Comparison of Integrated White Blood Cell α-Galactosidase A Activity Exposure Between Every-Other-Day Orally Administered Migalastat and Biweekly Infusions of Agalsidase Beta or Agalsidase Alfa

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Introduction
Fabry disease is an x-linked α-galactosidase deficiency: it involves progressive globotriaosylceramide (GL3) accumulation, which affects multiple organs and organ systems including the kidney and heart. Currently approved treatments include once-every-other-week infusions with enzyme replacement therapies 1 mg/kg agalsidase beta or 0.2 mg/kg agalsidase alfa. Mildly or unstable α-Gal A is degraded in the endoplasmic reticulum. Migalastat HCl is a low molecular weight iminosugar and is an analogue of the terminal galactose of GL3. Pre-clinical in vitro and in vivo studies have demonstrated that migalastat acts as a pharmacological chaperone for α-Gal A, selectively and reversibly binding, with high affinity, to the active site of both wild-type and specific mutant forms of α-Gal A, the genotypes of which are referred to as amenable mutations. In vitro and in vivo models bound migalastat stabilizes α-Gal A, slowing its denaturation at neutral pH and body temperature. Migalastat binding stabilizes these mutant forms of α-Gal A in the endoplasmic reticulum facilitating their proper trafficking to lysosomes where dissociation of migalastat allows α-Gal A to reduce GL3 storage material. In contrast, misfolded and/or unstable α-Gal A is recognized by the endoplasmic reticulum quality control system as aberrant and targeted for degradation, never reaching the lysosome. The PK of migalastat has been well-characterized. Migalastat is dose-proportional from 50 to 1250 mg, well absorbed in 3 hours, and has a terminal half-life of approximately 4 hours.x

Data Analysis Methods
The studies included in this data analysis were two Phase 3 studies, AT1001-011 and AT1001-012, and a Phase 2a study, AT1001-013. AT1001-011 was a randomized double-blind, placebo-controlled study, and AT1001-012, a randomized, open-label, comparator study with ERT and migalastat. Both Phase 3 studies were conducted in Fabry patients with amenable mutations, patients were dosed with migalastat every-other-day, and α-Gal A activity in WBCs were measured periodically for up to 24 months. AT1001-013 was an open-label, single-dose study in a fixed sequence with ERT alone first, and then co-administered with either 150 mg or 450 mg migalastat in male Fabry patients with any mutation. An additional arm with 150 mg migalastat alone was used to characterize the plasma PK in Fabry patients, the outcome of which was used in the current analyses: α-Gal A activity in WBCs was measured post-infusion, and at 2, 24, 168, and 336 hours post-start of infusion of agalsidase. The bianalytical method for determination of α-Gal A activity in WBCs was a fluorescence assay, which measured the rate of turn-over of an artificial substrate, 4MUG to 4MU. Circulating WBCs were selected as an example of tissue uptake because of ease of sampling, as well as excellent exposure to both agalsidase and migalastat. Importantly, migalastat-mediated changes in WBC α-Gal A levels were associated with similar changes in skin and kidney α-Gal A activity levels.x The data analysis methods comprised modeling and simulations to predict exposures of WBC α-Gal A activity following oral administration of 150 mg migalastat every-other-day for 7 doses, 14 days total, and noncomparative analyses to estimate mean WBC α-Gal A activity exposure following single infusions of 1 or 0.2 mg/kg agalsidase beta or alfa, respectively.

Migalastat administration results in more consistent levels of WBC α-Gal A Activity

![Figure 1. WBC α-Gal A Activity Following 150 mg Migalastat QOD X 7 Doses vs. Single-dose 1 mg/kg Agalsidase beta or 0.2 mg/kg Agalsidase alfa](image1)

<table>
<thead>
<tr>
<th>Treatment (N)</th>
<th>AUC [nmol/hr/mg]</th>
<th>Cmax [nmol/hr/mg]</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 mg migalastat HCl (79)</td>
<td>2969</td>
<td>39.9</td>
<td>Combined 01/012</td>
</tr>
<tr>
<td>1.0 mg/kg agalsidase β (9)</td>
<td>3091</td>
<td>105.9</td>
<td>AT1001-013</td>
</tr>
<tr>
<td>0.2 mg/kg agalsidase α (8)</td>
<td>485</td>
<td>4.83</td>
<td>AT1001-013</td>
</tr>
</tbody>
</table>

As shown in Figure 1, every-other-day dosing with migalastat suggests more consistent levels of α-Gal A activity compared to a 14-day ERT dosing interval. As shown in Table 1, simulated migalastat AUC for WBC α-Gal A activity is comparable to that seen following a single dose of 1 mg/kg agalsidase beta and is approximately 6-fold greater than that seen following a 0.2 mg/kg agalsidase alfa. Single doses of agalsidase beta resulted in higher Cmax values (mean of 105.9) with rapidly declining α-Gal A activity. The simulated AUC for migalastat represents an attenuated Cmax with more consistent levels of activity as a result of every-other-day dosing over the same 14-day interval. All baseline endogenous levels of activity were subtracted from each time point for estimation of PK parameters. The exposure values presented in the abstract were not baseline-corrected.

Proposed Relationship of Plasma Migalastat to WBC α-Gal A Activity

![Figure 2. Plasma Migalastat and WBC α-Gal Activity vs. Time (14 Days)](image2)

Conclusions Based on Modeling and Simulation and Limitations of the Analysis

Conclusions:
- Following Q14d single-dose infusions with agalsidase beta or alfa to Fabry patients, or 7 QOD oral administrations of 150 mg migalastat HCl to Fabry patients with amenable mutations over 14 days, α-Gal A in WBCs were:
  - Comparable between agalsidase beta and migalastat, but were 6-fold greater for migalastat compared to agalsidase alfa.
  - More consistent following QOD administration of migalastat, which provided lower Cmax values and higher Cavg values than single infusions of agalsidase which ultimately suggests more consistent cellular α-Gal A activity levels.

Limitations:
- Time of sampling relative to dosing for WBC activity data from Phase 3 studies AT1001-011 and -012 was not recorded.
- Therefore, a hypothetical activity level-time curve was constructed from actual data
- Selected activity levels from the combined 011 and 12 data sets were assigned to fit an assumed constant and rapid rate of increase and biphasic elimination rate based upon the characterization of α-Gal A in plasma
- WBCs are not a disease-relevant tissue for Fabry
- WBC α-Gal A activity may be overestimated following agalsidase administration to IgG positive patients who have greater uptake of α-Gal A into WBCs
- The hypothetical model and simulation presented here represents a mosaic of different amenable mutant forms
- Therefore, some individuals may have greater or lesser responses

References

[Insert references here]