

1018 - BCX4208 Synergistically Lowers Serum Uric Acid (sUA) Levels When Combined with Allopurinol in Patients with Gout: Results of a Phase 2 Dose-Ranging Trial

Monday, November 7, 2011: 9:00 AM-6:00 PM

Hall F2 - Poster Hall (McCormick Place West)

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**Presentation Number:** 1018

**Background/Purpose:** BCX4208 is an oral, once-daily, novel purine nucleoside phosphorylase inhibitor in clinical development for the chronic management of gout. Because BCX4208 blocks production of uric acid earlier in the metabolic pathway than xanthine oxidase inhibitors, there is a strong mechanistic rationale for expecting synergistic reduction of sUA when combined with xanthine oxidase inhibition. This is important because >50% of gout patients fail to meet the therapeutic goal of sUA <6.0 mg/dL during treatment with 300 mg allopurinol daily. This study assessed the dose-response relationship of BCX4208 on sUA when administered as monotherapy and in combination with allopurinol.

**Methods:** Adults (n=87) with gout and sUA ≥8.0 mg/dL were randomized to placebo (Plc) or 20, 40, or 80 mg/d BCX4208 in combination with Plc or with 100, 200, or 300 mg/d allopurinol using a 4 x 4 factorial study design. Drugs were administered in a double-blind manner for 3 weeks with weekly assessments of sUA and adverse events (AEs). The key efficacy endpoints were the change in sUA from baseline on Day 22 and the percentage of patients achieving the goal (sUA <6.0 mg/dL).

**Results:** When BCX4208 was combined with allopurinol, there was a synergistic reduction in sUA (by Combination Index test). BCX4208 produced a significant reduction in sUA compared with Plc when administered as monotherapy and in combination with allopurinol. Both BCX4208 and allopurinol demonstrated dose-related reductions in sUA and increases in the proportion of patients achieving goal sUA (Table).

<b>Table. Percentage of Patients Achieving sUA &lt;6.0 mg/dL at Day 22 (Per-Protocol Population)</b>				
<b>Cotreatment</b>	<b>Placebo</b>	<b>BCX4208</b>		
		<b>20 mg</b>	<b>40 mg</b>	<b>80 mg</b>
Placebo	(n=5) 0%	(n=4) 0%	(n=6) 17%	(n=5) 40%
Allopurinol 100 mg	(n=5) 0%	(n=4) 0%	(n=5) 60%	(n=5) 40%
Allopurinol 200 mg	(n=4) 0%	(n=5) 20%	(n=5) 80%	(n=5) 80%
Allopurinol 300 mg	(n=5) 40%	(n=4) 75%	(n=4) 100%	(n=5) 100%

Seventy-five percent to 100% of patients achieved sUA <6.0 mg/dL with BCX4208 in combination with 200 mg allopurinol (>20 mg BCX4208) or 300 mg allopurinol (≥20 mg BCX4208) daily. Patients in the 300 mg allopurinol monotherapy group had a 1.8 mg/dL reduction in sUA, whereas the addition of 20 mg BCX4208 to 300 mg allopurinol decreased sUA by 3.9 mg/dL. AE frequency and severity were comparable across dose groups. Common AEs in the BCX4208 group included diarrhea (12% vs 5% in Plc) and headache (6% vs 5% in Plc). No serious AEs were reported. Lymphocyte counts and subsets (CD4+, CD8+, CD20+ and CD56+) were reduced, with both baseline counts and dose of BCX4208 significant factors in multivariate models for all subsets. One patient on BCX4208 experienced a reduction in lymphocytes (grade 0 at baseline to grade 2, 500-599 cells/μL, at Day 22). No severe or opportunistic infections were observed.

**Conclusions:** BCX4208 combined with allopurinol produces synergistic reductions in sUA in patients with gout and permitted substantially higher achievement of goal sUA compared with commonly prescribed doses of allopurinol alone. BCX4208 once-daily dosing is well tolerated when used in combination. Positive results of this trial have led to the initiation of a 6-month add-on study of BCX4208 in patients who did not achieve goal sUA with 300 mg allopurinol daily.

**Keywords:** uric acid

**Disclosure:** **A. S. Hollister**, BioCryst Pharmaceuticals, Inc, 3 ; **M. A. Becker**, Takeda, Savient, Regeneron, URL Mutual, Novartis, Biocryst, Menarini, 5 ; **R. Terkeltaub**, Takeda, 5, URL, 5, ARDEA, 5, BioCryst, 5, Regeneron, 5, Novartis Pharmaceutical Corporation, 5, Pfizer Inc, 5, Metabolex, 5 ; **A. Waugh**, BioCryst Pharmaceuticals, Inc, 3 ; **S. Lyman**, BioCryst Pharmaceuticals, Inc, 3 ; **A. Flynt**, BioCryst Pharmaceuticals, Inc, 5 ; **D. Fitz-Patrick**, BioCryst Pharmaceuticals, Inc, 2 .