Dexmedetomidine Orally Dissolving Film (BXCL501) for the Treatment of Acute Agitation Associated With Schizophrenia or Bipolar Disorder: SERENITY I and SERENITY II Clinical Trials

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INTRODUCTION

- Patients with schizophrenia or bipolar disorder experiencing episodes of acute agitation may require early intervention to reduce the risk of patient or staff injury, disruption of care, and hospital stay prolongation[1,2]
- Dexmedetomidine orally dissolving film (ODF) is an investigational formulation of dexmedetomidine, a selective α_{2A} adrenergic receptor agonist
- Dexmedetomidine ODF is designed to rapidly dissolve and be absorbed sublingually or buccally, bypassing first-pass liver metabolism

OBJECTIVE

Determine if a 180 mcg or 120 mcg dose of dexmedetomidine ODF is more effective than placebo at reducing the symptoms of acute agitation in adults with schizophrenia or bipolar disorder

METHODS

- 2 randomized, double-blind, placebo-controlled Phase 3 trials including adults with acute agitation and DSM-5 diagnosis of schizophrenia or schizoaffective disorder (Serenity I) or bipolar disorder I or II (Serenity II)
- Participants were clinically agitated at screening and baseline, with a PEC total score ≥14 and baseline score of ≥4 on ≥1 of 5 PEC items
- Participants self-administered dexmedetomidine ODF 120 mcg, 180 mcg, or placebo

Assessments

- Screening, predose (within 15 minutes of the first dose), 10, 20, 30, 45, 60, 90 minutes and 2, 4, 6, and 8 hours after the first dose

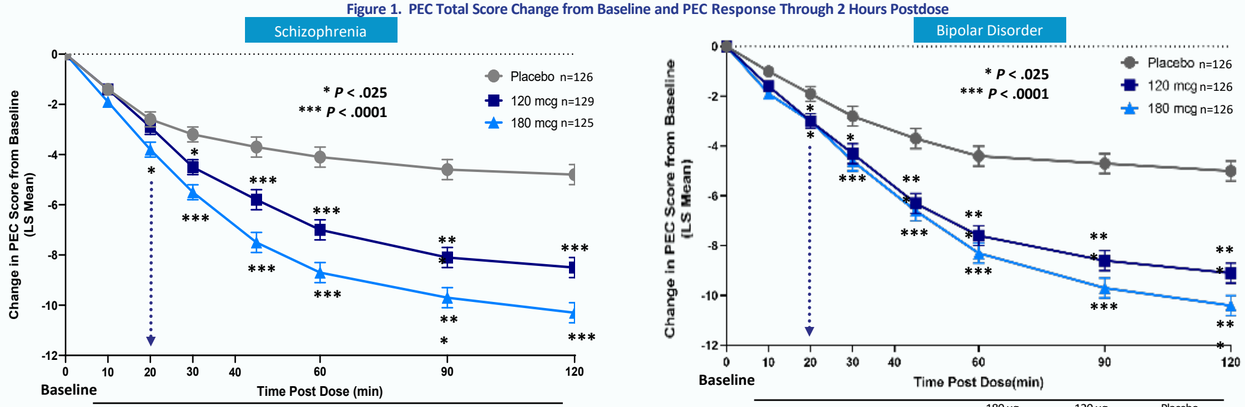
Endpoints

- Primary efficacy: least squares mean change from baseline on the PEC total score at 2 hours postdose
  - PEC scale items: scored from 1=minimum to 7=maximum; total score range 5-35
- Secondary efficacy: change from baseline in the PEC score at 10 minutes through 120 minutes postdose; secondary endpoints were tested using a hierarchical gatekeeping procedure (α>.025)
- Prespecified Exploratory: mean change from baseline in CGI-I and ACES; *P* values for exploratory endpoints were not corrected for multiple comparisons.

PARTICIPANTS

- Bipolar trial: 380 enrolled, 378 received at least 1 dose of study drug, and 362 completed the study
- Schizophrenia trial: 380 enrolled, 380 received at least 1 dose of study drug, and 372 completed the study
- Baseline agitation was mild to moderate [mean PEC scores 17.9-18.0 (bipolar trial) and 17.5-17.6 (schizophrenia trial)]
- In the schizophrenia trial the mean (SD) age was 45.6 years. Most participants identified as male (63.4%) and Black or African American (77.9%), with 19.7% White, and 90.3% Not Hispanic or Latino
- In the bipolar trial the mean (SD) age was 45.6 years. Most identified as female (207 [54.8%]) and Black or African American (212 [56.1%]), with 155 (41.0%) White, and 340 (89.9%) Not Hispanic or Latino

Figure 1. PEC Total Score Change from Baseline and PEC Response Through 2 Hours Postdose

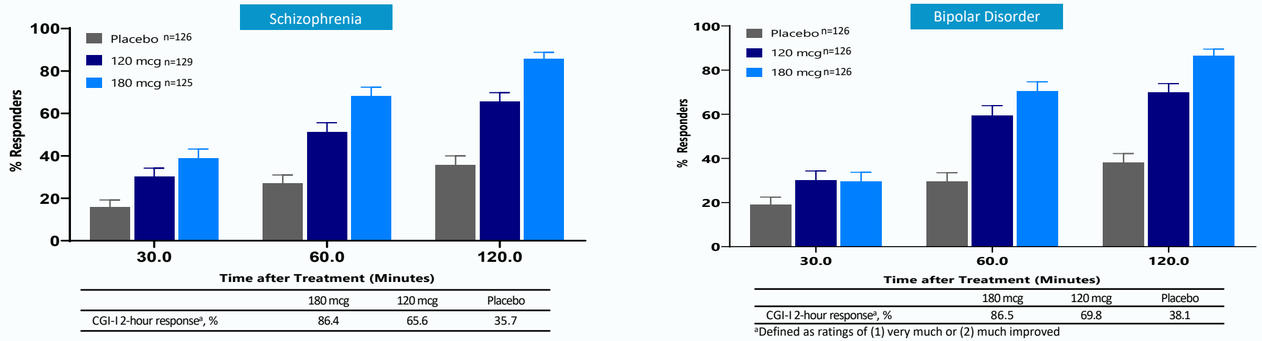


	180 µg	120 µg	Placebo
PEC 2-hour response[a], %	88.8	79.1	40.5

	180 µg	120 µg	Placebo
PEC 2-hour response[a], %	90.5	77.0	46.0

[a]Defined as a ≥40% PEC reduction from baseline

Figure 2. Clinical Global Impression-Improvement Scale (CGI-I) Response Through 2 Hours Postdose



	180 mcg	120 mcg	Placebo
CGI-I 2-hour response[a], %	86.4	65.6	35.7

	180 mcg	120 mcg	Placebo
CGI-I 2-hour response[a], %	86.5	69.8	38.1

[a]Defined as ratings of (1) very much or (2) much improved

Table 1. Adverse Events

	Number (%) of Patients		
	180 mcg (N=252)	120 mcg (N=255)	Placebo (N=252)
Number of TEAEs	170	168	62
At least 1 TEAE	92 (36.5)	95 (37.3)	41 (16.3)
TEAEs by severity			
Mild	68 (27.0)	78 (30.6)	38 (15.1)
Moderate	24 (9.5)	17 (6.7)	3 (1.2)
Severe	0	0	0
Serious AEs	0	1 (0.4)*	0
Discontinuation for AE	0	3 (1.2)	0
TEAEs in >2% of patients			
Dizziness	15 (6.0)	10 (3.9)	2 (0.8)
Dry mouth	11 (4.4)	19 (7.5)	3 (1.2)
Headache	6 (2.4)	12 (4.7)	12 (4.8)
Hypotension	13 (5.2)	14 (5.5)	0
Oral hypoaesthesia	12 (4.8)	7 (2.7)	1 (0.4)
Oral paresthesia	6 (2.4)	7 (2.7)	1 (0.4)
Orthostatic hypotension	13 (5.2)	7 (2.7)	1 (0.4)
Nausea	7 (2.8)	6 (2.4)	4 (1.6)
Somnolence	56 (22.2)	54 (21.2)	16 (6.3)

RESULTS

Efficacy: PEC Total Score and PEC Response

- In adults with schizophrenia or bipolar disorder (**Fig 1**):
  - Both 120 mcg and 180 mcg of dexmedetomidine ODF were more effective than placebo on the primary endpoint of change from baseline in PEC total at 2 hours postdose (*P*<.001)
  - Statistically significant Improvement began as early as 20 minutes at the 180 mcg dose in both trials
- Percent of responders on the PEC at 2 hours postdose was greater than placebo in both active treatment groups (*P*<.0001)

Efficacy: CGI– Improvement Scale

- In adults with schizophrenia or bipolar disorder (**Fig 2**):
  - Both 120 mcg and 180 mcg of dexmedetomidine ODF were more effective than placebo through 2 hours postdose, as measured by the CGI-I scale
  - Percent of responders on the CGI-I at 2 hours postdose was greater than placebo in both active treatment groups

KEY FINDINGS

Dexmedetomidine orally dissolving film, an investigational formulation of an α_{2A} adrenergic agonist being developed for the treatment of acute agitation associated with schizophrenia or bipolar disorder:

- Effectively treated acute agitation associated with schizophrenia or bipolar disorder, with an onset of action as early as 20 minutes at the 180 mcg dose
- Produced a calming effect without causing unarousable sedation
- There were no serious or severe drug-related AEs. Mild or moderate somnolence was the most common AE

References: 1. Citrome L. *Ther Clin Risk Manag.* 2013;9:235-245; 2. Montoya A, et al. *Health Qual Life Outcomes.* 2011;9:18. *Judged by investigator to be unrelated to study drug

Disclosures: This study was supported by funding from BioXcel Therapeutics. SH, LR, and RR are employed by BioXcel Therapeutics.