Novel Rapidly Effective Treatment of Agitation in Patients with Bipolar Disorders: BXCL501 – An Oral Dissolving Film

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ABSTRACT

BACKGROUND: Acute agitation occurs frequently in patients with bipolar disorder, requiring management in hospitals and emergency departments. Commonly used treatment options include injectable antipsychotics and/or benzodiazepines. BXCL501 is an oral dissolving film for sublingual or buccal use of dexmedetomidine, a highly selective alpha-2a receptor agonist. SERENITY II evaluated the efficacy, safety, and tolerability of BXCL501 for treating acute agitation in patients with bipolar disorder.

METHODS: This was a Phase 3, randomized, placebo-controlled study of BXCL501. Adults aged 18-75 years with a diagnosis of bipolar I or II disorder were eligible if they had a total score of ≥14 on the 5 items of the PANSS-Excited Component (PEC) scale at screening and baseline, and a score ≥4 on at least 1 of the 5 PEC items at baseline. Patients were excluded for agitation from use of benzodiazepines, other hypnotics or antipsychotics within 4 hours of receiving BXCL501. Patients were randomized 1:1:1 to a single dose of BXCL501 120 µg, BXCL501 180 µg or placebo. The primary endpoint was mean change from baseline in the PEC total score at 2 hours. Secondary endpoints were the earliest time of an effect on agitation as measured by the PEC scale, PEC response (≥40% reduction from baseline), and mean change from baseline to 2 hours on the Clinical Global Impression-Improvement Scale (CGI-I) and the Agitation and Calmness Evaluation Scale (ACES).

RESULTS: Of 380 patients randomized, 362 (95.3%) completed the study. Median age was 48 years, 55% were female, mean PEC total score was 18, and patients were comparable across groups. At 2 hours, the mean change from baseline for the PEC total score was -4.9, -9.0, and -10.4 for placebo, BXCL501 120 µg, and BXCL501 180 µg, respectively (LSM difference: -4.1 and -5.4 vs. placebo, p<0.0001). At 2 hours, PEC response rates were 92.1%, 78.6%, and 48.4% with BXCL501 180 µg and 120 µg and placebo (p<0.0001 vs. placebo). At 2 hours, significant improvement in the CGI-I was observed in the 120 µg and 180 µg groups vs. placebo (LSM difference: -0.9 and -1.3, respectively, p<0.0001). At 2 hours, significant improvement in the ACES score was observed with BXCL501 120 µg and 180 µg vs. placebo (LSM difference: 1.8 and 2.4, respectively, p<0.0001). Significant (p<0.01) improvement with BXCL501 vs. placebo was observed as early as 20 minutes for the PEC. Adverse events (AE) occurred in 34.9%, 35.7%, and 17.5% with BXCL501 120, 180, and placebo. All AEs were mild or moderate most commonly somnolence, dizziness, dry mouth, hypotension, orthostatic hypotension, and hypoaesthesia. No drug-related severe or serious AEs occurred.

CONCLUSION: BXCL501 demonstrated rapid, robust and clinically meaningful efficacy in bipolar I & II patients for ≥2 hours, and represents a novel, non-invasive and well tolerated treatment of agitation with potentially better patient outcomes.

INTRODUCTION

- Agitation associated with bipolar disorder is a serious condition that can require immediate clinical management
- Agitation may lead to patient or staff injuries, disrupts care, and can prolong hospital stays
- A rapidly effective non-invasive treatment is needed with a favorable side effect profile that may be self-administered to reduce agitation and potentially prevent escalating to aggression
- BXCL501 is an orally dissolving film formulation of the α_{2B}-adrenergic receptor agonist, dexmedetomidine
- Film administration of a discrete microdose bypasses first pass metabolism and results in more rapid and higher bioavailability of dexmedetomidine than ingested formulations

OBJECTIVE

- Evaluate the efficacy, safety, and tolerability of BXCL501 for the treatment of acute agitation in patients with bipolar disorder I or II

METHODS

- Randomized, double-blind, placebo-controlled, Phase 3 study (SERENITY II)

Selection Criteria

- Age 18-75 years with a diagnosis of bipolar I or II disorder (DSM-5), regardless of mood state (manic, mixed features, or depressed)
- Total score ≥14 on 5 items of the Positive and Negative Syndrome Scale (PANSS)-Excited Component (PEC) scale at screening and baseline, and score ≥4 on ≥1 of 5 PEC items at baseline

Treatments

- Randomized 1:1:1 to BXCL501 120 µg or 180 µg or matching placebo film; randomization stratified by age (<65, ≥65 years)
- For persistent or recurrent agitation, a repeat dose of BXCL501 90 µg or 60 µg (half of the 180 µg or 120 µg initial dose) could be given 2 hours after the first dose, if the PEC change from baseline was ≤40% and in the absence of safety concerns
- Maximum number of repeat doses was 2 during the 12 hours after the first dose

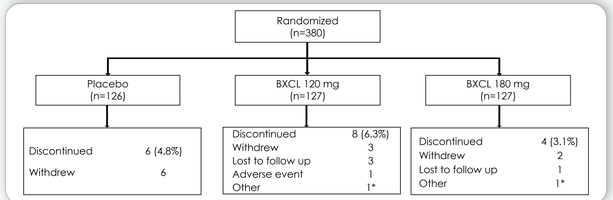
Study Outcomes

- Primary efficacy endpoint was absolute change from baseline in PEC total score at 2 hours
- Secondary endpoints
  - Change from baseline to 10, 20, 30, 45, 60, and 90 minutes up to 24 hours for PEC total score
  - Clinical Global Impressions-Improvement (CGI-I) score
  - Agitation-Calmness Evaluation Scale (ACES) score
  - PEC response rate (≥40% reduction in total score from baseline to 2 hours)
  - CGI-I response rate (score of 1 or 2 at 2 hours)
  - Young Mania Rating Scale (YMRS)
  - Time to rescue medication
  - Number of patients requiring rescue medication
  - Duration of calming effect (change from baseline for PEC total score)

RESULTS

- 380 patients were randomized and 362 (95.3%) completed the study (**Figure 1**)

Figure 1. Consort diagram of patient disposition



*1 patient in each group was randomized in error

- Baseline characteristics were comparable between treatment groups (**Table 1**)

Table 1. Baseline characteristics (safety population)

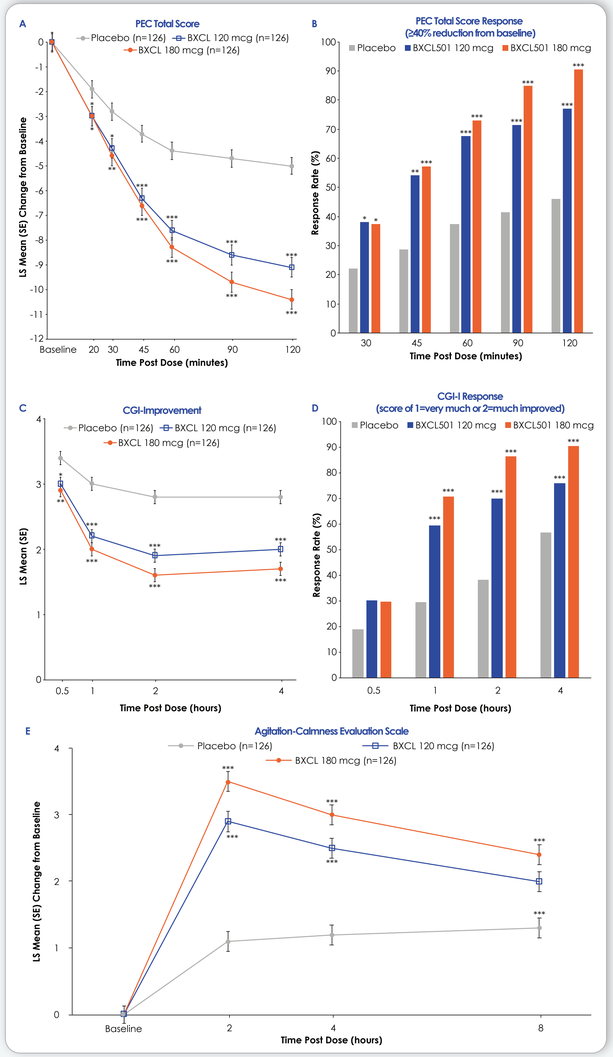
	Placebo (N=126)	BXCL501 120 µg (N=126)	BXCL501 180 µg (N=126)
Age, years[a]	44.8 ± 12.1	46.1 ± 11.5	45.9 ± 11.3
Age range, years	18 – 67	19 – 70	18 – 69
Female, n (%)	73 (57.9)	67 (53.2)	67 (53.2)
Race, n (%)			
White	50 (39.7)	56 (44.4)	49 (38.9)
Black or African American	72 (57.1)	68 (54.0)	72 (57.1)
Other	4 (3.2)	2 (1.6)	5 (4.0)
Hispanic or Latino, n (%)	11 (8.7)	12 (9.5)	15 (11.9)
Body weight, kg[a]	92.0 ± 20.7	91.8 ± 25.9	96.8 ± 26.0
Body mass index, kg/m^2[a]	32.5 ± 7.4	31.6 ± 8.0	33.3 ± 8.7
Diagnosis			
Depressed	26 (20.6)	20 (15.9)	28 (22.2)
Hypomania	10 (7.9)	14 (11.1)	5 (4.0)
Mania	63 (50.0)	58 (46.0)	59 (46.8)
Mixed episodes	22 (17.5)	27 (21.4)	30 (23.8)
Unspecified	5 (4.0)	7 (5.6)	4 (3.2)
Current agitation episode, days[a]	15.7 ± 21.9	21.8 ± 31.4	25.1 ± 74.3
Previous hospitalizations[a]	2.8 ± 3.7	3.5 ± 4.7	2.8 ± 4.5
Hours of sleep/night this week[a]	5.1 ± 1.5	5.3 ± 1.7	5.1 ± 1.5
Current smoker, n (%)	83 (65.9)	97 (77.0)	78 (61.9)
PEC[a]	17.9 ± 2.9	18.0 ± 2.7	18.0 ± 3.0
CGI-Severity[a]	4.1 ± 0.6	4.1 ± 0.5	4.1 ± 0.7

[a]Mean ± standard deviation
CGI = Clinical Global Impressions; PEC = Positive and Negative Syndrome Scale (PANSS)-Excitatory Component

Efficacy

- All patients were able to self-administered study drug
- At 2 hours, significant (p<0.0001) and clinically meaningful improvements from baseline in PEC total scores were observed with BXCL501 120 µg and BXCL501 180 µg vs. placebo. Mean changes from baseline were -9.0 and -10.4 points, respectively, versus -4.9 for placebo
  - Significant improvements were observed as early as 20 minutes with BXCL501 120 µg and BXCL 180 µg and persisted to 8 hours (**Figure 2A**)
- At 2 hours, mean PEC response rates were significantly (p<0.0001) higher with BXCL501 180 µg and 120 µg compared to placebo (**Figure 2B**)
- For the CGI-I, significant improvement was noted with BXCL501 vs. placebo at 30 minutes, and significant improvement was maintained at 1, 2, and 4 hours (**Table 2** and **Figure 2C**)
- CGI-I response rate was significantly (p<0.0001) greater with both doses of BXCL501 vs. placebo at 1, 2, and 4 hours (**Figure 2D**)
- At 2 hours, significantly (p<0.0001) greater improvements in ACES scores were observed with BXCL501 120 µg and 180 µg vs. placebo; effects persisted to 8 hours (**Table 2** and **Figure 2E**)
- Calmness (improvement in ACES of ≥1) at 2, 4 and 8 hours was 92%, 99%, and 94%, respectively, with BXCL501 180 µg, 83%, 92%, and 89%, respectively, with BXCL501 120 µg, and 56%, 79%, and 74% with placebo, respectively
- Improvement in YMRS total scores from baseline to 24 hours for BXCL510 180 µg and 120 µg groups were significantly greater vs. placebo (LSM difference: -3.1, p<0.0001 and -2.5, p<0.0005], respectively

Figure 2. A) LSM change from baseline for PEC total score; B) PEC response rate; C) LSM change for CGI-I improvement; D) CGI-I response rate; E) LSM change from baseline for ACES



*p<0.01, **p<0.005, ***p<0.0001 for BXCL501 versus placebo.

Table 2. Mean change from baseline for primary and secondary endpoints (ITT population)

	Placebo (N=126)	BXCL501 120 µg (N=126)	BXCL501 180 µg (N=126)
PEC Total Score			
Baseline[a]	17.9 ± 2.9	18.0 ± 2.7	18.0 ± 3.0
LSmean change (baseline – 2 hours)[b]	-5.0 ± 0.4	-9.1 ± 0.4	-10.4 ± 0.4
LSmean difference (97.5% CI)		-4.1 ± 0.5 (-5.3, -2.9)	-5.4 ± 0.5 (-6.6, -4.2)
p-value		<0.0001	<0.0001
CGI-I Scale			
LSmean score (baseline – 2 hours)[b]	2.8 ± 0.1	1.9 ± 0.1	1.5 ± 0.1
LSmean difference (95% CI)		-0.9 ± 0.1	-1.3 ± 0.1
p-value		<0.0001	<0.0001
ACES Score			
Baseline[a]	2.3 ± 0.7	2.2 ± 0.6	2.1 ± 0.5
LSmean change (baseline – 2 hours)[b]	1.1 ± 0.2	2.9 ± 0.2	3.5 ± 0.2
LSmean difference (95% CI)		1.8 ± 0.2 (1.3, 2.2)	2.4 ± 0.2 (1.9, 2.8)
p-value		<0.0001	<0.0001

[a]Mean ± standard deviation
[b]Mean ± standard error
CI = confidence interval; CGI-I = Clinical Global Impressions – Improvement; LSmean = least squares mean
P-value from a restricted maximum likelihood repeated measures mixed model on change from baseline values. Covariates were baseline PEC score, age stratum, study site, time point (including all 7 time points from 10 minutes to 2 hours post-dose), treatment group, baseline PEC score by time point interaction term, and treatment group by time point interaction term.

Safety

- The incidence of AEs with BXCL501 180 µg and 120 µg was 35.7% and 34.9%, respectively, and 17.5% with placebo (**Table 3**)
- Of the 53 patients (21%) reporting somnolence with BXCL501, 64% were mild and 36% were moderate

Table 3. Incidence of adverse events occurring in at least 2% of patients in either BXCL501 group (safety population)

	Number (%) of Patients		
	Placebo (N=126)	BXCL501 120 µg (N=126)	BXCL501 180 µg (N=126)
Any treatment-emergent AE	22 (17.5)	44 (34.9)	45 (35.7)
Any drug-related AE	15 (11.9)	41 (32.5)	39 (31.0)
Serious AE	0	1 (0.8)*	0
Discontinuation for AE	0	1 (0.8)*	0
Incidence of common AEs in ≥5%			
Dizziness	1 (0.8)	7 (5.6)	7 (5.6)
Dry mouth	1 (0.8)	9 (7.1)	6 (4.8)
Hypotension	0	6 (4.8)	8 (6.3)
Somnolence	6 (4.8)	26 (20.6)	27 (21.4)

* Considered by the Investigator to be unrelated to study drug

SUMMARY

- BXCL501 has a novel mechanism of action that differs from currently available agents
- In SERENITY II, BXCL501 demonstrated rapid, durable, and clinically meaningful improvements in agitation among adults with bipolar disorder
- BXCL501 represents a non-invasive and well-tolerated treatment for agitation in bipolar disorder that avoids the need for injections and can be self-administered by the patient

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The following information concerns a use that has not been approved by the U.S. Food and Drug Administration.

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