Background

- Hereditary angioedema (HAE) due to deficiency or dysfunction of C1 inhibitor (C1INH) is characterized by episodic swelling of the skin, pharynx, larynx, face, GI tract, genititals and extremities.
- Plasma kallikrein is a proven target for treatment of HAE.
- BCX7353, a once daily oral kallikrein inhibitor, was generally safe and well-tolerated in a phase 1 study in healthy subjects, dosed 350 mg QD for 14 days.
- Steady state drug levels were reached in approx. 1 week.
- APEX-1 (BCX7353-203, NCT02870972) was a Phase 2, double-blind, dose-ranging, placebo-controlled, parallel-group, proof-of-concept study.

Objectives

- To evaluate the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of oral once-daily BCX7353 in subjects with HAE.

Study Design/Methods

- Patients with HAE Type 1 or II were randomly into one of three study parts to receive BCX7353 or placebo.
- Efficacy was assessed by the number of independently adjudicated patients reported as attacks in the effective dosing period (EDP; Days 8 to 29, steady state), analyzed by ANCOVA adjusting for qualifying attack rate.
- Quality of life (QoL) outcomes were measured using the Angioedema (AE)-QoL score, at baseline and end of dosing. AE-QoL evaluates a 4-week look back time period.
- BCX7353 plasma levels and kallikrein inhibition were measured on Study Day 14.
- Safety was monitored by treatment-emergent adverse events (TEAEs), laboratory assessments, vital signs, physical exams and ECGs.

Key Inclusion Criteria:

- 18-70 years
- Laboratory confirmed diagnosis of HAE Type 1 or 2
- Historical attack rate ≥ 2 attacks per month (≥45 per week) for 13 consecutive months within last 6 months.

Key Exclusions:

- Intention-to-Treat (ITT) population: all subjects randomized who received at least 1 dose of study drug with post-baseline diary data
- Per Protocol (PP) population: subjects in ITT with ≥ 90% dosing compliance and no significant protocol deviations.

Analysis Definitions:

- Intention-to-Treat (ITT) population: all subjects randomized who received at least 1 dose of study drug with post-baseline diary data.
- Per Protocol (PP) population: subjects in ITT with ≥ 90% dosing compliance and no significant protocol deviations.
- Effective dosing period: Week 2-4 (Study Day 8-20 inclusive).

Study Design/Methods

- Screening
- 14-day Treatment
- Follow-up

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<th>Part</th>
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<tr>
<td>Total</td>
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Quality of Life Change from Baseline - PP

- For all subjects:
  - Overall average improvement was 19.7% in the BCX7353 group compared to placebo.
  - Improvement was seen in all domains: physical, role, and social functioning.

Conclusions

- BCX7353 was associated with clinically meaningful, statistically significant reductions in HAE attacks and improvements in quality of life at doses ≥ 250 mg QD for 28 days.
- Drug exposures at 250 mg and 350 mg were not necessary for efficacy and were associated with GI AEs that may have been misattributed as abdominal attacks.
- BCX7353 was generally safe and well-tolerated.
- These findings support evaluation of BCX7353 in studies of longer duration.