Dexmedetomidine Sublingual Film for Treatment of Acute Agitation Associated With Schizophrenia or Bipolar Disorder: SERNITY I and SERENITY II Trials

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INTRODUCTION

Sublingual dexmedetomidine is an orally dissolving film formulation of dexmedetomidine, a selective alpha$_2$ adrenergic receptor agonist

It is approved for sublingual or buccal administration for the treatment of adults with acute agitation associated with schizophrenia or bipolar disorder I or II

Acute agitation is common in psychiatric settings and should be managed urgently to lower the risk of escalation.[1] Previously, 2 randomized, placebo-controlled clinical trials showed that a single 120 mcg or 180 mcg dose of dexmedetomidine sublingual film effectively reduced agitation in adults with mild or moderate agitation associated with schizophrenia, schizoaffective disorder, or bipolar disorder.[2,3]

OBJECTIVE

Evaluate the efficacy and safety of dexmedetomidine 180 mcg or 120 mcg sublingual film in adults with moderate or severe symptoms of acute agitation associated with schizophrenia, schizoaffective disorder, or bipolar disorder in a post hoc analysis of pooled Phase 3 clinical trial data

METHODS

Design: Post hoc analysis of pooled data from two Phase 3 randomized, controlled studies in adults with schizophrenia or bipolar disorder experiencing acute agitation[2,3]

Participants: Adults (18-75) diagnosed with DSM-5 schizophrenia, schizoaffective disorder, or bipolar disorder I or II

Treatment: Participants self-administered 1 dose of sublingual dexmedetomidine 180 mcg, 120 mcg, or matching placebo

Primary Endpoint

Mean change from baseline on total score on the Positive and Negative Syndrome Scale (PANSS)-Excited Component (PEC)[4] at 2 hours postdose

Therapeutic response was defined as a ≥40% reduction in PEC total at 2 hours.

Secondary Endpoint: Earliest time of a statistically significant separation from placebo on the PEC

PARTICIPANTS

The 758 adults in the pooled population were treated with dexmedetomidine 180 mcg (n=251), dexmedetomidine 120 mcg (n=255), or placebo (n=252). The study population had a mean (SD) age of 45.0 (11.5) years and 54% identified as male and 59% as Black or African American (Table 1).

Mean (SD) PEC total scores were 17.8 (2.9) for sublingual dexmedetomidine 180 µg, 17.7 (2.6) for sublingual dexmedetomidine 120 µg, and 17.8 (2.6) for placebo.

Table 1. Participant Demographics and Baseline Characteristics

	Sublingual Dexmedetomidine		
	180 mcg (n=251)	**120 mcg (n=255)**	**Placebo (n=252)**
Age, years, mean (SD)	45.9 (11.6)	45.9 (11.4)	45.0 (11.6)
Age range, years	18, 71	19, 70	18, 68
Gender, self-identified, n (%)			
Female	110 (44)	119 (47)	117 (46)
Male	141 (56)	136 (53)	135 (54)
Race, self-identified, n (%)			
Black or African American	174 (69)	160 (63)	174 (69)
White	70 (28)	89 (35)	71 (28)
Other[a]	7 (3)	6 (2)	7 (3)
Body mass index, kg/m^2, mean (SD)	32.9 (8.3)	31.4 (7.8)	32.5 (7.4)
Number of hospitalizations, mean (SD)	3.6 (7.6)	4.1 (5.1)	3.4 (4.5)
Hours of sleep/night this week, mean (SD)	5.3 (1.6)	5.6 (1.7)	5.4 (1.7)
Current smoker, n (%)	160 (64)	193 (76)	185 (73)
PEC total score, mean (SD)	17.8 (2.9)	17.7 (2.6)	17.8 (2.6)

CGI, Clinical Global Impressions, severity of illness rated on a 7-point scale from 1 (normal) through to 7 (among the most severely ill patients); PEC, Positive and Negative Syndrome Scale-Excited Component, comprised of 5 items with a range of 5 (absence of agitation) to 35 (extremely severe); SD, standard deviation.
[a]Includes Native American, Alaska Native, Asian, Native Hawaiian or other Pacific Islander, and Multiple.

Safety

Treatment-emergent adverse events (AE) were experienced by 32.9%, 34.1%, and 11.9% of participants in the sublingual dexmedetomidine 180 mcg, 120 mcg, and placebo groups, respectively

The **most common** treatment-emergent adverse event was **somnolence**, which affected 22.2%, 21.2%, and 6.3% in the 180 mcg, 120 mcg, and placebo groups, respectively

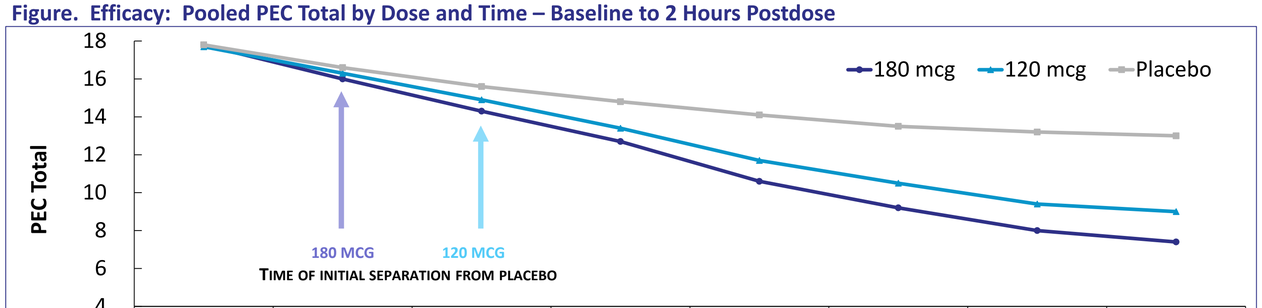
There were no severe AEs reported.

Table 2. Pooled Adverse Events (AE) by Treatment Group

	Sublingual Dexmedetomidine		
	180 mcg (n=252)	**120 mcg (n=255)**	**Placebo (n=252)**
Any Treatment Emergent AE	83 (32.9)	87 (34.1)	30 (11.9)
Serious AE	0	1 (0.4)	0
Discontinuation due to AE	0	3 (1.2)	0
Somnolence	56 (22.2)	54 (21.2)	16 (6.3)
Dry Mouth	11 (4.4)	19 (7.5)	3 (1.2)
Hypotension	13 (5.2)	14 (5.5)	0
Dizziness	15 (6.0)	10 (3.9)	2 (0.8)
Orthostatic Hypotension	13 (5.2)	7 (2.7)	1 (0.4)
Oral Hypoesthesia	12 (4.8)	7 (2.7)	1 (0.4)
Headache	6 (2.4)	12 (4.7)	12 (4.8)
Nausea	7 (2.8)	6 (2.4)	4 (1.6)
Oral Paresthesia	6 (2.4)	7 (2.7)	1 (0.4)

Subjects were counted once within a dexmedetomidine treatment group and once within a pooled treatment group (all dexmedetomidine or placebo). Data for 1 subject enrolled in the 120 ug and the 180 ug treatment group are reported in the 120 ug and 180 ug columns.

Figure. Efficacy: Pooled PEC Total by Dose and Time – Baseline to 2 Hours Postdose



	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	17.8	16.0	14.3	12.7	10.6	9.2	8.0	7.4
120 mcg	17.7	16.3	14.9	13.4	11.7	10.5	9.4	9.0
Placebo	17.8	16.6	15.6	14.8	14.1	13.5	13.2	13.0

Efficacy

Primary: At 2 hours postdose, the mean (SD) change from baseline in PEC total score was −10.4 (4.4) for sublingual dexmedetomidine 180 mcg, −8.7 (5.0) for sublingual dexmedetomidine 120 mcg, and −4.8 (4.7) for placebo. Both sublingual dexmedetomidine doses were more effective than placebo (*P*<.001) at reducing symptoms of agitation.

Secondary: The onset of treatment effect was 10 minutes postdose in the sublingual dexmedetomidine 180 µg group (−1.8 (3.13) vs −1.2 (2.02), *P*<.001) and 20 minutes postdose in the sublingual dexmedetomidine 120 µg group (−2.9 (3.92) vs −2.2 (3.11), *P*<.001).

PEC Scale

5 Items
1. Poor impulse control
2. Tension
3. Hostility
4. Uncooperativeness
5. Excitement

7-point Scale
1=minimum
7=maximum

Total Score
Sum of the 5 item scores (range 5-35)

Participants in This Analysis
≥14 PEC total score
≥4 on at least 1 PEC item

KEY POINTS

- Sublingual dexmedetomidine is an orally dissolving film formulation of dexmedetomidine, a selective alpha$_2$ adrenergic receptor agonist
- Post hoc analysis of pooled data from 2 Phase 3 Clinical Trials (N=506) of sublingual dexmedetomidine for the treatment of adults with acute agitation associated with schizophrenia or bipolar disorder I or II
- PEC Total was significantly lower than placebo from 20 minutes through 2 hours for both doses (Figure)
- Onset of treatment effect (Key Secondary Endpoint)
  - 10 minutes postdose for 180 mcg
  - 20 minutes postdose for 120 mcg
- The most common adverse events were somnolence, dry mouth, dizziness, hypotension, orthostatic hypotension, oral hypoesthesia, headache, nausea, oral paresthesia (Table 2)

References 1. Zeller SL, Citrome L. West J Emerg Med. 2016 Mar;17(2):165-72; 2. Preskorn SH et al. *JAMA*. 2022;327:727-736; 3. Citrome L, Preskorn SH, Lauriello J, et al. *J Clin Psychiatry*. (In Press); 4. Montoya A et al. *Health Qual Life Outcomes*. 2011;9:18.

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