≥3 (severe/very severe) for ISI Item-3 were included in this analysis. WASO2H was defined as minutes of wake during the interval from 240 minutes after lights off until lights on (based on 8hr time in bed). WASO2H was measured at Days 1/2 and 29/30 using polysomnography and averaged across consecutive nights; change from baseline was analyzed using mixed effect model repeated measurement analysis.

Results: Treatment groups were (number of subjects: treated/had ISI Item-3 scores ≥3) LEM5 (220/140), LEM10 (219/140), ZOL (216/158) and PBO (180/122). Baseline mean (standard deviation) WASO2H (minutes) ranged from 77.8-82.25 (30.3-35.5) across treatment groups. By Day 1/2, WASO2H improved significantly with LEM versus ZOL and PBO. Least-squares mean (LSM; standard error [SE]) WASO2H change from baseline at Day 1/2 was -15.56(2.3) (PBO), -34.19(2.2) (LEM5), -42.54(2.2) (LEM10), and -27.82(2.1) (ZOL); all P<0.0001 versus PBO, P=0.0222 and P<0.0001 for LEM5 and LEM10 versus ZOL, respectively. Improvements in WASO2H were maintained through Day 29/30. LSM (SE) change from baseline in WASO2H at Day 29/30 was -15.07(2.5) (PBO), -30.06(2.4) (LEM5), -34.30(2.4) (LEM10), -25.30(2.3) (ZOL); all P<0.002 versus PBO, P=0.1187 and P=0.0033 for LEM5 and LEM10 versus ZOL, respectively. ISI Item-3 improved from ≥3 at baseline to <3 for most LEM5 (97/137[70.8%]) and LEM10 (92/133[69.2%]) treated subjects.

Conclusion: LEM provided significant benefit in WASO2H versus PBO (LEM5 and LEM10) and versus ZOL (only LEM10 at Day 29/30) among subjects with severe/very severe problems with waking too early. Improvements reported for ISI Item-3 for LEM subjects supports this benefit.

Support (If Any): Eisai Inc.

0451

EFFECT OF LEMBOREXANT TREATMENT ON POLYSOMNOGRAPHIC SLEEP MEASURES IN OLDER ADULTS WITH INSOMNIA AND OBJECTIVE SHORT SLEEP

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Introduction: In Phase 3 Study 304 (NCT02783729), lemborexant (LEM) provided significant benefit versus placebo (PBO) on polysomnographic (PSG) and sleep diary-based sleep onset and maintenance outcomes over 1mo in subjects with insomnia disorder. Based on evidence that patients with insomnia and objective short sleep (ISS [total sleep time; TST] <6hrs) may respond less well to interventions such as cognitive behavioral therapy for insomnia (CBT-I) than patients with insomnia and objective long sleep (TST ≥6hrs), we conducted post-hoc analyses of LEM efficacy in the ISS subgroup (subjects with PSG TST<6hrs).

Methods: Study 304 was a 1mo, randomized, double-blind, PBO- and active-controlled, parallel-group study in female (age ≥55y) and male (age ≥65y) subjects (n=1006). Subjects received PBO, LEM 5mg (LEM5), LEM 10mg (LEM10), or zolpidem tartrate extended-release 6.25mg (ZOL). Latency to persistent sleep (LPS) and wake after sleep onset (WASO) were assessed at Nights (NT) 1/2 and NT29/30 using PSG and averaged; change from baseline (paired PSGs during single-blind PBO run-in) were analyzed using mixed-effect model repeated measurement analysis.

Results: The ISS subgroup comprised 710/1006 (70.58%) subjects. Mean (SD) baseline LPS was similar across treatments: PBO=52.80(35.73); ZOL=54.77(40.93); LEM5=54.28(39.30); LEM10=53.31(34.45). On NT1/2, LEM5/10 led to statistically significantly greater (P<0.05) decreases from baseline (PBO=−9.65[36.52]; ZOL=−17.78[36.34]; LEM5=−22.02[31.62]; LEM10=−25.42[34.73]) versus PBO and ZOL. On NT29/30, LEM5/10 led to statistically significantly greater (P<0.0005) decreases from baseline (PBO=−11.88[35.09]; ZOL=−12.57[38.50]; LEM5=−25.37[37.06]; LEM10=−28.20[34.75] versus PBO. ZOL was not different from PBO. Mean (SD) baseline WASO was similar: PBO=123.79(37.21); ZOL=128.37(38.94); LEM5=128.14(37.52); LEM10=129.07(37.98). On NT1/2, LEM5/10 led to statistically significantly greater (P<0.0001) decreases from baseline (LSM[SE]: PBO=−23.52[2.74]; ZOL=−54.74[2.47]; LEM5=−60.58[2.45]; LEM10=−69.35[2.41] versus PBO. LEM10 was significantly different than ZOL (P<0.0001). On NT29/30, LEM5/10 led to statistically significantly greater (P<0.0001) decreases from baseline (PBO=−29.62[3.09]; ZOL=−46.86[2.80]; LEM5=−52.67[2.74]; LEM10=−55.37[2.70] versus PBO. LEM10 was significantly different than ZOL (P<0.05).

Conclusion: The data support LEM as an effective therapy for older adult patients with ISS and suggest LEM may be more beneficial than ZOL, particularly for patients with ISS and sleep onset difficulties. These findings suggest that LEM may be a reasonable therapy to consider for treating older patients with ISS where CBT-I may have relatively limited efficacy.

Support (If Any): Eisai Inc.

0452

LEMBOREXANT TREATMENT OF OLDER ADULTS WITH INSOMNIA AND OBJECTIVE SHORT SLEEP: RATES OF RESPONSE AND REMISSION

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Introduction: In Phase 3 Study 304 (NCT02783729), lemborexant (LEM) provided significant benefit versus placebo (PBO) on polysomnographic (PSG) endpoints and sleep diary-based sleep onset and maintenance outcomes over 1mo in subjects with insomnia disorder. The study also included the Insomnia Severity Index (ISI) to ensure sufficient insomnia severity at baseline (ISI total score ≥13) and for use as an outcome measure. Subjects met criteria for insomnia disorder and were confirmed to spend between 7-9 hours in bed. Subjects had insomnia with objective short sleep (ISS; [total sleep time; TST] <6hrs) or objective long sleep (TST ≥6hrs). Since patients with ISS may respond less well to therapeutic approaches such as cognitive behavioral therapy for insomnia (CBT-I), we examined rates of response and remission with LEM as defined by the ISI in the ISS subgroup.

Methods: Study 304 was a 1mo, randomized, double-blind, PBO- and active-controlled, parallel-group study in female (age ≥55y) and male (age ≥65y) subjects (n=1006). Subjects received PBO, LEM 5mg (LEM5), LEM 10mg (LEM10), or zolpidem tartrate extended-release 6.25 mg (not reported). Baseline PSGs were obtained during a single-blind PBO run-in, followed by paired PSGs on Nights 1/2 and Nights 29/30. The ISI was given at baseline and end of treatment. For these post-hoc analyses, responders were defined as subjects whose decrease from baseline on the ISI was ≥7pts, while remitters achieved ISI total scores <8pts. LEM5 and LEM10 vs PBO differences were evaluated using chi-square tests.

Results: 525/743 (70.66%) of subjects in the PBO/LEM groups were in the ISS subgroup. For LEM5, 99/176 (56.25%) were responders and 49/176 (27.84%) were remitters. For LEM10, 97/180 (53.89%) were responders and 50/180 (27.78%) were remitters. For the PBO group, 59/140 (42.14%) were responders and 21/140 (15.00%) were remitters. The responder and remitter rates for

LEM5 and LEM10 were statistically significantly greater than those for PBO (all P<0.05).
Conclusion: Older adults with ISS achieved clinically meaningful improvement with LEM as assessed at the end of one month of treatment, with nearly 30% considered remitters and >50% considered treatment responders. LEM is a potential therapy for ISS patients who may have limited response to CBT-I.
Support (If Any): Eisai Inc.

0453

LEMBOREXANT EXPOSURE IS INDEPENDENT OF RACE

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Introduction: Some hypnotic treatments for insomnia require dosing consideration due to exposure differences based on patient characteristics. Lemborexant (LEM) is a dual orexin receptor antagonist approved in multiple countries for the treatment of adult insomnia. LEM is not associated with exposure differences based on sex, age, or BMI that impact dosing. The potential impact of race on exposure was determined in two stand-alone pharmacokinetic (PK) studies and by modeling data from studies comprising the LEM clinical development program, which included healthy subjects and insomnia patients.
Methods: Study 003 (NCT02039089) was a single-center, multiple-dose, randomized, double-blind, placebo-controlled, parallel-group study in healthy Japanese and White subjects. Study 014 (NCT04555733) was a phase 1, single center, open-label, single and multiple oral dose study in healthy Chinese subjects. Additionally, effect of race on LEM exposure was independently examined as part of a population PK analysis incorporating LEM data from 9 Phase 1 studies (n=407), and Studies 201 (NCT01995838; n=235), 303 (NCT02952820; n=726) and 304 (NCT02783729; n=524) (Lalovic et al., 2020). Plasma concentrations of LEM were quantified from plasma by validated liquid chromatography with tandem mass spectrometry. Adverse events (AE) were recorded.
Results: Exposure of LEM increased in an approximately dose-proportional manner across the dose range (2.5 mg to 25 mg) in studies 003 and 014. There were no significant exposure differences between Japanese and White subjects following single LEM10 administration on Day 1 in Study 003 (maximum concentration [Cmax] mean[SD], ng/mL: Japanese, 46.5[25.8]; White, 47.3[28.1]; area under the curve from time zero to 24h [AUC0-24] mean[SD], ng·h/mL: Japanese, 231[40.2]; White, 208[83.4]) or when comparing PK data from Chinese subjects in Study 014 following single dose administration on Day 1 (Cmax mean[SD], ng/mL: LEM5, 29.8[12.8]; LEM10, 56.2[16.9]; LEM25, 116[46.8]; AUC0-24 mean[SD], ng·h/mL: LEM5, 106[29.9]; LEM10, 205[35.6]; LEM25, 549[116]) to Japanese and White subjects in Study 003. These results are supported by the cross-study, population PK model-based analysis, indicating no significant clinical or statistical differences in LEM PK attributable to the intrinsic factor race.
Conclusion: LEM exposure is not significantly affected by race. Therefore, dosing of LEM can be consistent across patient populations from different racial groups.
Support (If Any): Eisai Inc.

0454

RESPONSE TO LEMBOREXANT IN OLDER SUBJECTS WITH INSOMNIA DISORDER AND COMORBID PAIN AT BASELINE

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Introduction: The reciprocal relationship between pain and poor sleep has been well established. Pain interferes with sleep, and insomnia increases pain sensitivity, thus reducing quality of life. Therefore, it is of clinical importance to evaluate whether a sleep-promoting drug such as the dual orexin receptor antagonist, lemborexant (LEM; approved in multiple countries to treat adults with insomnia) can improve sleep in older patients, in whom both sleep and ongoing pain are prevalent.
Methods: Study 304 (NCT02783729), was a 1-month, double-blind, PBO- and active-controlled study in subjects age ≥55y with insomnia (full analysis set [FAS]=1006). Those who also endorsed some/severe pain at baseline on the pain/discomfort dimension of the EuroQual-5 Dimension-3 Level scale (EQ-5D-3L; no problems/some problems/extreme problems) at baseline were eligible for these post-hoc analyses. Medical history of pain conditions and/or ongoing therapy were not required for eligibility and were not evaluated. Subjects were randomized to bedtime doses of placebo, LEM 5mg (LEM5),10mg (LEM10) or zolpidem tartrate extended release (not reported here). Changes from baseline (CFB) in objective sleep parameters assessed by polysomnography (latency to persistent sleep [LPS]; wake after sleep onset [WASO]) were analyzed by mixed-effect repeated measures analyses adjusted for relevant factors.
Results: Approximately 18% of the FAS reported some or extreme pain at baseline (PBO=55; LEM5=78; LEM10=50). For LPS, baseline median values (minutes) were 31.0, 29.4 and 42.1 for PBO, LEM5 and LEM10, respectively. Median CFB for LPS were larger and statistically significantly different for both LEM doses compared with PBO at the beginning of treatment (mean of Nights 1/2: +2.5; -8.4, -15.8; P<0.005); and were (mean of Nights 29/30: -7.1,-9.9, -9.0) at the end of treatment LEM5 (P=0.031), LEM10 (P=0.054). For WASO, baseline median values (minutes) were 101.0, 103.6 and 111.1 for PBO, LEM5 and LEM10, respectively. Median CFB for WASO were larger and statistically significantly different (P<0.001) for both LEM doses compared with PBO at the beginning (Nights 1/2; -1.5; -41.5, -64.4) and end of treatment (Nights 29/30; -1.1, -37.9, -52.5).
Conclusion: These data suggest that lemborexant can effectively treat insomnia in older adults with concomitant painful conditions.
Support (If Any): Eisai Inc.

0455

THE INSOMNIA DAYTIME SYMPTOMS AND IMPACTS QUESTIONNAIRE: AN ANALYSIS OF CLINICALLY MEANINGFUL CHANGE USING PHASE 3 CLINICAL TRIAL DATA

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Introduction: The Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) is a new validated patientreported outcome (PRO) instrument evaluating daytime functioning in people with