Safety, Acceptability, and Pharmacokinetics of Dexmedetomidine Orally Dissolving Film (BXCL501) for Treating Acute Agitation in Patients with Schizophrenia

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Introduction

- Agitation is common during acute exacerbations of schizophrenia; without prompt treatment, it can escalate into aggressive behavior[1]
- Dexmedetomidine orally dissolving film (ODF [BXCL501]) is an investigational formulation of dexmedetomidine, a selective α_{2A} adrenergic receptor agonist designed to completely dissolve in the sublingual or buccal area
- Dexmedetomidine ODF delivers a discrete microdose that bypasses first-pass liver metabolism

Objectives

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

Methods

Conduct

- Phase 3, randomized, placebo-controlled study of adults aged 18-75 years, inclusive
- Diagnosed with DSM-5 schizophrenia, schizoaffective, or schizophreniform disorder
- Clinically agitated at screening and baseline; Positive and Negative Syndrome Scale – Excited Component[2] (PEC) total score ≥14 and baseline score of ≥4 on ≥ 1 item. PEC scoring for each item ranges from 1 (minimum) to 7 (maximum).
- Participants were randomized (1:1:1) to dexmedetomidine ODF 180 mcg, dexmedetomidine ODF 120 mcg, or placebo and self-administered the study drug or identical matching placebo film

Assessments

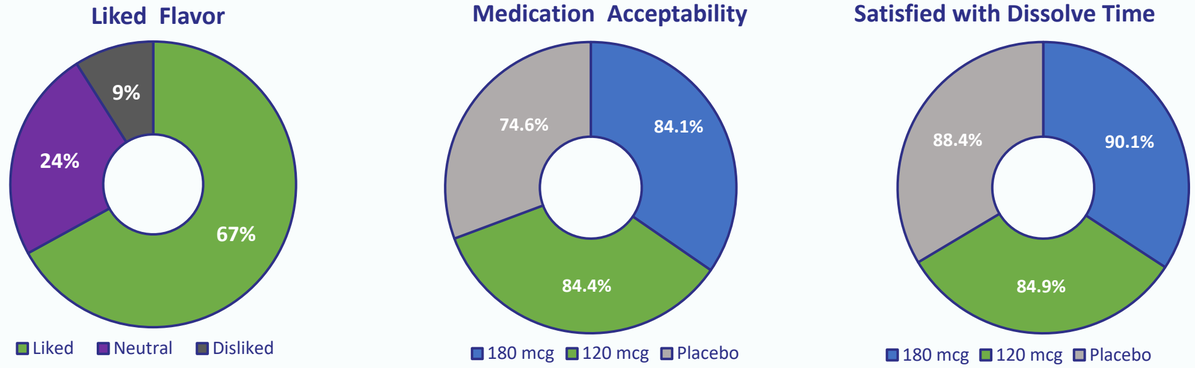
- Adverse events; clinical laboratory tests; electrocardiogram (ECG) with rhythm strip; ECG overreads by cardiologists; pulse oximetry; and vital signs, including resting and orthostatic vital sign parameters (systolic blood pressure [SBP], diastolic blood pressure [DBP], and heart rate [HR]) were monitored for safety and tolerability
- 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
- Patient opinion of study medication was assessed at 20 minutes postdose using a Likert-type scale (1=strongly disagree, 5=strongly agree) for 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 participants who received at least 1 dose of study drug; no formal hypothesis-testing of TEAE incidence rates was planned or performed

Participants

- 380 participants were enrolled, 380 received 1 or more doses of dexmedetomidine ODF, and 372 completed the study
- Demographic and baseline characteristics were comparable across treatment groups
- At screening, 84.5% of patients were diagnosed with schizophrenia and 15.5% of were diagnosed with schizoaffective disorder
- Baseline agitation was mild to moderate, with mean PEC total scores across treatment groups ranging from 17.5 to 17.6
- Mean participant (SD) age was 45.6 years. Most were male (63.4%) and Black or African American (77.9%), 19.7% were White, and 90.3% were Not Hispanic or Latino

Results

Figure 1. Acceptability at 20 Minutes Postdose



- > 84% rated dexmedetomidine ODF as acceptable
- 91% liked (67%) the flavor or were neutral (24%)
- > 80% were satisfied with the time it took the film to dissolve in the mouth
- > 90% said dexmedetomidine ODF did not have an unpleasant aftertaste; 99% reported no unpleasant scent

Table 1. Adverse Events Occurring in ≥2% of Participants[a]

	BXCL501 180 mcg (n=126)	BXCL501 120 mcg (n=126)	Placebo (n=126)
Any drug-related AE	44 (34.9)	46 (35.7)	15 (11.9)
Serious AE	0	0	0
Discontinuation for AE	0	2 (1.6)	0
Treatment-emergent AEs			
Any (≥1 event)	47 (37.3)	51 (39.5)	19 (15.1)
Dizziness	8 (6.4)	3 (2.3)	1 (.8)
Dry mouth	5 (4.0)	10 (7.8)	2 (1.6)
Headache	4 (3.2)	6 (4.7)	6 (4.8)
Hypoesthesia oral	7 (5.6)	5 (3.9)	0
Hypotension	5 (4.0)	8 (6.2)	0
Nausea	2 (1.6)	3 (2.3)	1 (.8)
Orthostatic hypotension	7 (5.6)	2 (1.6)	0
Paresthesia oral	3 (2.4)	5 (3.9)	1 (.8)
Somnolence	29 (23.0)	28 (21.7)	10 (7.9)

AE, adverse event
[a]In either treatment group

Blood Pressure

- At 2 hours postdose, subjects treated with dexmedetomidine ODF had decreases in SBP (180 µg: −16.8 [14.8]) mmHg, 120 µg: −12.8 [13.7]) mmHg); DBP (180 µg: −8.9 [10.2]) mmHg, 120 µg: −7.7 [8.5]) ; and HR (180 µg: −8.2 [10.3]) bpm, 120 µg: −7.6 [9.4]). These decreases were not observed in the placebo group
- Abnormal postural changes from supine to standing were ≤13% in all treatment groups. No cases of syncope or falls were reported
- At 2 hours and 24 hours postdose, there were no cardiac-related AEs; clinically meaningful changes from baseline for PR interval, QRS duration, or QTcF; or AEs related to ECG parameters, treatment-emergent arrhythmia, or a clinically significant ECG change from baseline

Local Irritation

- One patient in the 180 mcg treatment group (.8%) had local buccal irritation at 4 hours postdose
- No patient had irritation at 30 minutes, 2 or 24 hours postdose

Exposure

- A phase 1b randomized, double-blind, placebo-controlled, single ascending dose study trial enrolled 135 participants experiencing acute agitation associated with schizophrenia
- Patients were treated with a single 20 mcg, 60 mcg, 80 mcg, 120 mcg, or 180 mcg dose of dexmedetomidine ODF or matching placebo
- Plasma samples were collected over 24 hours postdose and analyzed by validated LC-MS /MS assay
- Maximum plasma concentrations were achieved within 2 hours
- Exposure was approximately dose proportional between 20 mcg - 180 mcg dose groups
- Plasma elimination half-life was between 2-3 hours
- Dose-dependent improvements in PEC total scores from baseline at 2 hours were significant with the 80 mcg, 120 mcg, and 180 mcg doses; the mean changes were −7.3, −9.2, and −10.8 points, respectively, and −4.5 for placebo

KEY FINDINGS

- In a Phase 3 randomized controlled trial, dexmedetomidine ODF, an investigational formulation, was well tolerated with no drug-related serious or severe AEs (Table 1)
- All participants self-administered study drug and the majority of participants rated the taste and dissolve time acceptable
- Results of a Phase 1b controlled trial demonstrated a dose-dependent increase in dexmedetomidine exposure after sublingual administration
- Dexmedetomidine ODF demonstrated dose- and exposure-dependent reduction in agitation in adults experiencing acute agitation associated with schizophrenia

References: 1. Citrome L. *Ther Clin Risk Manag*. 2013;9:235-245; 2. Montoya A et al. *Health Qual Life Outcomes*. 2011;9:18.

Disclosures : This study was supported by BioXcel Therapeutics. MK, AA, RR, and CL are employed by BioXcel Therapeutics.

Presented at: Midyear Clinical Meeting of the American Society of Health System Pharmacists; December 5-9, 2021