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

Scott Zeller, MD[1]; Leslie Citrome, MD, MPH[2]; Joseph F. Goldberg, MD[3]; Jeffrey Finman, PhD[4]; Michael De Vivo, PhD[5]; Frank D. Yocca, PhD[5]; Robert Risinger, MD[5]

[1]University of California-Riverside School of Medicine, Riverside, CA, USA; [2]New York Medical College, Valhalla, NY, USA; [3]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [4]Jupiter Point Pharma Consulting, LLC, Groton, CT, USA; [5]BioXcel Therapeutics, Inc., New Haven, CT, USA

Introduction

- Agitation occurs commonly with acute exacerbations of bipolar disorder and may escalate into aggressive behavior[1]
- BXCL501 is an investigational orally dissolving film formulation of dexmedetomidine, a selective α_{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

Objectives

- 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 treatment-emergent 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[4]
- Clinically agitated at screening and baseline (PEC total score ≥14), with a PEC baseline score of ≥4 on ≥ 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

	BXCL501 180 µg (n=126)	BXCL501 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

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

Table 2. Adverse Events Occurring in ≥2% of Subjects[a]

	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[b]	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
[a]In any treatment group; [b]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 group, 34.9% (44/126) in the BXCL501 120 µg group, and 17.5% (22/126) in the placebo group (**Table 2**)
- 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

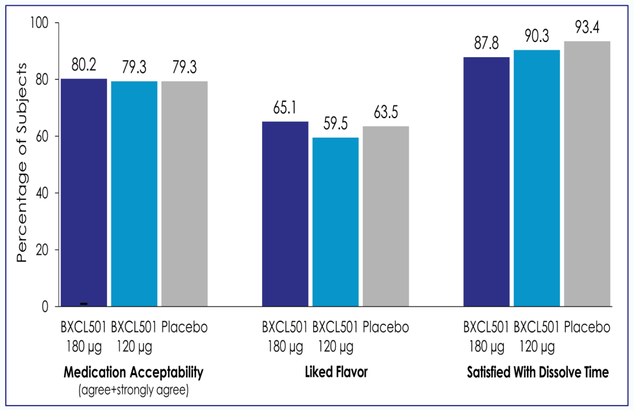
Local Irritation

- 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

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

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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