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

Abstract #41790
Poster #110

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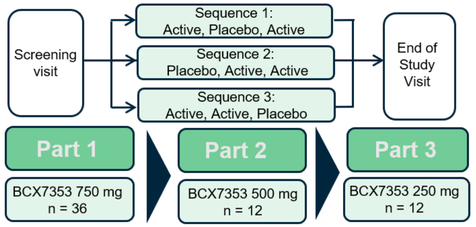
Introduction

- Hereditary angioedema (HAE) due to deficiency or dysfunction of C1 inhibitor (C1-INH) is a life-threatening disease characterized by periodic episodes or attacks of 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 given 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 ≥ 8 x EC_{50} (estimated concentration of drug for a half maximal response) for plasma kallikrein in all subjects from 30 minutes to at least 24 hours post dose[1]. The $t_{1/2}$ of BCX7353 is 70-80 hours[2].
- ZENITH-1 was a Phase 2 study that evaluated the efficacy and safety of single liquid doses of BCX7353 as an acute attack treatment in subjects with HAE (NCT03240133).

ZENITH-1 Study Design/Methods



- Double-blind study in adult subjects with Type I 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 ≥ 14 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 subject 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 symptom severity using a 3-symptom visual analog scale (VAS) and qualitative assessments prior to and at 1, 2, 3, 4, 8, and 24 hours after study drug dosing.

Subject Demographics and Attack Metrics

Demographics	Part 1 750 mg	Part 2 500 mg	Part 3 250 mg
Subjects randomized (n)	36	15	12
Age in years, mean (SD)	43.7 (13)	42.1 (11)	34.9 (11)
Sex, % female	52%	79%	64%
Subjects discontinued (n)	3	3	1
Usual symptoms of an HAE attack, n (%)			
Abdominal pain	30 (91)	12 (86)	10 (91)
Nausea	18 (55)	12 (86)	8 (72)
Substantial fatigue	21 (64)	10 (71)	7 (63)
Diarrhea	12 (36)	7 (50)	8 (73)
Vomiting	10 (30)	8 (57)	5 (46)
Difficulty swallowing	10 (30)	9 (64)	4 (36)
Difficulty breathing	10 (30)	7 (50)	3 (27)
Attack Metrics	**Part 1**	**Part 2**	**Part 3**
Attacks treated (active/placebo)	64/31	25/11	21/11
Subjects treating 0/1/2/3 attacks (n)	3/1/2/30	1/3/0/11	1/0/1/10
Mean pre dose composite VAS (active/placebo; mm)¥	14.0/15.0	17.7/13.5	14.6/11.3
Median time (minutes) from onset of symptoms to taking blinded study drug (active/placebo)	36/35	40/20	32/30
Proportion (%) of attacks where subjects used rescue medicine within 4 hours of symptom onset	5/95 (5%)	3/36 (8%)	0/32 (0%)

¥Composite VAS was calculated as the average of the VAS scores for abdominal pain, skin pain, and skin swelling.

Results—Part 1 Efficacy at 750 mg BCX7353

Endpoint	BCX7353 750mg n=64 attacks	Placebo n=31 attacks	Difference	p-value
Least-squares mean change from baseline in VAS score through 4 hours‡	-3.9	+3.1	-6.98	0.0024
Proportion of attacks requiring standard of care treatment through 24 hours	29.7%	61.3%	-31.6%	0.0029
Proportion of attacks with no or mild symptoms through 24 hours‡	64.1%	32.3%	+31.8%	0.0038
Time to standard of care acute attack treatment (median)	>24 hours	14 hours	>+10 hours	0.0043
Proportion of attacks with improved or stable symptoms through 24 hours‡	64.1%	35.5%	+28.6%	0.0092
Proportion of attacks with improved or stable VAS score through 24 hours‡	62.5%	35.5%	+27.0%	0.0125
Proportion of attacks with improved or stable symptoms through 4 hours‡	82.3%	60.0%	+22.3%	0.0192
Proportion of attacks with improved or stable VAS score through 4 hours‡	67.7%	46.7%	+21.0%	0.0387
Time to stable or improved VAS (median)‡	1 hour	2 hours	-1 hour	0.0452
Proportion of attacks with no or mild symptoms through 4 hours‡	69.4%	50.0%	+19.4%	0.0552
Time to ≥ 50% reduction in VAS through 24 hours (median)‡	8 hours	24 hours	-16 hours	0.0671
Time to initial symptom relief (median)‡	5.1 hours	19.4 hours	- 14.3 hours	0.0978
Time to almost complete symptom relief (median)‡	23.1 hours	23.6 hours	-0.5 hours	0.6767
Time to complete symptom relief (median)‡	35.1 hours	41.3 hour	-6.2 hours	0.8900

VAS = composite VAS
‡ Data censored for LSM or endpoint = failure (proportions) for timepoints after a subject took rescue medication

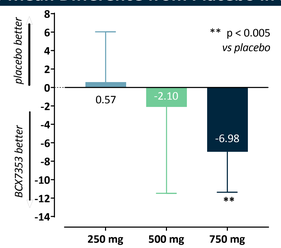
Results—Safety

Number of attacks	BCX7353 750 mg	BCX7353 500 mg	BCX7353 250 mg	All Placebo
Treated	64	25	21	53
With a treatment-emergent (TE) adverse events (AE)	16 (25%)	10 (40%)	10 (48%)	17 (32%)
With a drug-related TEAE	7 (11%)	5 (20%)	6 (29%)	6 (11%)
With a serious TEAE¥	0	1 (4.0%)	0	1 (1.9%)
With a drug-related serious TEAE	0	0	0	0
With TEAEs leading to permanent discontinuation from study drug	1 (1.6%)‡	1 (4.0%)€	0	1 (1.9%)§
With Grade 3 or 4 TEAEs	0	1 (4.0%)Δ	0	0
With Grade 3 or 4 TE lab abnormalities	0	0	0	0
Most common TEAEs				
Diarrhea	3 (4.7%)	3 (12%)	0	2(3.8%)
Abdominal pain	2 (3.1%)	3 (12%)	1 (4.8%)	1 (1.9%)
Nausea	2 (3.1%)	2 (8.0%)	2 (9.5%)	0
Nasopharyngitis	4 (6.3%)	0	0	1 (1.9%)
Headache	3 (4.7%)	0	3 (14%)	1 (1.9%)

¥ Motor vehicle accident and ankle fracture, neither related to study drug
‡ Discontinuation on BCX7353 occurred in a subject who developed a small red macule on the forearm 11 hours after taking BCX7353 for an HAE attack occurring in the same anatomic location. The macule lasted for 4 hours and resolved without treatment.
€ Discontinuation on BCX7353 occurred in a subject who experienced Grade 2 vomiting and nausea.
§ Discontinuation on placebo occurred in a subject who experienced abdominal pain on both active and placebo drug. The decision to stop study drug occurred after the placebo dose.
Δ Grade 3 unrelated ankle fracture

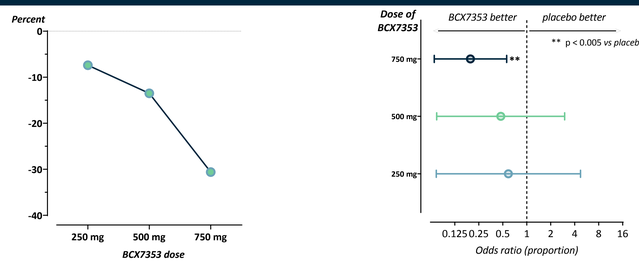
Results—Dose Response

Change from Baseline in 3-Composite VAS at 4 hours Post-dose (LS Mean Difference from Placebo in mm, 95% CI)



Attacks treated with approved standard of care rescue medication prior to 4 hours are censored

Use of Approved Standard of Care Medication Following BCX7353 Treatment for an HAE Attack (left panel: difference compared to placebo; right panel: model odds ratio)



Analyses were performed using a generalized logistic model including treatment, period and sequence as fixed effects, and subject within sequence as a random effect. Standard of care use was assessed in the 24 hours post-dose.

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 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
- 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

[1]Mathis A, et al. *Annals Allergy Asthma Immunol*, 2018; 121(5): S32.
[2]Cornpropst M, et al. *J Allergy Clin Immunol*, 2016; 137(2): AB401.
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