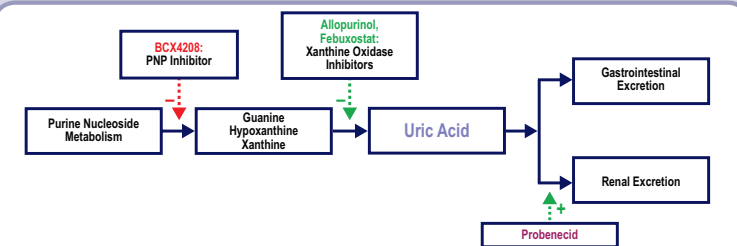


## BACKGROUND

- An estimated 8.3 million individuals (4%) in the United States are affected by gout<sup>1</sup>
- Sustained serum uric acid (sUA) elevations increase the risk for gout flares and joint damage
- Evidence-based guidelines recommend a target sUA concentration of <6 mg/dL (<360 μM)<sup>2</sup>
- Although allopurinol, a xanthine oxidase inhibitor (XOI), is considered the standard of care for chronic treatment of gout, <50% of patients achieve the target sUA level<sup>3</sup>
- BCX4208 is an oral, once-daily, novel purine nucleoside phosphorylase inhibitor in clinical development for the chronic management of gout
- BCX4208 blocks production of uric acid higher in the metabolic pathway than XOIs, so there is a mechanistic rationale for expecting synergy when combined with XOIs (Figure 1)



**Figure 1.** Summary of gout treatment targets in the purine nucleoside metabolic pathway. PNP, purine nucleoside phosphorylase.

## OBJECTIVES

- To assess the dose-response relationship of BCX4208 on sUA concentration when administered as monotherapy and in combination with allopurinol
- To evaluate the safety and tolerability of BCX4208 given in combination with allopurinol

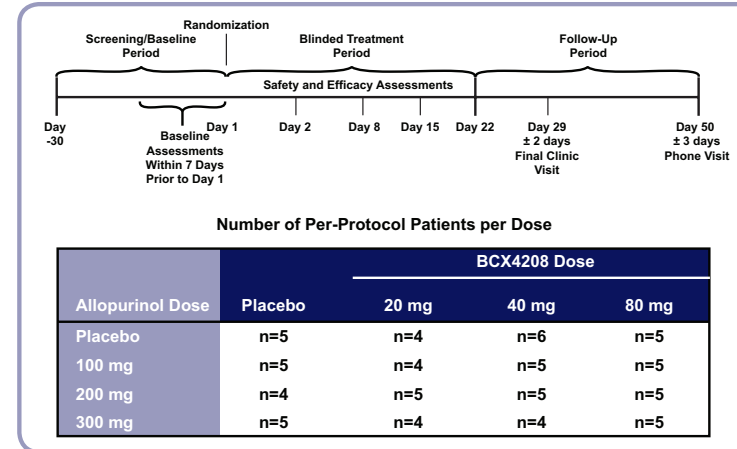
## METHODS

### Patient selection

- Gout patients 18 to 69 years old and sUA level >8.0 mg/dL
- Able to take colchicine or naproxen for flare prophylaxis
- CD4+ cell count ≥500 cells/μL

### Study design

- Randomized, double-blind, 4x4 factorial design (Figure 2)
- Patients received 3 weeks of placebo or BCX4208 20, 40, or 80 mg/d in combination with placebo or allopurinol 100, 200, or 300 mg/d
- Visits at screening, baseline, and days 1, 2, 8, 15, 22, and 29



**Figure 2.** Study schematic and dosing.

## Endpoints

- Change from baseline in sUA level at day 22, including the percent change and the proportion of patients with sUA level <6 mg/dL
- Safety via adverse events (AEs) and laboratory monitoring

## Statistical methods

- Per-protocol population analyzed: intent-to-treat population with confirmed drug levels of BCX4208 and oxypurinol on days 15 and 22
- Analysis of covariance for the primary endpoint
- Synergy was tested by the Combination Index test

## RESULTS

- Demographic and baseline characteristics were generally well balanced between dosing groups (Table 1)

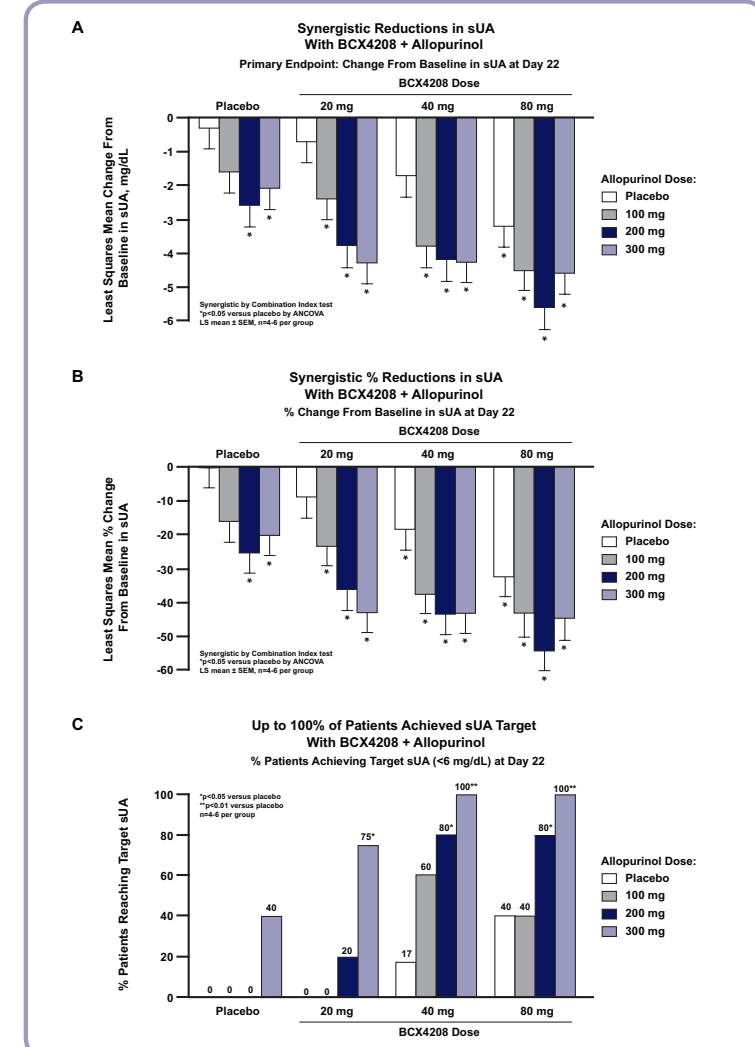
**Table 1.** Patient Demographic and Baseline Characteristics (Per-Protocol Population)

Parameter	Placebo (n=19)	BCX4208		
		20 mg/d (n=17)	40 mg/d (n=20)	80 mg/d (n=20)
Age, mean (SD), y	52 (11)	48 (10)	53 (10)	44 (11)
Sex, male:female, n	19:0	17:0	18:2	20:0
Race, n (%)				
White	12 (63)	10 (59)	15 (75)	15 (75)
Black	5 (26)	2 (12)	0	1 (5)
Asian	1 (5)	3 (18)	2 (10)	1 (5)
Other	1 (5)	2 (12)	3 (15)	3 (15)
Weight, mean (SD), kg	106 (21)	104 (26)	112 (17)	102 (26)
BMI, mean (SD), kg/m <sup>2</sup>	34 (6)	35 (7)	36 (6)	33 (7)
sUA concentration, mean (SD), mg/dL	9.5 (1.3)	10.5 (1.7)	10.0 (1.2)	10.1 (1.3)
Hypertension, n (%)	15 (79)	8 (47)	11 (55)	11 (55)
Diabetes, n (%)	4 (21)	1 (6)	2 (10)	4 (20)
Renal function, n (%)				
Normal (CrCl >90 mL/min)	16 (84)	12 (71)	15 (75)	15 (75)
Mildly impaired (CrCl ≥60 to 90 mL/min)	3 (16)	5 (29)	5 (25)	5 (25)
Hypercholesterolemia, n (%)	6 (32)	8 (47)	11 (55)	10 (50)

BMI, body mass index; SD, standard deviation; sUA, serum uric acid.

## Clinical efficacy

- Effect of BCX4208 on Serum Uric Acid (Per-Protocol Analysis; Figure 3)



**Figure 3.** (A) Mean change from baseline sUA level, (B) percent reduction in sUA level, and (C) percentage of patients achieving target sUA level <6.0 mg/dL are shown for the BCX4208 + allopurinol dosing groups. sUA, serum uric acid.

- All doses of BCX4208, given with or without allopurinol, reduced the mean sUA level at day 22 (Figure 3A)
  - Reductions apparent within 24 hours
  - Sustained reductions over 21-day dosing interval
- BCX4208 + allopurinol had a synergistic effect on sUA level by the Combination Index test (Figures 3A and 3B)
- BCX4208 increased the proportion of patients who reached target sUA when combined with allopurinol (Figure 3C)

## Clinical safety

- Incidence and severity of AEs were similar between the placebo and BCX4208 groups (Table 2)

**Table 2.** Overview of Adverse Events (ITT Population)

Parameter, n (%)	Placebo (n=21)	BCX4208 (n=66)
All AEs	13 (62)	33 (50)
Severity		
Mild	9 (43)	20 (30)
Moderate	3 (14)	13 (20)
Severe	1 (5)	0
Serious AEs	0	0
Discontinuation due to AE	1 (5)	2 (3)

AE, adverse event; ITT, intent to treat.

- 3 patients discontinued because of AEs
  - Placebo (n=1): ↑ creatine phosphokinase
  - BCX4208 (n=2): 1 headache and 1 vasculitic rash
- Most common AEs in BCX4208-treated patients included diarrhea (12%), infection (8%), and headache (6%; Table 3)
  - Diarrhea may be due to gout flare prophylaxis with colchicine

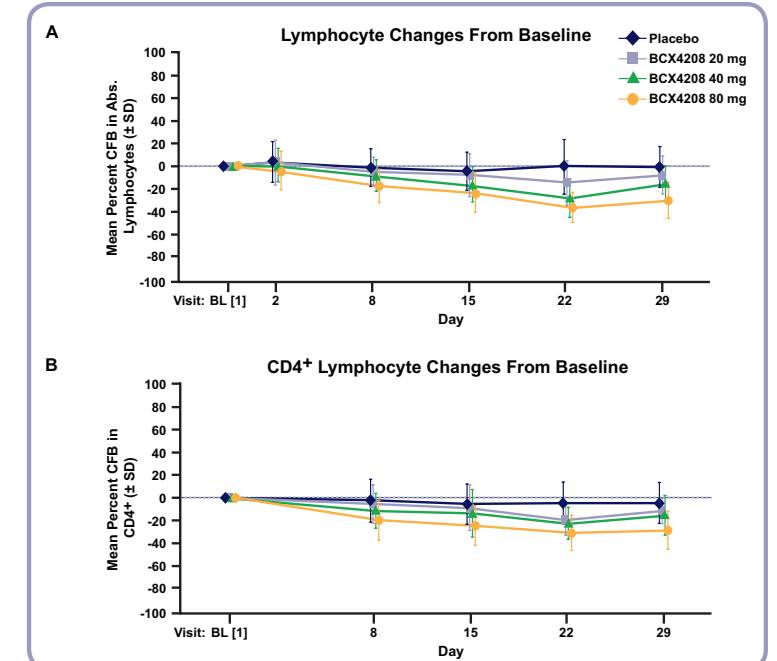
**Table 3.** Summary of Common Treatment-Emergent Adverse Events (≥2 Patients; ITT Population)

Adverse event, n (%)	Placebo (n=21)	BCX4208		
		20 mg/d (n=21)	40 mg/d (n=23)	80 mg/d (n=22)
Diarrhea	1 (5)	3 (14)	1 (4)	4 (18)
Headache	1 (5)	1 (5)	1 (4)	2 (9)
Infection	0	2 (10)	1 (4)	2 (9)
Creatine phosphokinase ↑	2 (10)	2 (10)	0	0
Dizziness	2 (10)	1 (5)	0	0
Lymphocyte count ↓	0	0	1 (4)	2 (9)
Rash	2 (10)	1 (5)	1 (4)	0
Abdominal pain	0	1 (5)	1 (4)	0
Blood pressure ↑	0	0	2 (9)	0
Tachycardia	0	2 (10)	0	0

ITT, intent to treat.

## Effects of BCX4208 on lymphocytes and lymphocyte subsets

- There were mild-to-moderate reductions in absolute lymphocyte count (Figure 4A) and CD4+ subset count (Figure 4B) for each BCX4208 dosing group
- 3 patients in the BCX4208 80-mg/d group experienced graded reductions in CD4+ cell count
  - 1 grade-1 reduction; 2 grade-2 reductions
- 4 patients in the BCX4208 groups experienced a CD4+ cell count <350 cells/μL
  - 1 patient in the 40-mg/d group and 3 patients in the 80-mg/d group
- CD8+, CD20+, and CD56+ lymphocytes displayed similar dose- and time-related reductions



**Figure 4.** (A) Percent change in absolute lymphocyte count and (B) CD4+ subset over time in patients treated with BCX4208. BL, baseline; CFB, change from baseline; SD, standard deviation.

## DISCUSSION AND CONCLUSIONS

- Synergistic mean and percent reductions in sUA level were observed with BCX4208 + allopurinol
  - All dose combinations were supra-additive or additive in the reduction of sUA level
- BCX4208 plus allopurinol 300 mg brought 75% to 100% of gout patients to target sUA level versus 40% for allopurinol 300 mg
- BCX4208 was generally safe and well tolerated; diarrhea and headache were the most commonly reported AEs
- Generally mild dose-related reductions in lymphocyte counts were observed; however, these were not temporally associated with AEs or infections

**Disclosures:** Support for this study was provided by BioCryst Pharmaceuticals, Inc. Assistance with medical writing and poster design was provided under the direction of the authors by MedThink SciCom, Inc. Preparation of this poster was supported by funding from BioCryst Pharmaceuticals, Inc.

**References:** 1. Zhu Y, Pandya BJ, Choi HK. *Arthritis Rheum*. 2011;63(10):3136-3141. 2. Zhang W, Doherty M, Bardin T, et al. *Ann Rheum Dis*. 2008;65(10):1312-1324. 3. Becker MA, Schumacher HR, Espinoza LR, et al. *Arthritis Res Ther*. 2010;12(2):R63.