A Novel Rapidly Effective Treatment of Agitation for Schizophrenia with the Oral Dissolving Film BXCL501

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ABSTRACT

BACKGROUND: Acute agitation can occur in patients with schizophrenia, and is often encountered in emergency departments and inpatient units. Treatment includes injectable antipsychotics or benzodiazepines. BXCL501 is an oral dissolving film for sublingual or buccal use of dexmedetomidine, a highly selective alpha-2a receptor agonist. SERENITY I evaluated the efficacy, safety, and tolerability of BXCL501 in patients with acute agitation associated with schizophrenia.

METHODS: This was a Phase 3, randomized, placebo-controlled study. Patients aged 18-75 years with a diagnosis of schizophrenia, schizoaffective or schizophreniform 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, with a score ≥4 on at least 1 of the 5 PEC items. Patients were randomized 1:1:1 to a single dose of BXCL501 120 mg, 180 mg 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, PEC response (≥40% reduction from baseline), improvement at 2 hours by Clinical Global Impression-Improvement Scale (CGI-I), and calming using the Agitation and Calmness Evaluation Scale (ACES).

RESULTS: Of 380 randomized patients, 372 (97.9%) completed the study. Baseline characteristics were similar across groups; median age was 45.6 years, 63% were male, and mean PEC total score was 17.6. LS Mean change from baseline to 120 minutes for the PEC total score was -4.8, -8.5, and -10.3 for placebo, BXCL501 120 mcg, and 180 mcg, respectively (LSM difference -3.7 and -5.5, p<0.0001 vs. placebo). At 1 and 2 hours post dose, significant (p<0.0001) improvement in the CGI-I was observed with BXCL501 120 µg and 180 µg vs. placebo. At 2 hours, PEC response rates were 89.6%, 80.6%, and 47.6% with BXCL501 180 µg, 120 µg and placebo (p<0.0001 vs. placebo). At 2 hours, significant improvement in ACES scores was observed with BXCL501 120 µg and 180 µg vs. placebo (LSM difference: 1.6 and 2.6, respectively, p<0.0001). Significant (p<0.05) improvements were observed with BXCL501 vs. placebo as early as 20 minutes on the PEC. The incidence of adverse events (AE) was 39.5%, 37.3%, and 15.1% with BXCL501 120 mg, 180 mg, and placebo groups. All AEs were mild or moderate, and the most common with BXCL501 were somnolence, dizziness, dry mouth, hypotension, orthostatic hypotension, hypoaesthesia, and paresthesia. No drug-related severe or serious AEs occurred.

CONCLUSION: BXCL501 demonstrated rapid, robust and clinically meaningful efficacy in the vast majority of patients sustained for at least 2 hours and represents a novel, versatile, non-invasive and well tolerated treatment of agitation with potentially better patient outcomes.

INTRODUCTION

- Agitation associated with schizophrenia is a serious condition that requires urgent clinical management
- Agitation impedes patient care, may lead to patient or staff injuries, disrupts healthcare settings and prolongs 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 escalation to aggression
- BXCL501 is an orally dissolving film formulation of the α_{2A}-adrenergic receptor agonist, dexmedetomidine; this formulation bypasses first pass metabolism to rapidly achieve high bioavailability of dexmedetomidine

OBJECTIVE

- Evaluate the efficacy, safety, and tolerability of BXCL501 for the treatment of acute agitation in patients with schizophrenia

METHODS

Study Design

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

Selection Criteria

- Age 18-75 years with a DSM 5 diagnosis of schizophrenia, schizoaffective or schizophreniform disorder and presenting with acute agitation
- 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

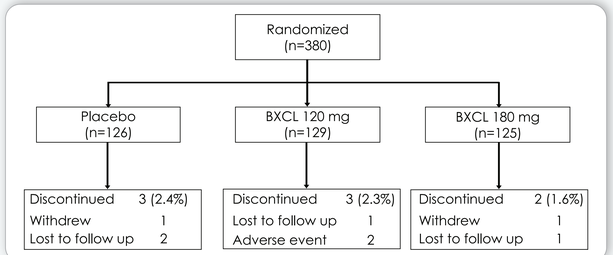
Study Outcomes

- Primary efficacy endpoint was absolute change from baseline in PEC total score at 2 hours
- Secondary endpoints
  - 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)
  - 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 enrolled and randomized and comprised the safety and ITT populations; 372 (97.9%) patients completed the study (**Figure 1**)

Figure 1. Patient disposition



- Treatment groups were comparable at baseline (**Table 1**)

Table 1. Baseline characteristics (safety population)

	Placebo (N=126)	BXCL501 120 µg (N=129)	BXCL501 180 µg (N=126)
Age, years[a]	45.1 ± 11.1	45.7 ± 11.3	46.0 ± 11.9
Age range, years	21 – 68	18 – 71	21 – 68
Female, n (%)	44 (34.9)	52 (40.3)	44 (34.9)
Race, n (%)			
White	21 (16.7)	33 (25.6)	21 (16.7)
Black or African American	102 (81.0)	92 (71.3)	103 (81.7)
Other	3 (2.3)	4 (3.1)	2 (1.6)
Hispanic or Latino, n (%)	7 (5.6)	17 (13.2)	13 (10.3)
Body mass index, kg/m²[a]	32.6 ± 7.4	31.2 ± 7.6	32.5 ± 7.9
Current schizophrenia, n (%)	96 (76.2)	97 (75.2)	90 (72.0)
Current smoker, n (%)	102 (81.0)	96 (74.4)	83 (65.9)
Days of current agitation[a]	18.3 (34.9)	25.4 (95.3)	22.9 (48.3)
PEC total score[a]	17.6 ± 2.3	17.5 ± 2.5	17.6 ± 2.7

[a]Mean ± standard deviation

Efficacy

- All patients self-administered BXCL501
- At 2 hours, significant improvements from baseline in PEC total scores were observed in BXCL501 120 µg and BXCL501 180 µg treatment groups compared to placebo (**Table 2**)

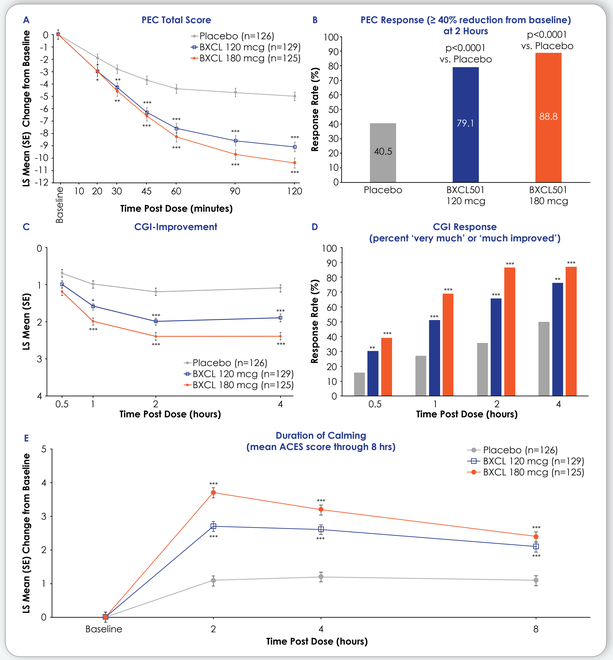
Table 2. Mean change for primary and secondary endpoints

	Placebo (N=126)	BXCL501 120 µg (N=129)	BXCL501 180 µg (N=125)
PEC Total Score			
Baseline[a]	17.6 ± 2.3	17.5 ± 2.5	17.6 ± 2.7
LSmean change (baseline – 2 hours)[b]	-4.8 ± 0.4	-8.5 ± 0.4	-10.3 ± 0.4
LSmean difference (97.5% CI)		-3.7 ± 0.5 (-4.9, -2.5)	-5.5 ± 0.5 (-6.7, -4.3)
p-value		<0.0001	<0.0001
CGI-I Scale			
LSmean score – 2 hours[b]	2.8 ± 0.1	2.0 ± 0.1	1.6 ± 0.1
LSmean difference (95% CI)		-0.8 ± 0.1 (-1.1, -0.6)	-1.3 ± 0.1 (-1.5, -1.0)
p-value		<0.0001	<0.0001
ACES Score			
Baseline[a]	2.3 ± 0.6	2.2 ± 0.7	2.3 ± 0.6
LSmean change (baseline – 2 hours)[b]	1.1 ± 0.2	2.7 ± 0.1	3.7 ± 0.2
LSmean difference (95% CI)		1.6 ± 0.2 (1.2, 2.0)	2.6 ± 0.2 (2.2, 3.0)
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.

- Mean changes from baseline were -8.5 and -10.3 points with BXCL501 120 µg and 180 µg, respectively, versus -4.8 for placebo. LSmean differences from placebo were -3.7 (p<0.0001) and -5.5 (p<0.0001) for BXCL501 120 µg and 180 µg
- A significant improvement in the PEC total score was observed as early as 20 minutes with BXCL501 180 µg and at 30 minutes with BXCL501 120 µg
- Significant (p<0.0001) improvements from baseline in PEC total scores were maintained at 4, 6, and 8 hours post dose with BXCL501 120 µg and 180 µg
- At 2 hours, PEC response rates were 79.1% and 88.8% with BXCL501 120 µg and 180 µg compared with 40.5% with placebo (p<0.0001 vs. placebo) (**Figure 2B**)
- Response rates were significantly (p=0.0001) higher with BXCL501 180 µg vs. placebo starting at 20 minutes post dose (34.4% versus 13.5%) (**Figure 2B**)
- For the CGI-I, significant improvements in agitation from baseline were observed at 30 minutes with BXCL501 120 µg and 180 µg (**Table 2**)
  - At 1 and 2 hours differences from placebo were significantly (p<0.01) greater with BXCL501 120 µg and 180 µg doses (**Figure 2C**)
- CGI-I response rate (very much improved or much improved) was significantly (p<0.01) greater with both doses of BXCL501 vs. placebo beginning at 30 minutes (**Figure 2D**)
- On ACES, an increase in calming effect was observed with BXCL501 120 µg and 180 µg vs. placebo (**Table 2**)
  - Mean scores at 2 hours with BXCL501 120 µg and 180 were 4.9 (mild calmness) and 6.0 (moderate calmness), respectively, vs. 3.3 (mild agitation) with placebo
  - Significantly (p<0.0001) greater improvements vs. placebo in ACES scores were observed with BXCL501 120 µg and 180 µg at 2 hours and maintained at 4 and 8 hours (**Figure 2E**)
  - At 2, 4, and 8 hours, the proportion who achieved a ACES score of ≥4 (normal – resolution of agitation) was 88%, 86%, and 80% with BXCL501 180 µg, 67%, 78%, and 70% with BXCL501 120 µg, and 33%, 55%, and 38% with placebo

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



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

Safety/Tolerability

- The incidence of AEs with BXCL501 120 µg and 180 µg was 39.5% and 37.3%, respectively, and 15.1% with placebo (**Table 3**)

Table 3. Incidence of adverse events occurring in at least 3% of patients in any treatment group (safety population)

	Number (%) of Patients		
	Placebo (N=126)	BXCL501 120 µg (N=129)	BXCL501 180 µg (N=126)
Any AEs	19 (15.1)	51 (39.5)	47 (37.3)
Any treatment-related AE	15 (11.9)	46 (35.7)	44 (34.9)
Individual AEs			
Dizziness	1 (0.8)	3 (2.3)	5 (4.0)
Dry mouth	2 (1.6)	10 (7.8)	5 (4.0)
Headache	6 (4.8)	6 (4.7)	4 (3.2)
Hypoaesthesia oral	0	5 (3.9)	7 (5.6)
Hypotension	0	8 (6.2)	5 (4.0)
Orthostatic hypotension	0	2 (1.6)	7 (5.6)
Paraesthesia oral	1 (0.8)	5 (3.9)	3 (2.4)
Somnolence	10 (7.9)	28 (21.7)	29 (23.0)

- No severe or serious AEs were reported in the study
- Somnolence, described as feeling "drowsy" or "sleepy" was reported by 57 (22%) of BXCL501 participants. Of these, 49 were mild and 8 were moderate severity.
- No clinically meaningful changes were observed for laboratory values. Post-dose oral exams revealed no local site tolerability findings
- There were no clinically meaningful mean changes from baseline at 2 hours or 24 hours post-dose for PR interval, QRS duration, and QTcF. Hypotension occurred in 5 (4.0%) patients in the BXCL501 180 µg group and 8 (6.2%) in the 120 µg group
- All patients were able to self-administer BXCL501 film
- 67.5% of patients in the BXCL501 180 µg group, 65.9% in the 120 µg group, and 64.3% in the placebo group liked the taste of the medication
- Over 90% of patients judged study medication as having no unpleasant aftertaste and approximately 99% said the medication did not have an unpleasant smell

SUMMARY

- BXCL501 was effective at 120 µg and 180 µg doses for treating acute agitation in patients with schizophrenia, with an onset of action as early as 20 minutes and effects that were sustained for at least 8 hours
- Importantly, BXCL501 produced a calming effect but no patient was unarousable after treatment.
- BXCL501 was well tolerated with somnolence the most commonly (22%) reported AE, all of which was rated as mild (86%) or moderate (14%) severity.
- BXCL501 possess a novel mechanism of action and differentiating route of administration that makes it potentially favored over currently existing therapeutic options for treating agitation

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