

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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November 8, 2011

Relevant Financial Relationships

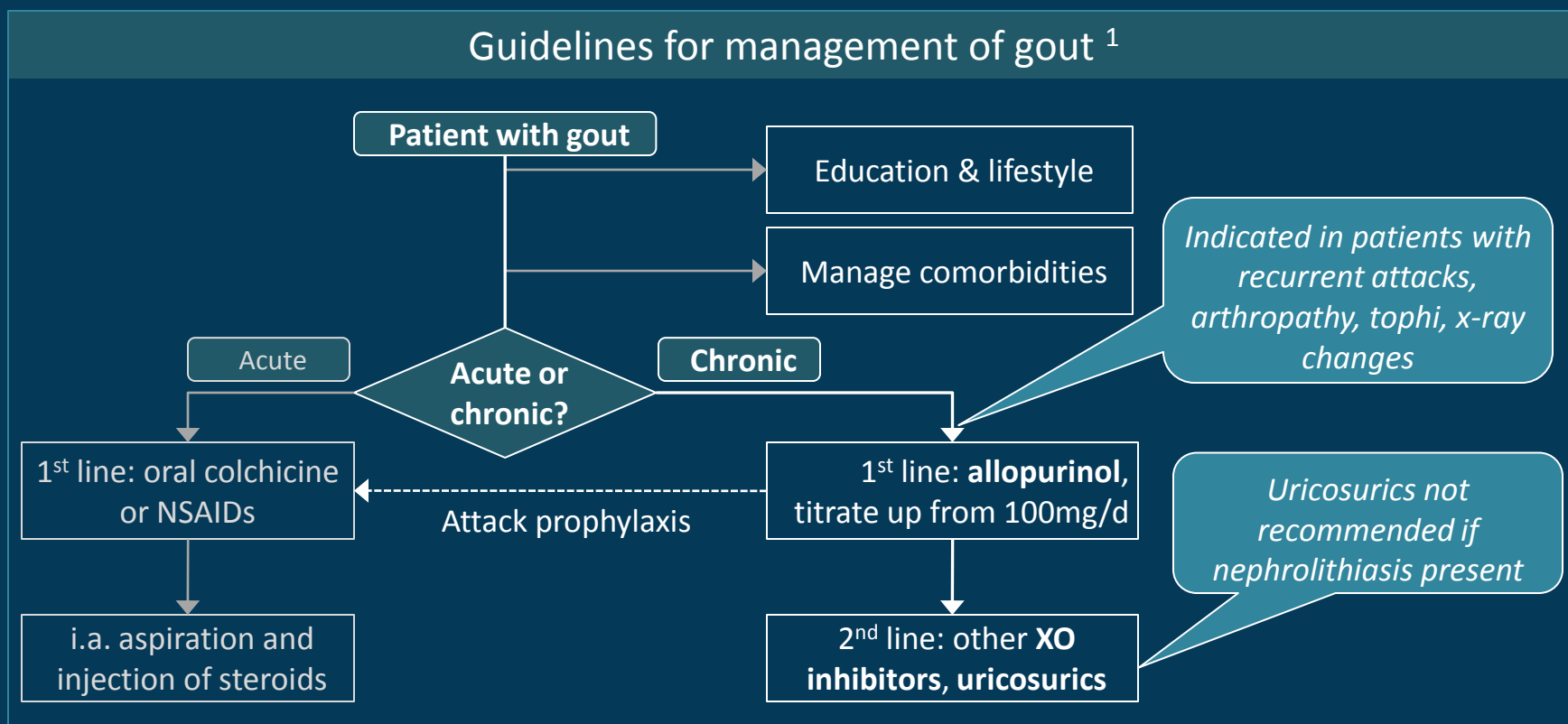
- Michael Becker
 - Consulting fees: Takeda, Savient, BioCryst, Ardea, Metabolex, URL/Mutual, Regeneron, Menarini
- Robert Terkeltaub
 - Consulting fees: Novartis, Regeneron, URL, Pfizer Inc, BioCryst, Takeda, ARDEA
- David Fitz-Patrick:
 - Research grants: BioCryst Pharmaceuticals, Inc, Ardea, Metabolex, Nuon, Novartis, Regeneron, Takeda, TAP
 - Consulting fees: Biocryst Pharmaceuticals, Inc, Takeda
- Richard Leff & Amy Flynt:
 - Consulting fees: BioCryst Pharmaceuticals, Inc
- Alan Hollister, Anita Waugh & William Sheridan:
 - Stock ownership: BioCryst Pharmaceuticals, Inc

Evidence-based medicine

- Review articles:
 - Zhang W et al. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 65(10):1312-24, 2006 Oct.
 - Burns, CM and Wortmann, RL. Gout therapeutics: new drugs for an old disease. *Lancet*. 377(9760):165-77, 2011 Jan 8.

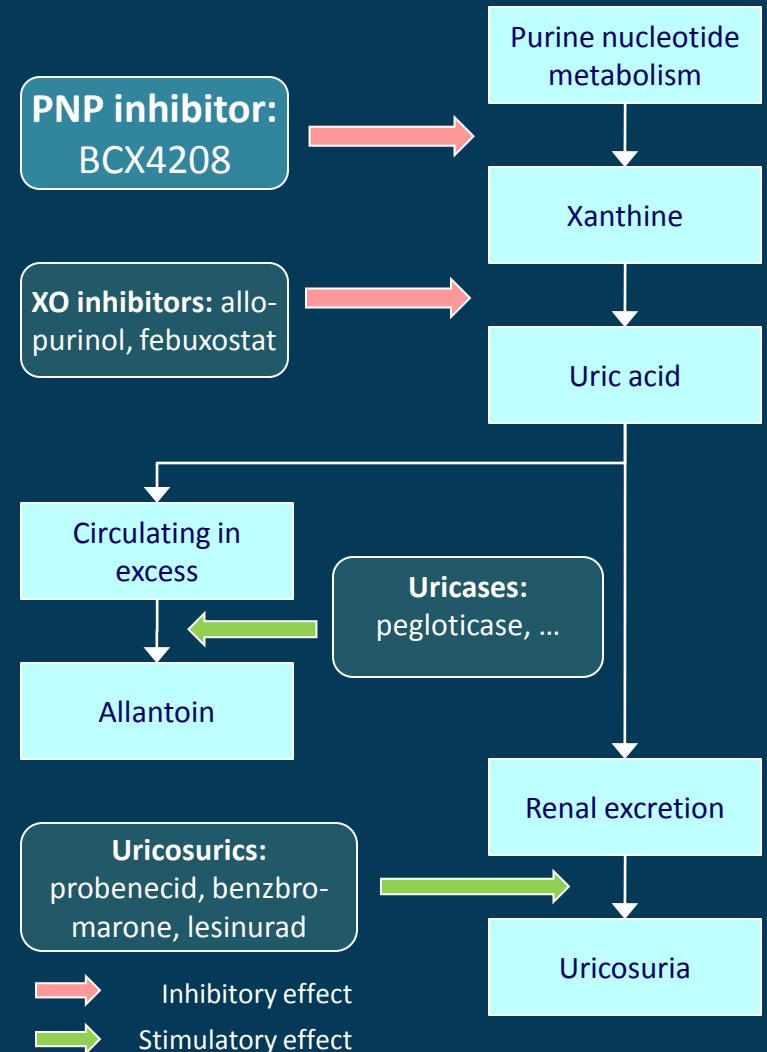
Background: management of gout

- Guidelines recommend urate lowering therapy for chronic gout
- Patients who fail XO inhibitors have few alternatives



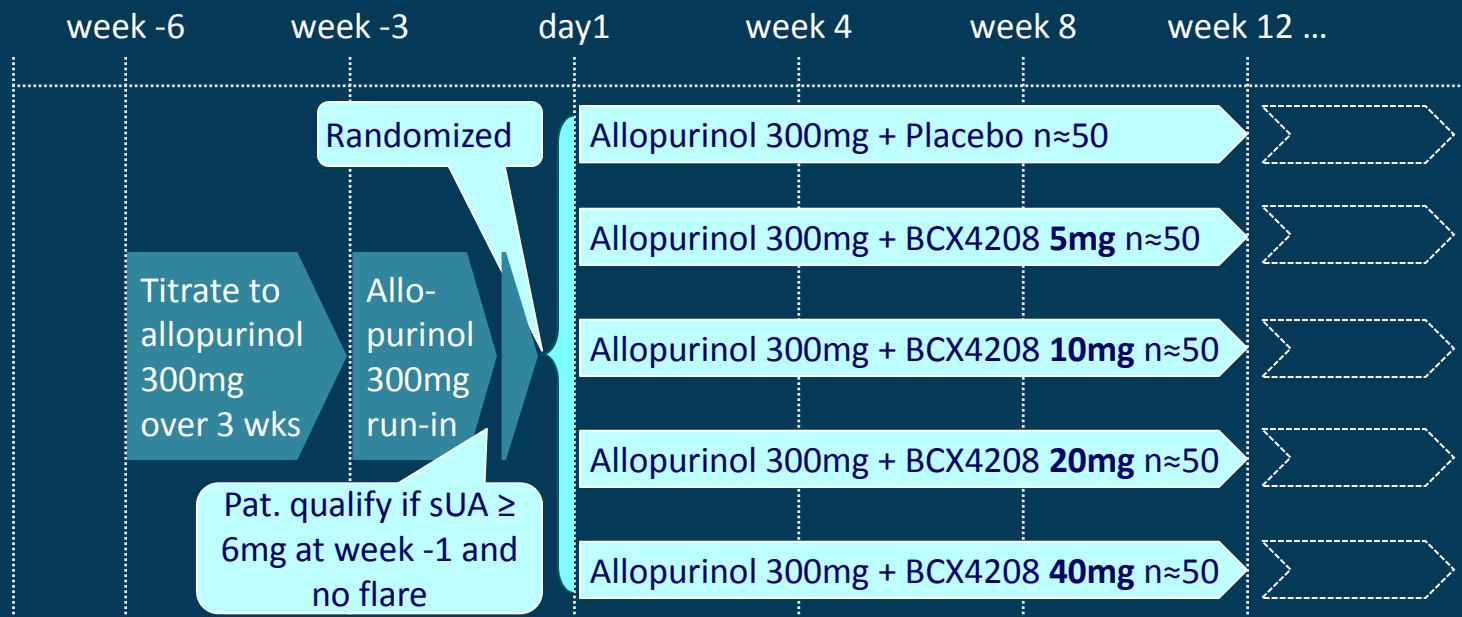
Background: BCX4208

- Purine nucleoside phosphorylase (PNP) inhibitor
- Inherited PNP deficiency leads to hypouricemia and decreased lymphocytes
- PNP inhibitors form a new class of therapy
 - Oral, once daily dosing
 - $t_{1/2}$ steady state: 17h
 - Clearance: renal



Objectives and study design

- To evaluate BCX4208 therapy added on to allopurinol 300mg in allopurinol inadequate responders
- 1^o endpoint: % patients with sUA < 6mg/dL at week 12
- Long-term extension is ongoing



Methods: Inclusion & exclusion criteria

Key inclusion criteria

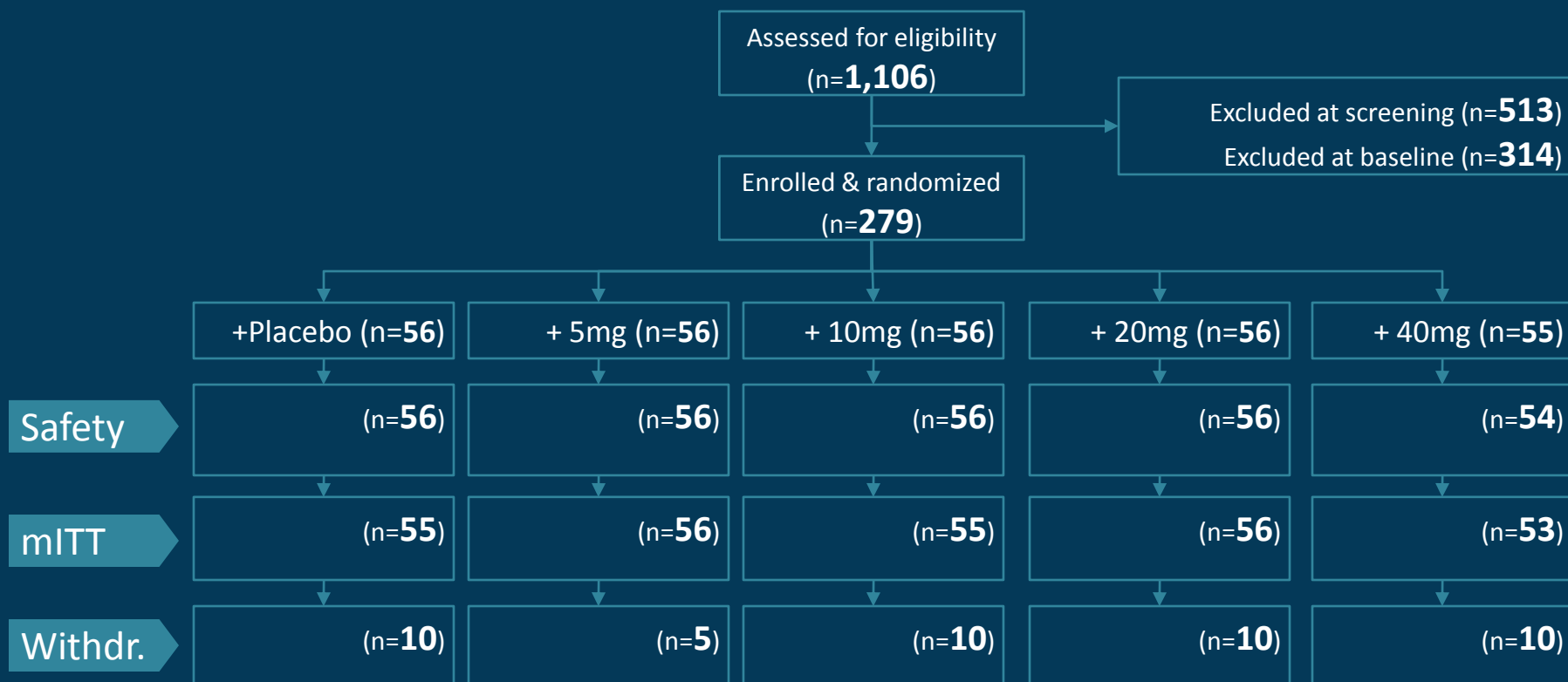
- Baseline sUA ≥ 6.0 mg/dL after 2 weeks on 300mg of allopurinol
- Documented diagnosis of gout (ARA 1977)
- Be willing and able to take prophylaxis for gout flares (colchicine or naproxen)

Key exclusion criteria

- Gout flare during 2 weeks prior to randomization
- CrCl < 60 ml/min
- ALT/AST > 2 x ULN
- CD4⁺ < 500 cells/mm³
- Hb < 10 g/dL or > 18 g/dL (> 17 g/dL for women)
- Abnormal WBC

Results: Screening and randomization

- Randomization was balanced across treatment groups



Results: Baseline demographics

- Half of the patients were obese and many had evidence of renal impairment

Characteristics	Allopurinol 300mg +				
	Placebo	BCX4208			
		5mg	10mg	20mg	40mg
N	56	56	56	56	54
Age, years: mean (min-max)	50 (28-68)	46 (21-69)	50 (19-69)	50 (30-69)	49 (29-68)
Female: n	1	3	2	3	3
Morbid obesity (BMI > 40)	17 (30%)	13 (23%)	13 (23%)	17 (30%)	10 (19%)
Mild-moderate renal impairment (IBW)	64%	61%	70%	70%	72%
sUA (mg/dL): mean (SD)	6.9 (1.02)	6.6 (0.99)	6.8 (1.05)	7.5 (1.64)	7.2 (1.13)

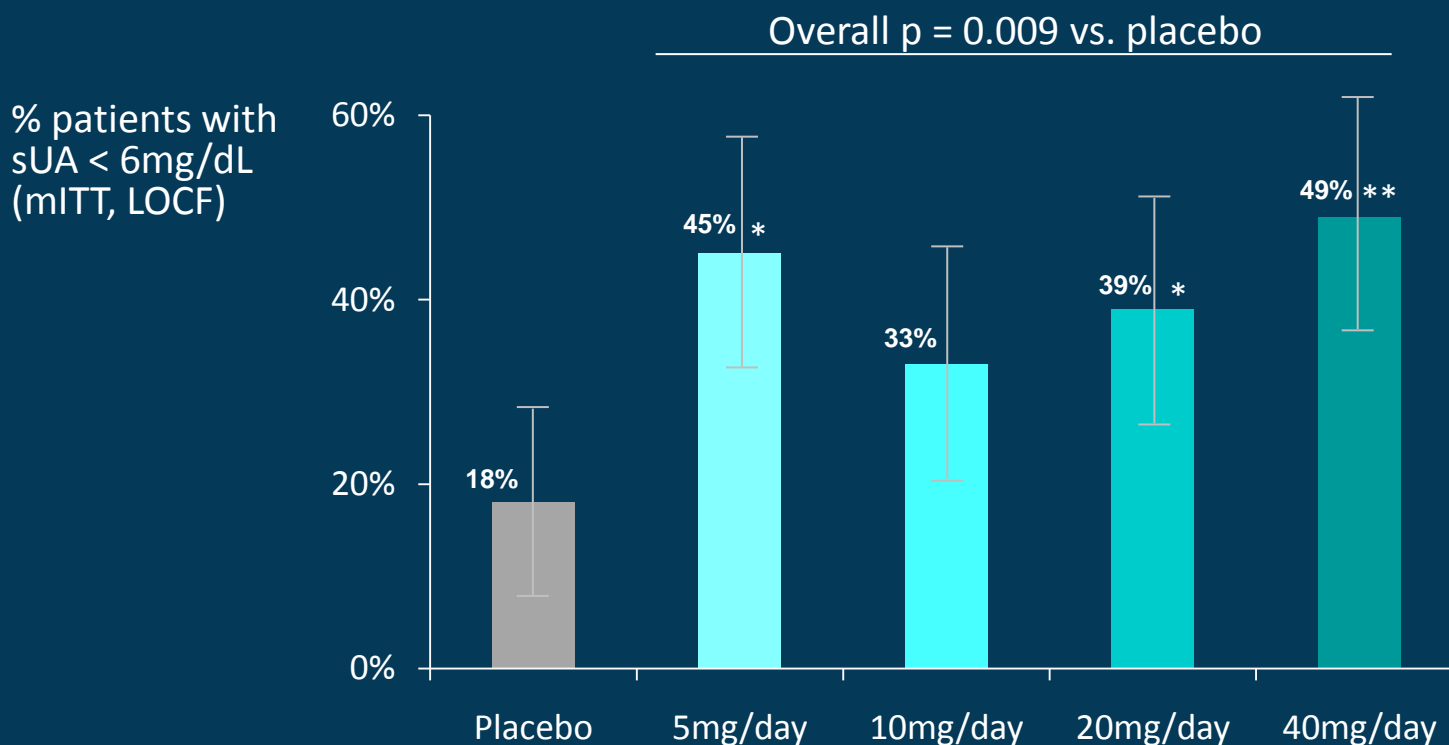
Results: Baseline comorbidities

- Metabolic and cardiovascular comorbidities were present in > 50% of the patient population

Characteristics	Allopurinol 300mg +				
	Placebo	BCX4208			
		5mg	10mg	20mg	40mg
N	56	56	56	56	54
Hypertension	33 (59%)	27 (48%)	36 (64%)	37 (66%)	28 (52%)
Hypercholesterolemia	19 (34%)	28 (50%)	25 (45%)	18 (32%)	18 (33%)
Diabetes	11 (20%)	10 (18%)	10 (18%)	7 (13%)	6 (11%)
Concomitant meds. median n	5	4	5	3	4
Total cholesterol, mg/dL (SD)	200 (44)	210 (52)	201 (45)	200 (38)	198 (49)
LDL cholesterol, mg/dL (SD)	118 (37)	118 (37)	125 (35)	122 (38)	123 (36)

Results: Primary endpoint

- BCX4208 added to allopurinol doubled the proportion achieving goal (sUA < 6mg/dL) at week 12



Results: Secondary endpoints

- BCX4208 added to allopurinol also achieved secondary endpoint of < 5mg/dL

Secondary endpoints	Allopurinol 300mg +					
	Placebo (N=56)	BCX4208				
	5mg (N=56)	10mg (N=56)	20mg (N=56)	40mg (N=54)	4208 All (N=222)	
sUA < 5mg/dL n(%)	0 (0%)	7* (13%)	3 (5%)	9* (16%)	6* (11%)	25 (11%)
Gout flares n (%)	3 (5%)	4 (7%)	3 (5%)	4 (7%)	6 (11%)	17 (8%)
sUA change from baseline: mean (SD)	0.2 (1.2)	-0.3* (1.1)	-0.1 (1.3)	-0.6* (1.9)	-0.8** (1.8)	-0.4* (1.6)
sUA % change from baseline: mean (SD)	4.2 (16.5)	-3.5* (17.9)	-0.7 (20.0)	-6.9* (22.2)	-10.3** (22.7)	-5.3 (20.9)

Results: Overall adverse events

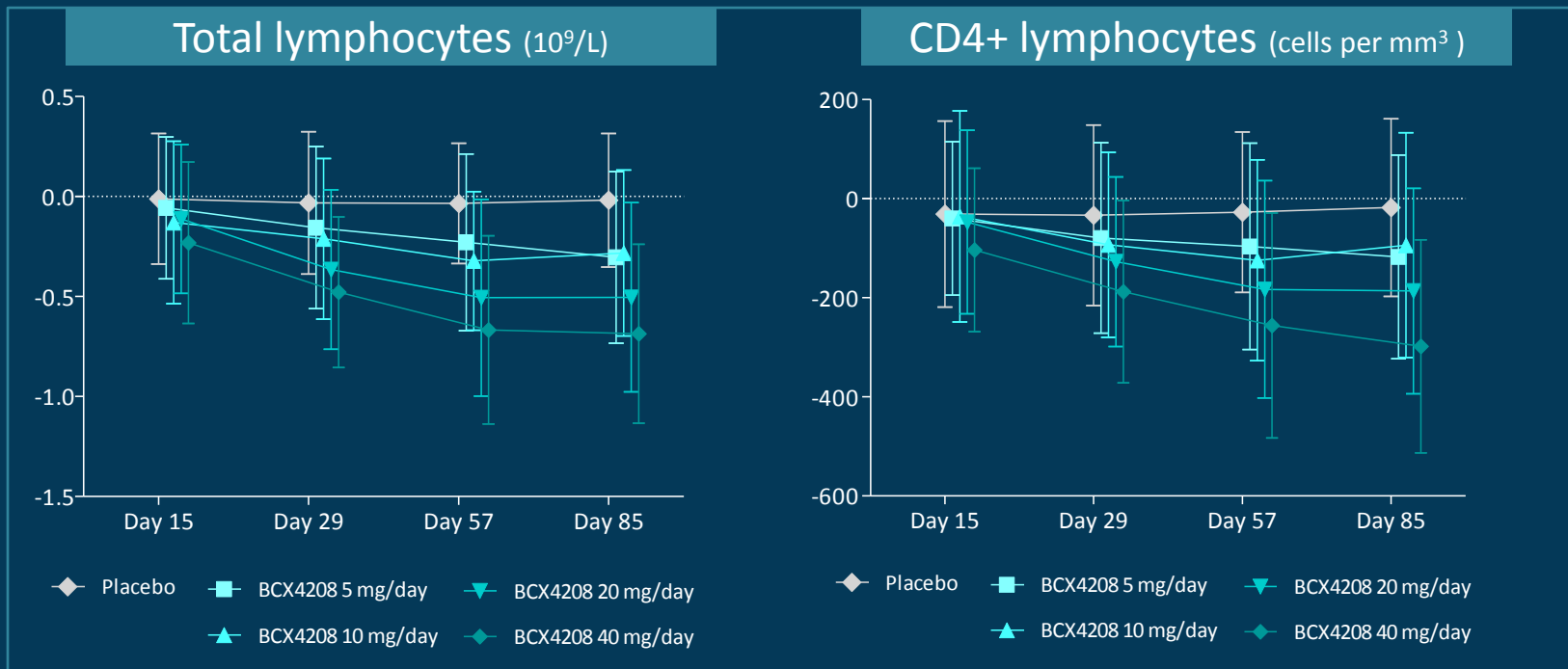
- Adverse events were balanced among groups
- No fatal or life-threatening adverse events were seen

Severity	Allopurinol 300mg +					4208 All (N=222)
	Placebo (N=56)	5mg (N=56)	10mg (N=56)	20mg (N=56)	40mg (N=54)	
Any AE N(%)	34 (61%)	29 (52%)	34 (61%)	33 (59%)	39 (72%)	135 (61%)
Mild	19 (34%)	13 (23%)	9 (16%)	9 (16%)	17 (31%)	48 (22%)
Moderate	11 (20%)	16 (29%)	19 (34%)	19 (34%)	18 (33%)	72 (32%)
Severe	4 (7%)	0	6 (11%)	5 (9%)	4 (7%)	15 (7%)
Life-threat. / fatal	0	0	0	0	0	0
Treatment emergent SAEs	0	0	2 (4%)	2 (4%)	2 (4%)	6 (3%)
Drug-related SAEs	0	0	0	0	0	0

*Investigator assessed Severity

Results: Change in lymphocyte counts

- Dose-related reductions in lymphocytes (total & subsets) reached plateau by day 85
- 10 patients met CD4+ stopping rule of $< 350/\text{mm}^3$ (40mg: n=8; 20mg: n=2)



Results: Grade change in lymphocytes

- Shifts in lymphocyte counts at any time were minor (DAIDS grade*)

Absolute lymphocyte counts	Allopurinol 300mg +					4208 Total (N=222)
	Placebo (N=56)	5mg (N=56)	10mg (N=56)	20mg (N=56)	40mg (N=54)	
Grade 1 ($0.600 \times 10^9 - 0.650 \times 10^9/L$)	-	-	1	-	3	4
Grade 2 ($0.500 \times 10^9 - 0.599 \times 10^9/L$)	-	-	-	-	-	-
Grade 3 ($0.350 \times 10^9 - 0.499 \times 10^9/L$)	-	-	-	-	1	1
Grade 4 ($< 0.350 \times 10^9 /L$)	-	-	-	-	-	-
CD4 ⁺ counts						
Grade 1 (300-400/ μ L)	-	3	6	6	5	20
Grade 2 (200-299/ μ L)	-	1	-	1	7	9
Grade 3 (100-199/ μ L)	-	-	-	-	-	-
Grade 4 ($< 100/\mu$ L)	-	-	-	-	-	-

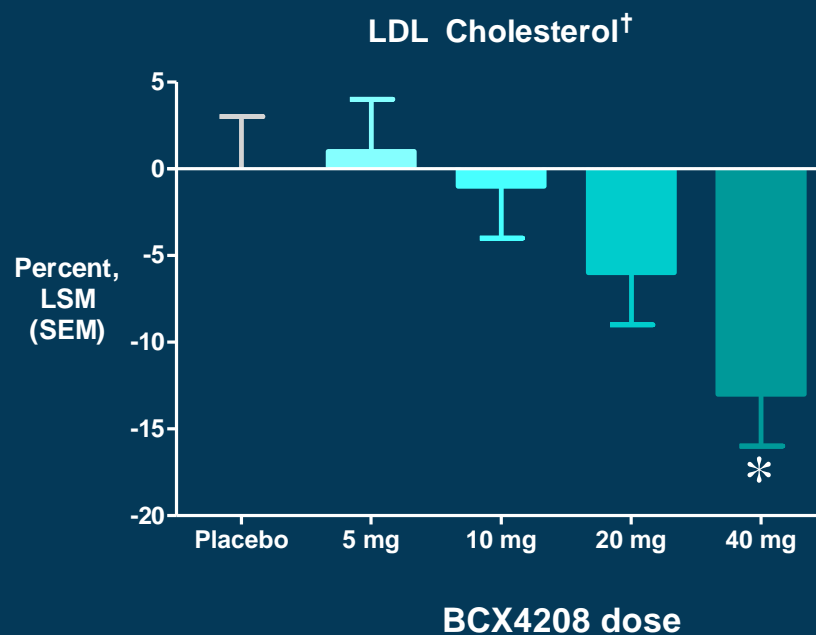
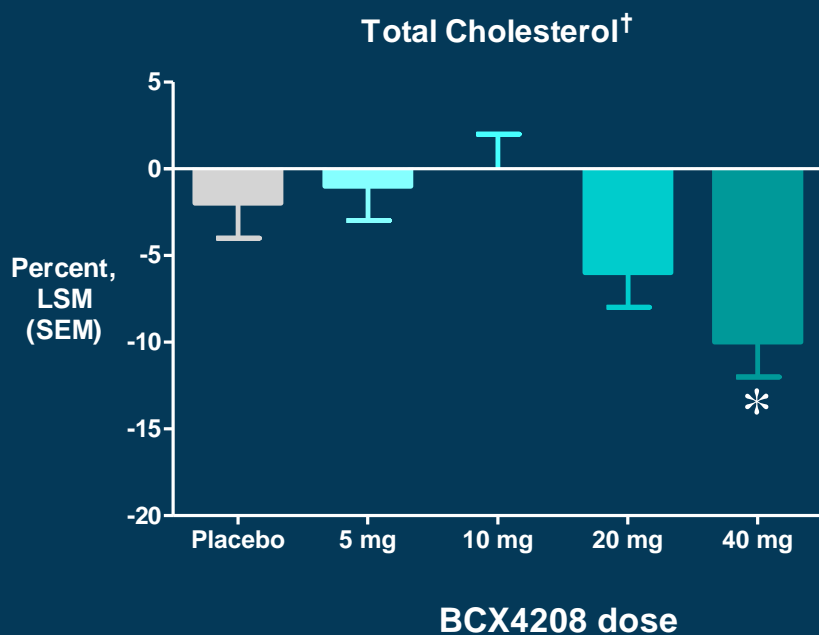
Results: Infectious adverse events

- Control and BCX4208 groups showed similar frequencies of infections

Infectious adv. events (AE)	Allopurinol 300mg +					4208 All (N=222)
	Placebo (N=56)	5mg (N=56)	10mg (N=56)	20mg (N=56)	40mg (N=54)	
Any infectious AE N(%)	11 (20%)	10 (18%)	10 (18%)	9 (16%)	11 (20%)	40 (18%)
Typical cold symptoms	6 (11%)	7 (13%)	2 (4%)	4 (8%)	4 (7%)	17 (8%)
Lower respiratory tract	2 (4%)	0	1 (2%)	0	1 (2%)	2 (<1%)
Bacterial /potentially bacterial	5 (9%)	2 (4%)	9 (16%)	5 (9%)	7 (13%)	23 (10%)
Viral / potentially viral	10 (18%)	9 (16%)	3 (5%)	4 (8%)	6 (11%)	22 (10%)
Fungal / potentially fungal	1 (2%)	1 (2%)	1 (2%)	1 (2%)	1 (2%)	4 (2%)

Results: Lipids

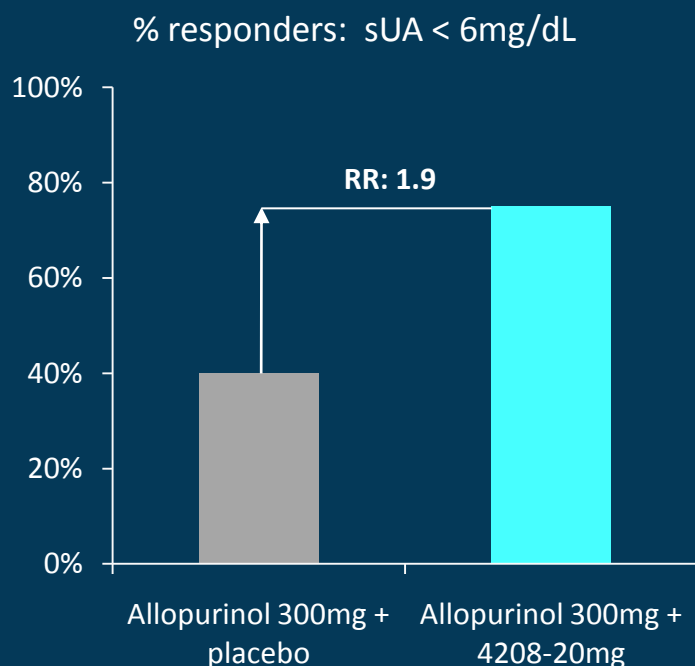
- BCX4208 administration was associated with reductions in total cholesterol and LDL cholesterol
- There were no significant changes in HDL cholesterol or triglycerides



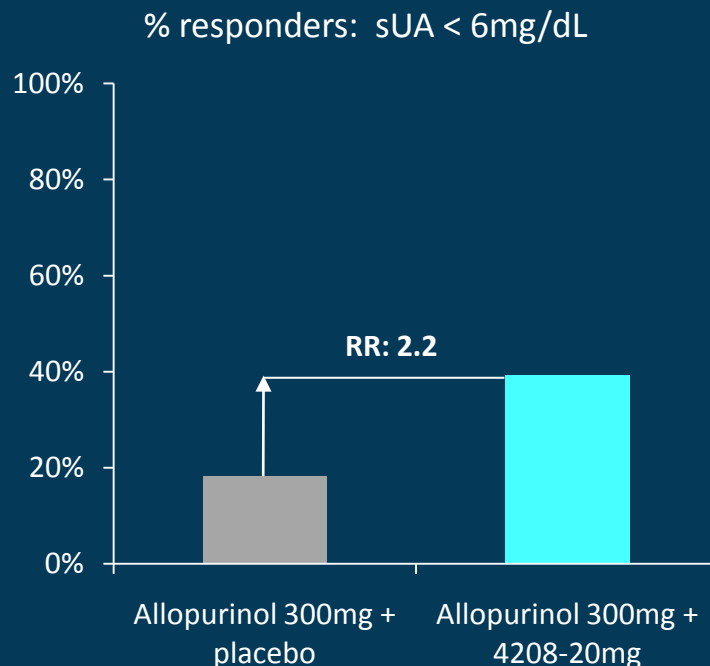
Discussion

- Relative response ratio in inadequate responders is consistent with previous BCX4208 findings in patients off ULT*

Study 202: patients off ULT



Study 203: inadequate responders



Conclusions

- BCX4208 was effective in a broad population of inadequate responders to allopurinol
- BCX4208 + allopurinol doubled the proportion of patients achieving goal of sUA <6 mg/dL compared to allopurinol alone
- BCX4208 was generally safe and well-tolerated
 - AEs frequency and severity was similar among all groups
 - There was no signal for infections
 - Reductions in lymphocyte counts reached a plateau by 12 weeks
- Based on these findings, phase 3 studies are currently in development

Acknowledgments

- The authors would like to acknowledge the invaluable assistance of the following site investigators in recruiting and following patients for this study:
 - Michael Adams - John Agaiby - Simir Azzam - Alan Wine - James Beach - Richard Beasley - David Burak - James Capo, Jr - James Chabala - Howard Chipman - Clinton Corder - Adnan Dahdul - Waymon Drummond - Jose Mari Elacion - William Ellison - Robert Ettliger - Marina Fernandez - Justus Fiechtner - David Fitz-Patrick - Michael Guice - Wayne Harper - John Hill - Troy Holdeman - Susan Hole - Randall Huling - Richard Jackson - Michael Jardula - William Jennings - Enrico Jones - Sukhinder Joshi - Boris Kerner - Alan Kivitz - Denny Lee - Dale Levinsky - Sean Lynd - Ray Mabaquiao - Kenneth Maynard - Jennifer McCallum - Robert McNeill - Stephanie Powell - Raul Romea - Lance Rudolph - David Bouda - Eric Sheldon - Teresa Sligh - Helen Stacey - Harry Studdard - Albert Tejada - Mark Turner - Henry West - Hayes Williams - Jonathan Williams

Adherence to study medications

- Adherence was defined as $\geq 85\%$ drug taken
- Overall, the 5 mg dose cohort had the highest adherence and the 10 mg cohort the lowest adherence
- Adherence to blinded study drug was higher than to allopurinol

