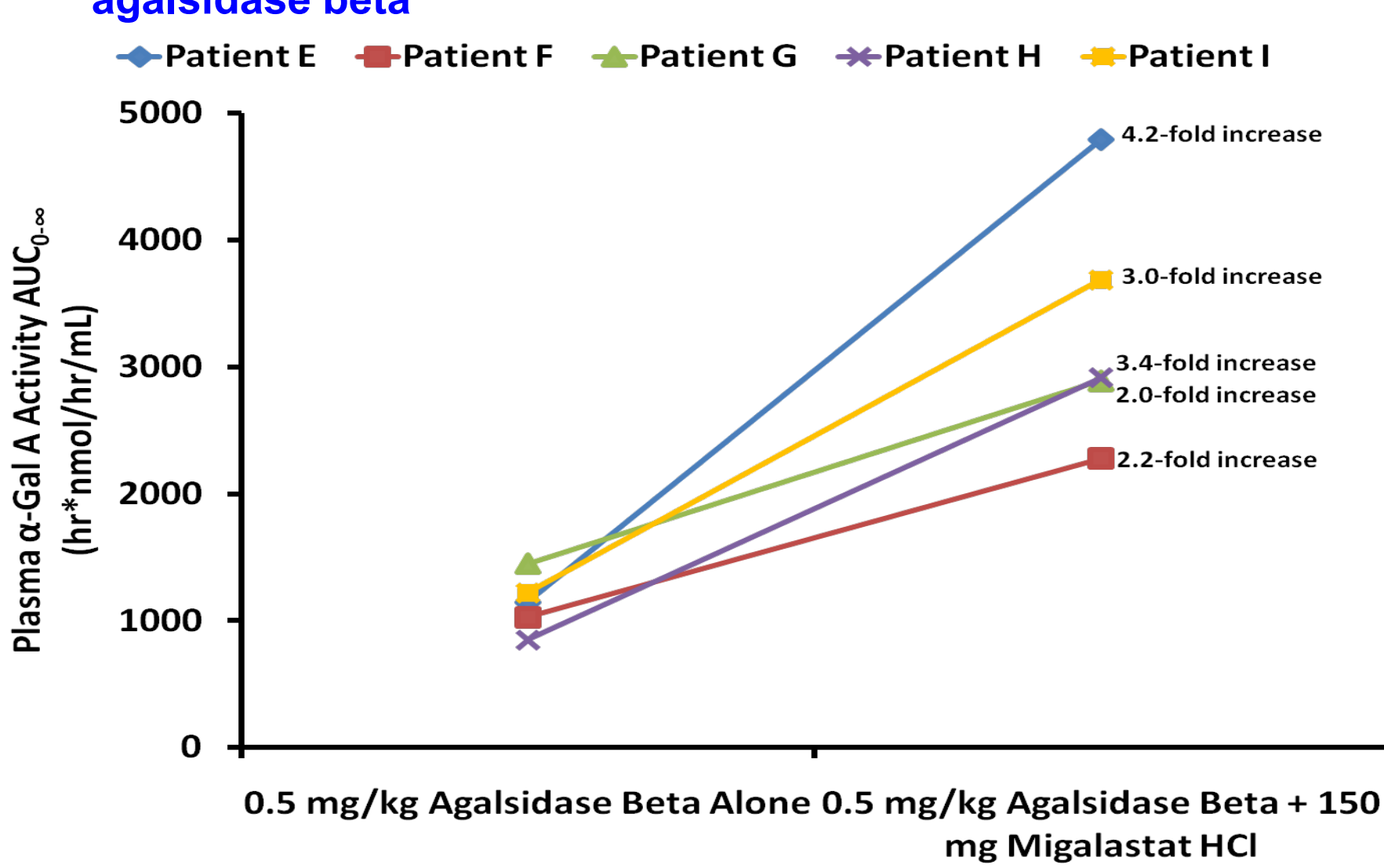


Figure 3. Plasma active enzyme AUC vs. Treatment with 1.0 mg/kg agalsidase beta

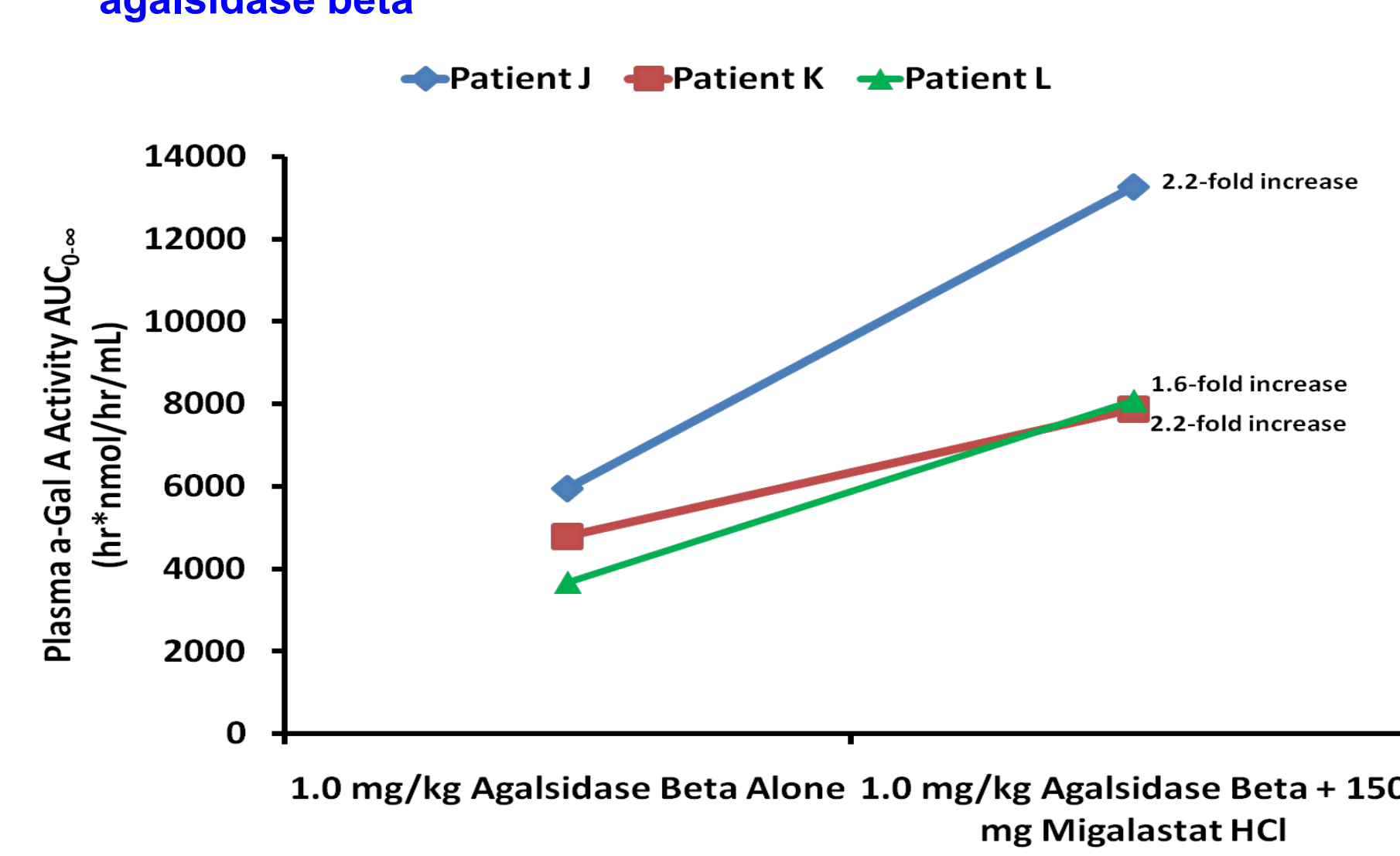


Figure 4. Mean (SD) Plasma Active Enzyme vs. Time for Each agalsidase Treatment Administered Alone

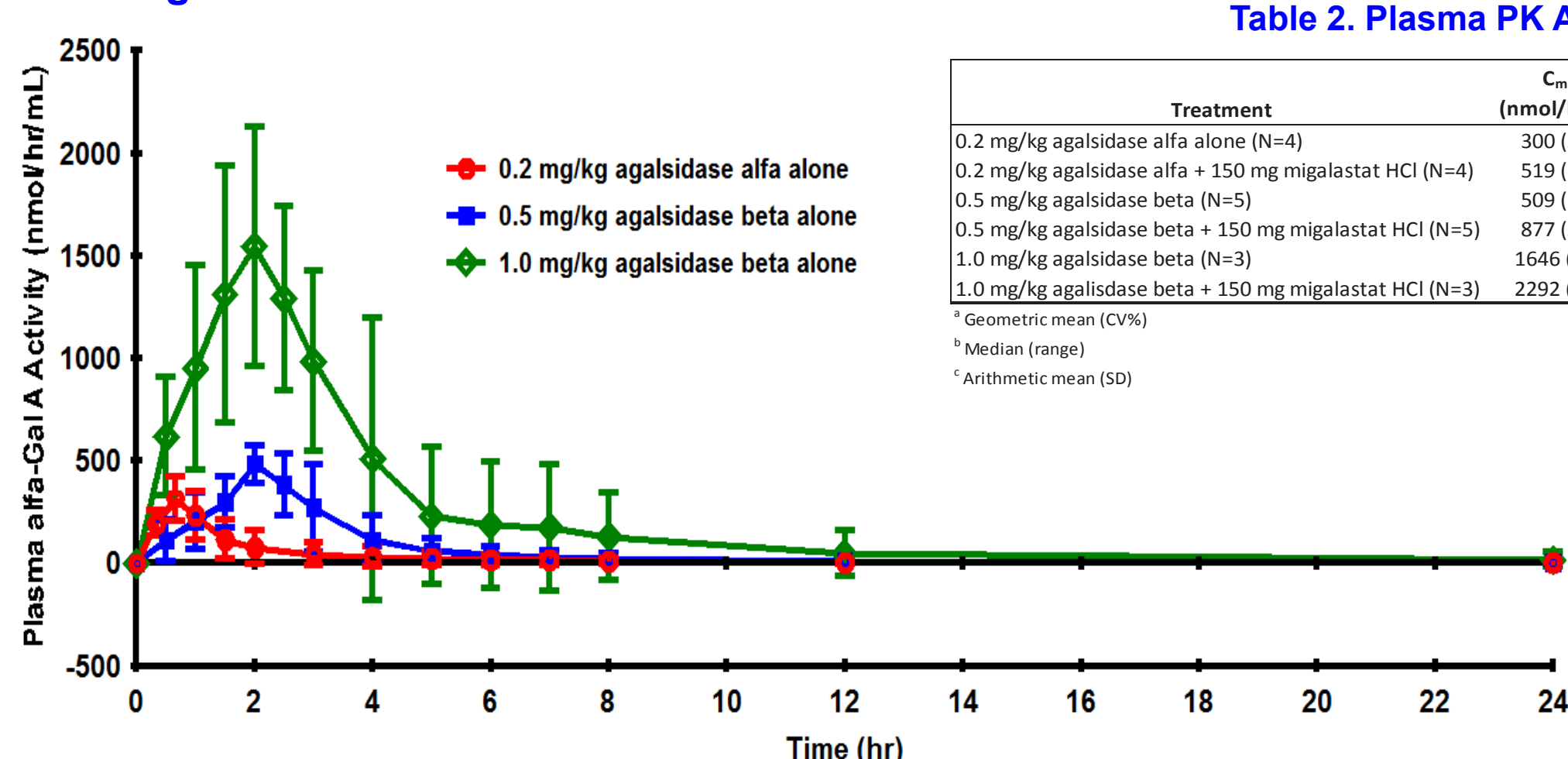
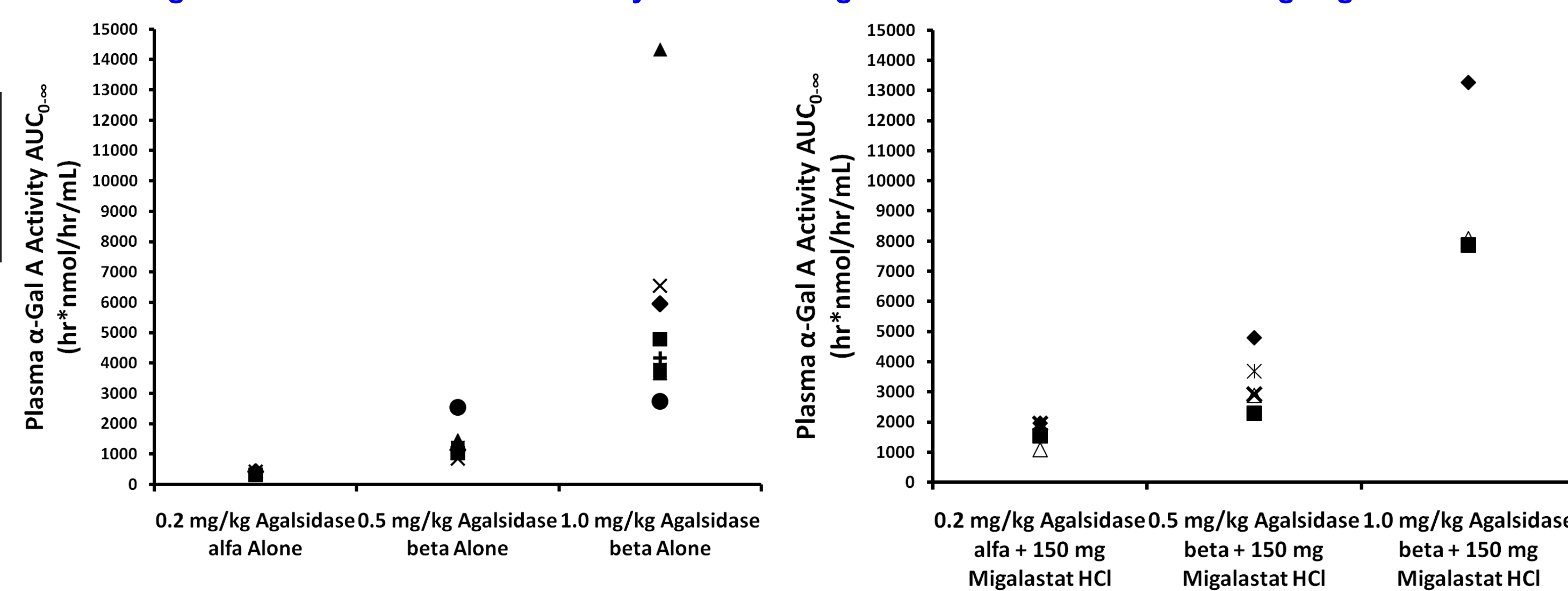


Table 2. Plasma PK Active Enzyme Summary

Treatment	C <sub>max</sub> <sup>a</sup> (nmol/hr/mL)	T <sub>max</sub> <sup>b</sup> (hr)	AUC <sub>0-24</sub> <sup>c</sup> (hr*nmol/hr/mL)	T <sub>1/2</sub> <sup>d</sup> (hr)	AUC Ratio <sup>e</sup>
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)
0.5 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)	4722 (33.3)	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)

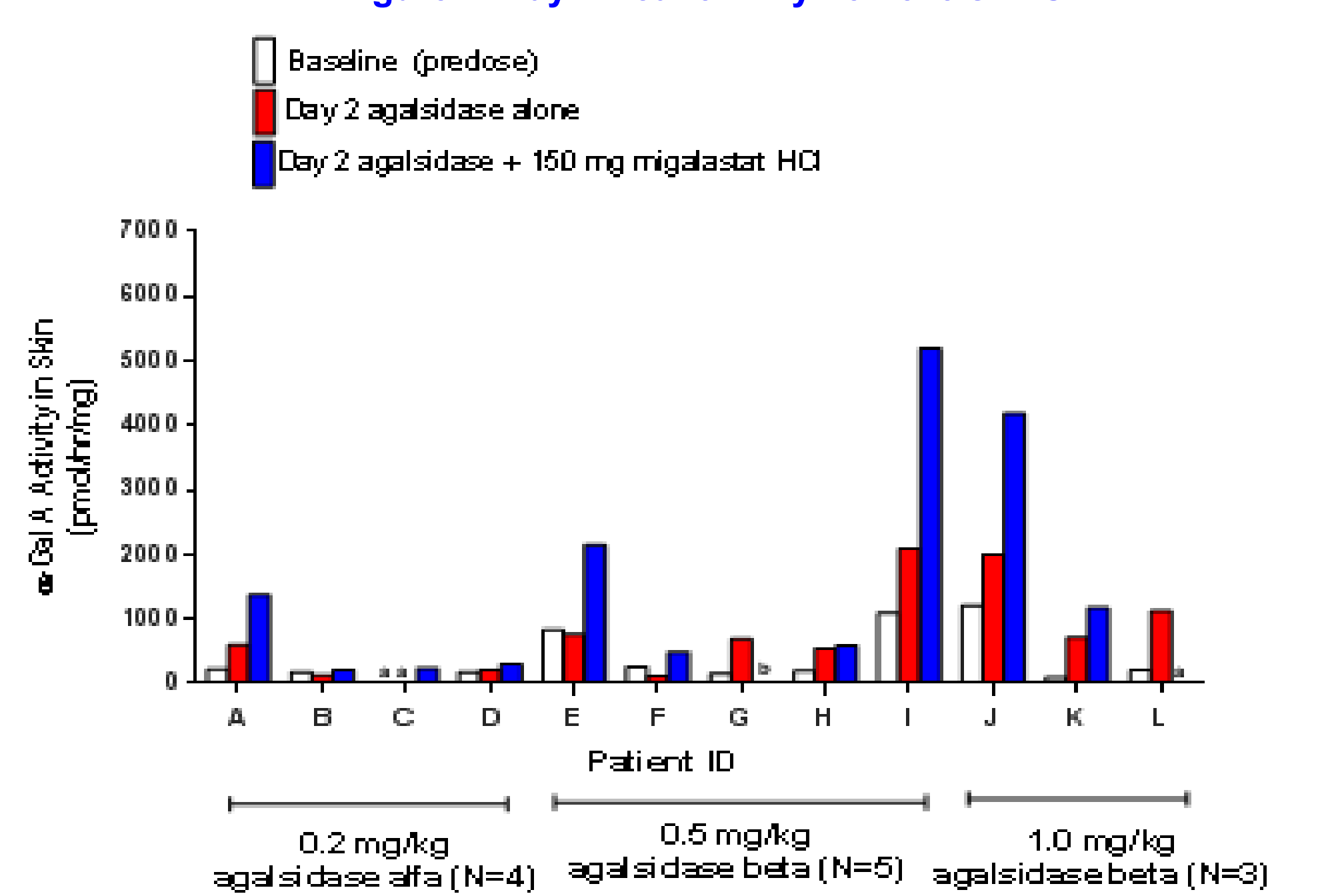
<sup>a</sup> Geometric mean (CV%)  
<sup>b</sup> Median (range)  
<sup>c</sup> Arithmetic mean (SD)

Figures 5 and 6. Plasma Active Enzyme AUC vs. agalsidase Alone and with 150 mg Migalastat HCl



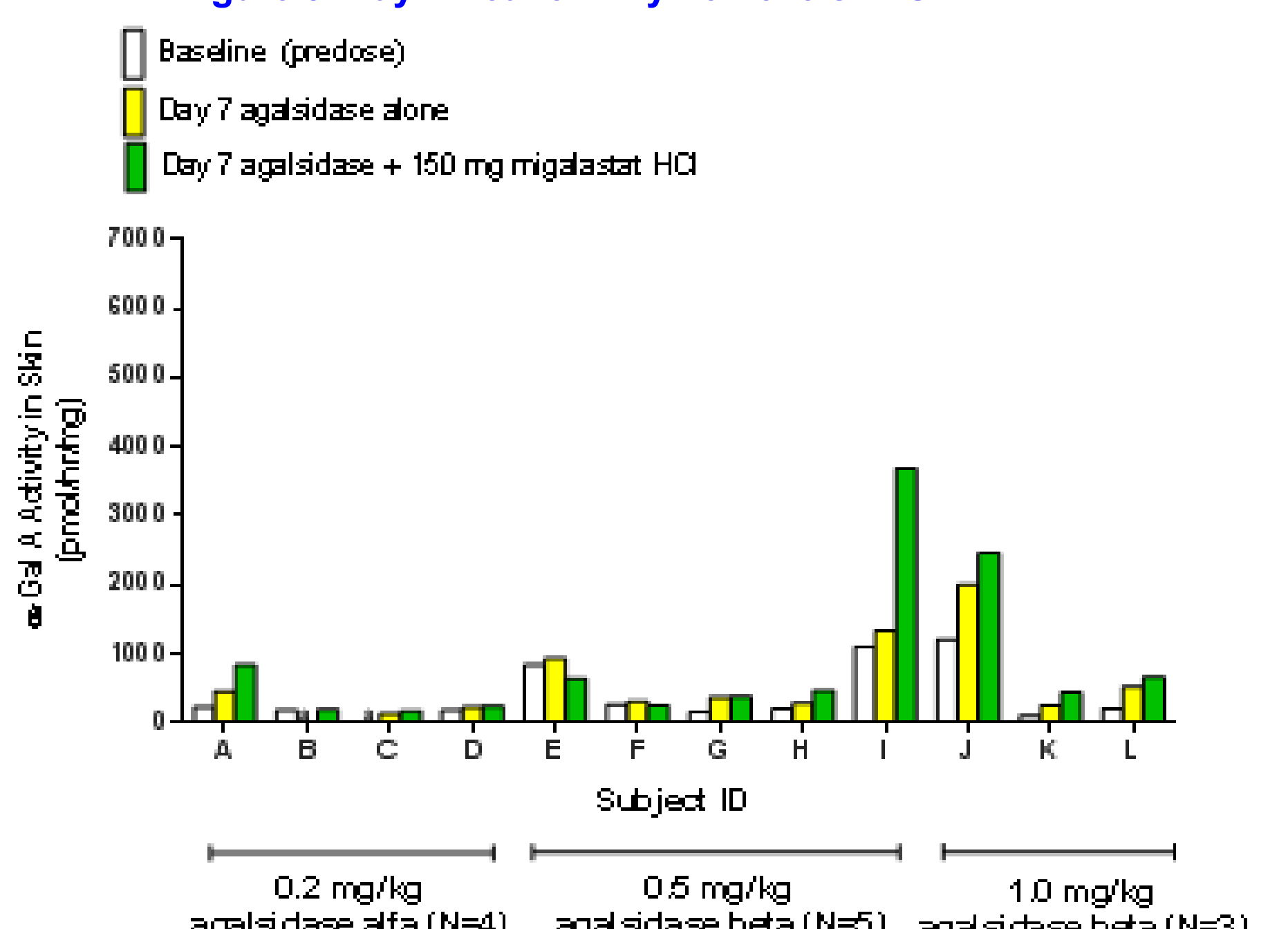
### Active Enzyme Levels in Skin

Figure 7. Day 2 Active Enzyme Levels in Skin



<sup>a</sup> Insufficient total  $\alpha$ -Gal A protein level from skin sample prohibited determination of  $\alpha$ -Gal A activity  
<sup>b</sup> Lost biopsy sample

Figure 8. Day 7 Active Enzyme Levels in Skin



<sup>a</sup> Insufficient total  $\alpha$ -Gal A protein level from skin sample prohibited determination of  $\alpha$ -Gal A activity

Table 3. Skin Active Enzyme Level Summary

Patient ID	Study Day	Fold Change (P2/P1)	Change from Baseline Ratio
A	1	2.6	2.6
A	2	2.3	6.1
A	7	2.0	2.0
B	1	1.8	3.2
B	2	1.7	0.7
B	7	-	1.2
B	7	-	1.1
C	1	2.2	-
C	2	2.2	-
C	7	-	-
C	7	-	-
D	1	2.2	1.2
D	2	1.4	1.7
D	7	1.3	1.3
D	7	1.1	0.9
E	1	2.2	0.9
E	2	2.8	2.6
E	7	1.1	1.1
E	7	0.7	0.8
F	1	2.2	0.5
F	2	3.9	1.8
F	7	1.2	1.2
F	7	0.8	0.9
G	1	2.2	4.5
G	2	-	2.4
G	7	1.0	2.5
H	1	2.2	2.7
H	2	1.1	3.0
H	7	1.1	1.5
H	7	1.6	2.4
I	1	2.2	1.9
I	2	2.5	4.8
I	7	1.7	1.2
I	7	2.8	3.4
J	1	2.2	1.7
J	2	2.1	3.5
J	7	1.7	1.7
J	7	1.2	2.0
K	1	2.2	-
K	2	1.6	-
K	7	1.7	-
K	7	-	-
L	2	-	5.4
L	7	-	2.5
L	7	1.3	3.2

## Summary of Results

**Safety:** To date, no deaths and two serious adverse events (SAEs) in one subject have occurred. One of the SAEs was a transient ischemic attack (TIA) which occurred during 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. The SAEs were deemed unrelated to study drug by the investigator. All other treatment emergent AEs were considered unrelated to study drug and except for one, were mild in intensity.

**PK:** Increases of 2-fold to 5-fold in plasma levels of active enzyme ( $\alpha$ -Gal A activity) AUC were observed following co-administration of 150 mg migalastat HCl with agalsidase relative to agalsidase alone. When agalsidase was administered alone, 0.2 mg/kg (Replagal<sup>®</sup>) had 3.0-fold lower active enzyme exposures than 0.5 mg/kg (Fabrazyme<sup>®</sup>), and both 0.2 mg/kg and 0.5 mg/kg had much lower active enzyme exposures, 12.7- and 4.2-fold, respectively, than 1.0 mg/kg (Fabrazyme<sup>®</sup>). When co-administered with agalsidase, 150 mg migalastat HCl increased 0.2 mg/kg active enzyme to levels similar to 0.5 mg/kg alone, increased 0.5 mg/kg active enzyme to levels similar to 1.0 mg/kg alone, and increased 1.0 mg/kg active enzyme levels by 2.0-fold. Generally, 150 mg migalastat HCl provided larger relative increases in plasma active enzyme exposure for the lower doses of agalsidase (0.2 mg/kg and 0.5 mg/kg) than 1.0 mg/kg. A similar trend is observed for increased tissue distribution of agalsidase into skin following co-administration with 150 mg migalastat HCl. Day 2 (24-hours post dose with 0.2 mg/kg) active enzyme levels increased 1.4- to 2.3-fold (mean 1.8-fold), 1.1- to 3.9-fold for 0.5 mg/kg (mean, 3.1-fold), and 1.6- to 2.1-fold for 1.0 mg/kg (mean, 1.9-fold). Generally, co-administration with 150 mg migalastat HCl had greater increases in active enzyme on Day 2 (3-fold) relative to baseline than agalsidase administered alone (2-fold). For Patients B, E, and F, agalsidase alone resulted in mild decreases (essentially no change) in active enzyme on Day 2 relative to baseline. Except for Patients I and J, active enzyme levels had returned to near-baseline levels by Day 7. Both of these patients tended to have higher baseline active enzyme levels than other patients. Although a positive drug-drug interaction is clearly demonstrated for the effect of migalastat on agalsidase, the plasma pharmacokinetics of migalastat administered with agalsidase relative to migalastat alone was negative for an interaction of agalsidase on migalastat C<sub>max</sub> and AUC (mean ratio of migalastat + agalsidase to migalastat alone = 1.0). [Note, all means presented are geometric means]

## Conclusions

- Preliminary results suggest 150 mg migalastat interaction with 0.2 mg/kg, 0.5 mg/kg, and 1.0 mg/kg agalsidase resulted in 2- to 5-fold increases in plasma active enzyme AUC. Plasma active enzyme AUC for 1.0 mg/kg agalsidase alone was 12.7- and 4.2 fold greater than 0.2 mg/kg and 0.5 mg/kg alone, respectively.
- Active enzyme levels from Day 2 skin biopsies demonstrated consistent increases following co-administration with 150 mg migalastat relative to agalsidase alone, verifying proof-of-concept of increased tissue uptake of ERT by means of a pharmacological chaperone.
- Co-administration of 150 mg migalastat HCl with agalsidase was generally well-tolerated.
- Further investigations are being conducted in the current study with 450 mg migalastat HCl with agalsidase alpha and beta.