LEM5, or LEM10 (SUNRISE-1 subjects could also be randomized to ZOL; not included in pooled analysis) following a 2-week PBO run-in. Changes from baseline (BL) in subjective sleep onset latency (sSOL), subjective sleep efficiency (sSE), and subjective wake after sleep onset (sWASO) were analyzed using mixed effect model repeated measurement analysis. Sleep onset and sleep maintenance responders were analyzed via Cochran–Mantel–Haenszel test stratified by study, region and age group.

RESULTS: The pooled analysis set comprised 1693 subjects (PBO, n=527; LEM5, n=582; LEM10, n=584). Reductions from BL in sSOL were significantly greater for LEM5 and LEM10 vs PBO during the first 7 days of treatment and at the end of Month 1 (all comparisons P<0.0001). Both doses of LEM significantly increased sSE from BL (P<0.001 both time points) more than PBO and reduced sWASO from BL (P<0.0001 first 7 days [both doses]; P<0.05 [LEM5] and P<0.001 [LEM10] at Month 1) more than PBO. After the first 7 days and at the end of Month 1, the proportion of sSOL responders (≤20 min if BL >30 min) was statistically significantly larger for LEM5 and LEM10 vs PBO (first 7 days: both P<0.0001; last 7 days of Month 1: both P<0.001) and the proportion of sWASO responders (≤60 minutes and a reduction from BL by >10 min, if BL >60 min) was statistically significantly larger for LEM5 and LEM10 vs PBO (first 7 days: both P<0.01; last 7 days of Month 1: both P<0.05). LEM was well tolerated. Most AEs were mild to moderate in severity, and rates of severe or serious AEs were low.

CONCLUSIONS: LEM improved sleep onset and sleep maintenance in adult and elderly subjects with insomnia disorder, and was well tolerated. Average values on sleep maintenance endpoints showed that subjects treated with LEM obtained >1 hour of additional sleep per night vs subjects who received PBO.

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Impact of Lemborexant on Insomnia Disease Severity and Fatigue: Results from the 6-Month Placebo-Controlled Period of the Phase 3 SUNRISE-2 Study

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ABSTRACT: Study Objective(s): This study examined the effects of lemborexant (LEM) compared with placebo (PBO) on subject-reported insomnia disease severity, assessed by the Insomnia Severity Index (ISI), and fatigue, assessed by the Fatigue Severity Score (FSS), from the 6-month PBO-controlled period of SUNRISE-2.

METHOD: SUNRISE-2 (NCT02952820; E2006-G000-303) was a 12-month randomized, double-blind, PBO-controlled (first 6-months) Phase 3 study. After an ~2-week PBO run-in, subjects were randomized to PBO, LEM 5mg (LEM5) or LEM 10mg (LEM10) for 6 months. The ISI and the FSS were administered at baseline [BL] and at the end of Months 1, 3, and 6. The ISI daytime functioning score (DFS), based on the ISI items that assess the impact of insomnia symptoms specific to daily functioning (items 4-7), was also evaluated. Mean changes from BL in ISI total score (ISI TS), ISI DFS, and FSS total score (FSS TS) were analyzed using a mixed-effect model repeated measurement analysis, adjusted for relevant factors and BL score (ISI TS, ISI DFS, or FSS TS) as a covariate.

RESULTS: 949 subjects (PBO, n=318; LEM5, n=316; LEM10, n=315) were included in the full analysis set. Median age was 55y (range 18-88y). Mean ISI TS at BL for PBO, LEM5, and LEM10 was 19.0, 19.6 and 19.1, respectively. While mean ISI TS decreased (improved) from BL for all groups, decreases were significantly larger for both LEM5 and LEM10 vs PBO at Month 1 (least squares mean treatment difference [LSM TD]: LEM5, −1.5 [P=0.001]; LEM10, −1.9 [P<0.0001]), Month 3 (LSM TD: LEM5, −2.0; LEM10, −2.6 [both P<0.0001]), and Month 6 (LSM TD: LEM5, −2.1; LEM10, −2.4 [both P<0.0001]). Decreases from BL in mean ISI DFS were also significantly larger for LEM5 and LEM10 vs PBO at Month 1 (LSM TD: LEM5, −0.7 [P=0.014]; LEM10, −0.9 [P=0.001]), Month 3 (LSM TD: LEM5, −1.2 [P=0.0001]; LEM10, −1.4 [P<0.0001]), and Month 6 (LSM TD: LEM5, −1.3; LEM10, −1.3 [both P<0.0001]).
Mean FSS TS at BL was 35.2, 37.4, and 36.0 for PBO, LEM5, and LEM10, respectively. Mean FSS TS decreased (improved) from BL in all groups at the end of Month 1 (decreases were larger and significant for LEM10 vs PBO [LSM TD: –2.0 (P=0.026)]), and Month 3 (decreases were larger and significant for LEM5 [LSM TD: –2.2 (P=0.021)] and LEM10 [LSM TD: –3.0; (P=0.001)] vs PBO). At Month 6, mean FSS TS remained improved from BL in all treatment groups (PBO, –6.3; LEM5, –10.1; and LEM10, –8.9). These decreases were larger and significant for LEM5 (LSM TD: –2.5 [P=0.013]) and LEM10 (LSM TD: –2.6 [P=0.013]) vs PBO. LEM was well tolerated with most adverse events mild to moderate in severity.

CONCLUSIONS: In SUNRISE-2, LEM5 and LEM10 significantly reduced subject-reported disease severity and

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fatigue vs PBO after 6 months of treatment. Reduced severity in insomnia symptoms with LEM5 and LEM10 also translated to improved daytime functioning.
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Post Market Rate of Seizures During TMS Treatment with NeuroStar® System Appears to Be Lower than Previously Estimated

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ABSTRACT: Objective: NeuroStar® Advanced Therapy System is a transcranial magnetic stimulation (TMS) device with FDA-clearance for the treatment of Major Depressive Disorder (MDD) in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode. With TMS, magnetic pulses are transmitted into the brain. Though the exact mechanism of action is unknown, it is postulated that resulting neuronal depolarization and changes in brain functional activity may be associated with various physiologic changes that lead to relief of depression in the indicated population. The type of magnetic field generated with TMS is not intended to induce a seizure during therapeutic use, but unintentional seizures have been reported during TMS treatment.
No seizures were reported with the use of the NeuroStar® system in clinical trials conducted prior to FDA clearance. The estimated risk of seizure in the NeuroStar® label is approximately 1 in 30,000 treatments or 1 in 1,000 patients. Since introduction of the NeuroStar® system into clinical practice, the rate at which seizures have been reported is even lower.

METHODS: We conducted a review of literature that named the NeuroStar® Advanced Therapy System as the device used for TMS treatment and reviewed all seizure events reported to Neuronetics, Inc., directly or through FDA MedWatch through June 30, 2019. Articles reporting seizures in subjects with epilepsy during TMS treatment were excluded.

RESULTS: Previous comprehensive reviews of seizures induced by treatment with any TMS device by Wasserman et al. (1998) and Rossi et al. (2009) revealed that the rate of seizures is low. Many subjects that developed seizures during TMS had either received stimulation at parameters beyond current recommendations or had been predisposed to develop seizures in some way. Some of the events reported as seizures may, in fact, have been non-epileptic events.
Our literature review and analysis of seizures reported to Neuronetics, Inc. revealed that the rate of seizures during TMS treatment with the NeuroStar® appears to be lower than the rate that is published in the NeuroStar® Advanced Therapy prescribing information.

CONCLUSIONS: Seizures that take place during TMS treatment with the NeuroStar® system are rare. The rate of seizures reported directly to Neuronetics, Inc. is lower than that included in the NeuroStar® prescribing information. Our literature review validated seizures during TMS treatment with the NeuroStar® system reported in published literature have described either non-epileptic events (syncope) or occurred with risk factors for seizure induction, such as other predisposing clinical factors or treatment parameters outside the guideline recommend "safe" ranges.
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Randomized, Double-Blind, Active-Controlled Study of Starting Aripiprazole Lauroxil with 1-Day Initiation in Acutely Ill Patients with Schizophrenia

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ABSTRACT: Objective: Evaluate efficacy and safety of a 2-month dose of aripiprazole lauroxil (AL) with a 1-day initiation regimen during hospitalization for an acute exacerbation of schizophrenia.

METHODS: In the phase 3b double-blind ALPINE study, adults with schizophrenia were randomized to AL (AL NanoCrystal® Dispersion + oral aripiprazole 30 mg day 1; AL 1064 mg day 8 and every 8 weeks) or paliperidone palmitate (PP 234 mg day 1; PP 156 mg day 8 and every 4 weeks). Patients were discharged after 2 weeks of hospitalization and followed through week 25. Primary

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