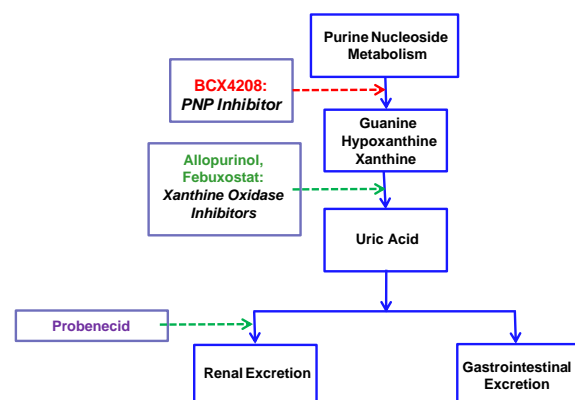


Background

- An estimated 15 million individuals in the United States and the European Union are diagnosed with gout.¹
- Gout symptoms, such as flares, can be controlled through sustained reduction in serum uric acid (sUA) concentrations.
- The sUA target recommended in evidence-based guidelines is <360 μM/L (<6 mg/dL).²
- Target sUA concentrations are not achieved in the majority of patients with gout despite treatment with current agents including allopurinol. In a recent study of 3363 patients receiving allopurinol, only 40% achieved the sUA target in a year.³
- BCX4208:
 - A novel enzyme inhibitor
 - Acts upstream of xanthine and hypoxanthine in the purine metabolic pathway to reduce sUA in patients with gout
 - Has a mechanism of action that complements the xanthine oxidase inhibitors allopurinol and febuxostat in reducing uric acid production
 - Dose-dependently reduced sUA when given as monotherapy in a randomized, double-blind study



Objectives

- To evaluate the sUA-lowering efficacy, tolerability, and safety of BCX4208 (20, 40, 80 mg) as monotherapy and in combination with allopurinol (100, 200, 300 mg)
- To evaluate the pharmacokinetics (PK) of BCX4208 given in combination with allopurinol

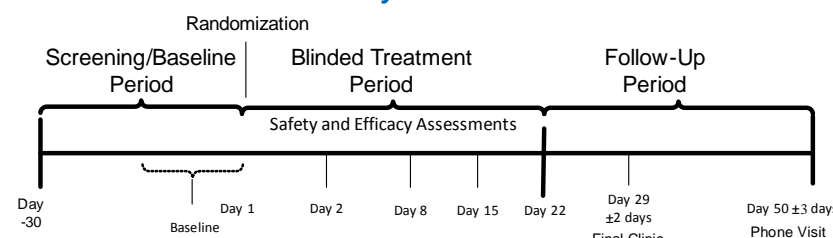
Endpoints

- Primary Efficacy:
 - Change from baseline in sUA at Day 22
- Secondary Efficacy:
 - % change from baseline in sUA at Day 22
 - % patients with sUA <6 mg/dL at Day 22
- Safety: laboratory tests, adverse events, clinical assessment
- PK of BCX4208, allopurinol, oxypurinol

Methods

- Design: randomized, double-blind, 4x4 factorial. Gout patients with sUA ≥8 mg/dL.
- Treatment: 3 weeks of placebo, 20, 40, or 80 mg/d BCX4208 in combination with placebo, 100, 200, or 300 mg/d allopurinol
- Procedures:
 - Gout flare prophylaxis with colchicine or naproxen
 - Weekly visits, first-dose PK, trough drug levels
 - Drop-outs and discontinuations replaced
 - Per-protocol analysis by ANCOVA and response surface analysis

Study Schematic



Numbers of Per-Protocol Patients Per Dose

Allopurinol Dose	BCX4208 Dose			
	Placebo	20 mg	40 mg	80 mg
Placebo	n=5	n=4	n=6	n=5
100 mg	n=5	n=4	n=5	n=5
200 mg	n=4	n=5	n=5	n=5
300 mg	n=5	n=4	n=4	n=5

Results

Demographics and Clinical Characteristics (Per-Protocol Population*) Were Generally Similar Across BCX4208 and Placebo Groups**

	Placebo (n=19)	BCX4208			
		20 mg (n=17)	40 mg (n=20)	80 mg (n=20)	
Mean age, y (SD)	52 (11.0)	48 (9.5)	53 (10.0)	44 (11.2)	
Sex, male/female	19/0	17/0	18/2	20/0	
Race, n					
White	12	10	15	15	
Black	5	2	0	1	
Asian	1	3	2	1	
Other	1	2	3	3	
Mean weight, kg (SD)	106 (21)	104 (26)	112 (17)	102 (26)	
Mean body mass index, kg/m ²	34.0 (6.5)	35.3 (7.3)	36.1 (6.3)	32.9 (6.9)	
Mean baseline sUA, mg/dL (SD)	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)	

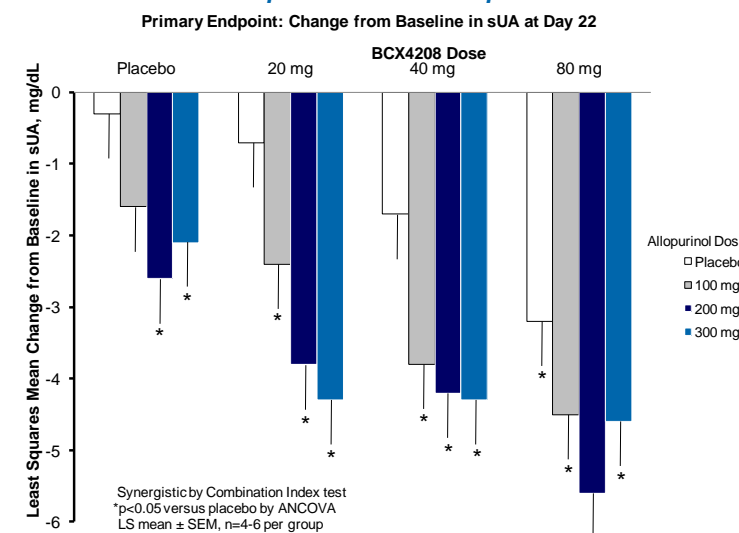
*Per-Protocol patients were ≥85% compliant, had confirmed drug levels, and had ≥1 post-baseline sUA measurement.
**Results combined across allopurinol dose groups

BCX4208, Allopurinol, Oxypurinol First-Dose PK: No Drug-Drug Interaction

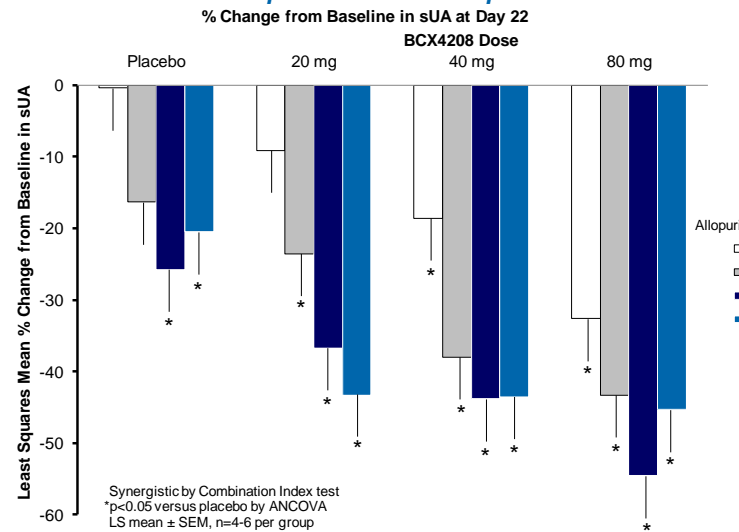
	n	C _{max} , ng/mL	AUC _{0-24h} , [*] ng-h/mL	t _{max} , h	C _{24h} , ng/mL
BCX4208					
20 mg	11	6.6 (2.6)	27 (10)	4	0.4 (0.3)
40 mg	16	10.0 (1.5)	130 (30)	4	7.3 (2.1)
80 mg	20	28.4 (3.8)	373 (40)	4	14.6 (3.2)
Allopurinol					
100 mg	20	191 (31)	427 (71)	2	0
200 mg	22	511 (55)	1329 (186)	2	0
300 mg	21	1062 (102)	3411 (353)	2	0
Oxypurinol					
100 mg	20	2161 (186)	37,580 (2800)	4	1308 (134)
200 mg	22	3687 (179)	67,250 (2580)	4	2354 (93)
300 mg	21	5678 (268)	109,810 (5513)	4	4052 (245)

*Drug-drug interactions: p=0.511 (ns)

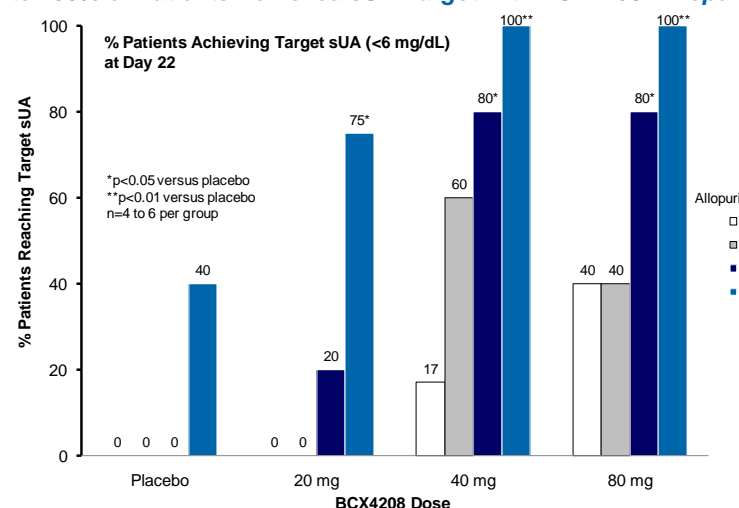
Synergistic Reductions in Mean sUA with BCX4208+Allopurinol Versus Allopurinol Alone



Synergistic % Reductions in sUA with BCX4208+Allopurinol Versus Allopurinol Alone



Up to 100% of Patients Achieved sUA Target with BCX4208+Allopurinol



BCX4208 Was Generally Safe and Well Tolerated

- The adverse event profile of BCX4208 with or without allopurinol was similar to that of placebo in this 3-week study.
- The frequencies and severities of adverse events were evenly distributed across dose groups.
- The most common adverse events were diarrhea (12% BCX4208, 5% placebo) and headache (6% BCX4208, 5% placebo).
- No serious adverse events were reported.
- Characteristic gout flares occurred in 1 placebo-treated patient, 1 patient receiving 20 mg/d BCX4208, 3 patients on 40 mg/d BCX4208, and 4 patients on 80 mg/d BCX4208.
- Additional safety information is available in Poster #THU0027 (this meeting).

Clinical Laboratory Findings

- Mild, dose-related reduction in lymphocytes and lymphocyte subsets were not associated with an increased rate of adverse events, including opportunistic infections.
- No clinically significant changes were observed in:
 - Hemoglobin, hematocrit, white blood cell counts, platelet counts
 - Renal function
 - Hepatic function

Conclusions

In this randomized, double-blind study:

- Synergistic mean reductions and % reductions in sUA were observed with BCX4208+allopurinol versus allopurinol alone.
- Up to 100% of patients achieved sUA target with BCX4208+allopurinol.
- BCX4208 and allopurinol first-dose PK revealed no drug-drug interaction.
- BCX4208 was generally well tolerated.
- Laboratory findings of mild, dose-related reductions in lymphocytes were not associated with adverse events.

References

- <http://gouteducation.org/medical-professionals/> and Decision Resources
- Zhang et al. *Ann Rheum Dis.* 2006;65:1312-1324.
- Pandya et al. *Curr Med Res Opin.* 2011;27:737-744.