**Supplemental Material.**

**Transdermal oestradiol and testosterone therapy for menopausal depression and mood symptoms: a retrospective cohort study.**

**S1. Summary statistics of Meno-D scores at baseline and follow up for the whole cohort and per subgroup (mean, standard deviation (SD), median, quartile 1 or 25th percentile (Q1), quartile 3 or 75th percentile (Q3), minimum, maximum and interquartile range (IQR).**

**S1a**. **Meno-D scores at baseline.**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Baseline Meno-D Score** | | | | | | | | |
|  | **Mean** | **SD** | **Median** | **Q1** | **Q3** | **Min** | **Max** | **IQR** |
| **Whole Cohort** | 19.86 | 7.71 | 20 | 14 | 25 | 2 | 44 | 11 |
| **MHT naïve** | 19.70 | 7.71 | 19 | 14 | 25 | 3 | 44 | 11 |
| **MHT user** | 20.02 | 7.72 | 20 | 14 | 25 | 2 | 43 | 11 |
| **Postmenopause** | 19.52 | 7.95 | 19 | 14 | 25 | 3 | 44 | 11 |
| **Perimenopause** | 20.13 | 7.38 | 20 | 15 | 25 | 2 | 40 | 10 |
| **Antidepressant naïve** | 19.31 | 7.62 | 19 | 14 | 24 | 2 | 44 | 10 |
| **Antidepressant user** | 22.23 | 7.69 | 22 | 17 | 28 | 5 | 43 | 11 |
| **E2 only** | 22.03 | 9.00 | 20 | 15 | 27 | 7 | 44 | 12 |
| **Combined MHT (E2 + P)** | 19.73 | 7.59 | 20 | 14 | 25 | 2 | 40 | 11 |
| **MHT naïve: E2 +/- P** | 18.93 | 7.39 | 19 | 14 | 24 | 3 | 44 | 10 |
| **MHT naïve: E2+/- P + TT** | 21.09 | 8.04 | 21.5 | 14 | 27 | 3 | 40 | 13 |
| **MHT user: E2 dose increase/change** | 18.38 | 8.83 | 17 | 11 | 24.25 | 3 | 37 | 13.25 |
| **MHT user: TT added** | 19.37 | 7.07 | 19 | 14 | 24 | 2 | 43 | 10 |
| **MHT user: E2 dose increase/change and TT added** | 20.67 | 7.82 | 21 | 15 | 26 | 3 | 40 | 11 |
| **Combined MHT: E2 + P4** | 19.61 | 7.59 | 20 | 14 | 25 | 2 | 40 | 11 |
| **Combined MHT: E2 + LNG-IUS** | 20.20 | 7.62 | 19.5 | 14.25 | 24 | 4 | 39 | 9.75 |

**MHT, menopausal hormone therapy; E2, 17β-oestradiol; P, progestogen; P4, micronised progesterone; LNG-IUS, levonorgestrel releasing intra-uterine system; TT, testosterone therapy.**

**S1b.** **Meno-D scores at follow-up.**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Follow Up Meno-D Score** | | | | | | | | |
|  | **Mean** | **SD** | **Median** | **Q1** | **Q3** | **Min** | **Max** | **IQR** |
| **Whole Cohort** | 10.62 | 6.97 | 9 | 5 | 15 | 0 | 39 | 10 |
| **MHT naïve** | 10.28 | 6.77 | 9 | 5 | 14 | 0 | 39 | 9 |
| **MHT user** | 10.95 | 7.16 | 10 | 5 | 16 | 0 | 38 | 11 |
| **Postmenopause** | 10.69 | 7.24 | 9 | 5 | 15 | 0 | 39 | 10 |
| **Perimenopause** | 10.64 | 6.49 | 9 | 6 | 15 | 0 | 35 | 9 |
| **Antidepressant naïve** | 10.08 | 6.61 | 9 | 5 | 14 | 0 | 36 | 9 |
| **Antidepressant user** | 12.96 | 7.99 | 12 | 6 | 18 | 0 | 39 | 12 |
| **E2 only** | 11.82 | 8.74 | 9 | 5 | 17.25 | 0 | 38 | 12.25 |
| **Combined MHT (E2 + P)** | 10.54 | 6.84 | 9 | 5 | 15 | 0 | 39 | 10 |
| **MHT naïve: E2 +/ P** | 10.18 | 6.87 | 9 | 5 | 13 | 0 | 39 | 8 |
| **MHT naïve: E2+/- P + TT** | 10.47 | 6.66 | 8.5 | 5 | 15 | 0 | 29 | 10 |
| **MHT user: E2 dose increase/change** | 11.00 | 7.57 | 9 | 5.75 | 15.25 | 1 | 31 | 9.5 |
| **MHT user: TT added** | 10.88 | 7.42 | 9 | 5 | 16 | 0 | 38 | 11 |
| **MHT user: E2 dose increase/change and TT added** | 11.00 | 6.96 | 10 | 6 | 16 | 0 | 31 | 10 |
| **Combined MHT: E2 + P4** | 10.48 | 6.68 | 9 | 5 | 14 | 0 | 35 | 9 |
| **Combined MHT: E2 + LNG-IUS** | 10.70 | 7.68 | 10 | 4.25 | 15 | 0 | 39 | 10.75 |

**MHT, menopausal hormone therapy; E2, 17β-oestradiol; P, progestogen; P4, micronised progesterone; LNG-IUS, levonorgestrel releasing intra-uterine system; TT, testosterone therapy.**

**Table S2. Summary statistics of change in Meno-D scores for the whole cohort and by subgroup (mean, standard deviation (SD), median, quartile 1 or 25th percentile (Q1), quartile 3 or 75th percentile (Q3), minimum, maximum and interquartile range (IQR).**

**S2a.** **Absolute change in Meno-D score.**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Meno-D Change Scores** | | | | | | | | |
|  | **Mean** | **SD** | **Median** | **Q1** | **Q3** | **Min** | **Max** | **IQR** | **p-value** |
| **Whole Cohort** | -9.24 | 7.15 | -9 | -14 | -4 | -36 | 16 | 10 | <0.001 |
| **MHT naïve** | -9.42 | 6.95 | -9 | -14 | -5 | -31 | 16 | 9 | <0.001 |
| **MHT user** | -9.07 | 7.35 | -8 | -14 | -4 | -36 | 10 | 10 | <0.001 |
| **Postmenopause** | -8.83 | 6.96 | -8 | -13 | -4 | -33 | 8 | 9 | <0.001 |
| **Perimenopause** | -9.49 | 7.39 | -9 | -14 | -4 | -36 | 16 | 10 | <0.001 |
| **Antidepressant naïve** | -9.24 | 6.95 | -9 | -14 | -4 | -36 | 11 | 10 | <0.001 |
| **Antidepressant user** | -9.27 | 8 | -8 | -15 | -4 | -29 | 16 | 11 | <0.001 |
| **E2 only** | -10.22 | 7.27 | -10 | -15 | -5 | -29 | 8 | 10 | <0.001 |
| **Combined MHT (E2 + P)** | -9.19 | 7.14 | -9 | -14 | -4 | -36 | 16 | 10 | <0.001 |
| **MHT naïve: E2 +/ P** | -8.75 | 6.69 | -9 | -13 | -4 | -28 | 16 | 9 | <0.001 |
| **MHT naïve: E2 +/- P + TT** | -10.62 | 7.22 | -10 | -15 | -6 | -31 | 8 | 9 | <0.001 |
| **MHT user: E2 dose increase/change** | -7.38 | 7.78 | -5.5 | -13 | -2 | -33 | 8 | 11 | <0.001 |
| **MHT user: TT added** | -8.49 | 6.69 | -8 | -12 | -4.5 | -29 | 10 | 7.5 | <0.001 |
| **MHT user: E2 dose increase/change and TT added** | -9.66 | 7.63 | -9 | -15 | -4 | -36 | 7 | 11 | <0.001 |
| **Combined MHT: E2 + P4** | -9.13 | 7.20 | -9 | -14 | -4 | -36 | 16 | 10 | <0.001 |
| **Combined MHT: E2 + LNG-IUS** | -9.5 | 6.85 | -9 | -14 | -5 | -30 | 6 | 9 | <0.001 |

**MHT, menopausal hormone therapy; E2, 17β-oestradiol; P, progestogen; P4, micronised progesterone; LNG-IUS, levonorgestrel releasing intra-uterine system; TT, testosterone therapy.**

**S2b**. **Percentage change in Meno-D score.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Meno-D Percentage Change Scores** | | | | | | | |
|  | **Mean** | **SD** | **Median** | **Q1** | **Q3** | **Min** | **Max** | **IQR** |
| **Whole Cohort** | -44.59 | 34.74 | -50 | -68.18 | -25 | -100 | 233.33 | 43.18 |
| **MHT naïve** | -46.38 | 32.03 | -50 | -68.05 | -30.43 | -100 | 145.45 | 37.61 |
| **MHT user** | -42.79 | 37.19 | -46.41 | -68.75 | -21.43 | -100 | 233.33 | 47.32 |
| **Postmenopause** | -43.45 | 36.53 | -48.15 | -68.75 | -23.67 | -100 | 233.33 | 45.08 |
| **Perimenopause** | -44.49 | 33.2 | -47.83 | -66.67 | -25 | -100 | 145.45 | 41.67 |
| **Antidepressant naïve** | -45.71 | 34.47 | -50 | -68.75 | -27.27 | -100 | 233.33 | 41.48 |
| **Antidepressant user** | -39.68 | 35.56 | -42.12 | -66.67 | -18.1 | -100 | 145.45 | 48.57 |
| **E2 only** | -47.61 | 31.49 | -50 | -69.06 | -32.5 | -100 | 80 | 36.56 |
| **Combined MHT (E2 + P)** | -44.47 | 34.93 | -48.28 | -68.18 | -25 | -100 | 233.33 | 43.18 |
| **MHT naïve: E2 +/- P** | -45.38 | 32.67 | -50 | -66.67 | -30.43 | -100 | 145.45 | 36.23 |
| **MHT naïve: E2+/- P + TT** | -48.53 | 30.71 | -53.14 | -69.42 | -31.89 | -100 | 80 | 37.53 |
| **MHT user: E2 dose increase/change** | -34.7 | 45.75 | -40.27 | -62.78 | -16.26 | -94.74 | 200 | 46.52 |
| **MHT user: TT added** | -43.93 | 33.82 | -46.67 | -69.62 | -20.71 | -100 | 100 | 48.9 |
| **MHT user: E2 dose increase/change and TT added** | -43.25 | 37.76 | -47.62 | -69.23 | -22.22 | -100 | 233.33 | 47.01 |
| **Combined MHT: E2 + P4** | -44.01 | 35.51 | -47.83 | -68.09 | -24.07 | -100 | 233.33 | 44.02 |
| **Combined MHT: E2 + LNG-IUS** | -47.84 | 29.63 | -50 | -69.23 | -29.75 | -100 | 27.27 | 39.48 |

**MHT, menopausal hormone therapy; E2, 17β-oestradiol; P, progestogen; P4, micronised progesterone; LNG-IUS, levonorgestrel releasing intra-uterine system; TT, testosterone therapy.**

**S3. Mean percentage change in Meno D scores with 95% Confidence Intervals for the whole cohort and per subgroup.**

|  |  |  |
| --- | --- | --- |
| **Group** | **Percentage Change** | **95% CI** |
| Whole Cohort | -44.59% | -46.83%, -42.34% |
| Perimenopause | -44.49% | -47.57%, -41.4% |
| Postmenopause | -43.45% | -46.89%, -40.01% |
| E2-only MHT | -47.61% | -55.74%, -39.47% |
| Combined MHT (E2 + P) | -44.47% | -46.81%, -42.12% |
| Combined MHT: E2 + P4 | -44.01% | -46.62%, -41.40% |
| Combined MHT: E2 + LNG-IUS | -47.84% | -53.15%, -42.53% |
| MHT naïve | -46.38% | -49.32%, -43.45% |
| MHT user | -42.79% | -46.2%, -39.38% |
| MHT naive: Initiated on E2 +/- P | -45.38% | -49.19%, -41.57% |
| MHT naive: Initiated on E2 +/- P + TT | -48.53% | -53.15%, -43.9% |
| MHT user: E2 dose increase/change in formulation | -34.70% | -47.98%, -21.41% |
| MHT user: TT added | -43.93% | -49.16%, -38.7% |
| MHT user: E2 dose increase/change in formulation AND TT added | -43.25% | -48.04%, -38.45% |
| Antidepressant naïve | -45.71% | -48.19%, -43.24% |
| Antidepressant user | -39.68% | -45.03%, -34.32% |

**MHT, menopausal hormone therapy; E2, 17β-oestradiol; P, progestogen; P4, micronised progesterone; LNG-IUS, levonorgestrel releasing intra-uterine system; TT, testosterone therapy.**

**S4. P values for the comparison in percentage change in Meno-D score within each subgroup.**

P values are derived by applying a linear model to the outcome percentage change for each subgroup.

|  |  |
| --- | --- |
| **Group** | **P-value** |
| MHT (user vs. naïve) | 0.0940 |
| Diagnosis (menopause vs. perimenopause) | 0.8052 |
| Antidepressant (user vs. naïve) | 0.0057 |
| MHT type (E2 only vs. combined MHT) | 0.7156 |
| MHT naïve (E2 +/- P vs. E2 +/- P + TT) | 0.4709 |
| MHT user (E2 dose increase/change vs. TT added vs. E2 dose increase/change AND TT added | 0.3819 |
| Combined MHT: P type (P4 vs LNG-IUS) | 0.3100 |

**MHT, menopausal hormone therapy; E2, 17β-oestradiol; P, progestogen; P4, micronised progesterone; LNG-IUS, levonorgestrel releasing intra-uterine system; TT, testosterone therapy.**

**S5. P values for the Chi-squared test of association between the symptom scores at baseline and follow up.**

|  |  |
| --- | --- |
| **Symptom** | **P-value** |
| Noticed reduced energy levels? | <0.001 |
| Experienced problems concentrating? | <0.001 |
| Experienced decreased libido? | <0.001 |
| Felt more irritable? | <0.001 |
| Noticed any memory related difficulties? | <0.001 |
| Experience sleep disturbance? | <0.001 |
| Your self-esteem been lowered? | <0.001 |
| Experienced physical symptoms? | <0.001 |
| Experienced heightened levels of anxiety? | <0.001 |
| Withdrawn socially? | <0.001 |
| Gained weight (in comparison with pre-menopause weight)? | <0.001 |
| Experienced increased paranoid thinking? | <0.001 |

**S6. Patients without symptoms at baseline (score 0) who remained without symptoms at follow-up (score 0), or who reported new-onset symptoms at follow-up (score 1-4).**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Symptom** | **Number of women without symptoms a baseline**  **(score 0).** | | **Number of women without symptoms both at baseline and follow-up**  **(score 0).** | | **Number of women without symptoms at baseline who reported an increase in symptom score at follow-up (new-onset symptom)**  **(score 1-4)** | |
|  | **n** | **%** | **n** | **%** | **n** | **%** |
| **Low energy** | 87 | 9.4 | 65 | 7.1 | 22 | 2.4 |
| **Paranoid thinking** | 503 | 54.6 | 463 | 50.3 | 40 | 4.3 |
| **Irritability** | 76 | 8.3 | 49 | 5.3 | 27 | 2.9 |
| **Self-esteem** | 213 | 23.1 | 180 | 19.5 | 33 | 3.6 |
| **Isolation** | 336 | 36.5 | 289 | 31.4 | 47 | 5.1 |
| **Anxiety** | 341 | 37.0 | 298 | 32.4 | 43 | 4.7 |
| **Somatic symptoms** | 228 | 24.8 | 182 | 19.8 | 46 | 5.0 |
| **Sleep disturbance** | 47 | 5.1 | 32 | 3.5 | 15 | 1.6 |
| **Weight** | 215 | 23.3 | 161 | 17.5 | 54 | 5.9 |
| **Sexual interest** | 167 | 18.1 | 140 | 15.2 | 27 | 2.9 |
| **Memory** | 107 | 11.6 | 87 | 9.4 | 20 | 2.2 |
| **Concentration** | 163 | 17.7 | 126 | 13.7 | 37 | 4.0 |

**S7. Patients whose symptoms stayed the same (no change in symptom score) or worsened (increase in symptoms score) across the study period.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Symptom** | **Number of women who reported no change in symptom score at follow-up** | | **Number of women who reported an increase in symptom score at follow-up** | |
|  | **n** | **%** | **n** | **%** |
| **Low energy** | 282 | 30.7 | 87 | 9.5 |
| **Paranoid thinking** | 548 | 59.6 | 64 | 7.0 |
| **Irritability** | 356 | 38.7 | 54 | 5.9 |
| **Self-esteem** | 354 | 38.5 | 78 | 8.5 |
| **Isolation** | 400 | 43.5 | 89 | 9.7 |
| **Anxiety** | 391 | 42.5 | 64 | 7.0 |
| **Somatic symptoms** | 345 | 37.5 | 104 | 11.3 |
| **Sleep disturbance** | 338 | 36.7 | 88 | 9.6 |
| **Weight** | 396 | 43.0 | 114 | 12.4 |
| **Sexual interest** | 318 | 34.6 | 61 | 6.6 |
| **Memory** | 371 | 40.3 | 53 | 5.8 |
| **Concentration** | 308 | 33.5 | 65 | 7.1 |