# Dexmedetomidine Orally Dissolving Film for Acute Agitation Associated with Schizophrenia or Bipolar Disorder: SERENITY I and SERENITY II Trials

Leslie L. Citrome, MD, MPH[1], Sheldon H. Preskorn, MD[2], Lavanya Rajachandran, PhD[3] and Robert Risinger, MD[3]

[1]New York Medical College, Valhalla, NY, USA, [2]University of Kansas School of Medicine-Wichita, Wichita, KS, USA, and [3]BioXcel Therapeutics, New Haven, CT, USA

**Abstract**

Episodes of acute agitation associated with psychiatric disorders are often managed in emergency and inpatient settings. These trials evaluated the efficacy, safety, and tolerability of dexmedetomidine orally dissolving film (ODF), an investigational treatment for acute agitation associated with schizophrenia (SERENITY I) or bipolar disorder (SERENITY II). Dexmedetomidine ODF is a highly selective agonist of alpha 2 adrenergic receptors that modulate norepinephrine release from the locus coeruleus. Two randomized, double-blind, placebo-controlled Phase 3 trials in 15 U.S. sites included participants aged 18 to 75 with acute agitation and a DSM-5 diagnosis of schizophrenia or schizoaffective disorder (Serenity I) or bipolar disorder I or II (Serenity II). Agitation was defined as ³14 on the Positive and Negative Syndrome Scale-Excited Component (PEC) at screening and baseline, and ³4 on at least 1 of the 5 PEC items (poor impulse control, tension, hostility, uncooperativeness, and excitement) at baseline. Randomization was 1:1:1 to dexmedetomidine ODF 120 or 180 mcg or matching placebo. All participants self-administered study drugs. For persistent or recurrent agitation after 2 hours, investigators could redose a half-dose. The primary endpoint was changed from baseline in PEC total at 2 hours. The secondary endpoint was the earliest time at which a statistically significant separation from placebo occurred.A total of 380 patients were randomized in each trial (N = 760). All doses of dexmedetomidine ODF met the primary endpoint of change from baseline in PEC at 2 hours vs placebo ($P < .001$). Statistically significant improvement in PEC occurred as early as 20 minutes with the 180 mcg dose in both trials. A second (half-strength) dose was given to 10 (4.0%) participants in the 180 mcg groups, 34 (13.3%) in the 120 mcg groups, and 58 (23.0%) in the placebo groups in Serenity 1 and Serenity 2. There were no drug-related serious or severe TEAEs in either trial. No participant was unarousable by the Agitation and Calmness Evaluation Scale. For dexmedetomidine 180 mcg, 120 mcg, and placebo, the incidence of TEAEs was 37.3%, 39.5%, and 15.1% in Serenity 1 and 35.7%, 34.9%, and 17.5% in Serenity 2. Somnolence was the most common TEAE in both trials (22% Serenity I; 21% Serenity 2). Of 110 somnolence reports, 75% were mild and 25% moderate. In 2 Phase 3 trials, the investigational treatment, dexmedetomidine ODF, effectively treated acute agitation associated with schizophrenia or bipolar disorder, with onset of action as early as 20 minutes at the 180 mcg dose. Both doses of dexmedetomidine ODF produced a calming effect without unarousable sedation. Mild or moderate somnolence was the most common AE. Dexmedetomidine ODF is a selective alpha-2 adrenergic receptor agonist that allows self-administration, making it a potential addition to noninvasive treatments for acute agitation associated with schizophrenia or bipolar disorder.

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# Randomized, Double-Blind, Placebo-Controlled, Fixed-Dose Study to Evaluate the Efficacy and Safety of the Amphetamine Extended-Release Tablet in Adults with Attention-Deficit/Hyperactivity Disorder

Andrew J. Cutler, MD[1,2], Ann C. Childress, MD[3], Antonio Pardo, MD[4], Eman Rafla, MD[4], Stephanie Duhoux, PhD[4], Judith C. Kando, PharmD, BCPP[4] and Lori Dansie, PhD, MBA[4]

[1]SUNY Upstate Medical University, Lakewood Ranch, FL, USA, [2]Neuroscience Education Institute, Carlsbad, CA, USA, [3]Center for Psychiatry and Behavioral Medicine, Las Vegas, NV, USA, and [4]Tris Pharma, Inc., Monmouth Junction, NJ, USA

**Abstract**

**Background.** Attention-deficit/hyperactivity disorder (ADHD) is a neurobehavioral disorder characterized by pervasive impairment in symptoms of inattention, hyperactivity, and impulsivity. Psychopharmacologic treatment is targeted at the management of symptoms of ADHD, and evidence exists that ADHD persists into adulthood. Clinical practice guidelines recommend a combination of behavior therapy and psychostimulant medication for the treatment of ADHD in children, adolescents, and adults. Psychostimulants are often prescribed for ADHD in adults, and amphetamine long has been considered a mainstay of treatment for this population. As adult patients seek relief from ADHD symptoms early in the workday and into the early evening hours, with fewer required doses, extended-release formulations with an early onset of efficacy and an extended duration of effect are considered very desirable. The amphetamine-extended release tablet (AMPH ER TAB) was developed to provide a portable, easy-to-use amphetamine tablet dosage option that can be chewed or swallowed whole.

**Objectives.** To evaluate the efficacy and safety of an Amphetamine Extended-Release Tablet (AMPH ER TAB) in adults with ADHD aged 18 to 60 years. Methods: In a 5-week forced dose-titration phase, eligible subjects were randomized to either oral

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double-blind AMPH ER TAB 5 mg starting dose or matching placebo, once daily in the morning beginning the day after the Baseline Visit. Subjects were titrated up (5 mg increments) each week. Safety and efficacy assessments were done weekly. After Visit 3, subjects received 20 mg for 14 (3) days before Visit 5 (V5). Subjects who could not tolerate study drugs discontinued. A Permanent Product Measure of Performance (PERMP) placement test was done at Screening or Baseline. At V5, efficacy assessments included the administration of serial PERMPs predose, 0.5, 1, 2, 4, 8, 10, 12, 13, and 14 hours postdose. The primary efficacy endpoint was the mean PERMP-T score across postdose time points during the Visit 5 serial PERMPs. Safety was monitored by AEs assessed at each visit, C-SSRS, vital signs, weight, and assessment of sleep, appetite, mood, and psychotic AEs.

**Results.** The mean postdose PERMP-T score over all postdose time points at V5 was statistically significantly higher in the AMPH ER TAB group vs placebo (302.8 vs 279.6; $P = .0043$). Common adverse events were decreased appetite, insomnia, and dry mouth. The majority of TEAEs were mild to moderate in severity, and no SAEs were reported.

**Conclusion.** The AMPH ER TAB demonstrated efficacy in the treatment of symptoms of ADHD in adults, with an anticipated safety profile.

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# Post Hoc Analysis of the Impact of Lemborexant on Patient-Reported Sleep and Insomnia Severity in Adults with Insomnia and Depression Histories

Larry Culpepper, MD, MPH[1], Andrew D. Krystal, MD[2], Kate Pinner, MSc[3] and Margaret Moline, PhD[4]

[1]Boston University School of Medicine, Boston, MA, USA, [2]University of California, San Francisco, San Francisco, CA, USA, [3]Eisai Ltd., Hatfield, United Kingdom, and [4]Eisai Inc., Woodcliff Lake, NJ, USA

**Abstract**

**Introduction.** The dual orexin receptor antagonist lemborexant (LEM) is approved in multiple countries including the United States, Japan, Canada, and Australia for insomnia treatment in adults. In phase 3 study E2006-G000-303 (Study 303; SUNRISE-2; NCT02952820), LEM provided significant benefit vs placebo (PBO) on subjective sleep outcomes over 6 months and was well tolerated. This post hoc analysis evaluated the effect of LEM on sleep outcome measures and insomnia severity as assessed by the Insomnia Severity Index (ISI) over 6 months in subjects with a lifetime history of depression (DepHx subgroup). We performed this analysis as insomnia in DepHx subjects could be a residual symptom of unresolved depression, and therefore, these subjects may respond differently to insomnia treatment.

**Methods.** Study 303 was a randomized, double-blind, 12 months global study in adults (≥18 years) with DSM-5 insomnia disorder. For 6 months (Treatment Period 1), subjects were randomized to PBO or LEM (5 mg [LEM5]; 10 mg [LEM10]). For the next 6 months (Treatment Period 2; not reported), PBO subjects were rerandomized to LEM and LEM subjects continued their original dose. The inclusion criteria allowed for participation of subjects with a lifetime DepHx, concomitant antidepressant medication use and/or mild depression (maximum Beck Depression Inventory II score of 19). Subjects had a baseline ISI total score (ISI-ts) ≥15.

**Results.** The Full Analysis Set comprised 949 subjects, including 112 subjects in the DepHx subgroup (PBO, n = 34; LEM5, n = 39; LEM10, n = 39). Baseline median subjective sleep onset latency (sSOL; minutes) was 52.9, 57.1, and 70.7 for PBO, LEM5, and LEM10, respectively. At 6 months, greater median decreases from baseline in sSOL were observed with LEM5 (−21.7) and LEM10 (−40.1) vs PBO (−12.9). Baseline mean subjective sleep efficiency (sSE; %) was 62.2, 59.2, and 62.4 for PBO, LEM5, and LEM10, respectively. At 6 months, greater mean (SD) increases from baseline in sSE were observed with LEM5 (17.2 [18.3]) and LEM10 (20.9 [19.0]) vs PBO (14.9 [15.4]). Baseline mean subjective wake after sleep onset (sWASO; minutes) was 123.7, 151.0, and 132.6 for PBO, LEM5, and LEM10, respectively. At 6 months, greater mean (SD) decreases from baseline in sWASO were observed with LEM5 (−52.7 [69.2]) and LEM10 (−68.8 [81.9]) vs PBO (−46.7 [69.4]). Mean baseline ISI-ts were 18.6, 19.9, and 19.0 PBO, LEM5, and LEM10, respectively. At 6 months, greater mean (SD) decreases from baseline in ISI-ts were observed with LEM5 (−9.1 [6.8]) and LEM10 (−10.0 [5.9]) vs PBO (−7.9 [5.6]). Treatment-emergent adverse event rates in the DepHx subgroup were similar to those in the overall study population.

**Discussion.** At 6 months, LEM improved patient-reported sleep outcomes and reduced patient-reported insomnia severity in subjects with DepHx. These results suggest that LEM may be a therapeutic option for patients with insomnia and DepHx.

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# Hyponatremia Secondary Treatment with SSRI Antidepressants in Adults and Elderly

Martin J. Mazzoglio y Nabar, MD, MSc[1], Milagros M. Muniz, MD, MSc[1,2], Christian A. Montivero, MD[1,2], Gabriel Schraier, MD[1,2] and Emmanuel E. Leidi Terren, MD, MSc[2]

[1]University of Buenos Aires, Buenos Aires City, Greater Buenos Aires, Argentina, and [2]Maimonides University, Buenos Aires City, Greater Buenos Aires, Argentina

**Abstract**

**Introduction.** Hyponatremia is an electrolyte disorder that can be caused by multiple factors, among which the syndrome of inappropriate antidiuretic hormone secretion (SIAHS) is one of the most frequent causes. Selective serotonin reuptake inhibitors (SSRIs) are the most widely used antidepressant drugs in all age

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