A Phase 2a Study to Investigate the Effect of AT2220 (Duvoglustat HCl) on the Pharmacokinetics of Acid α-Glucosidase in Subjects with Pompe Disease

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Objectives and Study Design

Pompe disease is caused by mutations in the gene that encodes the lysosomal enzyme acid α-glucosidase (GAA), which hydrolyzes glycogen. AT2220 (duvoglustat HCl) is a pharmacological chaperone that reversibly binds and stabilizes endogenous and exogenous forms of GAA. When co-administered with an Enzyme Replacement Therapy (ERT), such as recombinant human GAA (rhGAA), AT2220 is intended to bind to the infused enzyme, stabilizing it in its properly folded and active form. AT2220-010 is an open-label, non-randomized, 4-dose cohort, Phase 2a drug-drug interaction study to evaluate the safety and pharmacokinetic (PK) effects of a single oral dose of AT2220 (50 mg, 100 mg, 250 mg or 600 mg) co-administered with intravenous rhGAA in patients with Pompe disease. Patients received an IV infusion of ERT alone during Period 1. A single oral dose of AT2220 was co-administered 1 hour prior to the next IV infusion of ERT at the same dose and regimen during Period 2.

Preliminary Results

Patient Disposition and Demographics

Twenty-five patients gave consent and were enrolled into one of 4 dose cohorts as follows: 50 mg (N=6), 100 mg (N=6), 250 mg (N=6), and 600 mg (N=7).
Plasma and muscle rhGAA activity from Periods 1 and 2, and AT2220 concentrations from Period 2 were evaluated.

- All patients received rhGAA alone during Period 1; all patients were co-administered AT2220 1 hour prior to initiation of rhGAA infusion during Period 2.
- Cohort 1 patients are blinded as A, B, C, D, E, and F; Cohort 2 patients are blinded as G, H, I, J, K, and L; Cohort 3 patients are blinded as M, N, O, P, Q, and R, and Cohort 4 patients are blinded as S, T, U, V, W, X, and Y.
- Thirteen subjects were male and 12 were female with Pompe Disease aged 33-65 years, and weight ranged from 55.8 - 109 kg.

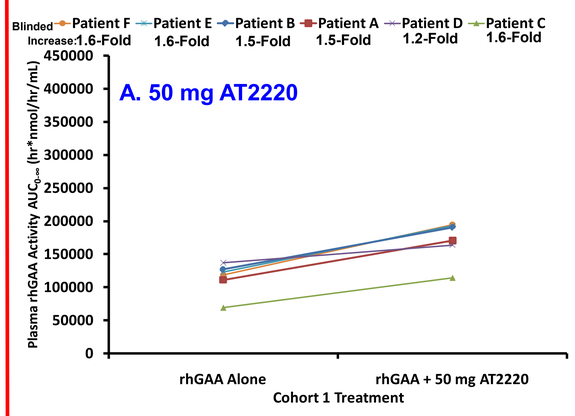
Available genotypes reported for each subject are presented in Table 1.

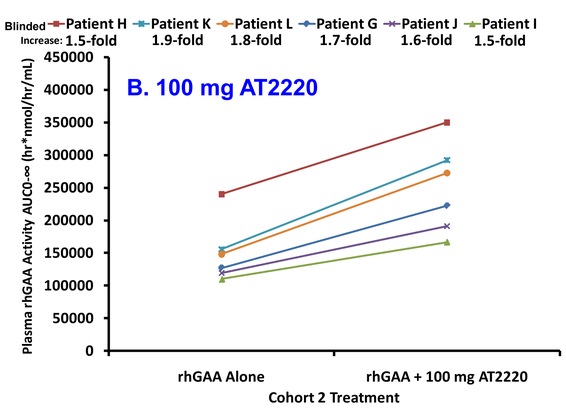
Table 1. *GAA* Genotypes

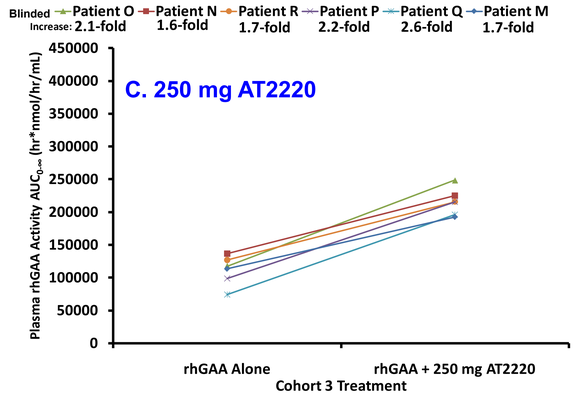
Patient ID	Reported Genotype
A	c.-32-13T>G
D	c.1222A>G / c.-32-13T>G
H	c.-32-13T>G / c.1445C>G
J	c.692+5G>T / c.1211A>G
L	c.-32-13T>G
N	c.-32-13T>G / c.1143delC
O	c.-32-13T>G / c.876C>T / c.1143delC
Q	c.-32-13T>G / c.2481+102 / c.2646+1del
R	c.-32-13T>G
S	IVS1-13T>G

AT2220 Increases Active Enzyme Levels in Plasma

Figure 1. Plasma Active Enzyme AUC vs. Treatment with 50 mg (Panel A), 100 mg (Panel B), 250 mg (Panel C), or 600 mg (Panel D) AT2220







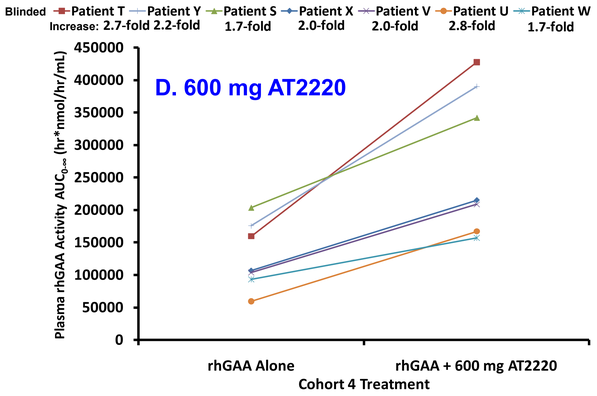
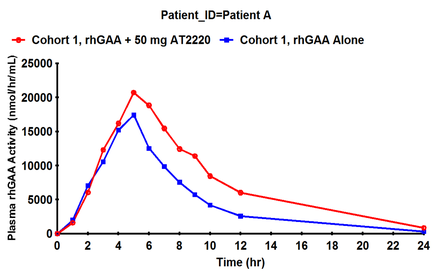


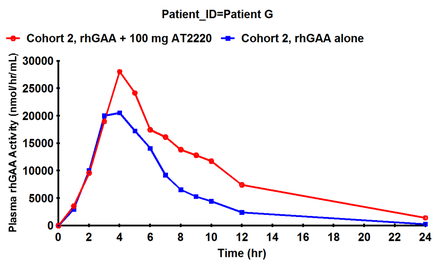
Table 2. Plasma PK Active Enzyme Summary

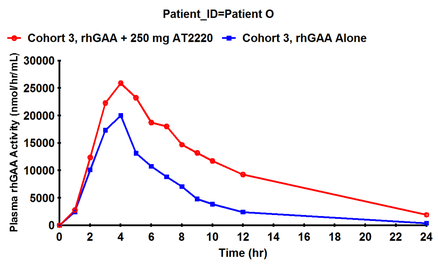
Period/Treatment	Cohort	Period	C_{max}[a] (nmol/hr/mL)	T_{max}[b] (hr)	$AUC_{0-\infty}$[a] (hr*nmol/hr/mL)	AUC Ratio[a]	$t_{1/2}$[c] (hr)
rhGAA Alone (N=6)	1	1	17269 (21.0)	4.5 (4 - 5)	111965 (20.6)	-	3.8 (0.4)
rhGAA + 50 mg AT2220 (N=6)	1	2	20539 (20.4)	4.5 (4 - 6)	168531 (17.9)	1.5 (11.0)	4.5 (0.8)
rhGAA Alone (N=6)	2	1	22785 (18.0)	4.0 (3 - 5)	144953 (31.5)	-	3.8 (0.6)
rhGAA + 100 mg AT2220 (N=6)	2	2	28607 (13.9)	4.0 (3 - 6)	241203 (27.5)	1.7 (10.1)	4.9 (0.8)
rhGAA Alone (N=6)	3	1	18986 (18.7)	4.0 (4 - 4)	109165 (20.0)	-	3.6 (0.5)
rhGAA + 250 mg AT2220 (N=6)	3	2	22651 (9.0)	4.0 (4 - 4)	214751 (9.5)	2.0 (19.7)	5.3 (1.1)
rhGAA Alone (N=7)	4	1	18628 (34.3)	4.0 (3 - 6)	119620 (40.0)	-	3.7 (0.8)
rhGAA + 600 mg AT2220 (N=7)	4	2	22505 (36.2)	4.0 (3 - 6)	253526 (40.9)	2.1 (20.8)	6.6 (1.4)

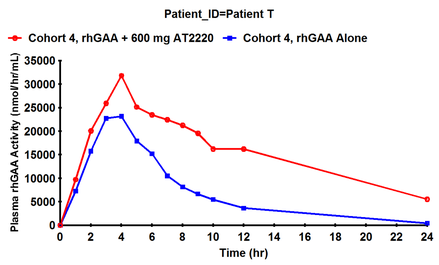
[a]Geometric mean (CV%)
[b]Median (range)
[c]Arithmetic mean (SD)

Figures 2a, 2b, 2c, and 2d. Representative Plots of Plasma Active Enzyme vs. Time









AT2220 Increases Uptake of Active Enzyme into Muscle

Figure 3a. Day 3 Active Enzyme Levels in Muscle

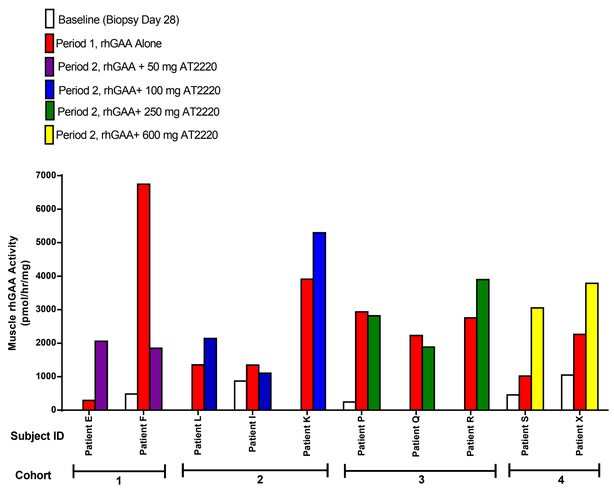
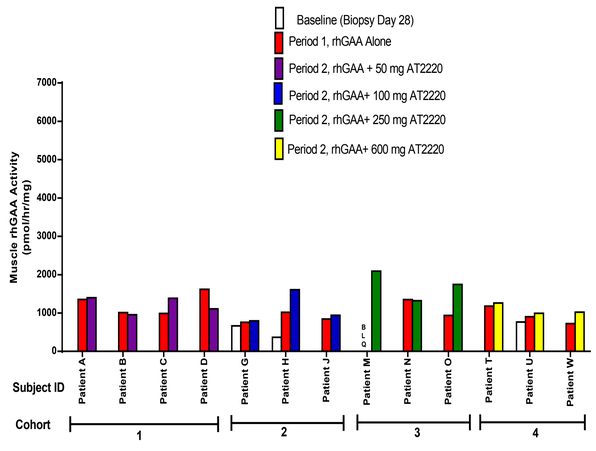


Figure 3b. Day 7 Active Enzyme Levels in Muscle



Dose-Related Increases Observed for Plasma AT2220 Pharmacokinetics

Figure 4a. Mean (SD) Plasma AT2220 Concentration-Time Profiles

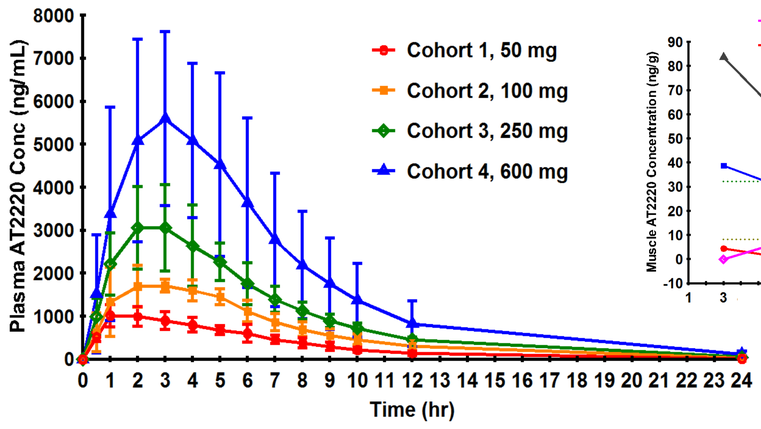
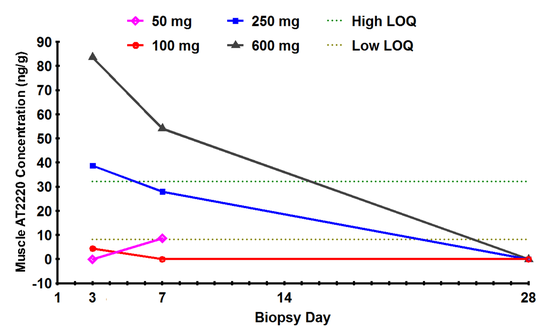


Figure 4b. Mean Muscle AT2220 Concentrations Decrease to Levels Near or Below the Limit of Quantification (LOQ)



Summary of Results and Conclusions

- Preliminary results show single doses of 50 mg, 100 mg, 250 mg and 600 mg AT2220 with an rhGAA dose of approximately 20 mg/kg increased active plasma rhGAA AUC levels by 1.5- to 2.8-fold in all Pompe patients (100%) relative to rhGAA administered alone.
- Following co-administration with AT2220, approximately 70% (16 out of 23) of patients had increased muscle rhGAA activity from Days 3 or 7 biopsy samples.
  - The increased rhGAA activity suggests more active rhGAA is taken up in muscle.
  - Increases in active rhGAA levels following co-administration appeared to be dose-dependent.
- Plasma AT2220 exposures (AUC) increased in a dose-related manner, however, were nonlinear.
  - Dose-related increases were observed for muscle AT2220 concentrations on Days 3 and 7.
  - However, all evaluable follow up samples (Day 28) were below the limit of quantification (8 ng/g).
    - Although complete clearance is desired, these data suggest AT2220 is gradually cleared from muscle to levels near or below the LOQ by Day 14.
  - The single dose pharmacokinetics in these Pompe patients were similar to results from healthy volunteers.
- Co-administration of AT2220 at doses of 50 mg, 100 mg, 250 mg and 600 mg with rhGAA was generally well-tolerated.
  - No changes in key safety data (e.g., urine glucose tetrasaccharide, CK, liver transaminases) were observed.
  - One serious adverse event (SAE) occurred in one subject. The SAE was deemed unrelated to study drug by the investigator.
    - The SAE was a QTc prolongation (473-493 msec) due to armodafinil-citalopram CYP2C19 interaction.
  - All other AEs were deemed unrelated to AT2220

Next Clinical Study Will Be Multiple Dose Co-administration with AT2220

- At least 2 to 3 doses will be selected in a minimum 3-month Phase 2b study in Pompe patients
- Route of AT2220 administration will be IV bolus
  - To characterize PK for later evaluation of infants and special populations
- AT2220 will be co-administered with rhGAA every 2 weeks
- In addition to rhGAA activity and AT2220 in plasma and muscle, key safety and efficacy data will be recorded including urine glucose tetrasaccharide, CK, liver transaminases, and rhGAA antibody titers

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