BXCL501 Demonstrates Significant Reduction in Agitation Across all Mood States (Depressed, Hypomanic, Manic) in Patients With Bipolar Disorder

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INTRODUCTION

- Acute agitation occurs frequently in patients with bipolar disorder, requiring early intervention to reduce the risk of patient or staff injuries, disruption of care, and prolongation of hospital stays
- BXCL501 is an investigational orally dissolving film formulation of dexmedetomidine, a selective α_{2A} adrenergic receptor agonist designed to completely dissolve in the sublingual or buccal area
- Film administration of a discrete microdose bypasses first-pass metabolism, resulting in more rapid and higher bioavailability of dexmedetomidine than ingested formulations

OBJECTIVES

- Determine if a single dose of BXCL501 180 µg or 120 µg effectively reduces symptoms of acute agitation associated with bipolar disorder up to 2 hours postdose compared to placebo
- Determine the effects of BXCL501 on acute agitation in patient subgroups identified by mood state, as defined by DSM-5

METHODS

- Phase 3, randomized, placebo-controlled study of adults (18-75) diagnosed with DSM-5 bipolar I or II
- Clinically agitated at screening and baseline with PANSS Excited Component (PEC) total score ≥14) and baseline score of ≥4 on ≥1 PEC item
- Subjects were randomized (1:1:1) to a single dose of BXCL501 120 µg, BXCL501 180 µg, or placebo and self-administered the study drug

Assessments

- The primary efficacy endpoint was mean change from baseline on the PEC total score at 2 hours postdose
- PEC scale includes 5 items (poor impulse control, tension, hostility, uncooperativeness, and excitement) scored on a scale ranging from 1=minimum to 7=maximum; total score was the sum of the 5 item scores (range 5-35)
- Assessments occurred at screening, predose (within 15 minutes of the first dose), 10, 20, 30, 45, 60, 90 minutes and 2, 4, 6, and 8 hours following the first dose
- In this post hoc analysis:
  - Subjects were stratified by DSM-5 mood state at baseline
  - Mood state subgroups included depression, hypomania, mania, mixed episodes, and unspecified
  - Mean change from baseline in PEC total score from 10 minutes to 8 hours postdose was analyzed; p-values are nominal

RESULTS

Subjects

- 380 subjects were enrolled, 378 received 1 or more doses of study drug, and 362 completed the study
- The most common diagnoses were mania (180 [47.6%]), mixed episodes (79 [20.9%]), and depressed (74 (19.6%)
- At baseline, most subjects had moderate agitation (mean PEC score range: 16.6-18.4)
- Demographic and baseline disease characteristics were generally comparable in all treatment groups (**Table 1**)
- Compared with the overall trial population, subjects in the unspecified subgroup were less likely to be:
  - Female
  - White
  - Severely agitated
  - Hospitalized

Table 1. Demographics and Baseline Characteristics

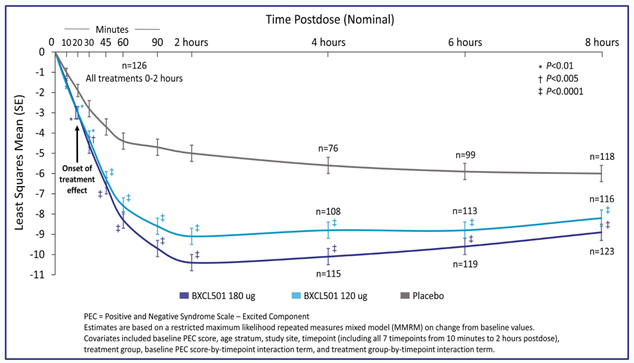
	BXCL501 Subgroup by DSM-5 Mood State (N=378)				
	Depressed n=74	Hypomania n=29	Mania n=180	Mixed n=79	Unspecified n=16
Age, years, mean (SD)	46.8 (11.2)	47.5 (10.7)	45.4 (11.4)	43.5 (12.5)	49.3 (12.4)
Sex, n (%)					
Female	43 (58)	17 (59)	103 (57)	37 (47)	7 (44)
Male	31 (42)	12 (41)	77 (43)	42 (53)	9 (56)
Race, n (%)					
Non-White*	42 (57)	14 (48)	107 (59)	49 (62)	11 (69)
White	32 (43)	15 (52)	73 (41)	30 (38)	5 (31)
Agitation severity, n (%)					
Moderate	61 (82)	23 (79)	128 (71)	55 (70)	15 (94)
Severe	13 (18)	6 (21)	52 (29)	24 (30)	1 (6)
Hospitalizations, n, mean (SD)	2.2 (3.5)	2.8 (4.9)	3.4 (4.3)	3.3 (4.5)	1.9 (5.4)
Sleep/night this week, h, mean (SD)	5.3 (1.5)	5.3 (1.5)	5.1 (1.6)	5.2 (1.6)	5.1 (1.3)

[a]Includes American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and Multiple

Efficacy: Overall and Mood State Subgroups

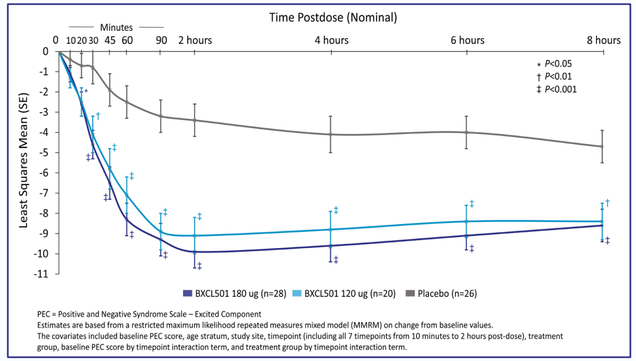
- In the overall population:
  - Mean 2-hour changes from baseline in PEC score were −10.4 for BXCL501 180 µg, −9.0 for BXCL501 120 µg, and −4.9 for placebo (both doses *P*<.0001 vs placebo)
  - Significant improvement from baseline in the PEC began at 20 minutes postdose and continued through 2 hours postdose (**Figure 1)**, and both BXCL501 treatment groups maintained improvements in PEC score at 4, 6, and 8 hours postdose
- In the depressed and mania subgroups (**Figures 2-5**), mean changes from baseline in PEC score were significantly superior to placebo:
  - Beginning at 20 minutes postdose (both doses *P*<.05 vs placebo)
  - At all timepoints through 8 hours postdose (both doses *P*<.05 vs placebo)
- Subjects in the unspecified subgroup had higher scores the those in the placebo group at all time points from 60 minutes through 8 hours postdose

Figure 1. Overall: PEC Total Change From Baseline 0 – 8 Hours Postdose



PEC = Positive and Negative Syndrome Scale – Excited Component
Estimates are based on a restricted maximum likelihood repeated measures mixed model (MMRM) on change from baseline values.
Covariates included baseline PEC score, age stratum, study site, timepoint (including all 7 timepoints from 10 minutes to 2 hours postdose), treatment group, baseline PEC score-by-timepoint interaction term, and treatment group-by-timepoint interaction term.

Figure 2. Depressed: PEC Total Change From Baseline 0 – 8 Hours Postdose



PEC = Positive and Negative Syndrome Scale – Excited Component
Estimates are based from a restricted maximum likelihood repeated measures mixed model (MMRM) on change from baseline values.
The covariates included baseline PEC score, age stratum, study site, timepoint (including all 7 timepoints from 10 minutes to 2 hours post-dose), treatment group, baseline PEC score by timepoint interaction term, and treatment group by timepoint interaction term.

Figure 3. Hypomania: PEC Total Change From Baseline 0 – 8 Hours Postdose

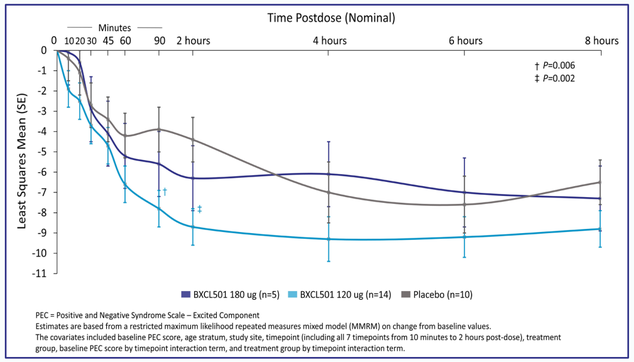


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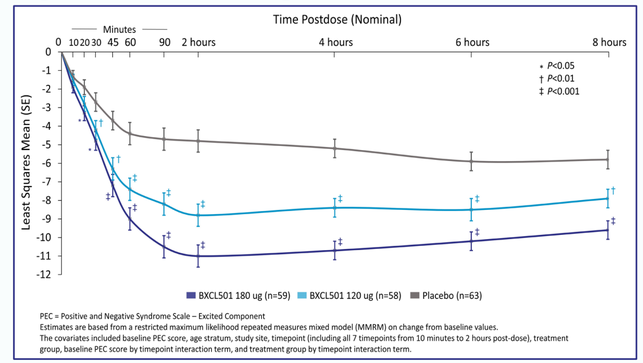
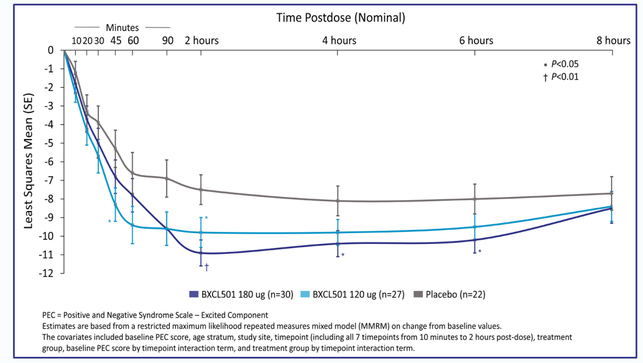
Figure 4. Mania: PEC Total Change From Baseline 0 – 8 Hours Postdose



PEC = Positive and Negative Syndrome Scale – Excited Component
Estimates are based from a restricted maximum likelihood repeated measures mixed model (MMRM) on change from baseline values.
The covariates included baseline PEC score, age stratum, study site, timepoint (including all 7 timepoints from 10 minutes to 2 hours post-dose), treatment group, baseline PEC score by timepoint interaction term, and treatment group by timepoint interaction term.

Figure 5. Mixed: PEC Total Change From Baseline 0 – 8 Hours Postdose



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CONCLUSIONS

- In the overall trial population, BXCL501 demonstrated rapid, durable, and clinically meaningful effects in acutely agitated subjects with bipolar disorder, with significant reductions from baseline as early as 20 minutes through 8 hours postdose in PEC total score
- This analysis demonstrated significant effects of BXCL501 across subgroups of patients regardless of bipolar mood state
- Among subjects in the depressed, hypomania, mania, and mixed episodes subgroups, both doses of BXCL501 provided significant benefits versus placebo as soon as 20 minutes postdose and through 8 hours postdose
- BXCL501 is an investigational, novel, non-invasive treatment of agitation for acute agitation in bipolar disorder

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