BXCL501 (Sublingual Dexmedetomidine) for Treatment of Agitation Associated With Bipolar Disorder or Schizophrenia in the Home Setting: a Phase 3 Study

Leslie Citrome[1], Lavanya Rajachandran[2], Robert Risinger[3], Michael De Vivo[2], Heather Robison[2], Dusan Kostic[2], Matt Mandel[2], Rashmi Deshpande[2], Frank Yocca[4]

[1]New York Medical College, [2]BioXcel Therapeutics, Inc., [3]BioXcel Therapeutics, Inc. (former), [4]Bioxcel Therapeutics, BioXcel Corporation

Introduction

- Patients with schizophrenia or bipolar disorder frequently experience episodes of agitation.
- In the home setting, where most episodes of agitation occur, there are no FDA-approved therapies for this indication.
- BXCL501 is a sublingual film formulation of dexmedetomidine, a selective alpha-2 adrenergic receptor agonist, which has been approved for treatment of agitation under the supervision of a healthcare provider. A Phase 3 safety trial of BXCL501 was initiated with the goal of expanding the indication into the unsupervised (home) setting.

Methods

- A randomized, double-blind, placebo-controlled, Phase 3, 12-week trial (SERENITY At-home, NCT05658510) in the home setting
- The primary outcome measure of the trial was the incidence of serious adverse events (SAEs) and treatment-emergent adverse events (TEAEs), defined as adverse events occurring within 24 hours of dosing.
- An exploratory objective was to evaluate whether repeated dosing would continue to provide treatment benefit. The exploratory outcome measures included a modified clinical global impression – severity (mCGI-S), scored by patients and by caregivers/informants, if present, on a scale of 0 (no agitation) to 3 (severe agitation)
- Patients could also use meditation, alcohol, cannabis, OTC medications etc. to reflect real-world coping strategies

INCLUDED PATIENTS

Male and female patients ages 18–75 years with bipolar I or II disorder, schizophrenia, schizoaffective, or schizophreniform disorder

On a stable psychotropic regimen for ≥30 days prior to screening

History of ≥3 agitation episodes in past 3 months

EXCLUDED PATIENTS

Unstable or serious medical illness (e.g., CHF, recent MI, hepatic disease)

Diagnosis of antisocial, borderline, or narcissistic personality disorder that predated schizophrenia or bipolar disorder

Moderate to severe substance use disorder in past 6 months

Agitation due primarily to acute intoxication or substance use

Results

- 246 patients randomized
  - 31 patients had no recorded episodes over 12 weeks
  - 7 patients did not take study treatment for their episodes
- 2437 agitation episodes were treated in 208 patients
- 81% of treated patients completed the study

Primary Outcome: Safety and Tolerability

- At home, adverse events frequencies with a single dose were similar to those observed under medical supervision in previously completed Phase 3 studies (Table 1)
- Over repeated administration, the incidence of adverse events did not increase (Tables 1 and 2)
- No patient in the active arm discontinued due to TEAE

Table 1: Most common TEAEs in SERENITY At-Home and comparison with studies done under medical supervision

Treatment-Emergent Adverse Event	SERENITY I & II[1]		SERENITY AT-HOME Adverse Event by Dose (Episode)[1]			
	SINGLE DOSE		FIRST DOSE		ALL DOSES	
	IGALMI™ 120 MCG (N=255) n (%)	PLACEBO (N=252) n (%)	BXCL501 120 MCG (N=102)[1] n (%)[2]	PLACEBO (N=106)[1] n (%)[2]	BXCL501 120 MCG (N=1160)[1] n (%)[2]	PLACEBO (N=1277)[1] n (%)[2]
Somnolence[3]	56 (22%)	16 (6%)	23 (22.5%)	18 (17.0%)	161(13.9%)	103 (8.1%)
Oral Paresthesia/Hypoesthesia	14 (6%)	2 (1%)	2 (2%)	1 (0.9%)	6 (0.5%)	1 (0.1%)
Dizziness	10 (4%)	2 (1%)	5 (4.9%)	1 (0.9%)	19 (1.6%)	2 (0.2%)
Dry Mouth	19 (7%)	3 (1%)	7 (6.9%)	1 (0.9%)	56 (4.8%)	24 (1.9%)
Nausea	6 (2%)	4 (2%)	1 (1.0%)	0 (0%)	6 (0.5%)	1 (0.1%)
Headache	12 (5%)	12 (5%)	0 (0%)	2 (1.9%)	4 (0.3%)	4 (0.3%)

[1]SERENITY I and II evaluated a single agitation episode in each patient. SERENITY AT-Home evaluated a total of 2437 episodes in 208 patients. Adverse events are presented on an episode basis. N denotes number of episodes. Only AEs observed in Serenity At-Home Pivotal Phase 3 trial are listed.
[2]Percent of TEAE events per dosing episode
[3]Includes fatigue

Table 2: TEAEs per dosed episode by dose numbers

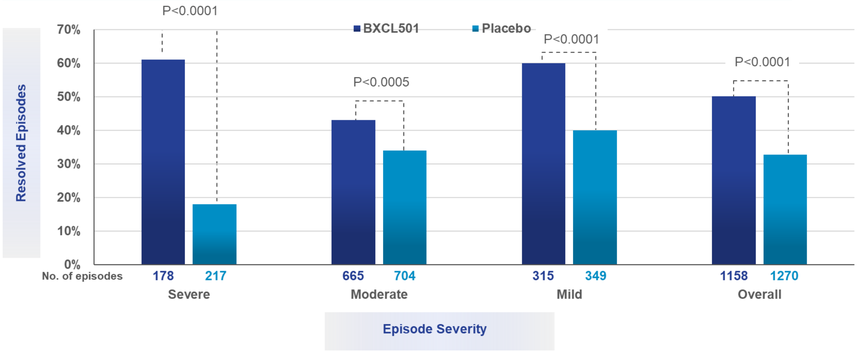
Treatment-Emergent Adverse Event	After Doses 1-3		After doses 4 to 12		After doses 13 and beyond	
	BXCL501 (N=266)[1] n (%)[2]	PLACEBO (N=274)[1] n (%)[2]	BXCL501 (N=398)[1] n (%)[2]	PLACEBO (N=485)[1] n (%)[2]	BXCL501 (N=496)[1] n (%)[2]	PLACEBO (N=518)[1] n (%)[2]
Somnolence[3]	58 (22.0%)	43 (16.0%)	61 (15.3%)	52 (10.8%)	42 (8.5%)	8 (1.5%)
Oral Paresthesia/Hypoesthesia	4 (1.5%)	1 (0.4%)	2 (0.5%)	0 (0%)	0 (0%)	0 (0%)
Dizziness	10 (3.8%)	1 (0.4%)	7 (1.8%)	1 (0.2%)	2 (0.4%)	0 (0%)
Dry mouth	14 (5.3%)	2 (0.7%)	29 (7.3%)	2 (0.4%)	13 (2.6%)	20 (3.9%)
Nausea	1 (0.4%)	1 (0.4%)	3 (0.8%)	0 (0%)	2 (0.4%)	0 (0%)
Headache	3 (1.1%)	2 (0.7%)	0 (0%)	2 (0.4%)	1 (0.2%)	0 (0%)

[1]Number of Dosed Episodes
[2]Percentage of Dosed Episodes
[3]Includes Fatigue

Exploratory Outcome: Efficacy

- Although not powered for efficacy, the reduction in mCGI-S score was greater in the active group compared with placebo (P<0.05)
- There was a mean reduction in mCGI-S score of 1.2 following the first 12 doses and a mean reduction of 1.4 following 13 or more doses of BXCL50, indicating no attenuation of benefit with repeat dosing.
- Complete resolution of agitation was significantly higher with BXCL501 compared to placebo across agitation episode severity (P<.0001, Figure 1)

Figure 1: Percent of fully resolved episodes by baseline severity and overall



Conclusions

- In this pivotal safety study, sublingual dexmedetomidine 120 mcg was safe and well tolerated over a 12-week treatment period when administered on an as-needed basis
- Over repeat dosing, no increase in TEAEs was observed
- The reduction in symptoms remained consistent throughout the duration of the trial
- Significantly more patients experienced full resolution of agitation symptoms with BXCL501 than with placebo