Supplement S2

eFigure 1. Study Design

A picture containing graphical user interface

Description automatically generated

Abbreviations: EZN, elinzanetant; N, number of participants; NTA, nighttime awakening; VMS, vasomotor symptoms.

eTable 1. Inclusion and Exclusion Criteria

|  |  |
| --- | --- |
| Inclusion criteria | Exclusion criteria |
| To be eligible for enrollment into the study, participants must have:   1. Been female, aged 40-65 years, inclusive, at screening visit 1. 2. Been able to understand and comply with the requirements of the study and give informed consent. 3. Been postmenopausal, defined as either (i) at least 12 months spontaneous amenorrhea, (ii) at least 6 months spontaneous amenorrhea with serum follicle-stimulating hormone levels >40 mIU/mL and serum estradiol <30 pg/mL, or (iii) at least 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy. 4. Had a body mass index between 18 and 38 kg/m2, inclusive, at screening visit 2. 5. Had a negative urinary pregnancy test at screening visit 2. 6. Been in good health, in the opinion of the Investigator, based on the medical history, physical examination, 12-lead ECG, vital signs, and clinical laboratory tests assessed at screening visit 2. 7. Completed the paper diary for at least 6 days between screening visits 1 and 2 and recorded an average of at least 8 moderate or severe VMS per day (including nighttime) over the last 5 days that the paper diary was completed (assessed at screening visit 2). 8. Completed the eDiary for at least 9 days between screening visit 2 and Day 1 and recorded an average of at least 7 moderate or severe VMS per day (including nighttime) over the last 7 days that the eDiary was completed (assessed at Baseline Visit). | To be eligible for enrollment in the study, participants must not have:   1. Used or been unwilling to wash-out use of any of the following hormonal therapies for the periods stated prior to screening visit 2:  * ≥1 week for vaginal hormonal products (rings, creams, gels, and including dehydroepiandrosterone or analogues thereof); * ≥4 weeks for transdermal estrogen alone or estrogen/progestin products; * ≥8 weeks for oral estrogen (including selective estrogen receptor modulators) and/or progestin therapy; * ≥8 weeks for intrauterine progestin therapy; * ≥3 months for progestin implants and estrogen alone injectable drug therapy; * ≥6 months for estrogen pellet therapy or progestin injectable drug therapy.  1. Used nonhormone prescription (e.g. paroxetine, other anti-depressants, alpha agonists [e.g. clonidine], methyldopa, gabapentin, pregabalin, medicinal cannabis) or over-the-counter/herbal treatments for the treatment of menopausal symptoms throughout the study. Participants had to have discontinued these drugs at least 28 days prior to screening visit 2. Participants may have been permitted to use these drugs if the dose had been stable for at least 4 weeks and they had been prescribed solely for the management of another disorder (e.g. neuropathic pain, depression). 2. Been unable to comply with the use of prohibited medications as described below:  * Use of digoxin was not allowed from screening visit 2 until 1 week after the last dose of IMP; * Use of known CYP3A4 substrates with a narrow therapeutic range was not allowed from screening visit 1 until after the last dose of IMP; * Use of strong or moderate inhibitors of CYP3A4 was not allowed from screening visit 2 until 1 week after the last dose of IMP; * Use of moderate or strong inducers of CYP3A4 was not allowed from screening visit 2 until week 12; * Use of know P-glycoprotein inhibitors was not allowed from screening visit 2 until 1 week after the last dose of IMP.  1. Had any prior or ongoing history of clinically relevant drug or alcohol misuse within 12 months of screening visit 1. 2. Had any clinically significant prior or ongoing history of arrhythmias, either determined through clinical history or on ECG evaluation. 3. Had any clinically significant abnormal laboratory test result(s) measured at screening visit 2. Specifically, severe hepatic impairment was excluded (United States only). 4. Had any active ongoing condition that could have caused difficulty in interpreting VMS such as: infection that could have caused pyrexia, pheochromocytoma, hyperthyroidism, carcinoid syndrome, alcohol misuse. 5. Had current history or previous (within the past 5 years) history of any malignancy (except basal and squamous cell skin tumors). 6. Had uncontrolled hypertension. 7. Had a history of hyperthyroidism or hypothyroidism. Treated hypothyroidism with normal thyroid function test results at screening visit 2 and a stable (for ≥3 months before screening visit 2) dose of replacement therapy was acceptable. 8. Had known hypersensitivity to elinzanetant or any of the excipients in the formulation. 9. Had concurrent (or within 2 months prior to screening visit 1) participation in a clinical study with an IMP. 10. Had concurrent (or within 1 month prior to screening visit 1) participation in an interventional clinical study. 11. Previously participated in a clinical study with elinzanetant. 12. Been a dependent of the Investigator, the Contract Research Organization(s) or Sponsor for education or employment. 13. Had any unexplained postmenopausal bleeding. |

Abbreviations: CYP3A4, cytochrome P450 3A4; ECG, electrocardiogram; IMP, investigational medicinal product; VMS, vasomotor symptoms.

eTable 2. Patient-reported Outcomes Methodology

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Insomnia Severity Index** | **Pittsburgh Sleep Quality Index** | **Menopause-specific Quality-of-Life Questionnaire Intervention version** |
| Overview | Assesses the nature, severity, and impact of insomnia | Assesses sleep quality and sleep disturbance | Measures condition-specific quality of life in menopausal women |
| Items/domains | 7 items that assess the perceived severity of difficulties initiating sleep, staying asleep, early morning awakenings, satisfaction with current sleep pattern, interference with daily functioning, noticeability of impairment attributed to the sleep problem, and degree of distress or concern caused by the sleep problem | 19 individual items to generate 7 component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction | 32 items across 4 domains (physical, vasomotor, psychosocial, and sexual) |
| Recall period | 2 weeks | 1 month | 1 month |
| Scoring | Each item is rated on a scale of 0 to 4 to give a total score ranging from 0 to 28 | Each component is scored on a scale of 0 (no difficulty) to 3 (severe difficulty) to give a global score ranging from 0 to 21 | The level of bother for each item is rated on a scale of 0 (not at all bothered) to 6 (extremely bothered) |
| Clinically meaningful benefit | Reduction of ≥647 | Unknown | Reduction of ≥148 |

eTable 3. Baseline Menopause Characteristics

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Parameter/Category** | **Placebo (N = 47)** | **Elinzanetant** | | | | |
| **40 mg (n = 31)** | **80 mg (n = 17)** | **120 mg (n = 52)** | **160 mg (n = 52)** | **Total elinzanetant (N = 152)** |
| Menopause characteristics | | | | | | |
| Age at menopause onset, mean (SD), years | 47.9 (6.5) | 46.3 (7.3) | 47.6 (7.7) | 47.5 (6.7) | 47.0 (7.4) | 47.1 (7.1) |
| Duration of menopause, mean (SD), yearsa | 7.79 (5.60) | 9.10 (8.53) | 8.40 (6.00) | 7.45 (7.73) | 8.12 (6.41) | 8.12 (7.26) |
| Menopause defined by at least, No. (%) |  |  |  |  |  |  |
| 12 months spontaneous amenorrhea | 33 (70) | 21 (68) | 12 (71) | 36 (69) | 40 (77) | 109 (71.7) |
| 6 months spontaneous amenorrheab | 6 (13) | 4 (13) | 2 (12) | 8 (15) | 3 (6) | 17 (11.2) |
| 6 weeks postsurgicalc | 8 (17) | 6 (19) | 3 (18) | 8 (15) | 9 (17) | 26 (17.1) |

Abbreviations: SD, standard deviation.

aDuration of menopause = (Informed Consent date -- Last menstrual period date + 1)/365.25.  
bWith serum follicle-stimulating hormone levels >40 mIU/mL and a serum estradiol concentration of <30 pg/mL.

cBilateral oophorectomy with or without hysterectomy.

eTable 4. Mean Change from Baseline in the Mean Daily Frequency of Moderate and Severe VMS

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Placebo (N = 47)** | **Elinzanetant** | | | |
| **40 mg (n = 31)** | **80 mg (n = 17)** | **120 mg (n = 52)** | **160 mg (n = 52)** |
| Baseline daily frequency of moderate and severe VMS, mean (SD) |  |  |  |  |  |
| Baseline | 11.82 (4.42) | 12.13 (8.81) | 14.55 (5.87) | 13.54 (7.17) | 12.92 (6.90) |
| Change from baseline of daily frequency of moderate and severe VMS by week, mean (SD) |  |  |  |  |  |
| Week 1 | -1.22 (3.07) | -1.61 (3.05) | -1.63 (3.56) | -3.22 (3.43) | -3.09 (3.76) |
| Week 2 | -2.19 (4.01) | -3.03 (3.95) | -3.47 (4.37) | -4.58 (4.70) | -3.78 (4.48) |
| Week 4 | -2.45 (3.65) | -4.19 (5.78) | -4.30 (6.45) | -6.76 (5.85) | -5.42 (5.36) |
| Week 8 | -4.33 (4.79) | -5.72 (6.18) | -5.94 (5.26) | -7.84 (5.95) | -5.58 (6.00) |
| Week 12 | -4.49 (4.29) | -6.48 (7.82) | -5.49 (5.31) | -7.91 (6.66) | -6.57 (5.83) |
| Week 16 | -3.95 (4.85) | -5.74 (9.45) | -2.01 (4.99) | -5.95 (6.95) | -2.78 (6.54) |
| Statistical analysis of change from baseline vs placebo (MMRM) |  |  |  |  |  |
| Change from baseline to week 1 |  |  |  |  |  |
| LS, mean (SE) | -1.39 (0.49) | -1.74 (0.60) | -1.42 (0.81) | -3.19 (0.46) | -3.08 (0.46) |
| Difference in LS means vs placebo (SE) | NA | -0.35 (0.77) | -0.03 (0.94) | -1.80 (0.67) | -1.69 (0.67) |
| 95% CI | NA | -1.86 to 1.17 | -1.89 to 1.84 | -3.12 to -0.48 | -3.01 to -0.37 |
| *P* value | NA | .65 | .98 | .008 | .01 |
| Change from baseline to week 2 |  |  |  |  |  |
| LS mean (SE) | -2.33 (0.62) | -3.16 (0.76) | -3.26 (1.02) | -4.55 (0.58) | -3.74 (0.58) |
| Difference in LS means vs placebo (SE) | NA | -0.83 (0.97) | -0.93 (1.20) | -2.22 (0.85) | -1.42 (0.85) |
| 95% CI | NA | -2.75 to 1.09 | -3.29 to 1.43 | -3.90 to -0.54 | -3.09 to 0.26 |
| P value | NA | .40 | .44 | .01 | .10 |
| Change from baseline to week 4 |  |  |  |  |  |
| LS means (SE) | -2.80 (0.74) | -4.32 (0.90) | -4.09 (1.22) | -6.73 (0.70) | -5.43 (0.71) |
| Difference in LS means vs placebo (SE) | NA | -1.52 (1.17) | -1.29 (1.43) | -3.93 (1.02) | -2.63 (1.03) |
| 95% CI | NA | -3.83 to 0.78 | -4.11 to 1.53 | -5.94 to -1.92 | -4.66 to -0.60 |
| *P* value | NA | .19 | .37 | < .001 | .01 |
| Change from baseline to week 8 |  |  |  |  |  |
| LS means (SE) | -4.65 (0.79) | -5.85 (0.95) | -5.73 (1.28) | -7.98 (0.74) | -5.57 (0.77) |
| Difference in LS means vs placebo (SE) | NA | -1.20 (1.23) | -1.07 (1.51) | -3.33 (1.08) | -0.92 (1.10) |
| 95% CI | NA | -3.63 to 1.24 | -4.05 to 1.90 | -5.46 to -1.21 | -3.09 to 1.25 |
| *P* value | NA | .33 | .48 | .002 | .40 |
| Change from baseline to week 12 |  |  |  |  |  |
| LS means (SE) | -4.81 (0.84) | -6.48 (1.02) | -5.58 (1.39) | -7.76 (0.79) | -6.59 (0.83) |
| Difference in LS means vs placebo (SE) | NA | -1.67 (1.32) | -0.77 (1.62) | -2.95 (1.15) | -1.78 (1.19) |
| 95% CI | NA | -4.28 to -0.95 | -3.97 to 2.44 | -5.22 to -0.67 | -4.12 to 0.56 |
| *P* value | NA | .21 | .64 | .01 | .13 |

Abbreviations: CI, confidence interval; LS, least square; MMRM, mixed-effect model repeated measures; NA, not applicable; SD, standard deviation; SE, standard error; VMS, vasomotor symptoms.

eTable 5. Mean Change from Baseline in the Mean Weekly Severity of Moderate and Severe VMS

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Placebo (N = 47)** | **Elinzanetant** | | | |
| **40 mg (n = 31)** | **80 mg (n = 17)** | **120 mg (n = 52)** | **160 mg (n = 52)** |
| Baseline weekly frequency of moderate and severe VMS, mean (SD) |  |  |  |  |  |
| Baseline | 2.54 (0.20) | 2.51 (0.26) | 2.63 (0.24) | 2.54 (0.24) | 2.54 (0.26) |
| Change from baseline of weekly frequency of moderate and severe VMS by week, mean (SD) |  |  |  |  |  |
| Week 1 | -0.24 (0.30) | -0.21 (0.20) | -0.22 (0.21) | -0.25 (0.28) | -0.26 (0.26) |
| Week 2 | -0.30 (0.39) | -0.32 (0.32) | -0.42 (0.58) | -0.38 (0.45) | -0.39 (0.54) |
| Week 4 | -0.31 (0.41) | -0.38 (0.54) | -0.44 (0.56) | -0.51 (0.57) | -0.54 (0.67) |
| Week 8 | -0.45 (0.58) | -0.48 (0.54) | -0.40 (0.61) | -0.52 (0.53) | -0.64 (0.72) |
| Week 12 | -0.41 (0.50) | -0.53 (0.64) | -0.26 (0.45) | -0.56 (0.68) | -0.73 (0.78) |
| Week 16 | -0.40 (0.57) | -0.48 (0.53) | -0.13 (0.37) | -0.41 (0.65) | -0.45 (0.53) |
| Statistical analysis of change from baseline vs placebo (MMRM) |  |  |  |  |  |
| Change from baseline to week 1 |  |  |  |  |  |
| LS means (SE) | -0.24 (0.04) | -0.20 (0.05) | -0.24 (0.06) | -0.25 (0.04) | -0.26 (0.04) |
| Difference in LS means vs placebo (SE) | NA | 0.04 (0.06) | 0.00 (0.07) | -0.01 (0.05) | -0.01 (0.05) |
| 95% CI | NA | -0.08 to 0.16 | -0.15 to 0.14 | -0.11 to -0.09 | -0.12 to -0.09 |
| *P* value | NA | .50 | .996 | .86 | .78 |
| Change from baseline to week 2 |  |  |  |  |  |
| LS means (SE) | -0.30 (0.07) | -0.32 (0.08) | -0.44 (0.11) | -0.37 (0.06) | -0.39 (0.06) |
| Difference in LS means vs placebo (SE) | NA | -0.01 (0.10) | -0.14 (0.13) | -0.07 (0.09) | -0.08 (0.09) |
| 95% CI | NA | -0.22 to 0.19 | -0.39 to 0.12 | -0.25 to 0.11 | -0.26 to 0.10 |
| *P* value | NA | .91 | .28 | .44 | .37 |
| Change from baseline to week 4 |  |  |  |  |  |
| LS means (SE) | -0.32 (0.08) | -0.37 (0.10) | -0.46 (0.13) | -0.51 (0.08) | -0.51 (0.08) |
| Difference in LS means vs placebo (SE) | NA | -0.05 (0.13) | -0.14 (0.16) | -0.19 (0.11) | -0.19 (0.11) |
| 95% CI | NA | -0.30 to 0.20 | -0.45 to 0.17 | -0.41 to 0.03 | -0.41 to 0.03 |
| *P* value | NA | .70 | .37 | .09 | .09 |
| Change from baseline to week 8 |  |  |  |  |  |
| LS means (SE) | -0.45 (0.09) | -0.47 (0.11) | -0.42 (0.14) | -0.51 (0.08) | -0.61 (0.09) |
| Difference in LS means vs placebo (SE) | NA | -0.02 (0.14) | 0.03 (0.17) | -0.06 (0.12) | -0.16 (0.12) |
| 95% CI | NA | -0.29 to 0.25 | -0.30 to 0.37 | -0.30 to 0.18 | -0.40 to 0.09 |
| *P* value | NA | .88 | .85 | .62 | .20 |
| Change from baseline to week 12 |  |  |  |  |  |
| LS means (SE) | -0.42 (0.10) | -0.51 (0.12) | -0.25 (0.16) | -0.56 (0.09) | -0.68 (0.09) |
| Difference in LS means vs placebo (SE) | NA | -0.09 (0.15) | 0.16 (0.18) | -0.15 (0.13) | -0.27 (0.13) |
| 95% CI | NA | -0.39 to 0.21 | -0.20 to 0.52 | -0.41 to 0.11 | -0.53 to -0.00 |
| *P* value | NA | .55 | .38 | .26 | .048 |

Abbreviations: CI, confidence interval; LS, least square; MMRM, mixed-effect model repeated measures; NA, not applicable; SD, standard deviation; SE, standard error; VMS, vasomotor symptoms.

eTable 6. Mean Change from Baseline in Mean Daily Nighttime Awakenings Secondary to VMS

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Placebo (n = 47)** | **Elinzanetant** | | | |
| **40 mg (n = 31)** | **80 mg (n = 17)** | **120 mg (n = 52)** | **160 mg (n = 52)** |
| Baseline daily nighttime awakenings secondary to VMS, mean (SD) |  |  |  |  |  |
| Baseline | 2.90 (1.64) | 2.41 (1.57) | 4.05 (1.86) | 2.76 (1.71) | 2.57 (1.54) |
| Change from baseline in mean daily frequency of nighttime awakenings secondary to VMS by week, mean (SD) |  |  |  |  |  |
| Week 1 | -0.57 (0.96) | -0.52 (1.07) | -0.63 (1.53) | -0.90 (1.03) | -0.68 (1.14) |
| Week 2 | -0.69 (1.03) | -0.75 (1.18) | -1.13 (1.89) | -1.18 (1.27) | -0.92 (1.38) |
| Week 4 | -0.89 (1.08) | -0.91 (1.26) | -1.33 (2.27) | -1.53 (1.19) | -1.01 (1.62) |
| Week 8 | -1.09 (1.36) | -1.50 (1.40) | -1.69 (2.21) | -1.79 (1.35) | -1.13 (1.86) |
| Week 12 | -1.31 (1.39) | -1.63 (1.46) | -1.70 (2.53) | -1.67 (1.27) | -1.32 (1.75) |
| Week 16 | -1.05 (1.19) | -1.29 (1.63) | -0.45 (2.05) | -1.19 (1.23) | -0.44 (1.62) |
| Statistical analysis of change from baseline vs placebo (MMRM) |  |  |  |  |  |
| Change from baseline to week 1 |  |  |  |  |  |
| LS means (SE) | -0.54 (0.14) | -0.66 (0.18) | -0.22 (0.25) | -0.93 (0.14) | -0.76 (0.14) |
| Difference in LS means vs placebo (SE) | NA | -0.12 (0.23) | 0.32 (0.28) | -0.39 (0.20) | -0.22 (0.20) |
| 95% CI | NA | -0.569 to 0.335 | -0.243 to 0.876 | -0.786 to -0.001 | -0.613 to 0.173 |
| *P* value | NA | .61 | .27 | .049 | .27 |
| Change from baseline to week 2 | | | | | |
| LS means (SE) | -0.69 (0.17) | -0.89 (0.21) | -0.72 (0.29) | -1.22 (0.16) | -0.98 (0.17) |
| Difference in LS means vs placebo (SE) | NA | -0.20 (0.28) | -0.03 (0.34) | -0.52 (0.24) | -0.29 (0.24) |
| 95% CI | NA | -0.743 to 0.345 | -0.704 to 0.636 | -0.997 to -0.052) | -0.767 to 0.180 |
| *P* value | NA | .47 | .92 | .03 | .22 |
| Change from baseline to week 4 | | | | | |
| LS means (SE) | -0.86 (0.19) | -1.04 (0.23) | -0.92 (0.31) | -1.56 (0.17) | -1.12 (0.18) |
| Difference in LS means vs placebo (SE) | NA | -0.19 (0.29) | -0.07 (0.36) | -0.70 (0.25) | -0.26 (0.26) |
| 95% CI | NA | -0.764 to 0.393 | -0.777 to 0.645 | -1.206 to -0.201 | -0.769 to 0.248 |
| *P* value | NA | .53 | .86 | .006 | .31 |
| Change from baseline to week 8 | | | | | |
| LS means (SE) | -1.08 (0.20) | -1.63 (0.25) | -1.29 (0.34) | -1.85 (0.19) | -1.26 (0.20) |
| Difference in LS means vs placebo (SE) | NA | -0.56 (0.32) | -0.21 (0.39) | -0.77 (0.28) | -0.18 (0.28) |
| 95% CI | NA | -1.188 to 0.075 | -0.986 to 0.563 | -1.320 to -0.219 | -0.743 to 0.380 |
| *P* value | NA | .08 | .59 | .006 | .53 |
| Change from baseline to week 12 | | | | | |
| LS means (SE) | -1.29 (0.20) | -1.77 (0.25) | -1.25 (0.34) | -1.67 (0.19) | -1.44 (0.20) |
| Difference in LS means vs placebo (SE) | NA | -0.48 (0.32) | 0.04 (0.40) | -0.39 (0.28) | -0.15 (0.29) |
| 95% CI | NA | -1.116 to 0.154 | -0.744 to 0.820 | -0.939 to 0.165 | -0.718 to 0.412 |
| *P* value | NA | .14 | .92 | .17 | .59 |

Abbreviations: CI, confidence interval; LS, least square; MMRM, mixed-effect model repeated measures; NA, not applicable; SD, standard deviation; SE, standard error; VMS, vasomotor symptoms.

eTable 7. Mean Change from Baseline in ISI Score

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Placebo (N = 47)** | **Elinzanetant** | | | |
| **40 mg (n = 31)** | **80 mg (n = 17)** | **120 mg (n = 52)** | **160 mg (n = 52)** |
| ISI score, mean (SD) |  |  |  |  |  |
| Baseline | 12.43 (5.09) | 13.23 (5.36) | 13.24 (8.04) | 12.63 (5.66) | 13.74 (5.89) |
| Week 4 | 10.67 (5.20) | 10.48 (4.95) | 9.59 (6.54) | 7.25 (5.31) | 7.70 (5.58) |
| Week 8 | 10.86 (6.00) | 9.48 (5.87) | 8.19 (6.59) | 6.60 (5.10) | 7.27 (5.39) |
| Week 12 | 10.67 (6.77) | 9.40 (5.68) | 6.81 (6.00) | 6.50 (5.06) | 5.62 (4.97) |
| Week 16 | 9.79 (6.70) | 9.47 (5.58) | 9.63 (7.17) | 8.32 (5.74) | 8.91 (6.26) |
| Change from baseline in ISI Score by week, mean (SD) |  |  |  |  |  |
| Change from baseline to Week 4 | -1.60 (2.98) | -2.74 (4.91) | -3.65 (6.03) | -5.14 (5.51) | -5.42 (5.42) |
| Change from baseline to Week 8 | -1.51 (3.64) | -3.74 (5.63) | -4.44 (6.17) | -6.20 (4.93) | -5.72 (5.14) |
| Change from baseline to Week 12 | -1.95 (4.70) | -3.80 (5.45) | -5.81 (5.86) | -6.12 (5.41) | -7.39 (5.82) |
| Change from baseline to Week 16 | -2.65 (4.32) | -3.73 (6.02) | -3.00 (3.72) | -4.34 (5.58) | -4.00 (5.49) |
| Statistical analysis of change from baseline vs placebo (MMRM) |  |  |  |  |  |
| Change from baseline to week 4 |  |  |  |  |  |
| LS mean (SE) | -1.90 (0.69) | -2.58 (0.78) | -3.49 (1.06) | -5.31 (0.62) | -5.19 (0.65) |
| Difference in LS means (SE) | NA | -0.68 (1.04) | -1.59 (1.26) | -3.41 (0.92) | -3.28 (0.95) |
| 95% CI | NA | -2.734 to 1.378 | -4.080 to 0.899 | -5.226 to -1.590 | -5.150 to -1.414 |
| *P* value | NA | .52 | .21 | < .001 | < .001 |
| Change from baseline to week 12 |  |  |  |  |  |
| LS mean (SE) | -2.13 (0.75) | -3.60 (0.86) | -5.91 (1.19) | -6.41 (0.68) | -6.99 (0.73) |
| Difference in LS means (SE) | NA | -1.46 (1.14) | -3.77 (1.40) | -4.27 (1.01) | -4.85 (1.05) |
| 95% CI | NA | -3.718 to 0.793 | -6.541 to -1.005 | -6.260 to -2.283 | -6.925 to -2.785 |
| *P* value | NA | .20 | .008 | < 0.001 | < 0.001 |

Abbreviations: CI, confidence interval; ISI, Insomnia Severity Index; LS, least square; MMRM, mixed-effect model repeated measures; NA, not applicable; SD, standard deviation; SE, standard error; VMS, vasomotor symptoms.

eTable 8. Mean Change from Baseline in Overall PSQI Score

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Placebo (N = 47)** | **Elinzanetant** | | | |
| **40 mg (n = 31)** | **80 mg (n = 17)** | **120 mg (n = 52)** | **160 mg (n = 52)** |
| PSQI score, mean (SD) | | | | | |
| Baseline | 10.80 (2.39) | 11.94 (3.11) | 11.35 (3.66) | 10.80 (3.00) | 11.44 (3.14) |
| Week 4 | 10.26 (2.67) | 10.06 (3.14) | 9.41 (3.71) | 8.02 (2.77) | 8.43 (2.86) |
| Week 8 | 9.66 (3.44) | 9.55 (3.59) | 8.81 (4.32) | 7.88 (2.95) | 8.02 (3.26) |
| Week 12 | 9.81 (3.43) | 9.47 (3.38) | 8.38 (3.84) | 7.36 (3.21) | 7.69 (3.86) |
| Week 16 | 9.14 (3.21) | 9.83 (3.50) | 9.81 (4.52) | 8.58 (2.91) | 9.40 (3.53) |
| Change from baseline in mean PSQI score by week, mean (SD) |  |  |  |  |  |
| Change from baseline to week 4 | -0.63 (2.02) | -1.87 (2.93) | -1.94 (2.68) | -2.70 (3.11) | -2.80 (2.84) |
| Change from baseline to week 8 | -1.36 (2.90) | -2.39 (3.63) | -2.38 (3.30) | -3.00 (3.23) | -3.14 (3.37) |
| Change from baseline to week 12 | -1.15 (2.95) | -2.47 (3.82) | -2.81 (2.97) | -3.39 (3.12) | -3.54 (4.12) |
| Change from baseline to Week 16 | -1.85 (2.46) | -2.10 (3.53) | -1.38 (3.26) | -2.24 (3.12) | -1.79 (2.69) |
| Statistical analysis of change from baseline vs placebo (MMRM) |  |  |  |  |  |
| Change from baseline to week 4 |  |  |  |  |  |
| LS mean (SE) | -0.83 (0.38) | -1.53 (0.44) | -1.86 (0.59) | -2.88 (0.34) | -2.72 (0.36) |
| Difference in LS means (SE) | NA | -0.71 (0.58) | -1.04 (0.70) | -2.05 (0.51) | -1.90 (0.52) |
| 95% CI | NA | -1.852 to 0.439 | -2.421 to 0.346 | -3.060 to -1.048 | -2.929 to -0.861 |
| *P* value | NA | .23 | .14 | < 0.001 | < .001 |
| Change from baseline to week 12 | | | | | |
| LS mean (SE) | -1.21 (0.49) | -2.18 (0.58) | -2.75 (0.79) | -3.67 (0.45) | -3.35 (0.49) |
| Difference in LS means (SE) | NA | -0.97 (0.76) | -1.54 (0.93) | -2.46 (0.67) | -2.14 (0.69) |
| 95% CI | NA | -2.472 to 0.527 | -3.376 to 0.292 | -3.777 to -1.145 | -3.507 to -0.773 |
| *P* value | NA | .20 | .10 | < .001 | .002 |

Abbreviations: CI, confidence interval; LS, least square; MMRM, mixed-effect model repeated measures; NA, not applicable; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation; SE, standard error; VMS, vasomotor symptoms.

eTable 9. Mean Change from Baseline in Overall MenQoL-I Score

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Placebo (N = 47)** | **Elinzanetant** | | | |
| **40 mg (n = 31)** | **80 mg (n = 17)** | **120 mg (n = 52)** | **160 mg (n = 52)** |
| MenQoL-I Score, mean (SD) |  |  |  |  |  |
| Baseline | 4.00 (1.06) | 4.38 (1.16) | 4.47 (1.25) | 4.17 (1.13) | 4.50 (1.23) |
| Change from baseline in mean MenQoL-I score by week, mean (SD) |  |  |  |  |  |
| Change from baseline to week 4 | -0.33 (0.90) | -0.62 (1.30) | -0.56 (0.87) | -1.29 (1.14) | -1.13 (1.09) |
| Change from baseline to week 8 | -0.62 (1.10) | -0.87 (1.25) | -0.91 (1.06) | -1.45 (1.18) | -1.50 (0.99) |
| Change from baseline to week 12 | -0.70 (1.03) | -0.81 (1.44) | -1.09 (0.76) | -1.54 (1.34) | -1.72 (1.32) |
| Change from baseline to week 16 | -0.68 (1.01) | -0.76 (1.33) | -0.69 (0.93) | -1.18 (1.13) | -1.00 (1.36) |
| Statistical analysis of change from baseline vs placebo (MMRM) |  |  |  |  |  |
| Change from baseline to week 4 |  |  |  |  |  |
| LS mean (SE) | -0.45 (0.15) | -0.56 (0.18) | -0.46 (0.24) | -1.33 (0.14) | -1.06 (0.14) |
| Difference in LS means (SE) | NA | -0.10 (0.23) | 0.00 (0.28) | -0.87 (0.20) | -0.61 (0.21) |
| 95% CI | NA | -0.558 to 0.353 | -0.557 to 0.551 | -1.271 to -0.471 | -1.020 to -0.199 |
| *P* value | NA | .66 | .99 | < 0.001 | .004 |
| Change from baseline to week 12 |  |  |  |  |  |
| LS mean (SE) | -0.80 (0.16) | -0.76 (0.19) | -0.98 (0.26) | -1.60 (0.15) | -1.57 (0.16) |
| Difference in LS means (SE) | NA | 0.03 (0.25) | -0.18 (0.31) | -0.80 (0.22) | -0.77 (0.23) |
| 95% CI | NA | -0.465 to 0.531 | -0.792 to 0.430 | -1.241 to -0.368 | -1.226 to -0.319 |
| *P* value | NA | .90 | .56 | < .001 | < .001 |

Abbreviations: CI, confidence interval; LS, least square; MenQoL-I, Menopause-specific Quality-of-Life questionnaire intervention version; MMRM, mixed-effect model repeated measures; NA, not applicable; SD, standard deviation; SE, standard error; VMS, vasomotor symptoms.