

Introduction

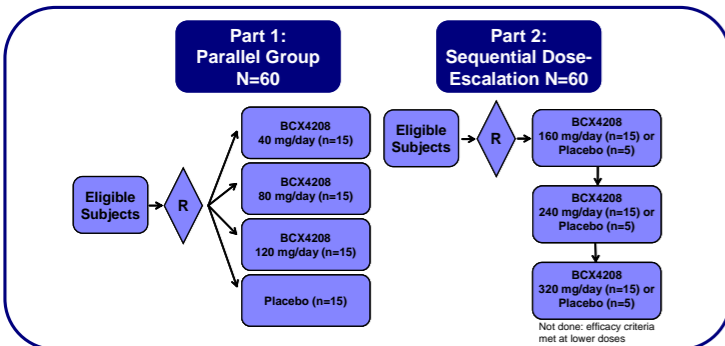
Gout is an inflammatory arthritis characterized by the presence of monosodium urate crystals in synovial fluid and is associated with hyperuricemia during the course of the disease (Bieber 2004). Urate crystal formation occurs when the extracellular uric acid concentration exceeds 6.8 mg/mL, and the goal of gout therapy is to reduce serum uric acid (sUA) concentrations to less than 6.0 mg/dL. Hyperuricemia is a risk factor for destructive arthritis, renal disease, hypertension, cardiovascular disease, and each of the components of the metabolic syndrome (Bieber 2004; Fieg 2008).

BCX4208 is a potent inhibitor of purine nucleoside phosphorylase (PNP), the enzyme that breaks down purine nucleosides to their bases and ribose 1-phosphate. The bases are subsequently metabolized to uric acid via xanthine oxidase. Inhibition of PNP leads directly to a reduction in sUA. The purpose of this study was to evaluate the sUA-lowering effects, safety and tolerability of BCX4208 40, 80, 120, 160, and 240 mg monotherapy administered orally once daily for 3 weeks in gout patients whose untreated sUA was >8.0mg/dL.

Methods

Eligible subjects

- Male or female, aged 18-69 with ARA diagnosis of gout and a baseline sUA > 8.0 mg/dL
- No active cardiac disease, gout flare, elevated liver enzymes, abnormal hemogram, or CD4+ cell count < 500 cells/mm³
- Estimated creatinine clearance >60 ml/min
- Able to tolerate colchicine or naproxen flare prophylaxis



Main Study Design and Assessments

- 30 day screening, with Baseline within 7 days of the start of 21 days treatment with study drug.
- Day 22 through 50 follow-up
- sUA and safety labs at Baseline, Days 2, 8, 15, 22, 29, 36, 43, and 50
- Lymphocyte subsets at Baseline, Days 2, 8, 15, 22, 29, 36, 43, and 50
- Sparse PK Day 1-2, and trough drug levels Days 8, 15, 22, 29, and 43
- AEs at every visit

Results

Study Subjects and Exposure

- 96% of placebo- and 95% of BCX4208-treated subjects completed the study
- One subject at 160 mg/day discontinued due to elevated CPK (also present at baseline)
- One subject at 240 mg/day discontinued on D16 due to diarrhea, and one on D2 due to an ectopic atrial rhythm.
- Gout flares of ≥ moderate severity requiring treatment occurred in 8 subjects (2 Placebo, 6 BCX4208) during the treatment phase, and 3 subjects (0 Placebo, 3 BCX4208) during follow-up to Day 50.

Table 1. Demographics and Baseline Values

	Placebo (N=24)	BCX4208					Total (N=75)
		40 mg/day (N=15)	80 mg/day (N=14)	120 mg/day (N=16)	160 mg/day (N=15)	240 mg/day (N=15)	
Age, mean (SD)	51 (9.9)	52 (11.9)	51 (11.7)	51 (13.6)	48 (10.5)	49 (10.9)	50 (11.6)
Male, n (%)	22 (92%)	15 (100%)	13 (93%)	15 (94%)	15 (100%)	15 (100%)	73 (97%)
White, n (%)	17 (71%)	10 (67%)	9 (64%)	10 (63%)	11 (73%)	8 (53%)	48 (64%)
Black/African American, n (%)	2 (8%)	3 (20%)	2 (14%)	1 (6%)	2 (13%)	2 (13%)	9 (12%)
Asian/Pacific Islander/Other	5 (21%)	2 (13%)	3 (21%)	5 (31%)	3 (20%)	5 (33%)	18 (24%)
BMI, kg/m ² , mean (SD)	34.9 (5.23)	34.6 (9.87)	33.7 (4.87)	35.4 (8.52)	33.6 (12.94)	32.8 (6.81)	34.1 (8.85)
Baseline sUA, mean (SD)	9.7 (1.04)	9.2 (0.71)	9.5 (0.84)	9.8 (1.36)	10.1 (1.76)	9.7 (1.51)	—
Baseline Lymphocyte Subsets, count/mm ³ , median (range)							
CD4+	887 (622, 1678)	837 (607, 2201)	801 (541, 1539)	870 (506, 1312)	1106 (524, 2135)	848 (505, 1483)	—
CD8+	477 (169, 788)	500 (230, 688)	421 (194, 704)	391 (171, 674)	504 (149, 1523)	406 (175, 697)	—
CD20+	273 (85, 649)	273 (81, 540)	216 (97, 714)	207 (73, 313)	281 (92, 690)	245 (107, 929)	—
CD56+	189 (54, 763)	254 (166, 623)	192 (61, 475)	163 (96, 390)	180 (103, 400)	283 (98, 472)	—

Efficacy: BCX4208 Monotherapy

Table 2. Absolute Values, Change from Baseline in Serum Uric Acid at Day 22

	Placebo (N=24)	BCX4208					
		40 mg/day (N=15)	80 mg/day (N=14)	120 mg/day (N=16)	160 mg/day (N=15)	240 mg/day (N=15)	
sUA Mean (SD), mg/dL	9.5 (1.35)	6.6 (1.13)	6.0 (0.89)	6.5 (1.50)	6.2 (1.72)	5.1 (1.46)	
CFB to Day 22	—	—	—	—	—	—	
LS Means (SEM) ^a , mg/dL	-0.2 (0.27)	-3.0 (0.35)	-3.6 (0.36)	-3.2 (0.33)	-3.6 (0.35)	-4.6 (0.34)	
Pairwise Comparisons to Placebo							
LS Mean Difference ^b , mg/dL	—	-2.8	-3.4	-3.1	-3.4	-4.4	
95% CI	—	-3.7, -1.9	-4.3, -2.5	-3.9, -2.2	-4.3, -2.6	-5.3, -3.5	

^aLeast Square (LS) Means from ANCOVA model with factors for treatment and baseline sUA.
^bp < 0.001 for overall treatment effect by ANCOVA.
^cp < 0.001 for pairwise differences between placebo and each BCX4208 dose.

Figure 2: Serum Uric Acid Percentage Change Over Time

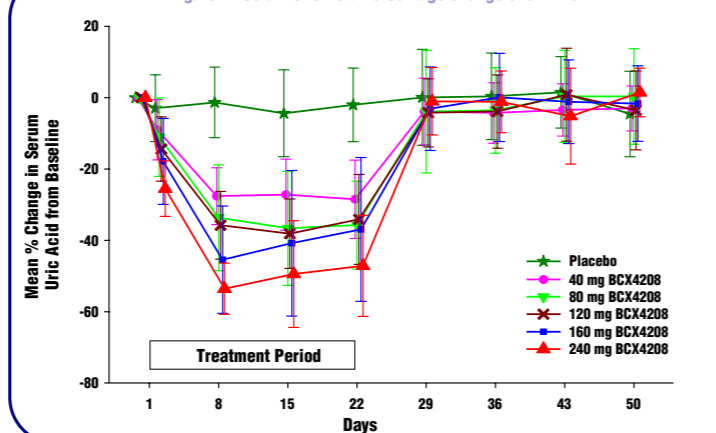


Table 3. Proportion of Subjects Achieving Serum Uric Acid Levels <6, <5, and <4 mg/dL at Day 22

	Placebo (N=24)	BCX4208				
		40 mg/day (N=15)	80 mg/day (N=14)	120 mg/day (N=16)	160 mg/day (N=15)	240 mg/day (N=15)
All Subjects						
Day 22						
<6.0 mg/dL ^a	0%	33%*	36%*	31%*	47%**	77%**
<5.0 mg/dL ^a	0%	0%	21%	25%	33%*	54%**
<4.0 mg/dL ^a	0%	0%	0%	6%	7%	23%
Subjects with BL sUA <10 mg/dL						
Day 22						
<6.0 mg/dL ^a	0%	38%	30%	63%*	29%	89%**
<5.0 mg/dL ^a	0%	0%	10%	50%*	29%	67%*
<4.0 mg/dL ^a	0%	0%	0%	13%	14%	33%

*P<0.001, **P<0.01 Overall Treatment Effect P-value by the Cochran-Armitage Trend Test.
^aP<0.01, **P<0.001 for comparison against placebo by Fisher's Exact Test.

Table 4. BCX4208 First-Dose Pharmacokinetic Parameters

BCX4208 Dose, mg/day	C _{max} , ng/mL Mean (SD)	t _{max} , hr Mean (SD)	AUC ₀₋₂₄ , ng·h/mL Mean (SD)	C ₂₄ , ng/mL Mean (SD)
40	13.0 (13.1)	3.9 (1.8)	327 (183)	10.6 (4.6)
80	22.8 (16.6)	4.5 (1.7)	453 (363)	17.1 (21.0)
120	35.2 (19.7)	4.4 (2.0)	547 (241)	12.7 (8.0)
160	46.5 (25.0)	4.1 (1.5)	678 (365)	18.4 (9.5)
240	71.3 (27.8)	4.0 (1.3)	1024 (385)	24.3 (12.0)

Safety: BCX4208 Monotherapy

Table 5. Overview of Adverse Events

Category	Number of subjects (%)	
	Placebo, N=24	BCX4208 (total), N=75
All AEs	15 (63%)	50 (67%)
All AEs at Least Possibly Related to Study Drug	6 (25%)	25 (33%)
All Severe AEs ^a	3 (13%)	2 (3%)
All Serious AEs	0	1 (1%)
Withdrawals from Study Medication Due to AEs	1 (4%)	3 (4%)
Deaths	0	0

All grades, all relationships to drug.
 Note: Subjects may fall into more than 1 category.
^aThe serious AE was hemorrhoidal bleeding 11 days after treatment with 40 mg/d BCX4208.

Table 6. Adverse Events that Occurred in >1 Subject Per Dose Group, N(%)

	Placebo (N=24)	BCX4208				
		40 mg/day (N=15)	80 mg/day (N=14)	120 mg/day (N=16)	160 mg/day (N=15)	240 mg/day (N=15)
Any adverse event						
Decreased lymphocytes	1 (4%)	0	2 (14%)	0	2 (13%)	1 (7%)
Blood CPK increased	2 (8%)	0	1 (7%)	0	1 (7%)	1 (7%)
Blood glucose increased	0	0	0	2 (13%)	0	1 (7%)
Back pain	2 (8%)	1 (7%)	1 (7%)	2 (13%)	0	4 (5%)
URTI	1 (4%)	1 (7%)	2 (14%)	2 (13%)	0	1 (7%)
Nasopharyngitis	3 (13%)	1 (7%)	1 (7%)	1 (6%)	0	3 (4%)
Gastroenteritis	3 (13%)	0	0	0	0	0
Edema peripheral	0	1 (7%)	1 (7%)	2 (13%)	1 (7%)	2 (13%)
Fatigue	3 (13%)	0	2 (14%)	1 (6%)	1 (7%)	0
Headache	4 (17%)	5 (33%)	1 (7%)	2 (13%)	0	2 (13%)
Diarrhea	2 (8%)	1 (7%)	0	1 (6%)	1 (7%)	3 (20%)
Cough	0	0	0	0	2 (13%)	0
Rash	0	1 (7%)	0	0	0	2 (13%)
Hypertension	1 (4%)	2 (13%)	0	0	0	2 (3%)

All grades, all relationships to drug

Figure 3: Lymphocyte Subset Change from Baseline Over Time

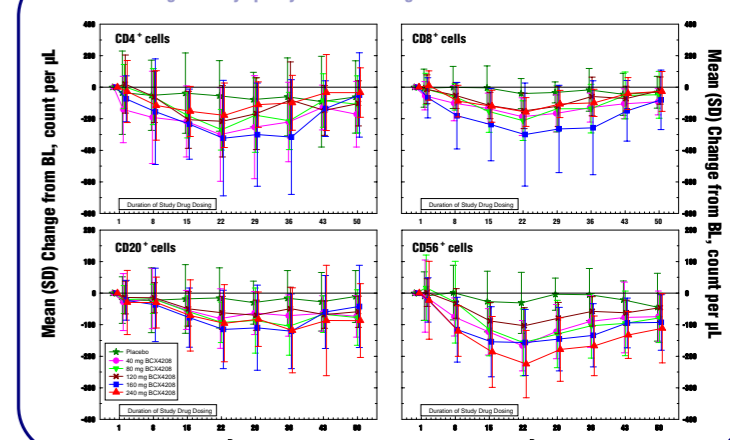


Table 7. Lymphocyte Subset Percent Change from Baseline at Day 22 – Median (Range in %)

	Placebo (N=24)	40 mg/day (N=15)	80 mg/day (N=14)	120 mg/day (N=16)	160 mg/day (N=15)	240 mg/day (N=15)
CD4+ ^a	-9% (-38, 61)	-29% (-52, 5)	-31% (-71, -1)	-28% (-65, 17)	-37% (-59, 17)	-25% (-57, 21)
CD8+ ^a	-7% (-47, 45)	-49% (-58, -8)	-44% (-77, -8)	-36% (-59, 1)	-56% (-76, 7)	-44% (-71, 6)
CD20+ ^a	-6% (-47, 87)	-23% (-55, 4)	-37% (-81, -2)	-36% (-51, 66)	-37% (-68, 18)	-38% (-61, 46)
CD56+ ^a	-5% (-58, 109)	-56% (-76, -26)	-74% (-91, -47)	-65% (-92, -12)	-78% (-91, -31)	-82% (-97, -50)

**P<0.001, by ANCOVA with factors for treatment and baseline subset counts.

Table 8. Categorical Summary of CD4+ Cell Counts <350 Cells/µL

	Placebo (N=24)	BCX4208				
	40 mg/day (N=15)	80 mg/day (N=14)	120 mg/day (N=16)	160 mg/day (N=15)	240 mg/day (N=15)	
Day 22	0/24 (0%)	0/15 (0%)	2/14 (14%)	0/16 (0%)	1/15 (7%)	1/13 (8%)
At Any Time	0/24 (0%)	0/15 (0%)	3/14 (21%)*	3/16 (19%)	1/15 (7%)	1/13 (8%)

*P<0.05, for comparison to placebo by Fisher's Exact Test.
 No subject discontinued the drug treatment for a confirmed CD4+ cell count of less than 350 cells/µL.

Conclusions

- BCX4208 at 40, 80 120, 160, and 240 mg/day rapidly and significantly reduced sUA in gout subjects.
- There was a dose-related increase in the proportion of subjects who reached sUA <6.0 mg/dL and lower.
- First-dose exposures of BCX4208 were dose proportional between 40 and 240 mg/day.
- BCX4208 was safe and well-tolerated
 - AEs were similar in frequency and severity between BCX4208 and placebo.
 - Measured lymphocyte subsets were reduced by BCX4208 therapy.
- These results demonstrate the potential for BCX4208 in the treatment of gout.

REFERENCES

Bieber JD, Terkeltaub RA. Gout: on the brink of novel therapeutic options for an ancient disease. Arthritis Rheum. 2004;50:2400-14.
 Feig DL, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med 2008;359:1811-21.