Oral Plasma Kallikrein Inhibitor BCX7353 is Safe and Effective as an On-Demand Treatment of Hereditary Angioedema (HAE) Patients: Results of the ZENITH-1 Trial

Introduction

Hereditary angioedema (HAE) due to deficiency or dysfunction of C1 inhibitor (C1-INH) is a life-threatening condition characterized by periodic episodes of attacks or swelling.

Plasma kallikrein is a proven target for treatment of HAE attacks. BCX7353 is an investigational oral kallikrein inhibitor in Phase 3 studies for prevention of HAE attacks, administered in a capsule formulation once daily.

When a 750 mg dose was administered as a liquid to HAE patients in a pharmacokinetic study, BCX7353 was rapidly absorbed, with concentrations 2 x EC (estimated concentration of drug for a half-life) for 120 minutes (peak) for plasma kallikrein.

Results—Part 1 Efficacy at 750 mg BCX7353

<table>
<thead>
<tr>
<th>BCX7353 dose</th>
<th>250 mg</th>
<th>500 mg</th>
<th>750 mg</th>
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<tbody>
<tr>
<td>n=31 attacks</td>
<td>n=64 attacks</td>
<td>n=30 attacks</td>
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</table>

- A single dose of BCX7353 750 mg resulted in significant improvements compared to placebo in multiple subject endpoints that evaluated reductions in symptom severity and use of rescue medication in the 24 hours following treatment of attacks.
- A dose response in efficacy was observed across the 250 mg to 750 mg dose range.

Results—Safety

- BCX7353 750 mg dose resulted in significantly more adverse events compared to placebo.
- The most common adverse events were abdominal pain, nausea, and headache.

Conclusions

- The ZENITH-1 Phase 2 placebo-controlled trial was a novel, early-intervention trial of self-administered oral BCX7353 for the treatment of HAE attacks.
- A single dose of BCX7353 750 mg resulted in significant improvements compared to placebo in multiple subject-reported endpoints that evaluated reduced symptoms and use of rescue medication in the 24 hours following treatment of attacks.
- A dose response in efficacy was observed across the 250 mg to 750 mg dose range.
- Across dose levels, BCX7353 was generally safe and well-tolerated with no notable differentiation from the adverse event profile of placebo.
- These results support selection of the 750 mg dose level for further evaluation in Phase 3 studies.

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Abstract #41790

ZENITH-1 Study Design/Methods

- Double-blind study in adult subjects with Type 1 or II HAE
- Subjects treated 3 separate attacks, 2 with BCX7353 and 1 with placebo in a randomized sequence.
- Each treated attack was separated by ≥ 4 days.
- Investigators approved attacks by phone that were reported to be without airway involvement or vomiting and were within 1 hour of symptom onset prior to self-administration with study drug.
- Where possible, subjects were asked to refrain from taking their usual attack medication for at least 4 hours post-study drug.
- Subjects recorded HAE symptoms severity using a 3 symptom visual analog scale (VAS) with a range from 0 to 100 mm (0, no symptom; 100, worst symptom).