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BCX4208 Development Program in Gout: Study 203 Top-Line Results

October 5, 2011

BIOCRYST PHARMACEUTICALS, INC.

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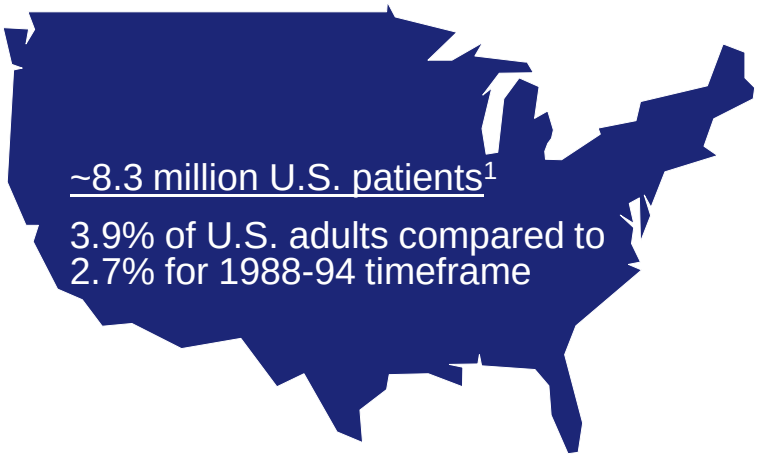
Gout is a global disease with increasing prevalence

In 2008, approximately 17.6 million patients were diagnosed with gout in the major markets



6.4 million patients in 5EU[4]

2.9 million patients in Japan[4]

- Gout prevalence is markedly rising[2]
- Gout now affects ~5% elderly women in U.S. and >7% of elderly men[3]

1. NHANES 2007-2008 Data
2. Zhu Y et al. Arthritis Rheum Vol. 63, No. 10, October 2011, pp 3136–3141
3. Saag KG, et al. Arthritis Res Ther. 2006;8 Suppl 1:S2.]
4. Decision Resources Data

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Goals for treating gout are well established

Acute Treatment:

- ✓ Ease the pain associated with acute gout flare attacks

Chronic Treatment:

- ✓ Decrease serum uric acid (sUA) levels
- ✓ Prevent future attacks
- ✓ Avoid the formation of tophi and kidney stones
- ✓ Reduce the risk of long-term joint destruction and erosion

With early medical attention and treatment, most gout patients will not progress to the advanced disabling stages of gout

Source: Adapted from Gout and Uric Acid Education Society

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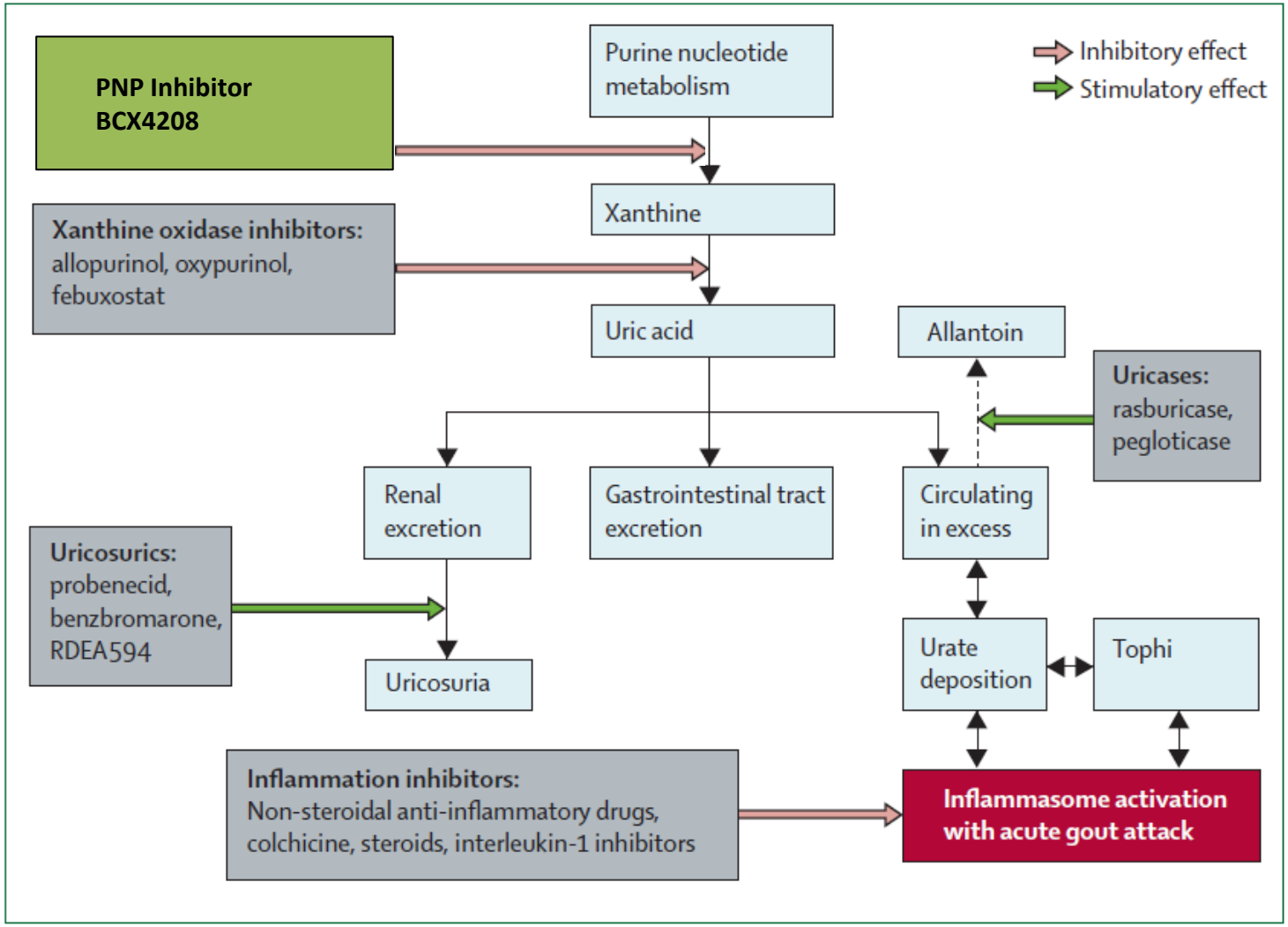
PNP inhibition represents an innovative approach to urate-lowering therapies



Burns et all, Gout therapeutics :new drugs for an old disease. Aug17,2010 DOI:10.1016/so140-6736

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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 3-month Extension Study	Daily chronic dosing extension, vaccine response	Evaluate long-term safety	Total treatment period 6 months	Safety profile	~150 patients	Ongoing & Top-line Expected Early 2012

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Synergistic reductions in mean sUA with BCX4208 and allopurinol in lowering sUA

Proportion of Subjects with day 22 sUA <6.0 mg/dL

	0 mg BCX4208	20mg BCX4208	40mg BCX4208	80mg BCX4208
0 mg allopurinol	0%	0%	17%	40%
100 mg allopurinol	0%	0%	60%	40%
200 mg allopurinol	0%	20%	80%§	80%§
300 mg allopurinol	40%	80%§	80%§	83%§

Change in sUA from Baseline on Day 22

	0 mg BCX4208	20 mg BCX4208	40 mg BCX4208	80 mg BCX4208
300 mg allopurinol	-2.1	-4.3	-4.3	-4.6

Overall BCX4208 dose-response effect, $p < 0.001$
Overall allopurinol dose-response effect, $p < 0.001$
§ $p < 0.05$ vs placebo

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Study 203 inclusion & exclusion criteria selected a more challenging patient population compared to 202

- Key inclusion criteria:
  - **Baseline sUA ≥6.0 mg/dL after 2 weeks on 300 mg of allopurinol**
  - Documented diagnosis of gout - ARA 1977 criteria
  - Prophylaxis for gout flares - colchicine or naproxen

- Key exclusion criteria:
  - Gout flare during 2 weeks prior to randomization
  - Moderate or severe renal impairment
  - Liver transaminases > 2 times upper limit of normal
  - $CD4^+$ lymphocyte subset < 500 cells/mm^3
  - Abnormal hemoglobin or white blood cell counts

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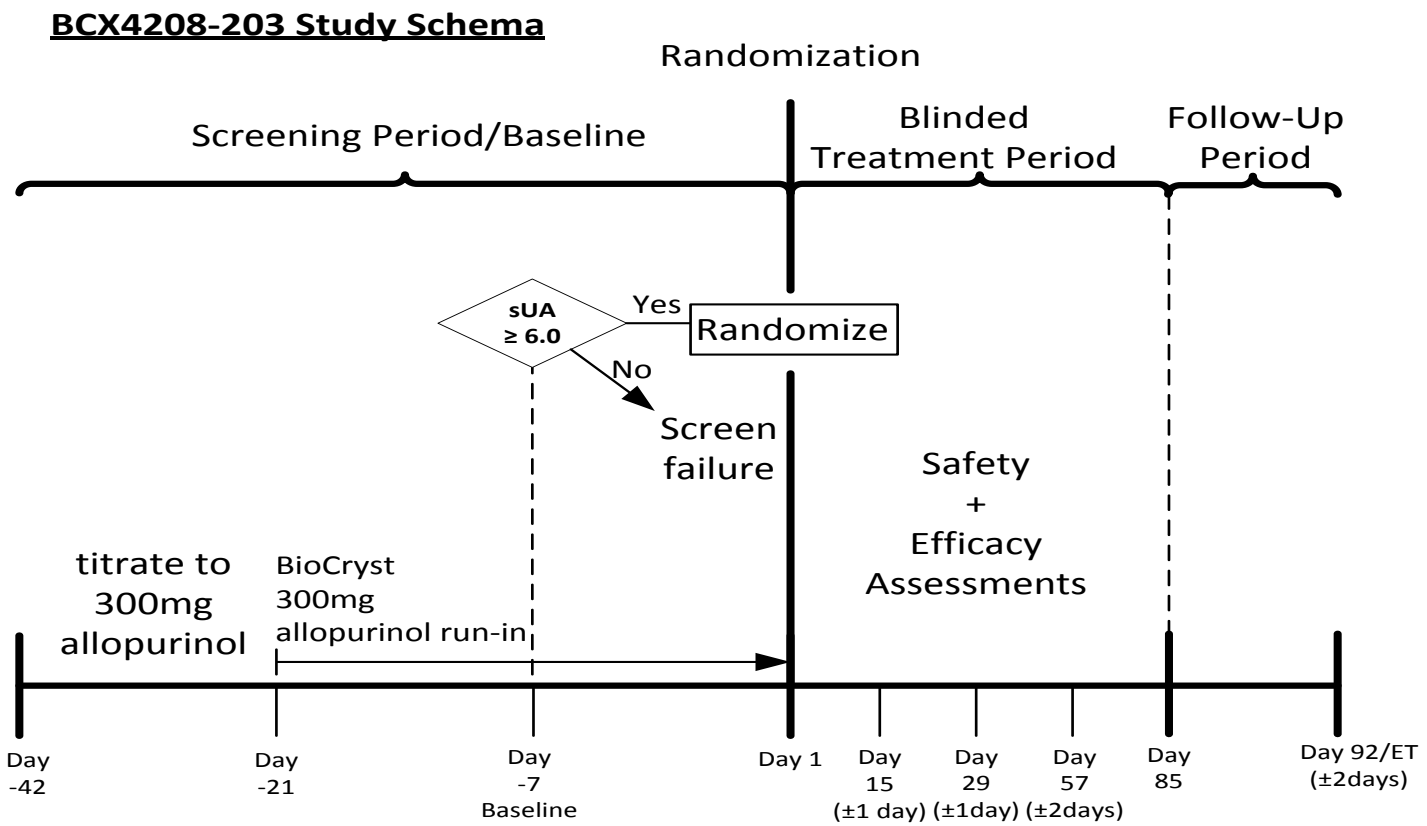
Patients were followed for 12 weeks on study for this analysis



Primary Endpoint: proportion of subjects with sUA <6.0 mg/dL at day 85

Study 203 demographic and baseline characteristics showed a population with multiple comorbidities

		BCX4208 Treatment Groups			
	Placebo (N=56)	5mg/day (N=56)	10mg/day (N=56)	20mg/day (N=56)	40mg/day (N=54)
Males	55 (98%)	53 (95%)	54 (96%)	53 (95%)	51 (94%)
Age, yr*	50 (10.2)	46 (10.8)	50 (9.4)	50 (10.6)	49 (9.9)
BMI, kg/m^2*	37.3 (7.63)	35.1 (6.76)	36.1 (7.41)	36.2 (6.69)	34.5 (6.68)
Obese: BMI > 30	29 (52%)	29 (52%)	28 (50%)	31 (55%)	23 (43%)
Morbidly Obese: BMI > 40	17 (30%)	13 (23%)	13 (23%)	17 (30%)	10 (19%)
Hypertension	33 (59%)	27 (48%)	36 (64%)	37 (66%)	28 (58%)
Hyper-cholesterolemia	19 (34%)	28 (50%)	25 (45%)	18 (32%)	18 (33%)
Diabetes	11 (20%)	10 (18%)	10 (18%)	7 (13%)	6 (11%)
Median # of Concomitant Medications	5	4	5	3	4

**Mean (SD)*

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The 203 study met its primary efficacy endpoint

In a population of gout subjects failing to achieve target sUA of <6mg/dL on allopurinol alone:

- The primary endpoint of the study was the proportion of patients with sUA <6 mg/dL at day 85
- The primary endpoint of the study was successfully achieved
- When added to allopurinol 300 mg, BCX4208 was superior to allopurinol plus placebo (p=0.009 overall)
- BCX4208 doses evaluated in the study showed response rates ranging from 33% to 49%, compared to 18% for placebo

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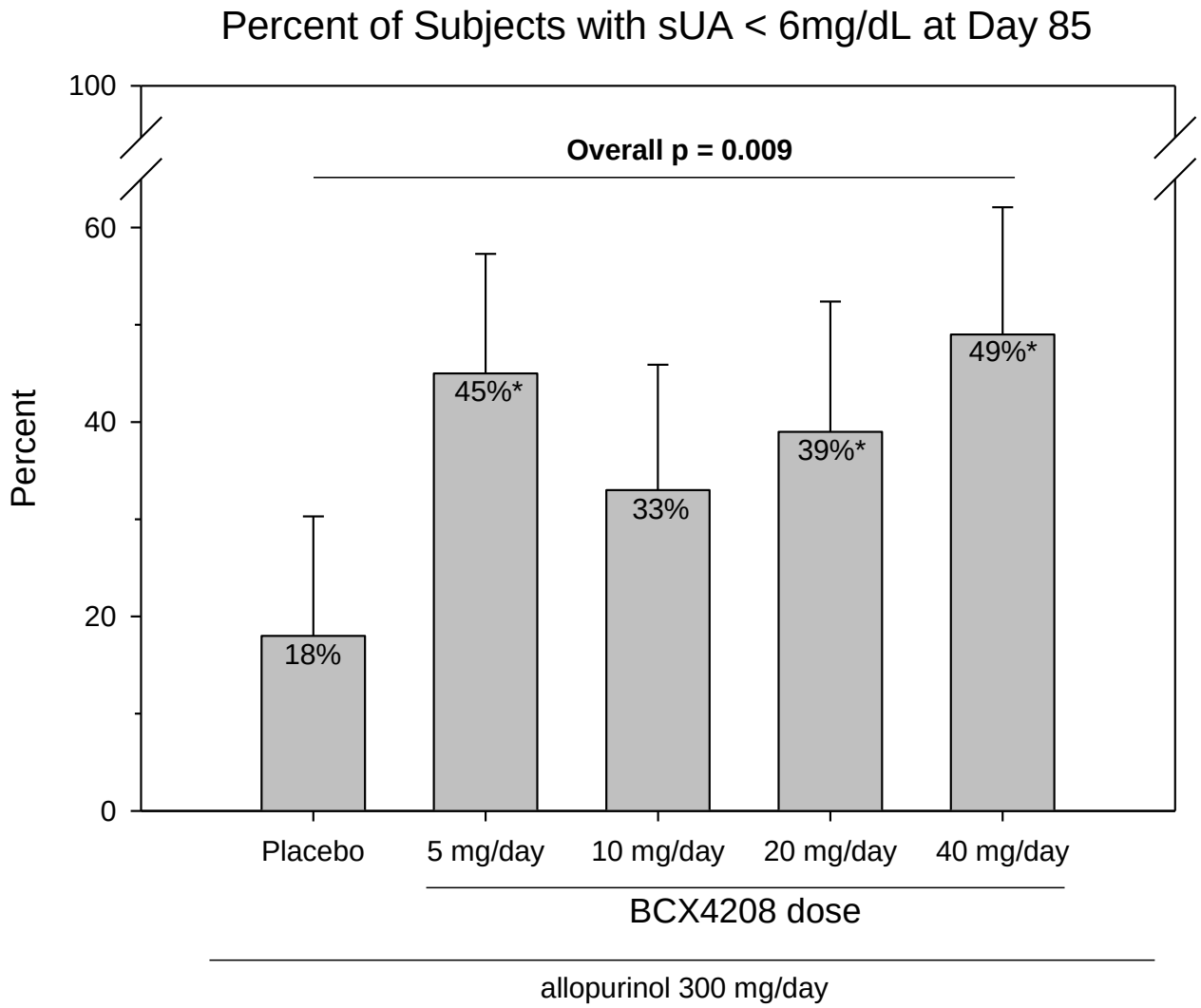
BCX4208 added to allopurinol increased the proportion of patients achieving goal in patients failing allopurinol alone



BCX4208 was generally safe and well-tolerated, with no significant safety signals at the doses studied

- **Overall, BCX4208 was generally safe and well-tolerated**
  - Frequency and severity of AEs was similar between placebo and each dose of BCX4208
  - SAEs were infrequent and showed no drug or dose relationship
- **No signal for infections**
  - Incidence and types of infections, and the pattern of severity were similar across placebo and BCX4208 dose groups
  - No opportunistic or unusual infections were observed
- **The lymphocyte counts appear to plateau within 12 weeks**
- **Within the first 12 weeks, 10 of 222 BCX4208 patients met the CD4+ stopping rule**
  - Two patients on 20 mg/day and eight on 40 mg/day met stopping rule
  - No patients on placebo, 5 or 10 mg/day BCX4208 met the stopping rule

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Incidence and types of infections were similar across placebo and BCX4208 dose groups

Infection and Infestations SOC	Placebo (N=56)	5mg/day (N=56)	10mg/day (N=56)	20mg/day (N=56)	40mg/day (N=54)	BCX4208 Total (N=222)
Any infectious AE	11 (20%)	10 (18%)	10 (18%)	9 (16%)	11 (20%)	40 (18%)
Event representing Typical cold symptoms[1]	6 (11%)	7 (13%)	2 (4%)	4 (8%)	4 (7%)	17 (8%)
Events representing lower respiratory tract infections [2]	2 (4%)	0	1 (2%)	0	1 (2%)	2 (<1%)
Bacterial and potentially bacterial infections[3]	5 (9%)	2 (4%)	9 (16%)	5 (9%)	7 (13%)	23 (10%)
Viral and potentially viral infections[4]	10 (18%)	9 (16%)	3 (5%)	4 (8%)	6 (11%)	22 (10%)
Fungal and potentially fungal infections[5]	1 (2%)	1 (2%)	1 (2%)	1 (2%)	1 (2%)	4 (2%)

1. *PTs representing cold symptoms: URI, Nasopharyngitis, Viral infection, Sinusitis, Pharyngitis*
2. *PTs representing lower respiratory tract symptoms: Influenza, Pneumonia*
3. *PTs representing bacterial infections: Sinusitis, Gastroenteritis, Pharyngitis, Pharyngitis Streptococcal, Tooth infection, Urinary tract infection, Bactiuria, Cellulitis, Diverticulitis, Ear infection, Folliculitis, Hordeolum, Oral infection, Otitis externa, Pneumonia, Prostate infection, Pyelonephritis, Tooth abscess*
4. *PTs representing viral infections: URI, nasopharyngitis, sinusitis, Gastroenteritis, influenza, pharyngitis, gastroenteritis viral, gastrointestinal viral infection, Herpes simplex, Viral infection*
5. *PTs representing fungal infections: Tinea versicolor, Body tinea, Otitis externa, Tinea cruris*

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Pattern of severity of infection was similar across placebo and BCX4208 groups

Infection and Infestations severity	Placebo (N=56)	5mg/day (N=56)	10mg/day (N=56)	20mg/day (N=56)	40mg/day (N=54)	BCX4208 Total (N=222)
All infectious adverse events	11 (20%)	10 (18%)	10 (18%)	9 (16%)	11 (20%)	40 (18%)
Mild	7 (13%)	3 (5%)	3 (5%)	4 (7%)	6 (11%)	16 (7%)
Moderate	3 (5%)	7 (13%)	5 (9%)	4 (7%)	5 (9%)	21 (9%)
Severe	1 (2%)	0	2 (4%)	1 (2%)	0	3 (1%)
Life-threatening	0	0	0	0	0	0

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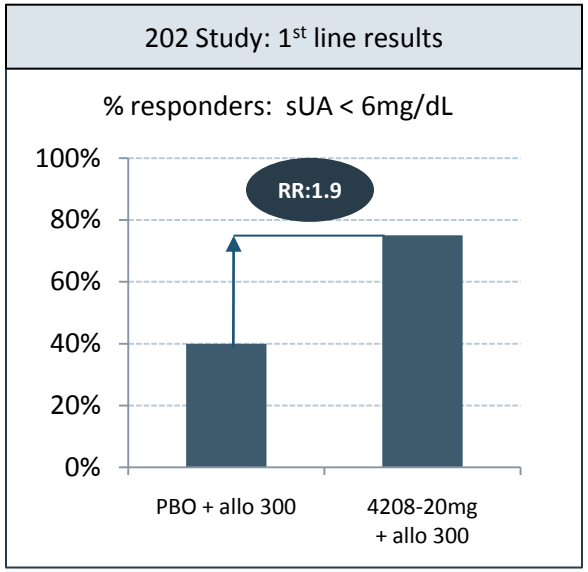
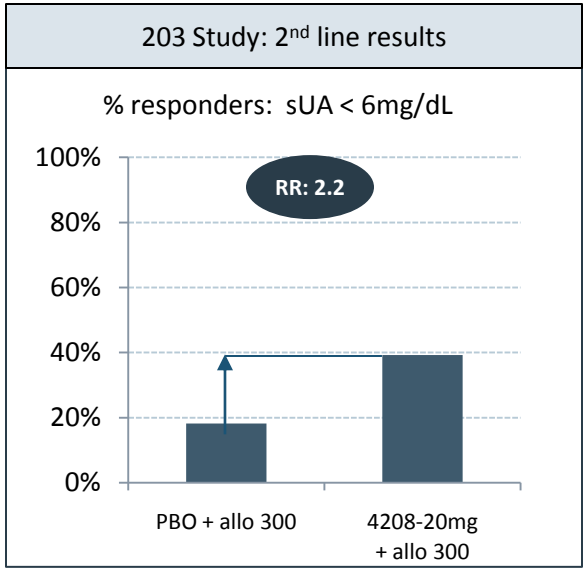
BCX4208-203 added to allopurinol doubled the response rate in both 1st and 2nd line therapy

- Study 203 response ratio in allopurinol failures is consistent with study 202 findings in 1st line therapy





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Study Summary

- Primary efficacy met: BCX4208 + allopurinol increased the proportion of patients achieving goal of sUA <6 mg/dL overall, compared to placebo + allopurinol
- BCX4208 was generally safe and well-tolerated
- No signal for infections
- Additional study results to be submitted for presentation at an upcoming medical meeting
- On track to conclude BCX4208 Phase 2 program during 1H:12
- Plan to discuss study results in more detail with regulatory authorities and potential partners

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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 Mechanisms 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

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BCX4208: Important progress & next steps

- ✓ Additional data from Phase 2 BCX4208/allopurinol combination study in gout at EULAR (May)
- ✓ Begin collecting BCX4208 long-term safety data in gout (2Q:11)
- ✓ **Report data from Phase 2b BCX4208/allopurinol add-on study (Early 4Q:11)**
- ❑ **Complete BCX4208 ADME study (Late 2011)**
- ❑ **Report initial six-month safety data for BCX4208 (Early 2012)**
- ❑ **Complete renal impairment study (1H:12)**
- ❑ **End of Phase 2 regulatory discussions for BCX4208 (Mid-2012)**

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