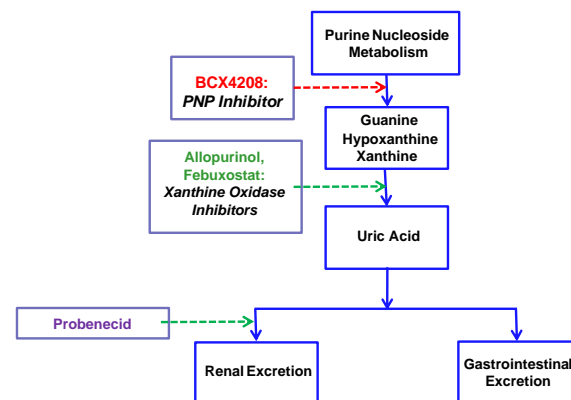


Background

BCX4208:

- An enzyme inhibitor being developed for the treatment of gout
- Has a mechanism of action that complements the xanthine oxidase inhibitors allopurinol and febuxostat by acting upstream of xanthine and hypoxanthine in the purine metabolic pathway



- In 2 randomized, double-blind, placebo-controlled, 3-week trials, BCX4208 20 mg to 240 mg/day:

- Significantly lowered serum uric acid (sUA) versus placebo
- Increased the proportion of patients achieving the sUA target of <6.0 mg/dL versus placebo
- Demonstrated additive and synergistic sUA-lowering efficacy with allopurinol

Objective

To describe the tolerability and safety profiles of BCX4208 during daily use for up to 3 weeks

Methods

- Data from two 3-week studies were pooled and summarized by BCX4208 dose.

- Designs were randomized, double-blind, placebo-controlled.
- Eligibility included adults with gout and sUA ≥8 mg/dL.
- Flare prophylaxis consisted of colchicine 0.6 mg/day or naproxen 250 mg twice daily.

Studies:

- BCX4208-201
 - Parallel-group study followed by sequential dose escalation
 - Safety Population: BCX4208 n=75; placebo n=24
 - BCX4208 40 mg, 80 mg, 120 mg, 160 mg, or 240 mg, or placebo
- BCX4208-202
 - 4x4 factorial design
 - Safety Population: BCX4208 n=66; placebo n=21
 - Combination of BCX4208 placebo, 20 mg, 40 mg, or 80 mg and allopurinol placebo, 100 mg, 200 mg, or 300 mg

Measures

- Safety was assessed by the type and frequency of adverse events reported by patients or observed by investigators and changes from baseline in clinical laboratory assessments.
- Adverse events were assessed from the time of informed consent and blood samples for laboratory tests were taken at weekly clinic visits and at a follow-up visit approximately 1 week after the end of the treatment period.
- Adverse events were graded by the investigator as mild, moderate, severe, or potentially life threatening. Lab abnormalities were graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (December, 2004). Lab toxicity shifts from baseline to last visit were summarized by treatment group.

Demographics and Clinical Characteristics Were Generally Similar Among Dose Groups

	Placebo (n=45)	BCX4208					
		20 mg (n=21)	40 mg (n=38)	80 mg (n=36)	120 mg (n=16)	160 mg (n=15)	240 mg (n=15)
Mean (SD) age, y	52 (10.4)	47 (8.9)	51 (11.8)	47 (11.6)	51 (13.6)	48 (10.5)	49 (10.9)
Male, n (%)	43 (96)	21 (100)	36 (95)	35 (97)	15 (94)	15 (100)	15 (100)
Race, n (%)							
White	31 (69)	11 (52)	27 (71)	26 (72)	10 (63)	11 (73)	8 (53)
Black	7 (16)	2 (10)	3 (8)	3 (8)	1 (6)	1 (7)	2 (13)
Asian	2 (4)	3 (14)	2 (5)	2 (6)	2 (13)	2 (13)	2 (13)
Other	5 (11)	5 (24)	6 (16)	5 (14)	3 (19)	1 (7)	3 (20)
Mean body mass index, kg/m ²	34.2 (5.8)	36.6 (8.5)	35.9 (7.9)	33.0 (6.3)	35.4 (8.5)	32.9 (6.1)	32.8 (6.8)
Mean (SD) baseline sUA, mg/dL	9.6 (1.1)	10.5 (1.5)	9.7 (1.2)	9.8 (1.2)	9.8 (1.4)	10.1 (1.8)	9.7 (1.5)
Comorbidities, n (%)							
Obesity	31 (69)	17 (81)	28 (74)	24 (67)	11 (69)	9 (60)	8 (53)
Hypertension	33 (73)	10 (48)	19 (50)	20 (56)	10 (63)	6 (40)	6 (40)
Diabetes	7 (16)	1 (5)	2 (5)	5 (14)	3 (19)	0 (0)	0 (0)
Hypercholesterolemia	25 (56)	11 (52)	23 (61)	16 (44)	6 (38)	6 (40)	9 (60)
Chronic kidney disease	8 (18)	5 (24)	9 (24)	9 (25)	2 (13)	3 (20)	3 (20)
Coronary heart disease	1 (2)	0 (0)	1 (3)	0 (0)	1 (6)	0 (0)	1 (7)
Flare prophylaxis during study, n (%)							
Colchicine	33 (73)	14 (67)	27 (71)	21 (58)	10 (63)	12 (80)	7 (47)
Naproxen	5 (11)	4 (19)	3 (8)	8 (22)	3 (19)	2 (13)	4 (27)
Colchicine and naproxen	3 (7)	3 (14)	6 (16)	4 (11)	1 (6)	0 (0)	2 (13)

The Incidence of Adverse Events Was Generally Similar Among Dose Groups

	Placebo (n=45)	BCX4208					
		20 mg ¹ (n=21)	40 mg ¹ (n=38)	80 mg ¹ (n=36)	120 mg (n=16)	160 mg (n=15)	240 mg (n=15)
	n (%)						
Any adverse event	28 (62)	14 (67)	20 (53)	18 (50)	10 (63)	10 (67)	11 (73)
Severity							
Mild	14 (31)	8 (38)	14 (37)	8 (22)	3 (19)	6 (40)	5 (33)
Moderate	10 (22)	6 (29)	6 (16)	10 (28)	7 (44)	4 (27)	4 (27)
Severe	4 (9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 ³ (13)
Serious adverse event	0 (0)	0 (0)	1 ² (5)	0 (0)	0 (0)	0 (0)	0 (0)
Adverse event leading to discontinuation of study medication	2 (4)	0 (0)	2 (5)	2 (6)	0 (0)	1 (7)	2 (13)

¹BCX4208 20 mg, 40 mg, and 80 mg were administered both with and without allopurinol. ²The serious adverse event was a hemorrhoidal bleed that resolved and was not considered related to study medication. ³The severe adverse events were diarrhea and diverticulitis.

The Adverse Event Profile of BCX4208 Was Not Affected by Concomitant Administration of Allopurinol

	Placebo (n=45)	BCX4208		
		20 mg (n=21)	40 mg (n=38)	80 mg (n=36)
	Proportion (%)			
No allopurinol (n=30)	18/30 (60)	4/5 (80)	14/21 (67)	12/20 (60)
Allopurinol 100 mg (n=5)	3/5 (60)	4/5 (80)	3/6 (50)	1/5 (20)
Allopurinol 200 mg (n=5)	3/5 (60)	1/6 (17)	2/6 (33)	1/5 (20)
Allopurinol 300 mg (n=5)	4/5 (80)	5/5 (100)	1/5 (20)	4/6 (67)

- Adverse events of moderate severity were infrequent with BCX4208 administered in combination with allopurinol.
- No severe adverse events were reported with the combination of BCX4208 and allopurinol at any active dose.
- The types of adverse events were similar in recipients of placebo, allopurinol, BCX4208, or both drugs combined.

Results

The Most Common Adverse Events Were Diarrhea** and Headache

	Placebo (n=45)	BCX4208						
		20 mg ¹ (n=21)	40 mg ¹ (n=38)	80 mg ¹ (n=36)	120 mg (n=16)	160 mg (n=15)	240 mg (n=15)	Total (n=141)
	n (%)							
Diarrhea	3 (7)	3 (14)	2 (5)	4 (11)	1 (6)	1 (7)	3 (20)	14 (10)
Headache	5 (11)	1 (5)	6 (16)	3 (8)	2 (13)	0 (0)	2 (13)	14 (10)
Peripheral edema	0 (0)	1 (5)	1 (3)	1 (3)	2 (13)	1 (7)	2 (13)	8 (6)
Lymphocyte count decreased	1 (2)	0 (0)	1 (3)	4 (11)	0 (0)	2 (13)	1 (7)	8 (6)
Upper respiratory tract infection	1 (2)	0 (0)	1 (3)	3 (8)	2 (13)	0 (0)	1 (7)	7 (5)
Blood creatine phosphokinase increased	4 (9)	2 (10)	0 (0)	1 (3)	0 (0)	1 (7)	1 (7)	5 (4)
Rash	2 (4)	1 (5)	2 (5)	0 (0)	0 (0)	0 (0)	2 (13)	5 (4)
Cough	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (13)	0 (0)	2 (1)
Tachycardia	0 (0)	2 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)

¹BCX4208 20 mg, 40 mg, and 80 mg were administered both with and without allopurinol. ^{**}Diarrhea likely due to high rate of colchicine use.

The Incidence and Severity Profile of Infections Were Similar Between BCX4208 and Placebo**

Infections	Placebo (n=45)	BCX4208						
		20 mg ¹ (n=21)	40 mg ¹ (n=38)	80 mg ¹ (n=36)	120 mg (n=16)	160 mg (n=15)	240 mg (n=15)	Total (n=141)
	n (%)							
Any infection	7 (16)	2 (10)	4 (11)	6 (17)	4 (25)	0 (0)	2 (13)	18 (13)
Upper respiratory tract	4 (9)	0	2 (5)	5 (14)	3 (19)	0	1 (7)	11 (8)
Mild	3 (7)	0	2 (5)	3 (8)	0	0	1 (7)	6 (4)
Moderate	1 (2)	0	0	2 (6)	3 (19)	0	0	5 (4)
Severe	0	0	0	0	0	0	0	0
Potentially life-threatening	0	0	0	0	0	0	0	0
Viral	0	0	1 (3)	1 (3)	1 (6)	0	0	3 (2)
Mild	0	0	1 (3)	0	1 (6)	0	0	2 (1)
Moderate	0	0	0	1 (3)	0	0	0	1 (1)
Severe	0	0	0	0	0	0	0	0
Potentially life-threatening	0	0	0	0	0	0	0	0
Abdominal/gastrointestinal	3 (7)	0	0	0	0	0	1 (7)	1 (1)
Mild	1 (2)	0	0	0	0	0	0	0
Moderate	2 (4)	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	1 (7)	1 (1)
Potentially life-threatening	0	0	0	0	0	0	0	0

¹BCX4208 20 mg, 40 mg, and 80 mg were administered both with and without allopurinol. ^{**}Additional infections reported as adverse events in 1 patient in a dosing group were mild tooth abscess, oral herpes, tinea pedis, and a moderate otitis externa in BCX4208-treated patients and 1 mild urinary tract infection in a placebo-treated patient.

The Incidences of Adverse Events of Special Interest and Lab Abnormalities Were Low

- Mild-to-moderate reductions in absolute lymphocyte counts as well as counts for CD4+, CD8+, CD20+, and CD56+ subsets were observed.
- A decrease of ≥1 grade in total lymphocyte counts was observed in 3/141 BCX4208-treated patients (2.1%).
- A decrease of ≥1 grade in CD4+ lymphocytes was observed in 21/141 BCX4208-treated patients (15%).
- Baseline absolute lymphocyte count and BCX4208 dose were each significantly (p<0.001) associated with absolute lymphocyte counts at Day 22 in multivariate regression analyses that examined the contributions of age, gender, weight, race, and baseline sUA, CrCl, and lymphocyte count to the change in lymphocyte count.

- DAIDS grading data were available for absolute lymphocyte counts and CD4+ counts:

	Placebo (n=42)	BCX4208					
		20 mg (n=20)	40 mg (n=36)	80 mg (n=35)	120 mg (n=16)	160 mg (n=15)	240 mg (n=13)
	Absolute Lymphocyte Counts: Number of Patients with DAIDS Grade Shifts from Normal Baseline at Day 22 Visit						
No shift	42	20	36	33	16	15	13
Grade 1 (0.600x10 ⁹ -0.650x10 ⁹ /L)	0	0	0	1	0	0	0
Grade 2 (0.500x10 ⁹ -0.599x10 ⁹ /L)	0	0	0	1	0	0	0
Grade 3 (0.350x10 ⁹ -0.499x10 ⁹ /L)	0	0	0	0	0	0	0
Grade 4 (<0.350x10 ⁹ /L)	0	0	0	0	0	0	0
	CD4+ Counts: Number of Patients with DAIDS Grade Shifts from Normal Baseline at Day 22 Visit						
	BCX4208						
No shift	43	19	34	27	15	13	10
Grade 1 (300-400/μL)	0	1	2	6	1	1	3
Grade 2 (200-299/μL)	0	0	0	1	0	1	0
Grade 3 (100-199/μL)	0	0	0	1	0	0	0
Grade 4 (<100/μL)	0	0	0	0	0	0	0

- Very few patients met stopping rules for absolute lymphocyte counts or CD4+ counts during treatment:

	Placebo (n=45)	BCX4208					
		20 mg ¹ (n=21)	40 mg ¹ (n=38)	80 mg ¹ (n=36)	120 mg (n=16)	160 mg (n=15)	240 mg (n=15)
	Absolute Lymphocyte Counts <500/μL and CD4+ Counts <350/μL or that Met Stopping Rules						
Absolute lymphocyte count <500/μL	0	0	0	0	0	0	0
Met stopping rules ²	0	0	0	0	0	0	0
CD4+ count <350/μL	0	0	1	8	3	1	1
Met stopping rules ³	0	0	0	1* (2.8)	0	1* (6.7)	2 (1.4)

¹BCX4208 20 mg, 40 mg, and 80 mg were administered both with and without allopurinol. ²Stopping rule: If absolute lymphocyte cell count values fall <500/μL, retest to confirm. If values remain <500/μL then stop study drug immediately, withdraw from study, and follow up until resolution. ³Stopping rule: If CD4+ flow cytometer cell count values fall to <350/μL, retest to confirm. If values remain <350/μL, stop study drug, withdraw from study, and follow up until resolution. *Patient met stopping rules at day 17.

- No opportunistic infections were reported.
- The frequency of grade changes in other laboratory analytes was generally similar between BCX4208 and placebo with no evidence of drug effect or dose relationship.

Conclusions

In 2 randomized, double-blind, placebo-controlled studies:

- BCX4208 was generally safe and well tolerated when administered at doses up to 240 mg/day for 21 days.
- The combination of BCX4208 and allopurinol was generally safe and well tolerated at daily doses of 20 mg, 40 mg, and 80 mg for BCX4208 and 100 mg, 200 mg, and 300 mg for allopurinol.
- No clinical impact of the reduction in lymphocyte subsets was observed.
 - The rate of infections was similar between BCX4208 and placebo.
 - No opportunistic infections were reported.
- In the 141 patients treated, no safety signals were identified.
- Based on the results of these studies, a longer-term safety study is warranted and is in progress.