



BCX4208 for the chronic management of gout

**Results of the phase 2b extension to 24 weeks
January 9, 2012**

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BCX4208 phase 2 gout program is nearing completion

Study	Design	Goal	Duration & Population	Primary Outcome Measure	Enrollment	Timeline
201 Monotherapy Dose-ranging Phase 2a	Randomized, double-blind, placebo-controlled 40-240 mg/d	Dose-response + Safety	21-day All comers sUA >8 mg/dL	Reduction in uric acid	99 patients	Reported 2H:10
202 Combination therapy Phase 2a	4X4 factorial design 0,20,40,80 mg/d BCX4208 + 0,100,200,300 mg/d allopurinol	Dose-response + Safety Interactions	21-day All comers sUA >8 mg/dL	Reduction in uric acid	87 patients	Top-line Reported 3Q:10
203 Add-on therapy Phase 2b	RDBPC study 300 mg allopurinol +/- 0,5,10,20,40 mg/d BCX4208	Dose-response + Safety	12 weeks Inadequate response to allopurinol	Proportion of responders: sUA <6mg/dL	279 patients	Top-line Reported 4Q:11
203 Extension to 24 weeks Phase 2b	Daily chronic dosing extension, vaccine response	Evaluate long-term safety	Total treatment period 24 weeks	Safety profile	160 patients	Top-line Reported 1Q:12

Positive outcomes from the BCX4208 extension study to 24 weeks



BCX4208 was generally safe and well-tolerated; no clinical adverse event signals were seen; the rate, severity, pattern and types of infections were similar for BCX4208 and placebo



Patients generated healthy immune responses to a vaccine challenge at 16 or 20 weeks of BCX4208 treatment, similar to patients who received placebo



Over 900 patient-months of drug exposure established a promising longer-term safety profile of BCX4208



BCX4208 sustained sUA control over time, doubling patients' chances of achieving sUA levels below 6 mg/dL

- Data from the robust Phase 2 program supports moving into Phase 3

Study 203 was extended to 24 weeks to further assess the safety profile of BCX4208

12-week analysis objectives

- Evaluate dose-response of BCX4208
- Establish comparative efficacy of BCX4208 add-on to allopurinol in reducing sUA levels, with testing for statistical significance
- Evaluate safety and tolerability
- Evaluate effects of BCX4208 on lymphocytes and subsets
- Evaluate frequency & severity of gout flares

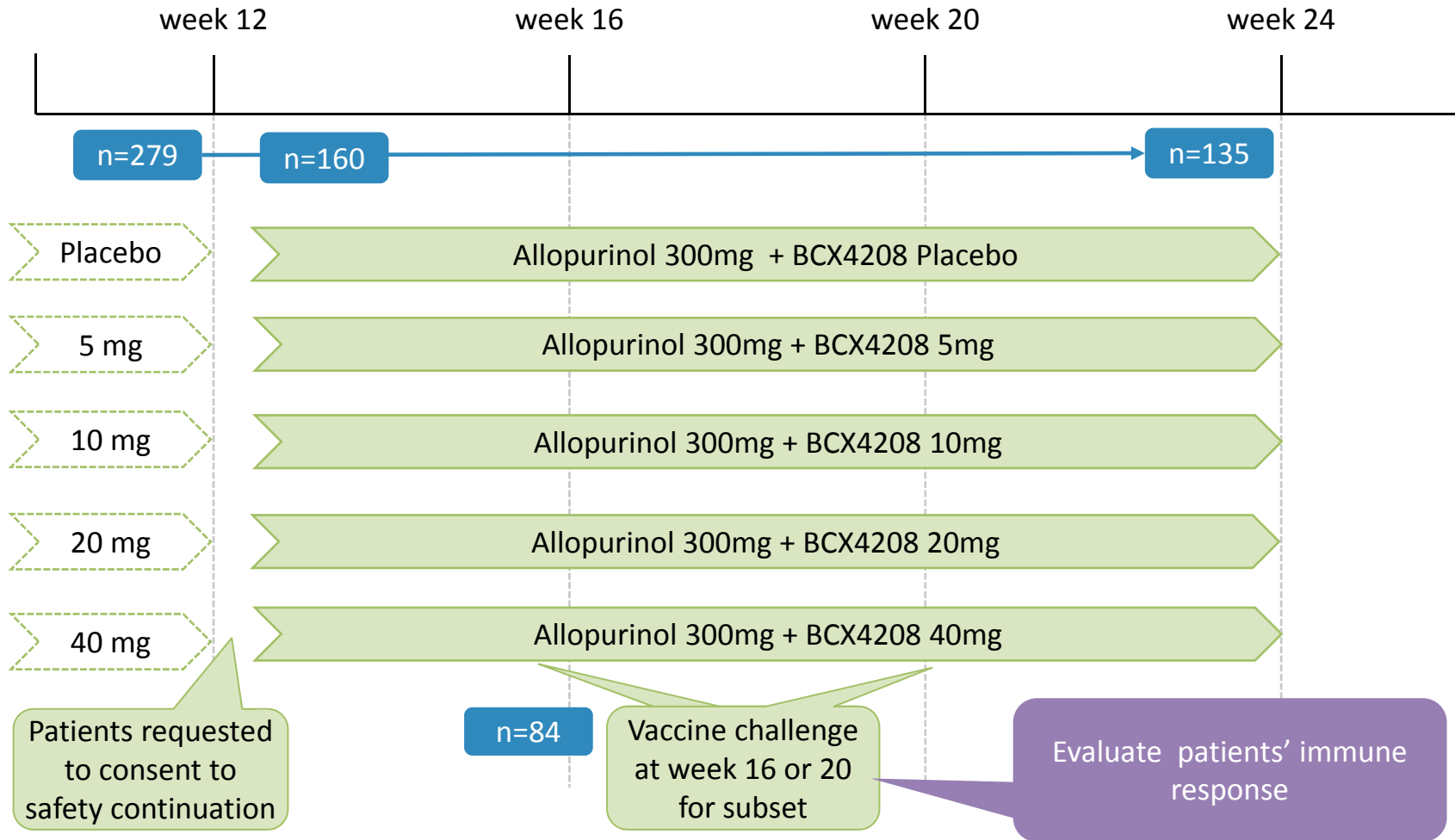
24-week analysis objectives

- Assess longer-term rates of adverse events, especially infections
- Confirm stabilization of lymphocyte counts
- Evaluate immune responses to vaccine challenge
- Confirm continuing impact of BCX4208 on laboratory measures (sUA)

- The design of the 24-week extension allowed for exploratory analyses with the benefit of increased exposure time

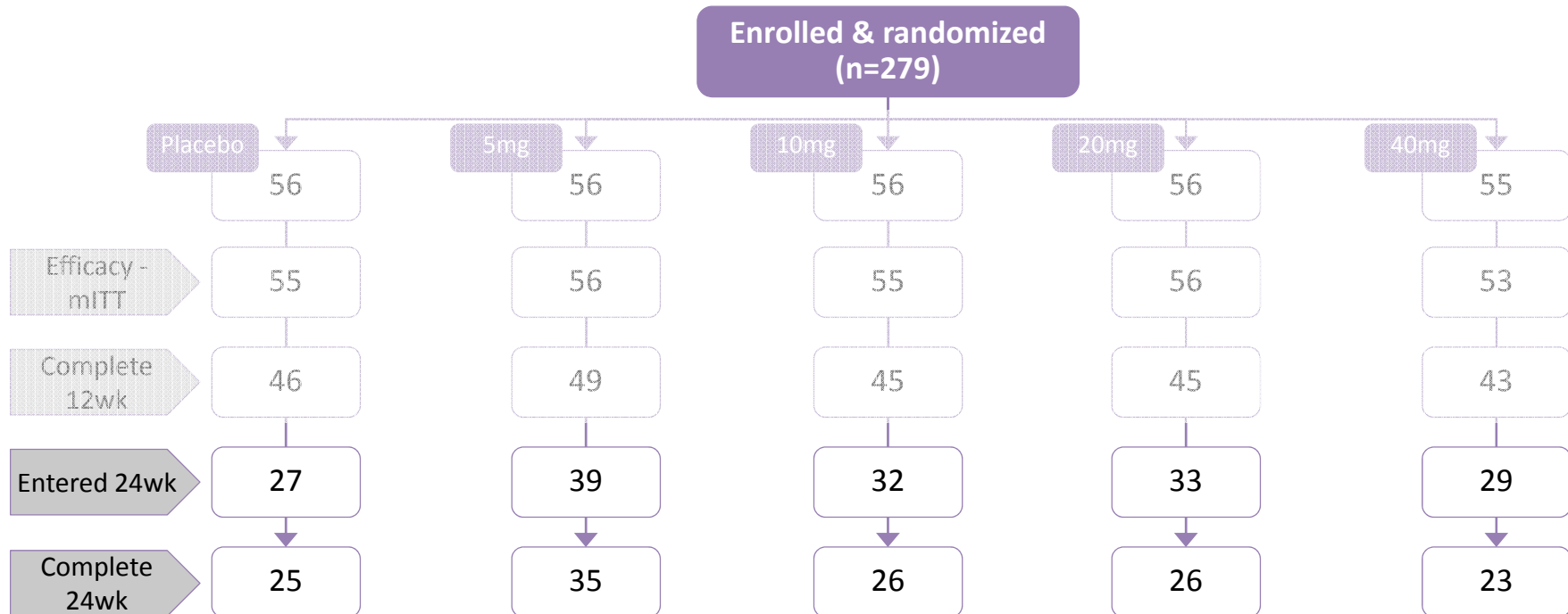
Patients were invited to enroll for another 12 weeks to increase the safety experience on BCX4208

Study 203 safety continuation: design



A large percentage (160 of 228: 70%) agreed to continue blinded treatment assignment in the extension

Study 203: Simplified CONSORT diagram for 24-week safety extension



- A sufficient number of patients continued in each treatment arm to evaluate the 24-week safety of BCX4208

Patients continuing into 24-week extension were representative of the overall study population

Characteristics	<u>In</u> safety continuation (N=160)	<u>Not</u> in safety continuation (N=115)
Age, years: mean (min-max)	49 (19 - 69)	49 (21 - 69)
Female: n	6 (4%)	6 (5%)
Body mass index: mean (min – max)	35.9 (22.8 – 62.2)	36.0 (24.7 – 55.6)
Mild-moderate renal impairment (BSA) : n (%)	72 (45%)	49 (42%)
Diabetes: n (%)	22 (14%)	22 (19%)
White race: n (%)	126 (79%)	75 (65%)

- Patients consenting to 24-week safety extension were not different from those who did not continue

Adverse event rates remained balanced among groups over the 24-week study period

Adverse event rate per 100 patient-months	Allopurinol 300 mg +	Allopurinol 300 mg + BCX4208				
	Placebo (N=56)	5mg/day (N=56)	10mg/day (N=56)	20mg/day (N=56)	40mg/day (N=54)	4208 Total (N=222)
Total patient-months [1]	218	258	220	225	210	912
Any adverse event	45.3	33.8	41.0	41.3	58.2	43.0
Mild	27.5	19.0	15.5	19.1	30.0	20.7
Moderate	15.1	14.4	21.4	17.3	23.8	19.0
Severe	2.7	0.4	4.1	4.9	4.3	3.3

[1] This is used as the denominator to calculate rate of adverse events. The body of the table shows Number of Events per 100 patient-months (Rate of Adverse Events).

- Adverse event rates are similar to placebo

Rates of infections were balanced among groups over the 24-week study period

Infectious AE rate per 100 patient-months	Allopurinol 300 mg +	Allopurinol 300 mg + BCX4208				
	Placebo (N=56)	5mg/d (N=56)	10mg/d (N=56)	20mg/d (N=56)	40mg/d (N=54)	4208 Total (N=222)
Total patient-months ^[1]	218	258	220	225	210	912
Any infectious AE	8.3	6.3	6.5	7.3	5.1	6.3
Mild	5.2	1.8	1.6	3.6	3.0	2.5
Moderate	2.2	4.1	4.1	3.2	2.1	3.4
Severe ^[2]	0.9	0.4	0.8	0.4	0.0	0.4

[1] This is used as the denominator to calculate rate of adverse events. The body of the table shows Number of Events per 100 patient-months (Rate of Adverse Events).

[2] Severe infections were for placebo: sinusitis and influenza, 5mg: gastroenteritis, 10mg: pyelonephritis and pneumonia, 20mg: diverticulitis

- Distribution between mild, moderate and severe infections is similar among treatment arms

There were no imbalances across treatment groups in the types of infections

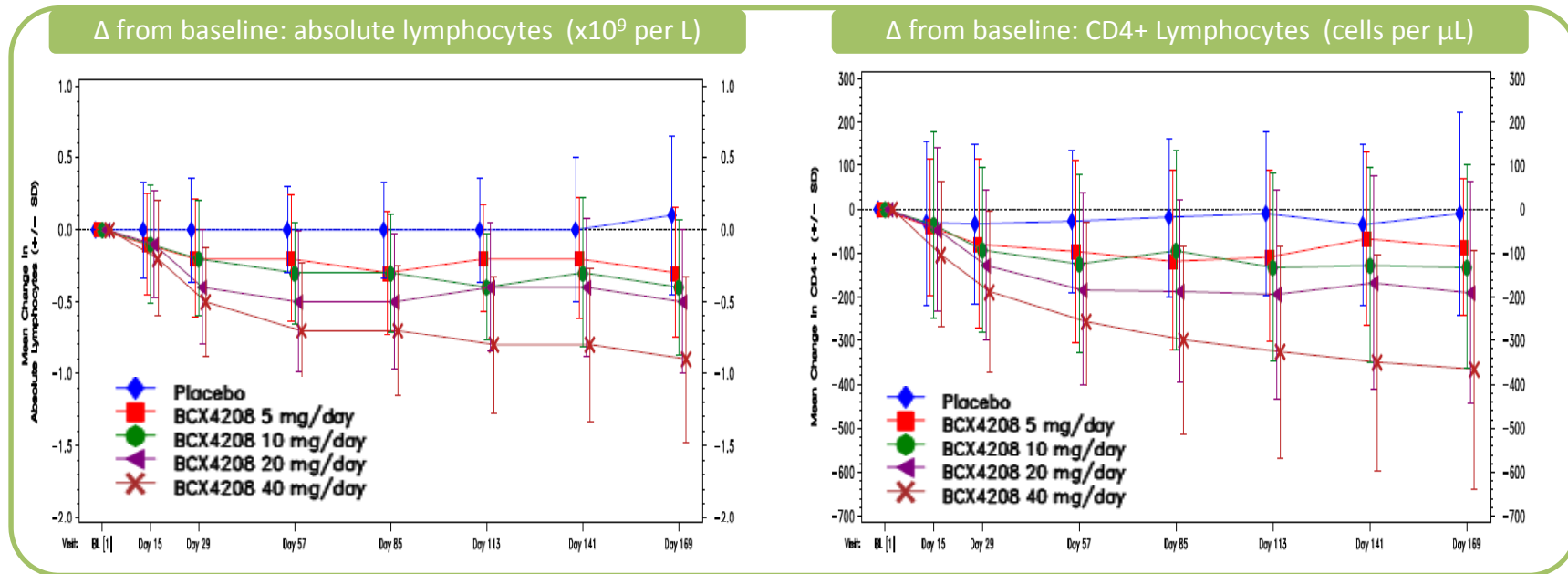
Infectious AE rate per 100 patient-months	Allopurinol 300 mg +	Allopurinol 300 mg + BCX4208				
	Placebo (N=56)	5mg/d (N=56)	10mg/d (N=56)	20mg/d (N=56)	40mg/d (N=54)	4208 Total (N=222)
Total patient-months ^[1]	218	258	220	225	210	912
Cold Symptoms	5.2	4.1	1.6	4.0	1.7	2.9
Lower Respiratory Tract Symptoms	0.9	0.0	0.8	0.4	0.4	0.4
Bacterial Infections	3.5	1.8	5.3	3.6	3.0	3.4
Viral Infections	7.0	5.2	2.0	4.8	2.5	3.7
Topical fungal Infections	0.4	0.4	0.4	0.4	0.8	0.5
Systemic fungal infections	0.0	0.0	0.0	0.0	0.0	0.0

[1] This is used as the denominator to calculate rate of adverse events. The body of the table shows Number of Events per 100 patient-months (Rate of Adverse Events).

The lymphocyte plateau reached at 12 weeks remained unchanged in the 5, 10 and 20 mg BCX4208 arms

- Dose-related reductions in lymphocytes reached a plateau by day 85 (p = non-significant by Helmert transformation)
- Lymphocyte related withdrawals & infection rates:

	Placebo	5 mg	10 mg	20 mg	40 mg
CD4+ withdrawals	0	0	0	4	11
Infection Rate*	8.3	6.3	6.5	7.3	5.1



*Per 100 patient months exposure

The 24-week results confirm that BCX4208 was generally safe and well-tolerated

12-week safety conclusions

- There was no signal for infection
- The lymphocyte counts appear to plateau by 3 months
- Within the first 12 weeks, 10 of 220 BCX4208 subjects met the CD4+ stopping rule
- No subjects on 5 or 10 mg/day met the stopping rule
- The proportion of patients with gout flares was slightly higher for BCX4208 vs. control

24-week safety conclusions

- No clinical adverse event signals were seen
- Over 900 patient-months of drug exposure established a promising safety profile of BCX4208 for longer-term treatment of chronic gout
- The previously observed lymphocyte plateau reached by 12 weeks of treatment remained unchanged in the 5, 10 and 20 mg BCX4208 arms through 24 weeks

- BCX4208 doses of 5 mg, 10 mg and 20 mg are being considered for continued development

A vaccine challenge sub-study was initiated to test the functional competence of lymphocytes in mounting an immune response

Objectives

- To estimate the proportion of subjects who generate an antibody response to pneumococcal polysaccharide vaccine (PPSV) or tetanus toxoid vaccine or both

T-cell functionality

- ≥ 4 -fold antibody response to tetanus toxoid or seroconversion to > 0.15 IU/mL

B-cell functionality

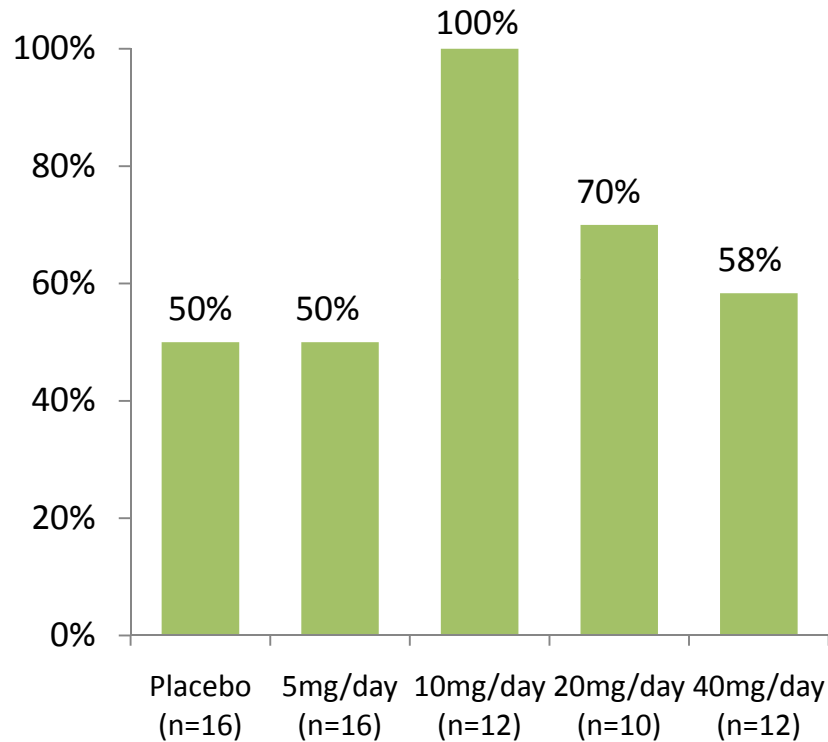
- ≥ 2 -fold antibody response or a seroconversion to detectable levels to ≥ 4 of 6 pneumococcal serotypes

Key exclusion criteria

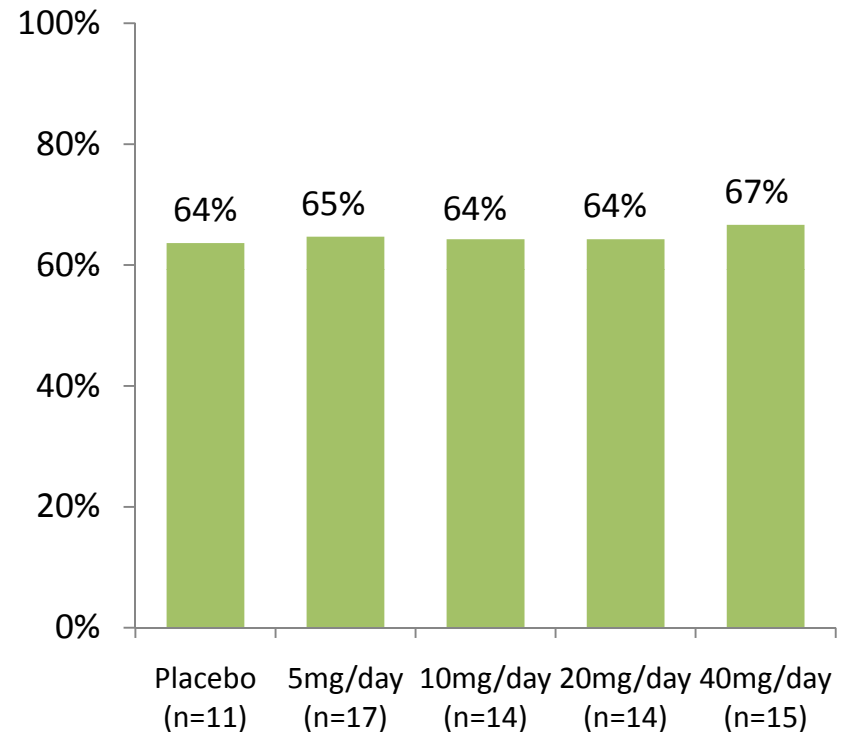
- Previous adverse reaction to PPSV or tetanus toxoid vaccination or allergy
- Diagnosis of pneumococcal infections within the previous 6 months
- Prior vaccinations with PPSV (< 5 y), tetanus (< 10 y) or any vaccination (< 3 mo)

Patients were able to mount a healthy immune response to vaccination

% responding to tetanus toxoid vaccine



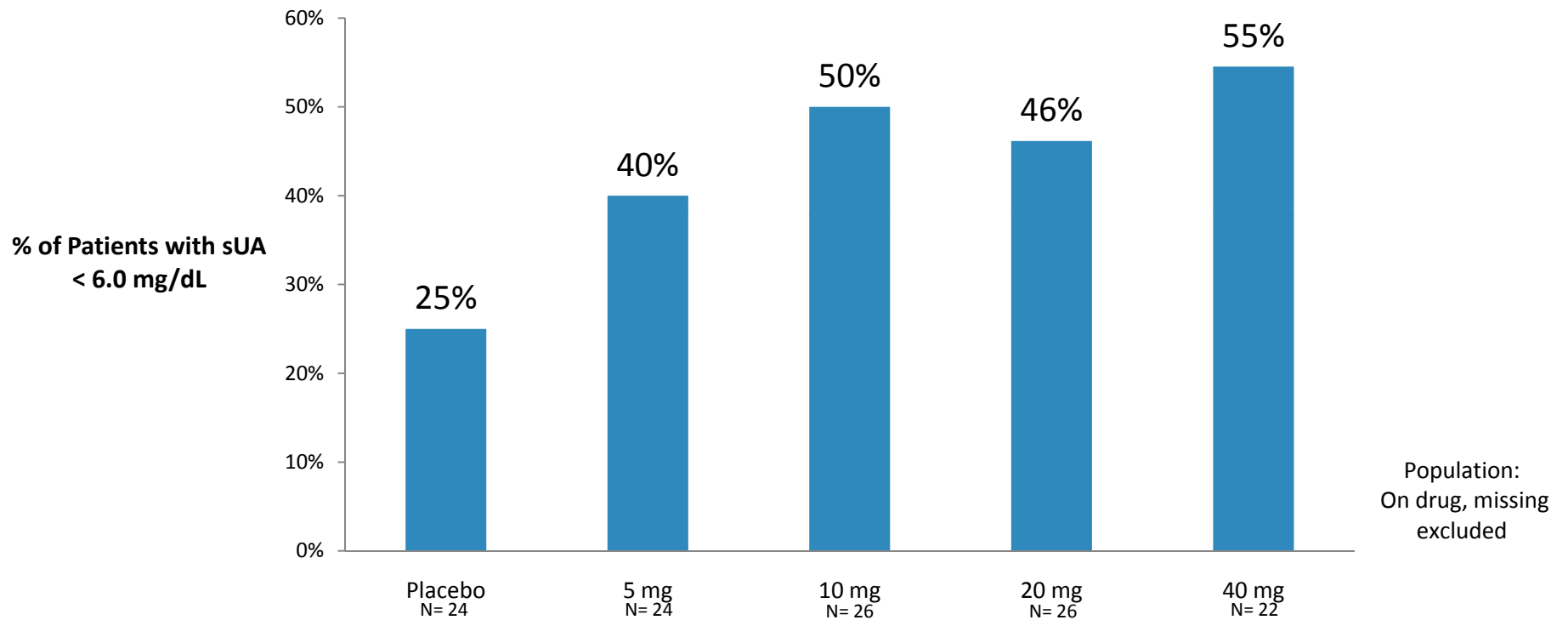
% responding to PPSV vaccine



- Patients generated a healthy immune response to tetanus toxoid (T-cell) or PPSV (B-cell), irrespective of treatment assignment
- Results are consistent with normal responses reported in the literature

BCX4208 add-on to allopurinol maintained an increased proportion of patients reaching goal at week 24

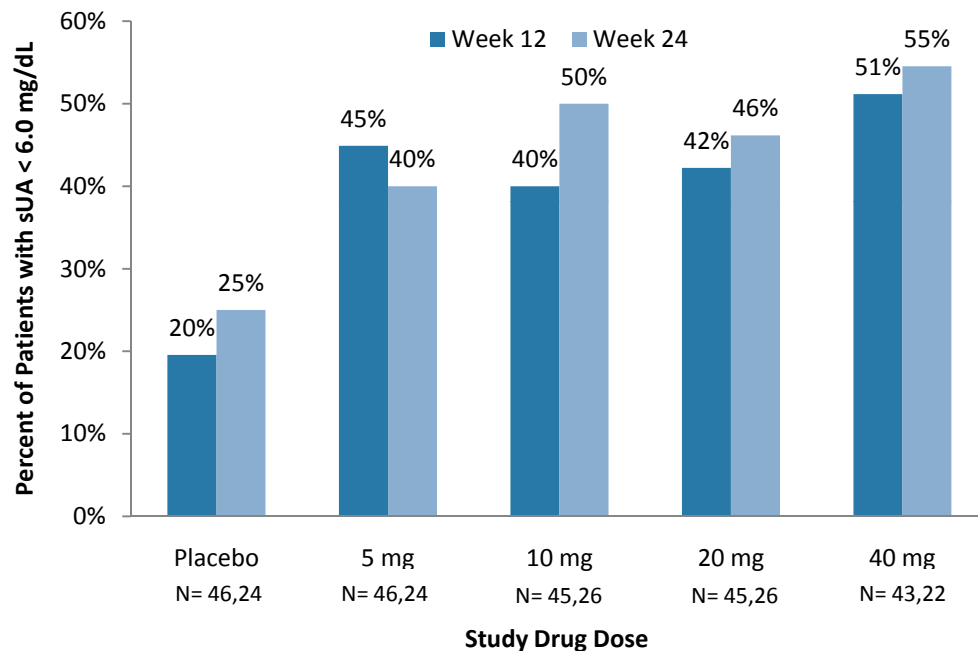
Study 203 results: % patients responding with sUA < 6mg/dL at week 24



Proportion of patients meeting target sUA in the primary population analysis was similar to that in the 24-week extension

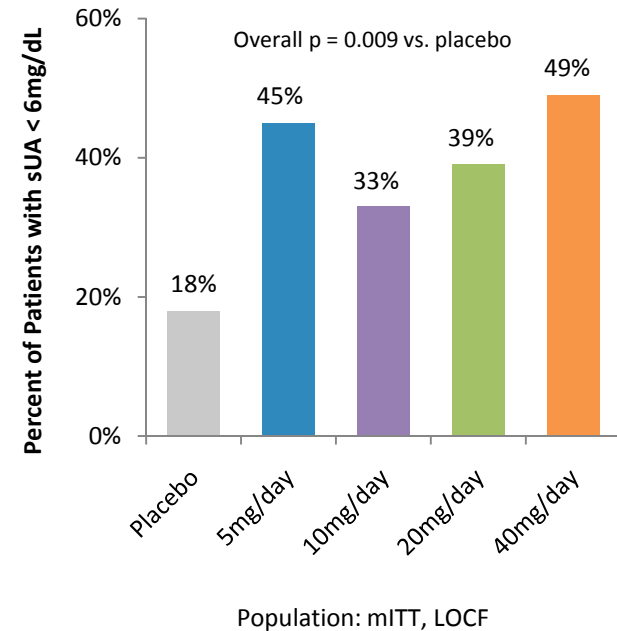
Study 203 results: % patients responding with sUA < 6mg/dL at week 12 & 24

Patients Achieving Goal at 12 and 24 weeks



Population: On drug, missing excluded

Patients Achieving Goal at 12 weeks



Population: mITT, LOCF

- BCX4208 approximately doubled patients' chance of responding to treatment when added to allopurinol

A mild and expected increase in gout flares was observed with increasing dose

- Protocol-defined gout flares
 - Pain to reach a maximum ≥ 2 on the 5-point Likert pain scale within 24 hours
 - ≤ 10 days duration
 - Requires drug therapy
 - Composite score of ≥ 5 on 3 scales for pain, swelling and tenderness

Through week 24	Allopurinol 300 mg +	Allopurinol 300 mg + BCX4208			
	Placebo (N=55)	5mg/day (N=56)	10mg/day (N=55)	20mg/day (N=56)	40mg/day (N=53)
Flares: n (%)	3 (5%)	4 (7%)	4 (7%)	9 (16%)	8 (15%)

BCX4208 has the opportunity to meet unmet medical needs

Gout market challenges:

How BCX4208 may address unmet needs:

1

Improved efficacy

- Only 40% patients reach goal on common doses of XO-inhibitors
- BCX4208 combined with allopurinol increases response rate

2

Innovative mechanism of action (MOA)

- BCX4208 is the only novel MOA in reducing sUA
- BCX4208 demonstrated synergy with allopurinol

3

Patients treated for many chronic diseases

- BCX4208 should not cause drug-drug interactions
- Physicians should not need to adjust concomitant medications

4

20-40% of patients have kidney stones

- BioCryst has included patients with kidney stones in clinical trials
- Approved uricosuric drugs are contraindicated in patients with uric acid kidney stones

1. Shimizu T. Journal of Rheumatology. 36 (9) (pp 1958-62), 2009- The prevalence of nephrolithiasis in patients with primary gout: A cross-sectional study using helical computed tomography; 2. Zhu Y. Choi H. Individuals in the US general population with gout and hyperuricemia have significantly higher comorbidities; NHANES 2007-08; 3. Alvarez-Nemegyei J. Journal of Rheumatology. 32 (11) (pp 2189-91), 2005- Prevalence and risk factors for urolithiasis in primary gout- Is a reappraisal needed



Next steps for BCX4208



- **Regulatory meetings to occur in coming months**
 - FDA (End of Phase 2), EMEA (End of Phase 2) & PMDA (Clinical Trials Consultation)



- **Advancement of the BCX4208 partnering process for Phase 3 development and commercialization**



- **Extension of BCX4208-203 study to 52 weeks of treatment**



- **Continuation of BCX4208 renal impairment and ADME studies**
 - Completion not necessary prior to end of Phase 2 meetings