# An Ongoing Phase 2a Study to Investigate the Effect of AT2220 (Duvoglustat HCl) on the Pharmacokinetics of Acid α-Glucosidase in Subjects with Pompe Disease: Preliminary Results

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## Introduction

Pompe disease is caused by mutations in the gene that encodes the lysosomal enzyme acid α-glucosidase (*GAA*), which hydrolyzes glycogen. AT2220 (1-deoxynojirimycin [DNJ] hydrochloride [HCl] ) is an iminosugar that is a potent, competitive inhibitor of GAA. We have shown that AT2220 can increase GAA enzyme activity and protein processing in cell lines derived from Pompe patients and in COS-7 cells that transiently express various mutant forms of GAA. AT2220 has also been shown to stabilize human recombinant GAA (rhGAA, alglucosidase alfa) *in vitro* and co-administration of AT2220 with rhGAA results in significant increases in muscle GAA levels and decreases in glycogen levels in a mouse model of Pompe disease.

## Objectives

**Primary Objectives**

- To evaluate the safety of single ascending oral doses of AT2220 administered 1 hour before administration of alglucosidase alfa in patients with Pompe disease
- To evaluate the effect of single ascending oral doses of AT2220 on the plasma pharmacokinetics of rhGAA

**Secondary Objectives**

- To assess rhGAA enzyme activity and protein levels in skeletal muscle at Day 3 or Day 7 following a single intravenous infusion with alglucosidase alfa alone and after pre-administration of single ascending oral doses of AT2220
- To evaluate the concentration of AT2220 in skeletal muscle on Day 3 or Day 7

## Study Design and Methods

AT2220-010 is an ongoing, open-label, non-randomized, fixed-sequence, single-ascending dose study comprised of 2 periods per dose level in patients with Pompe disease.

- Period 1: IV infusion of rhGAA alone
- Period 2: AT2220 orally administered 1 hour prior to IV infusion of rhGAA (at the same dose and infusion duration as in period 1)

Each period is separated by a minimum 14-day rhGAA dosing interval. AT2220 dose cohorts 1 – 4 (N of 4 to 6 patients per cohort) evaluated: 50 mg, 100 mg, 250 mg, and 600 mg administered as an oral solution.

Preliminary results are available for Cohorts 1 and 2 (50 mg and 100 mg) for Periods 1 and 2:

- Subjects receive their current dose and regimen of rhGAA alone as an IV infusion (approximately 20 mg/kg for 3 - 6 hrs) followed by oral AT2220 administered one hour prior to the next rhGAA infusion.
- IV infusions of rhGAA are balanced each period for dose and duration of infusion

Further details regarding study design and methods are presented in Poster #244.

## Preliminary Results

### Patient Disposition and Demographics

**Four patients from Cohort 1 (50 mg) and 6 patients from Cohort 2 (100 mg) with plasma and muscle rhGAA activity, total protein levels, and AT2220 concentrations from Periods 1 and 2 were evaluated**.

- All patients received rhGAA alone during Period 1; all patients were co-administered with either 50 mg or 100 mg AT2220 1 hour prior to initiation of rhGAA infusion during Period 2.
- Cohort 1 patients are identified as A, B, C, and D, and Cohort 2 patients are identified as E, F, G, H, I, and J.
- Four subjects were male and 6 were female with Pompe Disease aged 43-63 years, weight ranged from 55.8 - 109 kg and estimated eGFR ranged from 90-234 mL/min.

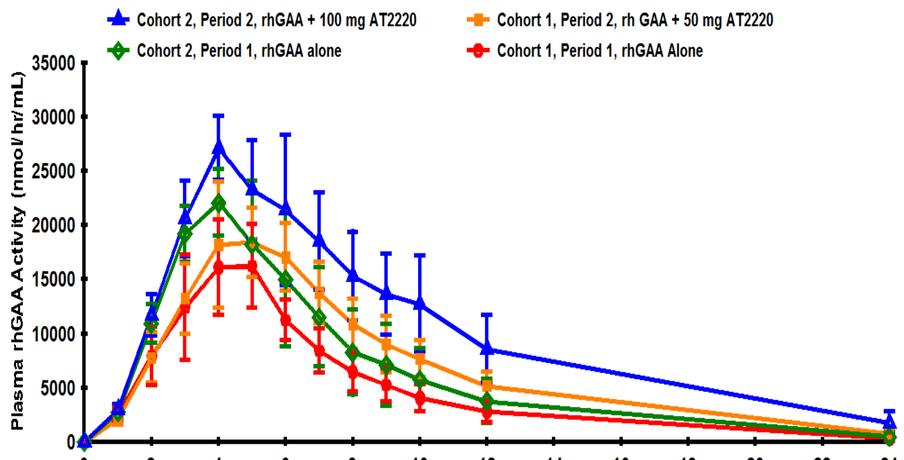
The genotype, including nucleotide and amino acid changes, for each subject (where available) is presented in Table 1.

**Table 1. *GAA* Genotypes**

| Patient ID | Nucleotide Change | Amino Acid Change |
|---|---|---|
| A | c.-32-13T>G | Splicing Mutation |
| B | Not Available | - |
| C | Not Available | - |
| D | c.1222A>G / c.-32-13T>G | M408V / Splicing Mutation |
| E | c.-32-13T>G | Splicing Mutation |
| F | Not Available | - |
| G | c.-32-13T>G / c.1445C>G | Splicing Mutation / P482R |
| H | Not Available | - |
| I | c.692+5G>T / c.1211A>G | Splicing Mutation / D404G |
| J | Not Available | - |

## Plasma rhGAA Activity

**Figure 3. Mean (SD) Plasma rhGAA Activity Over Time Profiles for Cohorts 1 and 2**




**Tables 2 and 3. Mean (SD) Plasma rhGAA Activity and Plasma AT2220 PK Summary for Cohorts 1 and 2**

| Period/Treatment | Cohort | $C_{max}$[a] (nmol/hr/mL) | $T_{max}$[b] (hr) | $AUC_{0-T}$[a] (hr*nmol/hr/mL) | $AUC_{0-\infty}$[a] (hr*nmol/hr/mL) | AUC Ratio[a] | $t_{½}$[c] (hr) |
|---|---|---|---|---|---|---|---|
| rhGAA Alone (N=4) | 1 | 16441 (31.6) | 5.0 (4 - 5) | 105834 (30.7) | 107707 (31.1) | - | 3.9 (0.6) |
| rhGAA + 50 mg AT2220 (N=4) | 1 | 19922 (24.4) | 5.0 (4 - 6) | 152207 (21.3) | 157162 (22.4) | 1.5 (13.2) | 4.2 (0.8) |
| rhGAA Alone (N=6) | 2 | 22785 (18.0) | 4.0 (3 - 5) | 142415 (30.4) | 144953 (31.5) | - | 3.8 (0.6) |
| rhGAA + 100 mg AT2220 (N=6) | 2 | 28607 (13.9) | 4.0 (3 - 6) | 229434 (25.3) | 241203 (27.5) | 1.7 (10.1) | 4.9 (0.8) |

[a]Geometric mean (CV%)

[b]Median (range)

[c]Arithmetic mean (SD)

**AT2220 PK Summary Table**

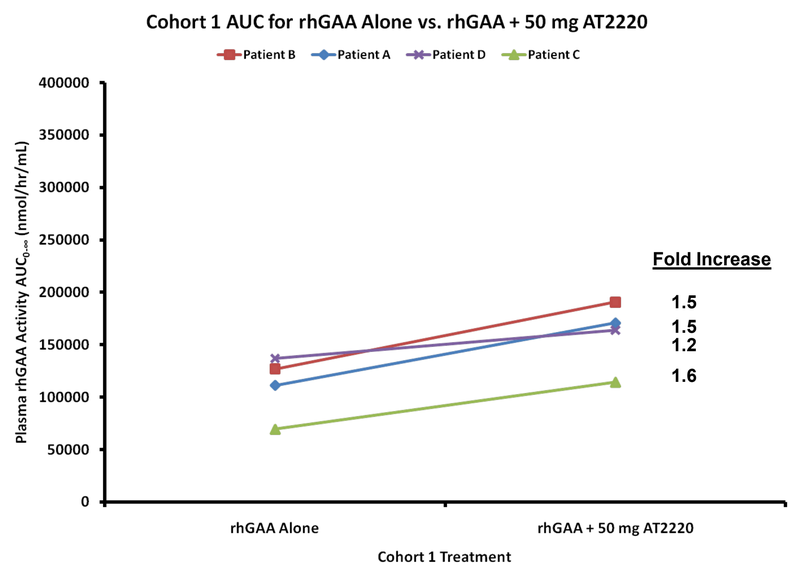
| AT2220 Dose | $C_{max}$[a] (ng/mL) | $T_{max}$[b] (hr) | $AUC_{0-T}$[a] (ng·hr/mL) | $AUC_{0-\infty}$[a] (ng·hr/mL) | $AUC_{0-\infty}$ Ratio | $t_{½}$[c] (hr) |
|---|---|---|---|---|---|---|
| 50 mg (N=4) | 1035 (25.0) | 2.0 (1 - 3) | 6972 (28.1) | 7008 (28.2) | - | 3.1 (0.2) |
| 100 mg (N=6) | 1863 (13.1) | 3.0 (1 - 4) | 13003 (18.9) | 13137 (19.2) | 1.9 | 3.4 (0.3) |

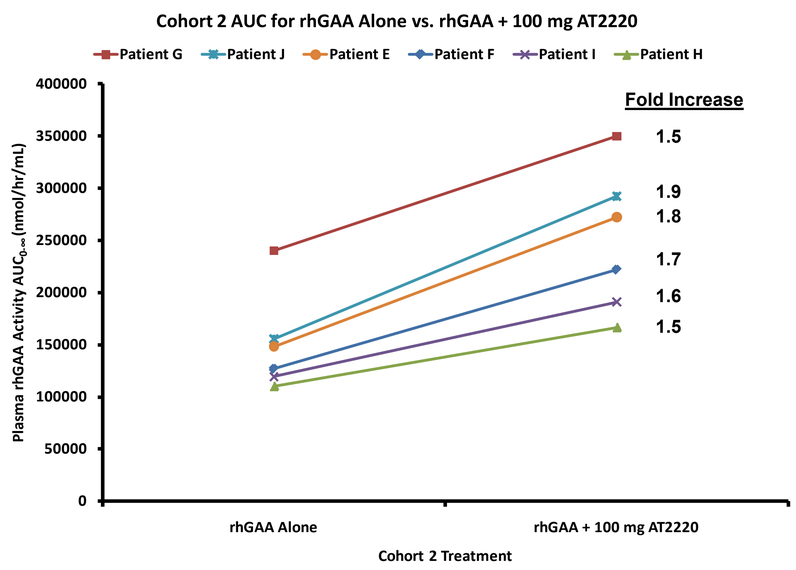
[a]Geometric mean (CV%)

[b]Median (range)

[c]Arithmetic mean (SD)

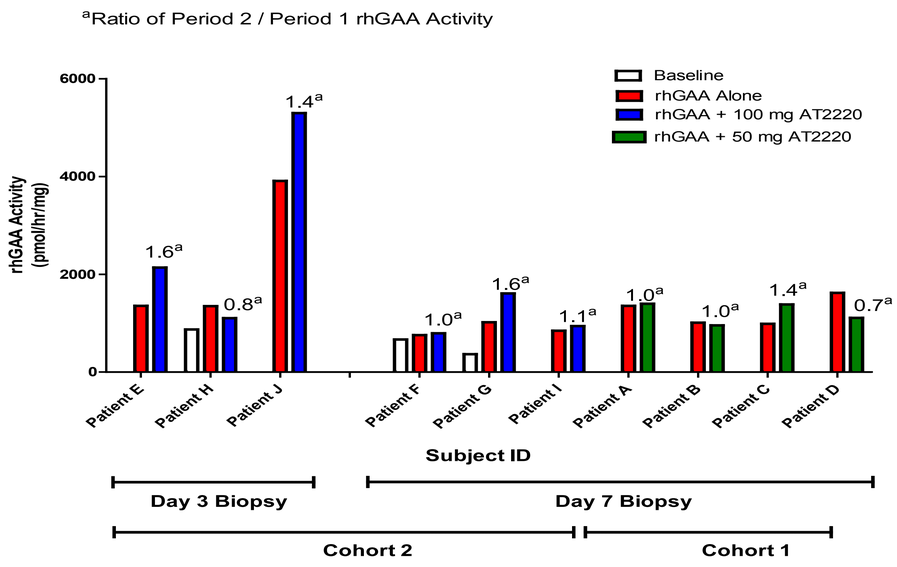
**Figures 4 and 5. Plasma AUC rhGAA Activity Vs. Treatment with 20 mg/kg Alglucosidase alfa for Cohorts 1 and 2**




## Muscle rhGAA Activity

**Figure 6. Muscle rhGAA Activity on Days 3 and 7**




## Plasma and Muscle AT2220 Concentrations

**Figure 7. Mean (SD) Plasma AT2220 Concentrations**

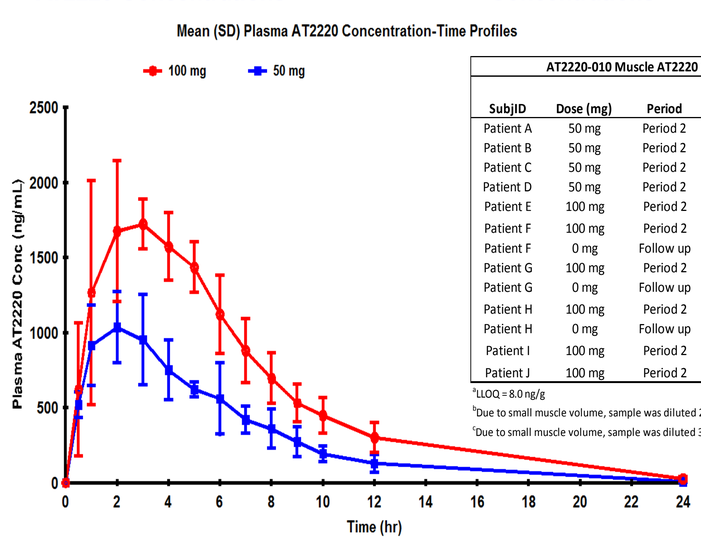



**Table 4. Individual Muscle AT2220 Concentrations**

| AT2220-010 Muscle AT2220 Conc for Cohort 2 | | | | |
|---|---|---|---|---|
| SubjID | Dose (mg) | Period | Study Day | Muscle AT2220 Conc (ng/g)[a] |
| Patient A | 50 mg | Period 2 | Day 7 | 11.8 |
| Patient B | 50 mg | Period 2 | Day 7 | 10.0 |
| Patient C | 50 mg | Period 2 | Day 7 | 13.1 |
| Patient D | 50 mg | Period 2 | Day 7 | BLQ |
| Patient E | 100 mg | Period 2 | Day 3 | 17.8 |
| Patient F | 100 mg | Period 2 | Day 7 | BLQ[b] |
| Patient F | 0 mg | Follow up | Baseline | BLQ |
| Patient G | 100 mg | Period 2 | Day 7 | BLQ |
| Patient G | 0 mg | Follow up | Baseline | BLQ |
| Patient H | 100 mg | Period 2 | Day 3 | BLQ[b] |
| Patient H | 0 mg | Follow up | Baseline | BLQ |
| Patient I | 100 mg | Period 2 | Day 7 | BLQ[b] |
| Patient J | 100 mg | Period 2 | Day 3 | BLQ[c] |

[a]LLOQ = 8.0 ng/g

[b]Due to small muscle volume, sample was diluted 2-fold, therefore LLOQ = 16.0 ng/g

[c]Due to small muscle volume, sample was diluted 3-fold, therefore LLOQ = 32.0 ng/g

## Total rhGAA Protein by Western Blot

**Figure 8. Plasma Total rhGAA Protein Concentration Profiles**

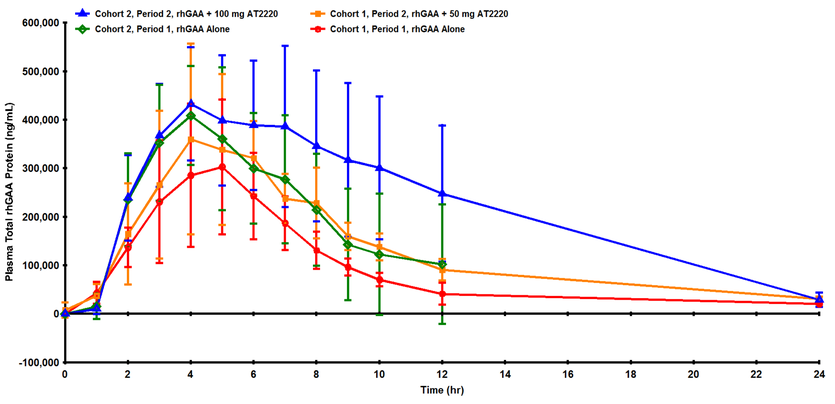



**Table 5. Total rhGAA Protein PK Summary Table**

**Cohorts 1 and 2 Plasma rhGAA Protein PK Summary**

| Period/Treatment | Cohort | $C_{max}$[a] (nmol/hr/mL) | $T_{max}$[b] (hr) | $AUC_{0-T}$[a] (hr*nmol/hr/mL) | $AUC_{0-T}$[a] Ratio | $AUC_{0-\infty}$[a] (hr*nmol/hr/mL) | $T_{½}$[c] (hr) |
|---|---|---|---|---|---|---|---|
| rhGAA Alone (N=4) | 1 | 283118 (45.9) | 5.0 (5 - 5) | 1979695 (19.4) | - | 2172404 (12.8) | 4.8 (3.7) |
| rhGAA + 50 mg AT2220 (N=4) | 1 | 354035 (47.3) | 5.5 (4 - 6) | 2796515 (17.7) | 1.4 (9.2) | 3124625 (13.1) | 4.8 (2.2) |
| rhGAA Alone (N=6) | 2 | 399623 (25.8) | 4.0 (4 - 5) | 2315249 (44.3) | - | 2862876 (86.8) | 3.9 (4.5) |
| rhGAA + 100 mg AT2220 (N=6) | 2 | 430738 (30.5) | 4.0 (4 - 7) | 3841773 (44.5) | 1.7 (18.5) | 5123518 (42.3) | 6.1 (3.2) |

[a]Geometric mean (CV%)

[b]Median (range)

[c]Arithmetic mean (SD)

## Safety

To date, 20 adverse events (AEs) have been reported, one of which was serious. The serious AE, prolonged QTc interval from 473 to 493 msec, which occurred after the screening visit, but prior to dosing, was moderate in severity, and was considered unrelated to study drug by the investigator. All other AEs were mild in severity, all considered unrelated to study drug, and resolved without treatment. Urine hexose tetrasaccharide A (urine Hex 4) and serum CPK levels are presented for each patient in Figures 1 and 2.

**Figure 1. Urine Hex 4 Levels by Study Day**

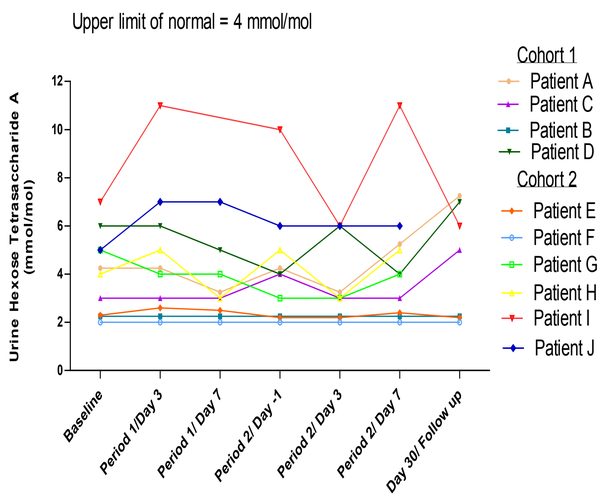
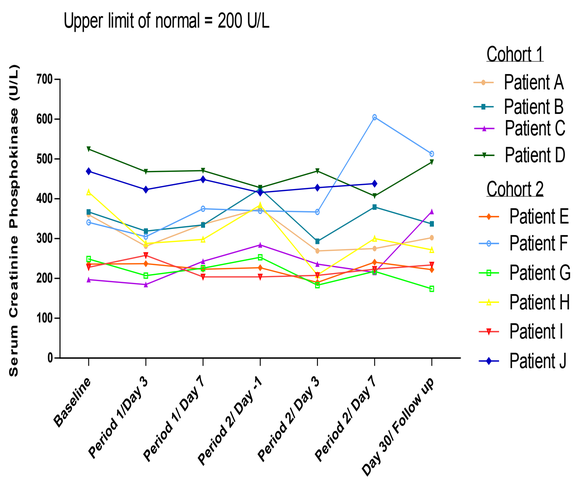



**Figure 2. Serum CPK Levels by Study Day**




**Disclosure Statement:** Authors footnoted #1 – 11 above are currently participating investigators in the ongoing clinical trial, AT2220-010. Authors footnoted #12 are full-time employees of Amicus Therapeutics and are stockholders.

## Summary of Results

To date, single doses of 50 mg and 100 mg AT2220 have been found safe and well-tolerated in patients with Pompe Disease. Only mild, transient AE's have been reported, none of which were related to AT2220. One serious AE was reported of citalopram-induced QTc prolongation. The QTc prolongation attenuated following citalopram dose reduction. Generally, urine hex 4 levels either did not change from baseline, or did not show any consistent trend following a single dose of AT2220 (Fig. 1). Additionally, CPK levels did not appreciably change from baseline in Cohorts 1 and 2 (Fig. 2).

Plasma rhGAA activity AUC increased for all patients for both co-administered doses relative to alglucosidase alfa alone (Figs. 4 and 5). Increases in AUC were primarily driven by prolonged plasma half-life due to increases in rhGAA activity at post-$T_{max}$ time points (Table 2, Fig. 3). The increases in plasma rhGAA activity AUC suggest an increase in stabilized rhGAA uptake for tissue distribution.

Muscle biopsies were taken on Day 7 for all four Cohort 1 patients, and on Day 3 or Day 7 for each of 3 of the 6 Cohort 2 patients. Three patients from Cohort 2 had an optional Day 30 muscle biopsy, that was used as a baseline for those patients. Of the Cohort 1 patients, following co-administration of 50 mg AT2220, one had a 40% increase in muscle rhGAA activity, two showed no change, and one had a 30% decrease in rhGAA activity relative to rhGAA alone (Fig. 6). Of the Cohort 2 patients, following co-administration of 100 mg AT2220, two patients had 60% and 40% increases in rhGAA activity relative to rhGAA alone, but one was decreased by 20% from biopsies taken on Day 3. From biopsies taken on Day 7, two were increased by 60% and 10%, and one showed no change in rhGAA activity (Fig. 6).

The pharmacokinetics of plasma AT2220 are approximately linear for the 50 mg and 100 mg doses evaluated at this point in the study. An approximate 2-fold increase in $C_{max}$ and AUC is observed with dose (Table 3, Fig. 7). The rate of absorption ($T_{max}$) is 2 to 3 hours indicating all bioavailable drug has been absorbed early on during the infusion of rhGAA. Muscle AT2220 concentrations from Day 3 or Day 7 biopsies were either below or near the lower limit of quantitation of 8 ng/g (Table 4).

Total plasma rhGAA protein by Western blot followed a similar trend as plasma rhGAA activity in terms of AT2220 dose-related increases (Fig. 8, Table 5).

## Preliminary Conclusions

- AT2220 was safe and well-tolerated at both 50 mg and 100 mg dose levels evaluated to date.
- Plasma rhGAA activity increased 20% to 40% and 50% to 90% following single dose of 50 mg and 100 mg AT2220, respectively.
- At the 50 mg dose level, 1 of 4 patients had increased rhGAA activity in muscle; however, at 100 mg AT2220, 4 of 6 patients had up to 60% increases in rhGAA activity in muscle.
- Plasma AT2220 demonstrated approximately linear PK for the 2 doses evaluated to date.
- AT2220 concentrations in muscle were either below or just above the lower limit of quantification from Day 3 or 7 biopsies suggesting AT2220 may not accumulate following multiple dosing every 14 days.
- Plasma total rhGAA protein PK followed a similar trend to rhGAA activity PK.