BCX4161, an Oral Kallikrein Inhibitor: Safety and Pharmacokinetic Results of a Phase 1 Study in Healthy Volunteers

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Background

- Hereditary angioedema (HAE) is an autosomal dominant disorder characterized by episodic swelling of the skin, pharynx, larynx, GI tract, genitals and extremities.1

- Acute HAE attacks are due to kallikrein-mediated cleavage of high molecular weight kininogen to bradykinin.

- Plasma kallikrein is a proven target in the treatment of acute attacks of HAE.

- BCX4161 is a potent small molecule inhibitor of plasma kallikrein, showing prolonged kallikrein inhibition in rats following oral doses of BCX4161 in healthy volunteers.

Methods

- Two part, double-blind, randomized, placebo-controlled dose-escalation study in healthy volunteers.

  - Part 1: Single dose cohorts of 50 mg, 125 mg, 250 mg, 500 mg, 1000 mg BCX4161 or placebo: n = 6 active and n = 2 placebo/cohort.

  - Part 2: Oral dose cohorts of 100 mg, 200 mg, 400 mg, and 800 mg BCX4161 or placebo administered every 8 hours (p.o.) for 6 days and a morning dose on Day 7: n = 10 active and n = 2 placebo/cohort.

  - In each study part, safety and plasma PK from current dose was reviewed prior to advancement to a higher dose.

  - Plasma kallikrein activity (PK) was assessed with an ellagic acid-induced contact activation assay.2 (See Poster P-143)

  - After a 2-week washout, a second 500 mg dose was given after a high-fat meal to subjects in Part 1 Cohort 4 to enable assessment of a PK food effect.

Results

Part 1 Safety Findings

- 41 subjects enrolled, 1 subject replaced due to noncompliance.

- 12 treatment-emergent adverse events (TEAEs) in 31 BCX4161 subjects, 5 TEAEs in 10 placebo subjects.

- Mild headache, in 4 BCX4161 subjects & 2 placebo, was the only TEAE reported in > 1 subject in Part 1.

- No serious AE (SAEs) or other clinically significant findings.

Part 2 Safety Findings

- 48 subjects enrolled, 1 subject not replaced due to noncompliance.

- Increased incidence of mild lower GI symptoms at 800 mg q8h.

- No serious AE or other clinically significant findings.

Plasma Pharmacokinetics of BCX4161

- Relatively dose-proportional AUC through 500 mg (Part 1) and 400 mg q8h (Part 2) with acceptable between-subject variability.

- 30% accumulation in exposure was observed with multiple dosing to steady-state.

- AUC_{max} and C_{max} values were decreased 28% and 47% with food; within-subject BCX4161 at 6-9 hours unchanged with food.

Conclusions

- BCX4161 was generally safe and well-tolerated at single doses up to 1000 mg and for 7 days at 800 mg q8h.

- Plasma kallikrein inhibition:

  - had acceptable between-subject variability within a dose

  - were at or above the EC_{50} for kallikrein inhibition over a dosing interval of 200 mg q8h.

  - met or exceeded the target range predicted for efficacy as an prophylactic HAE treatment.

- BCX4161 400 mg tid is currently being tested in the OPUS-1 proof-of-concept study in HAE patients (NCT01984788).


Disclosures: P. Collis, T. Cornpropst and M. Sheridan are current employees of BioCryst Pharmaceuticals, Inc. J. Collier is a current employee of Quotient Clinical.