Oral Migalastat HCl as an Investigational Therapy Evaluated in Females with Fabry Disease


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BACKGROUND

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by mutations in the α-galactosidase A (α-Gal A) gene. This results in accumulation of globotriaosylceramide (GL3) in tissues and body fluids, leading to multi-organ disease. Heterozygote females may develop significant multi-system pathology, but generally later than males. Many females require supportive and enzyme replacement therapies.

STUDY OBJECTIVES

Primary: To evaluate the safety and tolerability of oral migalastat HCl (AT1001/GR181413A) 50, 100, or 250 mg once every other day in female patients with FD.

Secondary: To evaluate pharmacokinetics (PK) and pharmacodynamics (PD) of migalastat HCl, including assessing changes in α-Gal A activity and GL3.

STUDY DESIGN

FAB-CL-204 (NCT00304512) was a Phase 2, multicenter, open-label trial of migalastat HCl in female patients with FD. The trial included a 12-week treatment phase and an optional 36-week treatment extension.

Eligible patients were females, 18 to 65 years old with Fabry disease and documented end-organ dysfunction, missense GLA mutations, and an α-Gal A activity (mutant and/or wild type) in an ex vivo lymphocyte-based assay. Written informed consent, approved by Institutional Review Boards/Ethics Committee, was obtained from all patients prior to any study procedures. Each patient was randomized to receive 50, 100, or 250 mg migalastat HCl once every other day throughout the study.

This study was conducted according to globally accepted standards of Good Clinical Practice (ICH-GCP) and in agreement with the Declaration of Helsinki.

SAFETY & PD PARAMETERS

Adverse events (AEs), serious AEs, vital signs, clinical laboratory tests (hematology, serum chemistry, and urine analysis), electrocardiograms, and use of concomitant medications; heart, kidney, and CNS evaluations; α-Gal A activity in peripheral blood mononuclear cells (WBC α-Gal A activity), kidney, and skin; GL3 in urine (uGL3), kidney, plasma, and skin.

RESULTS

Table 1: Demographic and Baseline Disease Characteristics of Female Patients with Fabry Disease

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age at diagnosis</th>
<th>GLA Mutation</th>
<th>Medical History and/or Baseline Disease Characteristics</th>
<th>α-Gal A activity (U/L)</th>
<th>WBC α-Gal A activity (U/L)</th>
<th>Kidney GL-3 Deposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>01-01</td>
<td>62</td>
<td>PS29R</td>
<td>Hypertension, Abdominal pain, Depression</td>
<td>27.5</td>
<td>0.5</td>
<td>BLISS Score Score Score</td>
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<td>01-05</td>
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<td>L32P</td>
<td>Hypertension, Abdominal pain, Depression</td>
<td>27.5</td>
<td>0.5</td>
<td>BLISS Score Score Score</td>
</tr>
</tbody>
</table>

Baseline disease characteristics were similar between females with amenable and non-amenable GLA mutations.

No adverse events (SAEs) related to treatment were reported. Two SAEs unrelated to treatment were reported:

1) Cardiac tamponade occurred during the screening period following cardiac biopsy; 2) Muscular chest pain occurred after 1 month of study treatment; an ECC and laboratory tests ruled out cardiac etiology.

All patients completed 48 weeks of treatment. No patients interrupted, reduced, or discontinued study drug dosing due to an AE.

All treatment-related AEs (TEAEs) were mild or moderate in severity. Two of those AEs were reported as possibly or probably related to study drug: 1) arteriolar block was reported at Week 4 and resolved without any intervention while patients continued migalastat HCl treatment; 2) Abdominal discomfort. All other TEAEs were unrelated or likely not related to study drug.

SUMMARY and CONCLUSIONS

In females this study had significant manifestations of FD despite relatively high baseline WBC α-Gal A activity. Low GL3 but in kidney interstitial capillary cells was in contrast to heavily affected podocytes, probably due to different cell turnover rates.

The earliest and most consistent declines in urine GL3 were seen in three patients with amenable mutations, at all dose levels. No consistent reduction in urine GL3 was seen in females with non-amenable mutations, at any dose. Females with amenable GLA mutations who were on the 150 or 250 mg dose of migalastat HCl demonstrated reduction in urine GL3 when compared to baseline at each treatment visit.

No changes in podocyte GL3 inclusions were detected after treatment period of 48 weeks. No consistent reduction in urine GL3 was seen in females with non-amenable mutations, at any dose. Four out of 5 females with amenable mutations demonstrated a decline in GL3 inclusions in interstitial capillary cells in their last available kidney biopsy.

No changes in podocyte GL3 inclusions were detected after treatment period of 48 weeks. No consistent reduction in urine GL3 was seen in females with non-amenable mutations, at any dose. Four out of 5 females with amenable mutations demonstrated a decline in GL3 inclusions in interstitial capillary cells in their last available kidney biopsy.

SAFETY SUMMARY

The earliest and most consistent declines in urine GL3 were seen in three patients with amenable GLA mutations, treated with 150 or 250 mg migalastat HCl. These three patients also demonstrated a decrease in GL3 inclusions in interstitial capillary cells.

No consistent reduction in urine GL3 was seen in females with non-amenable mutations, at any dose. Four out of 5 females with amenable mutations demonstrated a decline in GL3 inclusions in interstitial capillary cells in their last available kidney biopsy.

No changes in podocyte GL3 inclusions were detected after treatment period of 48 weeks. No consistent reduction in urine GL3 was seen in females with non-amenable mutations, at any dose. Four out of 5 females with amenable mutations demonstrated a decline in GL3 inclusions in interstitial capillary cells in their last available kidney biopsy.

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ACKNOWLEDGMENT

Alexander Bragat and Johanna Smysler for study design; site clinical research personnel and patients.