A STUDY TO EVALUATE THE PHARMACODYNAMICS, PHARMACOKINETICS AND SAFETY OF ARHALOFENATE IN COMBINATION WITH FEBUXOSTAT WHEN TREATING HYPERURICEMIA ASSOCIATED WITH GOUT

Alexandra Steinberg, Yun-Jung Choi, Robert Martin, Charles McWherter, Pol Boudes
CymaBay Therapeutics, Newark, CA

www.cymabay.com

Introduction

Arhalofenate is a novel, once-daily, oral Urate-Lowering Anti-FlareTherapy (ULaFT) for the treatment of gout. It has a unique dual mechanism of action: it lowers serum uric acid (sUA) by blocking UATE1 and also reduces gout flares by blocking the local release of IL-1β. Febuxostat is a xanthine oxidase (XO) inhibitor that is recommended as a first-line therapy for gout patients. Arhalofenate in combination with febuxostat provides three actions: 1) inhibition of UA production and 2) increased UA excretion 3) prevention of gout flares. The sUA lowering activities of arhalofenate and febuxostat are complementary.

This study evaluated the sUA lowering activity, drug-drug interaction and safety of arhalofenate in combination with febuxostat.

Objectives

- Measure the sUA reductions in gout patients treated with arhalofenate, febuxostat and their combinations
- Determine inter- and intraday fractional excretion of uric acid (FEUA) after arhalofenate treatment
- Evaluate the potential pharmacokinetic (PK) and pharmacodynamic (PD) interaction between arhalofenate and febuxostat
- Assess the safety and tolerability of the combination

Methods

This was an open label Phase 2 study (NCT02252833) at a single center with two cohorts of gout patients (n = 16 each). Subjects were treatment-naive or willing to discontinue uric acid lowering therapy. Dosing was once daily oral and included flax seed prophylaxis with colchicine.

The 600 mg cohort received arhalofenate 600 mg for 2 weeks followed by sequential one week periods of co-administration of febuxostat 80 mg and 40 mg. During the final two weeks, febuxostat 80 mg was administered alone. The 800 mg cohort received arhalofenate 900 mg for 2 weeks, followed by sequential one week periods of co-administration of febuxostat 40 mg and 80 mg. During the final two weeks, febuxostat 80 mg was administered alone. sUA, 24 hr FEUA and urate clearance were assessed on multiple study days. The PK of arhalofenate (800 mg) and febuxostat (80 mg) were determined to assess the potential for an interaction. Oxypurines (xanthine and hypoxanthine) were determined to assess PD interactions between arhalofenate and febuxostat.

Study Design

<table>
<thead>
<tr>
<th>Weeks</th>
<th>1-2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort</td>
<td>Arhalofenate 600 mg</td>
<td>Arhalofenate 800 mg</td>
<td>Febuxostat 40 mg</td>
<td>Febuxostat 80 mg</td>
<td></td>
</tr>
</tbody>
</table>

Results

Patient Demographics

<table>
<thead>
<tr>
<th>Cohort</th>
<th>At Baseline</th>
<th>N</th>
<th>Age (yrs)</th>
<th>Gender (%)</th>
<th>Flare (%)</th>
<th>BMI (kg/m²)</th>
<th>sUA (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>600 mg</td>
<td>16</td>
<td>49 ± 12</td>
<td>Male (50%)</td>
<td>33 ± 0.5</td>
<td>8.4 ± 1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>800 mg</td>
<td>16</td>
<td>51 ± 12</td>
<td>Male (54%)</td>
<td>34 ± 0.4</td>
<td>6.2 ± 1.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Changes in Serum Uric Acid

Arhalofenate + Febuxostat Potentially Lower sUA

Changes in Serum Uric Acid (mg/dL)

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>Arhalofenate 600 mg</th>
<th>Arhalofenate 800 mg</th>
<th>Febuxostat 40 mg</th>
<th>Febuxostat 80 mg</th>
<th>Combination 600 mg</th>
<th>Combination 800 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7.13</td>
<td>9.13</td>
<td>0.3</td>
<td>0.3</td>
<td>7.13</td>
<td>9.13</td>
</tr>
<tr>
<td>4</td>
<td>6.56</td>
<td>8.64</td>
<td>1.29</td>
<td>1.29</td>
<td>6.56</td>
<td>8.64</td>
</tr>
<tr>
<td>8</td>
<td>6.21</td>
<td>8.38</td>
<td>2.41</td>
<td>2.41</td>
<td>6.21</td>
<td>8.38</td>
</tr>
<tr>
<td>12</td>
<td>5.93</td>
<td>8.06</td>
<td>3.22</td>
<td>3.22</td>
<td>5.93</td>
<td>8.06</td>
</tr>
<tr>
<td>24</td>
<td>5.60</td>
<td>7.85</td>
<td>4.22</td>
<td>4.22</td>
<td>5.60</td>
<td>7.85</td>
</tr>
</tbody>
</table>

Pharmacokinetics

Exposures Maintained in Combination

<table>
<thead>
<tr>
<th>Analysis (Plasma)</th>
<th>Arhalofenate 600 mg</th>
<th>Arhalofenate 800 mg</th>
<th>Febuxostat 40 mg</th>
<th>Febuxostat 80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Alone</td>
<td>Combination</td>
<td>Alone</td>
<td>Combination</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>7.57 ± 3.04</td>
<td>5.20 ± 2.56</td>
<td>1.21 ± 0.31</td>
<td>1.86 ± 1.28</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>146 ± 33.8</td>
<td>155 ± 30.8</td>
<td>3.60 ± 1.96</td>
<td>4.36 ± 1.06</td>
</tr>
<tr>
<td>AUC0→inf (ng*h/mL)</td>
<td>2950 ± 730</td>
<td>3150 ± 871</td>
<td>11.1 ± 2.34</td>
<td>9.59 ± 2.27</td>
</tr>
</tbody>
</table>

Oxyurines

Xanthine
Hypoxanthine

Safety Overview

Discontinuation for adverse events (n=2)
- Uncontrolled hypertension deemed unrelated to study drugs
- OI symptoms, myalgia, headache attributed to colchicine

Adverse events (n=3):
- No serious adverse events
- Stevens-Johnson, uncontrolled hypertension
- Moderate (4)
- Mild (29)

Recall (n=1)
- Rash (1)
- Febuxostat 40 mg (2)
- Arhalofenate 600 mg (1)

Laboratory
- One elevation of transaminase occurred on febuxostat initiation
- No patient had a creatinine increase of >1.5X or a creatinine value greater than the upper limit of normal

Conclusions

- The arhalofenate and febuxostat combination was well tolerated and appeared safe
- The sUA lowering of each agent was by complementary mechanisms
- Arhalofenate increases FEUA by its uricosuric activity
- Febuxostat: Increases oxypurines by xanthine oxidation inhibition
- The combination of mechanisms led to greater decreases in sUA
  Arhalofenate 800 mg plus Febuxostat 40 mg
  - 100% of patients achieved sUA < 6 mg/dL
  - Arhalofenate 800 mg plus Febuxostat 80 mg
  - 100% of patients achieved sUA < 6 mg/dL
  - 93% of patients achieved sUA < 5 mg/dL
  - 75% of patients achieved sUA < 4 mg/dL
- Arhalofenate and FeBuXostat gradually decreased sUA over 2 weeks with low intraday variability in sUA levels
- Arhalofenate treatment increased FEUA toward the normal range in both trough and 24-hr levels
- There was no meaningful pharmacodynamic interaction between arhalofenate and febuxostat
- Arhalofenate is being developed in combination with febuxostat for the management of hyperuricemia and prophylaxis of flares in gout patients.

References