

[2011] [THU0011] BCX4208 SHOWS SYNERGISTIC REDUCTIONS IN SERUM URIC ACID IN GOUT PATIENTS WHEN COMBINED WITH ALLOPURINOL

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Background: Greater than 50% of gout patients treated with allopurinol fail to meet the therapeutic goal of serum uric acid (sUA) <6.0 mg/dL (<360 mM), so additional treatments to reduce sUA are needed. Purine nucleoside phosphorylase (PNP) controls the generation of the precursors of uric acid at an earlier step in the metabolic pathway. BCX4208 is a potent, orally bioavailable PNP inhibitor that reduced sUA by a mean of 49% at doses of 240 mg once daily in gout patients.

Objectives: The goal of this study was to determine the dose-response relationship of BCX4208 on sUA when administered as monotherapy and in combination with allopurinol. The key efficacy endpoints were the change in sUA levels from baseline on Day 22 and the proportion of subjects at goal sUA <6.0 mg/dL.

Methods: 87 adult subjects (M:F =85:2) with gout and a sUA ≥8.0 mg/dL were randomized to a 4 X 4 factorial study design using placebo, 20 mg, 40 mg, or 80 mg per day BCX4208 in combination with placebo, 100 mg, 200 mg, or 300 mg daily allopurinol. Drugs were administered in a double-blind manner for three weeks with weekly assessments of sUA, safety parameters, adverse events, and first dose abbreviated pharmacokinetics (PK). All subjects received colchicine 0.6 mg/d or naproxen 220-250 mg BID for gout flare prophylaxis. The per protocol population analyses are presented.

Results: BCX4208 produced a significant reduction in sUA levels compared to placebo when administered as monotherapy and as combination therapy with allopurinol. Both BCX4208 and allopurinol demonstrated dose-related reductions in sUA and increases in the proportion of subjects reaching goal. When BCX4208 was combined with allopurinol, there was an additive or synergistic reduction in sUA.

Table 1. Percent Reduction in Serum Uric Acid at Day 22				
Per protocol population, N=4-6 per cell				
Least Square Means (SE)				
Allopurinol	Placebo	BCX4208		
		20 mg	40 mg	80 mg
Placebo	0.7 (5.2)	-11.3 (5.8)	-18.8 (4.6)	-32.1 (5.1)
100 mg	-16.5 (5.1)	-24.6 (5.6)	-43.9 (5.1)	-43.7 (5.1)
200 mg	-24.7 (5.6)	-37.4 (5.2)	-43.3 (5.2)	-55.0 (5.1)
300 mg	-20.0 (5.2)	-41.0 (5.7)	-45.7 (5.6)	-56.4 (5.0)

75% to 100% of subjects achieved sUA <6.0 mg/dL when treated with combinations of both 40 mg and 80 mg BCX4208 with either 200 mg or 300 mg allopurinol, and 20 mg BCX4208 with 300 mg allopurinol. BCX4208 showed statistically significant increases in the proportion of subjects achieving sUA <6.0 mg/dL (p<0.001), <5.0 mg/dL (p=0.003), and <4.0 mg/dL (p=0.01) compared to placebo. First dose PK for BCX4208 and the active metabolite of allopurinol, oxypurinol, were roughly dose proportional for C_{max} and AUC₀₋₂₄, and did not indicate a drug-drug PK interaction. BCX4208-treated subjects showed generally mild reductions in lymphocyte subsets during the drug administration. Adverse event frequency and severity were evenly distributed across all dose groups.

Conclusions: BCX4208 combined with allopurinol produces additive or synergistic reductions in sUA in gout patients. Combinations of BCX4208 with allopurinol bring a greater proportion of gout patients to goal sUA levels than allopurinol alone. Three weeks of BCX4208 daily dosing is generally safe and well tolerated when used in

combination with allopurinol.

Disclosure of Interest: A. Hollister Employee of: BioCryst Pharmaceuticals, Inc., M. Becker Consultant for: BioCryst, Takeda, Savient, URL/Pharma, Ardea, Regeneron, Metabolex, R. Terkeltaub Consultant for: BioCryst, Regeneron, Ardea, Novartis, A. Waugh Employee of: BioCryst Pharmaceuticals, Inc., S. Lyman Employee of: BioCryst Pharmaceuticals, Inc., A. Flynt Consultant for: BioCryst, D. Fitz-Patrick Grant/Research support from: BioCryst

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Bone diseases other than osteoporosis, metabolic diseases and crystal diseases