Effect of BXCL501 for Treating Acute Agitation 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 dexmedetomidine bypasses 1st pass metabolism resulting in more rapid & higher bioavailability 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

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
- Participants 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
- Secondary endpoints — change from baseline in the PEC score at 90 through 10 minutes postdose — were tested using a hierarchical gatekeeping procedure (α> 0.025)
- Prespecified exploratory endpoints included mean change from baseline in Clinical Global Impressions-Improvement (CGI-I) and Agitation-Calmness Evaluation Scale (ACES); p-values for exploratory endpoints are nominal
- 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

RESULTS

Subjects

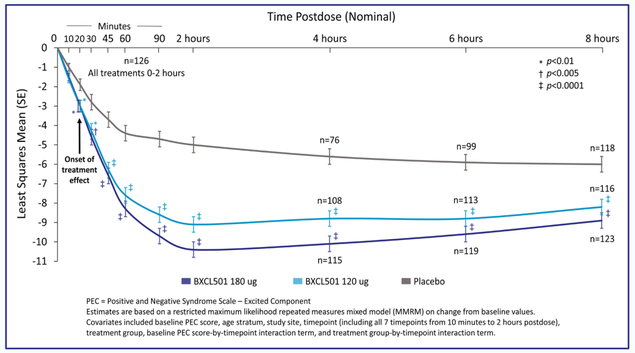
- 380 subjects were enrolled, 378 received 1 or more doses of study drug, and 362 completed the study
- Demographic and baseline disease characteristics were comparable and balanced in all treatment groups (**Table 1**)
- The most common diagnoses were mania (180 [47.6%]) and mixed episodes (79 [20.9%])
- At baseline, subjects in all treatment groups had moderate agitation (mean PEC score range: 17.9-18.0)

Table 1. Demographics and Baseline Characteristics

	180 µg (n=126)	120 µg (n=126)	Placebo (n=126)
Age, years, mean (SD)	45.9 (11.3)	46.1 (11.5)	44.8 (12.1)
Sex, n (%)			
Female	67 (53.2)	67 (53.2)	73 (57.9)
Male	59 (46.8)	59 (46.8)	53 (42.1)
Race, n (%)			
Black or African American	72 (57.1)	68 (54.0)	72 (57.1)
White	49 (38.9)	56 (44.4)	50 (39.7)
Other[a]	5 (4.0)	2 (1.6)	4 (3.2)
Ethnicity, n (%)			
Hispanic or Latino	15 (11.9)	12 (9.5)	11 (8.7)
Not Hispanic or Latino	111 (88.1)	114 (90.5)	115 (91.3)
Diagnosis, n (%)			
Depressed	28 (22.2)	20 (15.9)	26 (20.6)
Hypomania	5 (4.0)	14 (11.1)	10 (7.9)
Mania	59 (46.8)	58 (46.0)	63 (50.0)
Mixed episodes	30 (23.8)	27 (21.4)	22 (17.5)
Unspecified	4 (3.2)	7 (5.6)	5 (4.0)
Current agitation, days, mean (SD)	25.1 (74.3)	21.8 (31.4)	15.7 (21.9)
Hospitalizations, n, mean (SD)	2.8 (4.45)	3.5 (4.70)	2.8 (3.66)
Sleep/night this week, h, mean (SD)	5.1 (1.51)	5.3 (1.65)	5.1 (1.49)

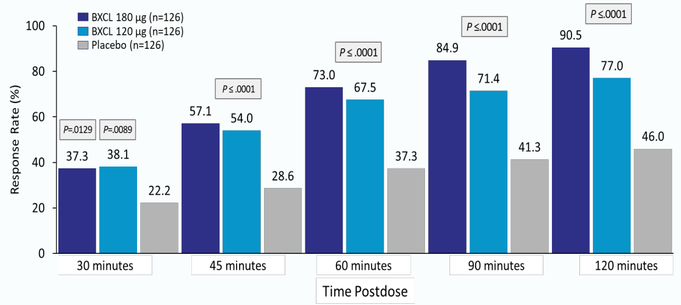
[a]Includes American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, and Multiple

Figure 1. Change from Baseline in PEC Total Score, 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. PEC Response Rate Through 2 Hours Postdose



Efficacy: PEC Total, CGI-I, and ACES

- 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, as shown in **Figure 1**
- Both BXCL501 treatment groups maintained significant improvements in PEC score at 4, 6, and 8 hours postdose (*P*<.0001 vs placebo)
- Mean PEC response rates in both BXCL treatment groups were greater than placebo from 30 minutes through 2 hours postdose (Figure 2), resulting in a number needed to treat versus placebo of 3 (95% CI 2 - 3) for BXCL501 180 µg and 4 (95% CI 3 - 6) for BXCL501 120 µg
- On the CGI-I and ACES (**Table 2**), subjects in both BXCL treatment groups were improved versus baseline at 2 hours postdose (*P*<.0001)

Table 2. CGI-I at 2 Hours & ACES Change Baseline to 2 Hours Postdose

	180 µg (n=126)	120 µg (n=126)	Placebo (n=126)
CGI-I			
LS mean ± SE	1.5 ± 0.1	1.9 ± 0.1	2.8 ± 0.1
LS mean difference ± SE	-1.3 ± 0.1	-0.9 ± 0.1	
P-value	<.0001	<.0001	
ACES			
LS mean change ± SE	3.5 ± 0.2	2.9 ± 0.2	1.1 ± 0.2
LS mean difference ± SE	2.4 ± 0.2	1.8 ± 0.2	
P-value	<.0001	<.0001	

CGI-I, Clinical Global Impressions – Improvement; LS, least squares; ACES, Agitation and Calmness Evaluation Scale

Safety

- The incidence of AEs was 35.7% with BXCL501 180 µg, 34.9% with 120 µg, and 17.5% with placebo
- The most common AEs with BXCL501 were somnolence, dry mouth, hypotension, and dizziness (**Table 3**)
- Of 53 patients reporting somnolence with BXCL501, the event was mild in 64% and moderate in 36%, as judged by the investigator
- No severe adverse events AEs were reported
- No clinically meaningful changes in laboratory values were observed

Table 3. Incidence of Adverse Events Reported in ≥2% in Either BXCL501 Group (Safety Population)

	Number (%) of Patients		
	180 µg (n=126)	120 µg (n=126)	Placebo (n=126)
Any treatment emergent AE	45 (35.7)	44 (34.9)	22 (17.5)
Any drug-related AE	39 (31.0)	41 (32.5)	15 (11.9)
Serious AE	0	1 (0.8)*	0
Discontinuation due to AE	0	1 (0.8)	0
Incidence of Common AES in ≥5%			
Somnolence	27 (21.4)	26 (20.6)	6 (4.8)
Dry Mouth	6 (4.8)	9 (7.1)	1 (0.8
Dizziness	7 (5.6)	7 (5.6)	1 (0.8)
Hypotension	8 (6.3)	6 (4.8)	0

*Considered by the investigator to be unrelated to study drug

CONCLUSIONS

- BXCL501 demonstrated rapid, durable, and clinically meaningful effects at 2 hours that were sustained to 8 hours among acutely agitated patients with bipolar disorder
- Significant reductions were seen as early as 20 minutes postdose in PEC total score and efficacy results were confirmed by CGI-I and ACES scores
- The most common TEAEs were somnolence, dry mouth, dizziness, and hypotension.
- BXCL501 is an investigational, novel, non-invasive treatment of agitation for acute agitation in bipolar disorder

References 1. Citrome L. *Ther Clin Risk Manag*. 2013;9:235-245; 2. Montoya A et al. *Health Qual Life Outcomes*. 2011;9:18; 3. Young RC et al. *Br J Psychiatry*. 1978;133:429-435; 4. Sheehan DV et al. *J Clin Psychiatry*. 1998;59 Suppl 20:22-33.

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