

# Safety and Patient Acceptability of BXCL501 for Treating Acute Agitation in Patients with Bipolar Disorder

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#### INTRODUCTION

- Agitation occurs commonly with acute exacerbations of bipolar disorder and may escalate into aggressive behavior<sup>1</sup>
- BXCL501 is an investigational orally dissolving film formulation of dexmedetomidine, a selective  $\alpha_{2A}$  adrenergic receptor agonist designed for sublingual or buccal administration
- BXCL501 is a small, solid-dose rectangular film 22 x 13 mm wide (0.7 mm thick) designed to completely dissolve (solubilize) in the sublingual or buccal space
- Delivers 180 µg or 120 µg of dexmedetomidine per dose

#### **O**BJECTIVES

- Determine the safety profile of BXCL501, as measured by reports of adverse events (AEs) and vital signs
- Describe the overall tolerability of BXCL501 in terms of treatmentemergent AE (TEAE) reports and local site tolerability of oral film
- Determine subject opinion about the acceptability, flavor, and likability of BXCL501

#### **METHODS**

#### Conduct

- Phase 3, randomized, placebo-controlled study
- Adults aged 18-75 years, inclusive
- Diagnosed with DSM-5 bipolar I or II disorder using the Mini-International Neuropsychiatric Interview<sup>4</sup>
- Clinically agitated at screening and baseline (PEC total score  $\geq$ 14), with a PEC baseline score of  $\geq 4$  on  $\geq 1$  item
- subjects were randomized (1:1:1) to BXCL501 120 µg, BXCL501 180 µg, or placebo and self-administered the study drug or identical matching placebo film

#### Assessments

- The following were monitored for safety and tolerability: Adverse events (AEs); Clinical laboratory tests; Electrocardiogram (ECG) with rhythm strip, ECG overreads by cardiologists; Pulse oximetry; Vital signs, including resting and orthostatic vital sign parameters (systolic blood pressure [SBP], diastolic blood pressure [DBP], and heart rate [HR])
- The application site of the sublingual preparation (buccal mucosa) was inspected at 30 minutes, 2, 4, and 24 hours postdose for any signs of local (oral/sublingual) irritation
- subject opinion of study medication was assessed at 20 minutes postdose using a Likert-type scale (1=strongly disagree, 5=strongly agree) based on subject response to statements about study drug acceptability ("the medication is acceptable") and flavor ("I like the taste of the medication"); opinions about unpleasant aftertaste and aroma and satisfaction with dissolve time were asked as yes/no questions
- The safety population included all subjects who received at least 1 dose of study drug; no formal hypothesis-testing of TEAE incidence rates was planned or performed

# RESULTS

# **Subjects**

- In total, 380 subjects were enrolled, 378 received 1 or more doses of study drug, and 362 completed the study
- Demographic and baseline characteristics were comparable in all treatment groups, except for a higher number of agitation days in the BXCL501 180 µg dose group (**Table 1**)
- The most common diagnoses were mania (180 [47.6%]) and mixed episodes (79 [20.9%])

#### **Table 1. Demographics and Baseline Characteristics**

180 μg (n=126)	120 µg (n=126)	Placebo (n=126)
45.9 (11.3)	46.1 (11.5)	44.8 (12.1)
67 (53.2)	67 (53.2)	73 (57.9)
59 (46.8)	59 (46.8)	53 (42.1)
72 (57.1)	68 (54.0)	72 (57.1)
49 (38.9)	56 (44.4)	50 (39.7)
5 (4.0)	2 (1.6)	4 (3.2)
15 (11.9)	12 (9.5)	11 (8.7)
111 (88.1)	114 (90.5)	115 (91.3)
28 (22.2)	20 (15.9)	26 (20.6)
5 (4.0)	14 (11.1)	10 (7.9)
59 (46.8)	58 (46.0)	63 (50.0)
30 (23.8)	27 (21.4)	22 (17.5)
4 (3.2)	7 (5.6)	5 (4.0)
25.1 (74.3)	21.8 (31.4)	15.7 (21.9)
2.8 (4.45)	3.5 (4.70)	2.8 (3.66)
5.1 (1.51)	5.3 (1.65)	5.1 (1.49)
	(n=126) 45.9 (11.3) 67 (53.2) 59 (46.8) 72 (57.1) 49 (38.9) 5 (4.0) 15 (11.9) 111 (88.1) 28 (22.2) 5 (4.0) 59 (46.8) 30 (23.8) 4 (3.2) 25.1 (74.3) 2.8 (4.45) 5.1 (1.51)	$130 \ \mu g$ $120 \ \mu g$ $(n=126)$ $(n=126)$ $45.9 (11.3)$ $46.1 (11.5)$ $67 (53.2)$ $67 (53.2)$ $59 (46.8)$ $59 (46.8)$ $72 (57.1)$ $68 (54.0)$ $49 (38.9)$ $56 (44.4)$ $5 (4.0)$ $2 (1.6)$ $15 (11.9)$ $12 (9.5)$ $111 (88.1)$ $114 (90.5)$ $28 (22.2)$ $20 (15.9)$ $5 (4.0)$ $14 (11.1)$ $59 (46.8)$ $58 (46.0)$ $30 (23.8)$ $27 (21.4)$ $4 (3.2)$ $7 (5.6)$ $25.1 (74.3)$ $21.8 (31.4)$ $2.8 (4.45)$ $3.5 (4.70)$ $5.1 (1.51)$ $5.3 (1.65)$

### **Blood Pressure**

- At 2 hours postdose, dose-dependent decreases in SBP (-14.8 and -18.1 mmHg), DBP (-8.8 and -11.5 mmHg), and HR (-7.9 and -9.2 bpm) were observed in the 120 µg and 180 µg treatment groups; no decreases were observed in the placebo group
- Abnormal postural changes from supine to standing were ≤15% in all treatment groups; no cases of syncope or falls were reported
- At 2 through 24 hours postdose, there were no reports of cardiac-related AEs; no clinically meaningful changes from baseline observed for PR interval, QRS duration, or QTcF; and no subjects had an AE related to ECG parameters, treatment-emergent arrhythmia or a clinically significant abnormal ECG

	BXCL501 180 μg (n=126)	BXCL501 120 μg (n=126)	Placebo (n=126)	
Any drug-related AE	39 (31.0)	41 (32.5)	15 (11.9)	
Serious AE <sup>b</sup>	0	1 (0.8)	0	
Discontinuation for AE	0	1 (0.8)	0	
Treatment-emergent AEs				
Any (≥1 event)	45 (35.7)	44 (34.9)	22 (17.5)	
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	
Orthostatic hypotension	6 (4.8)	5 (4.0)	1 (0.8)	
Nausea	5 (4.0)	3 (2.4)	3 (2.4)	
Hypoesthesia oral	5 (4.0)	2 (1.6)	1 (0.8)	
Bradycardia	3 (2.4)	2 (1.6)	0	
Paresthesia oral	3 (2.4)	2 (1.6)	0	
AE, adverse event <sup>a</sup> In any treatment group; <sup>b</sup> Occurred on Day 7 postdose and judged to be unrelated to study drug.				
The incidence of TEAEs was 35.7% (45/126) in the BXCL501 180 μg				

- One serious adverse event in the 120 µg group (agitation recurrence at Day 7) was judged by the investigator to be unrelated to study drug
- The most common events in the active treatment groups were somnolence, dry mouth, hypotension, and dizziness
- Among subjects reporting somnolence with BXCL501 (n=53), investigators judged that no events were severe, 64% were mild, and 36% were moderate
- All adverse events were considered by investigators mild or moderate and not clinically meaningful and all subjects recovered without medical intervention
- In the BXCL501 180 μg and 120 μg treatment groups, the proportions of subjects who experienced hypotension, orthostatic hypotension, or bradycardia were similar
- No clinically meaningful changes in laboratory values were observed

# Local Irritation

- On buccal exam, 1 subject (0.8%) in the 180 μg group, 2 subjects (1.6%) in the 120 µg group and no subject in the placebo group had local irritation to study drug at 30 minutes postdose
- No subject had irritation at 2 or 24 hours postdose

# Table 2. Adverse Events Occurring in ≥2% of Subjects<sup>a</sup>

group, 34.9% (44/126) in the BXCL501 120 µg group, and 17.5% (22/126) in the placebo group (**Table 2**)

# Acceptability

- At 20 minutes postdose more than 80% of subjects in the study rated BXCL501 as acceptable
- 62% of subjects said that they liked the flavor and 28% were neutral about the taste
- A large majority of subjects were satisfied with the time it took the film to dissolve in the mouth (Figure 1)
- More than 90% of subjects said BXCL501 did not have an unpleasant aftertaste
- 99% reported that the film did not have an unpleasant smell



# Figure 1. Acceptability, Flavor, and Satisfaction

# **CONCLUSIONS**

- BXCL501 was well tolerated with no drug-related serious AEs and local site irritation in 1 and 2 subjects in the 180 µg and 120 µg groups, respectively
- The majority of subjects reported that they liked the taste, there was no unpleasant smell or aftertaste, and that the time to dissolve in the mouth was acceptable
- BXCL501 is a potential non-invasive treatment for acute agitation associated with bipolar disorders