Dexmedetomidine Sublingual Film: Post Hoc Analysis of PANSS-Excited Component Items in Acute Agitation Associated With Schizophrenia or Bipolar Disorder

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INTRODUCTION

- Individuals with schizophrenia or bipolar disorder experiencing episodes of acute agitation often require timely intervention to reduce the risk of patient or staff injury, disruption of care, and hospital stay prolongation[1,2]
- Dexmedetomidine is a selective α_{2A} adrenergic receptor agonist
- Dexmedetomidine sublingual film 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 sublingual film is more effective than placebo at reducing the symptoms of acute agitation in adults with schizophrenia or bipolar disorder measure by the PANSS-Excited Component (PEC) total and individual scale components.

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 sublingual dexmedetomidine 120 mcg, 180 mcg, or matching 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: mean change from baseline on the PEC total score at 2 hours postdose
  - Poor impulse control, tension, hostility, uncooperative, excitement)
  - 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)

Post Hoc Analysis

- Mean change from baseline in individual PEC component scores

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 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 age was 45.6 years. Most identified as female (54.8%) and Black or African American (56.1%), with 41.0% White, and 89.9% Not Hispanic or Latino

Figure 1. 2-Hour PEC Component Scores by Treatment Group

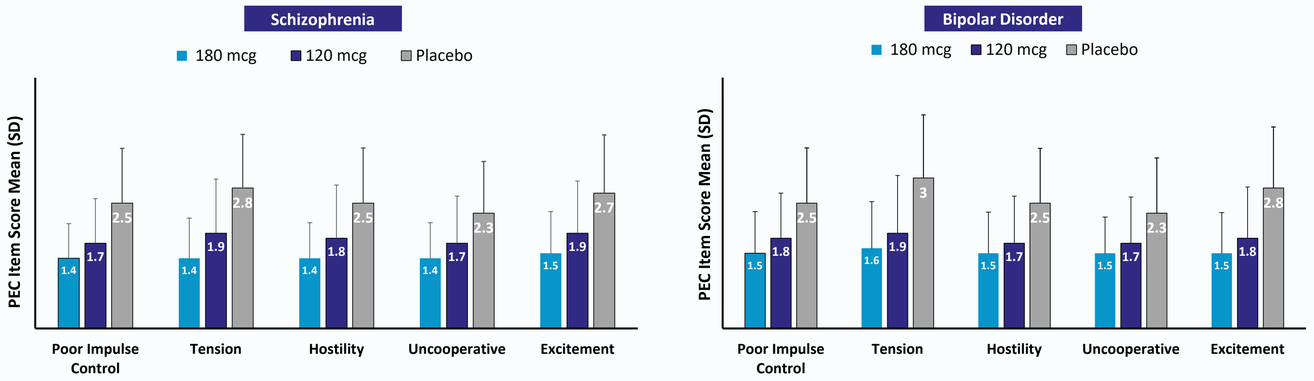


Figure 2. Pooled PEC Components Change from Baseline to 2 Hours

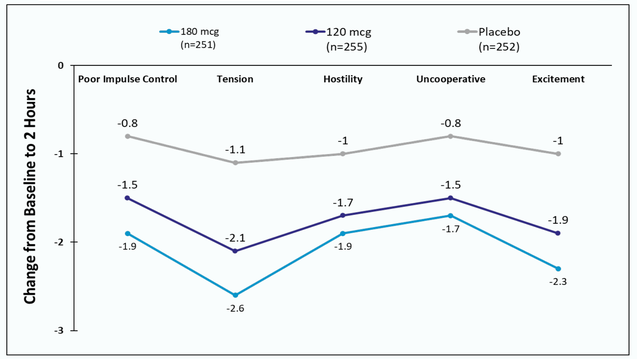
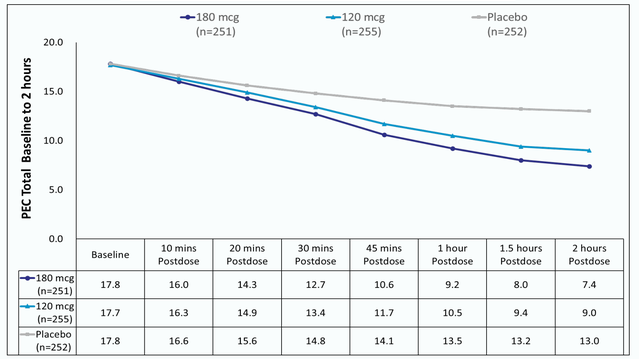


Figure 3. Pooled PEC Total Baseline to 2 hours



	Baseline	10 mins Postdose	20 mins Postdose	30 mins Postdose	45 mins Postdose	1 hour Postdose	1.5 hours Postdose	2 hours Postdose
180 mcg (n=251)	17.8	16.0	14.3	12.7	10.6	9.2	8.0	7.4
120 mcg (n=255)	17.7	16.3	14.9	13.4	11.7	10.5	9.4	9.0
Placebo (n=252)	17.8	16.6	15.6	14.8	14.1	13.5	13.2	13.0

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

- Two-hour change from baseline in individual PEC items was significantly higher for both dexmedetomidine sublingual film dose groups compared to placebo (*P*<.001.). **Figure 1**
- The largest decreases in both doses were in the tension and excitement items. Across the 5 PEC items, decrease from baseline ranged from 1.7 to 2.6 in the 180 mcg group and 1.5 to 2.1 in the 120 mcg group, compared to 0.8 to 1.1 with placebo. **Figure 2**
- At the 180 mcg dose, change from baseline relative to placebo was statistically significant (*P*<.05) as early as 10 minutes for Poor Impulse Control, Tension, and Hostility and as early as 20 minutes for Uncooperative and Excitement.
- Pooled PEC total scores statistically separated from placebo as early as 10 minutes at 180 mcg and as early as 20 minutes at 120 mcg. **Figure 3**
- There were no serious or severe treatment related adverse events (TEAEs). The most common adverse events (AEs) were somnolence, dry mouth, hypotension, dizziness, orthostatic hypotension, oral hypoesthesia, nausea, and oral paresthesia. **Table 1.**

KEY FINDINGS

Dexmedetomidine sublingual film

- Effectively reduced symptoms of acute agitation associated with schizophrenia or bipolar disorder, with an onset of action as early as 10 minutes at the 180 mcg dose and 20 minutes at the 120 mcg dose.
- Produced statistically significant reductions in each component of the PANSS-Excited Component (PEC) scale compared to placebo.
- Produced a calming effect without causing unarousable sedation.
- Was not associated with serious or severe TEAEs. 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

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