

L10 - BCX4208 Combined with Allopurinol Increases Response Rates in Patients with Gout Who Fail to Reach Goal Range Serum Urate on Allopurinol Alone: A Randomized, Double-Blind, Placebo-Controlled Trial

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Background/Purpose: BCX4208, a purine nucleoside phosphorylase inhibitor, blocks uric acid production at a step preceding xanthine oxidase and reduces serum urate (sUA) in gout patients synergistically when combined with allopurinol. A phase 2b clinical trial in gout patients with sUA levels ≥ 6.0 mg/dL during treatment with 300 mg/d allopurinol was designed to assess response to the addition of either placebo or 4 BCX4208 doses. The primary endpoint was the proportion of BCX4208-treated subjects achieving the sUA goal (< 6.0 mg/dL) at 12 weeks compared with placebo. Study subjects completed the trial in September. We present the primary efficacy and safety information.

Method: 278 adult subjects (M:F = 266:12) with gout and sUA ≥ 6.0 mg/dL on allopurinol 300 mg/d for at least 2 weeks were randomized and received oral BCX4208 5, 10, 20, or 40 mg/d or placebo for 12 weeks while continuing allopurinol 300 mg/d. sUA, safety parameters, adverse events, and trough plasma BCX4208 and oxypurinol concentrations were assessed at 2, 4, 8, and 12 weeks of treatment. Subjects received colchicine 0.6 mg/d or naproxen 220 mg to 250 mg BID for gout flare prophylaxis. Subjects who received > 1 dose of study drug and had at least one sUA assessment (modified intention-to-treat [mITT] population) were analyzed using the last observation carried forward method.

Result: Demographic, comorbid, and gout characteristics of the study population were evenly distributed in the study arms. Mean (SD) age was 49 (10) years and BMI was 36 (7) kg/m² in the predominantly white (73%) population, with high prevalences of hypertension (58%), diabetes (16%), and hypercholesterolemia (39%). BCX4208 added to allopurinol 300 mg/d brought more patients to goal range sUA compared with placebo (Table).

Table. Percent Goal Range sUA Attainment at 12 Weeks (mITT Population)					
Parameter	Allopurinol 300 mg/d				
	BCX4208				
	Placebo	5 mg/d	10 mg/d	20 mg/d	40 mg/d
Subjects, n	55	56	55	56	53
Subjects with sUA < 6.0 mg/dL	18%	45%	33%	39%	49%
P value compared with placebo	—	0.004	0.125	0.021	< 0.001
Overall treatment effect, $P = 0.009$ vs placebo					

33% to 49% of subjects not at goal sUA while receiving allopurinol 300 mg/d reached the goal when BCX4208 was added, compared with 18% of subjects after the addition of placebo. Differences between the BCX4208 5-, 20-, and 40-mg/d arms and placebo were significant. Five to 11% of subjects per arm experienced gout flares during treatment. Frequency and severity of adverse events, including infections, were evenly distributed across dose groups, and no opportunistic infections occurred. BCX4208 treatment showed dose-related reductions in lymphocytes and lymphocyte subsets during drug administration that appeared to plateau within 12 weeks. Eight subjects in the BCX4208 40-mg/d arm and 2 subjects in the 20-mg/d arm were discontinued for confirmed CD4+ cell counts < 350 cells/mm³. No subjects in the placebo or the BCX4208 5- and 10-mg/d arms were discontinued because of low CD4+ cell counts.

Conclusion: Addition of BCX4208 to allopurinol 300 mg/d allows a significantly greater proportion of gout patients to reach the sUA goal range than does placebo. Twelve weeks of BCX4208 daily dosing is generally safe and well tolerated when combined with allopurinol.

Keywords: gout and uric acid

Disclosure: **M. A. Becker**, Takeda, Savient, BioCryst, Ardea, Metabolex, URL/Mutual, Regeneron, Menarini, Teijin, Chugai, 5 ; **A. S. Hollister**, BioCryst Pharmaceuticals, Inc, 3 ; **R. Terkeltaub**, Novartis Pharmaceutical Corporation, 5, Regeneron, 5, URL, 5, Pfizer Inc, 5, BioCryst, 5, Takeda, 5, ARDEA, 5 ; **A. Waugh**, BioCryst Pharmaceuticals, Inc, 3 ; **R. L. Leff**, BioCryst, 5 ; **A. Flynt**, BioCryst Pharmaceuticals, Inc, 5 ; **D. Fitz-Patrick**, BioCryst Pharmaceuticals, Inc, 2 ; **W. P. Sheridan**, BioCryst Pharmaceuticals, Inc., 3 .