**SUPPLEMENTARY TABLE 2*.*** *Number and percentage of participants reporting no, mild, moderate severe genitourinary symptoms of menopause, in the E4 2.5, 5, 10, 15 mg and placebo groups, and for all participants (total) (last observation carried forward)*

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **E4 2.5 mg (n = 53)a** | **E4 5 mg (n = 47)** | **E4 10 mg (n = 53)** | **E4 15 mg (n = 48)a** | **Placebo (n = 55)** | **Total (n = 256)** |
|  |  | n | % | n | % | n | % | n | % | n | % | n | % |
| **Vaginal dryness**  |  |  |  |  |  |  |  |  |  |  |  |
| Baseline | None | 21 | 39.6 | 9 | 19.1 | 19 | 35.8 | 19 | 39.6 | 17 | 30.9 | 85 | 33.2 |
| Mild | 14 | 26.4 | 19 | 40.4 | 17 | 32.1 | 12 | 25.0 | 15 | 27.3 | 77 | 30.1 |
| Moderate | 17 | 32.1 | 13 | 27.7 | 14 | 26.4 | 12 | 25.0 | 13 | 23.6 | 69 | 27.0 |
| Severe | 1 | 1.9 | 6 | 12.8 | 3 | 5.7 | 5 | 10.4 | 10 | 18.2 | 25 | 9.8 |
| End of treatment | None | 32 | 60.4 | 26 | 55.3 | 35 | 66 | 31 | 64.6 | 25 | 45.5 | 149 | 58.2 |
| Mild | 14 | 26.4 | 11 | 23.4 | 12 | 22.6 | 12 | 25.0 | 14 | 25.5 | 63 | 24.6 |
| Moderate | 6 | 11.3 | 9 | 19.1 | 5 | 9.4 | 5 | 10.4 | 11 | 20.0 | 36 | 14.1 |
| Severe | 1 | 1.9 | 1 | 2.1 | 1 | 1.9 | 0 | 0 | 5 | 9.1 | 8 | 3.1 |
| **Vaginal and/or Vulvar Irritation/Itching** |  |  |  |  |  |  |  |  |  |  |  |
| Baseline | None | 31 | 58.5 | 28 | 59.6 | 29 | 54.7 | 35 | 72.9 | 28 | 50.9 | 151 | 59.0 |
| Mild | 7 | 13.2 | 10 | 21.3 | 12 | 22.6 | 4 | 8.3 | 13 | 23.6 | 46 | 18.0 |
| Moderate | 13 | 24.5 | 7 | 14.9 | 11 | 20.8 | 8 | 16.7 | 12 | 21.8 | 51 | 19.9 |
| Severe | 2 | 3.8 | 2 | 4.3 | 1 | 1.9 | 1 | 2.1 | 2 | 3.6 | 8 | 3.1 |
| End of treatment | None | 41 | 77.4 | 31 | 66.0 | 41 | 77.4 | 36 | 75.0 | 35 | 63.6 | 184 | 71.9 |
| Mild | 10 | 18.9 | 12 | 25.5 | 9 | 17.0 | 6 | 12.5 | 11 | 20.0 | 48 | 18.8 |
| Moderate | 1 | 1.9 | 4 | 8.5 | 2 | 3.8 | 6 | 12.5 | 9 | 16.4 | 22 | 8.6 |
| Severe | 1 | 1.9 | 0 | 0 | 1 | 1.9 | 0 | 0 | 0 | 0 | 2 | 0.8 |

 *Continued on next page*

**SUPPLEMENTAL TABLE 2 (CONTINUED).***Number and percentage of participants reporting no, mild, moderate severe genitourinary symptoms of menopause, in the E4 2.5, 5, 10, 15 mg and placebo groups, and for all participants (total) (last observation carried forward)*

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **E4 2.5 mg (n=53)a** | **E4 5 mg (n=47)** | **E4 10 mg (n=53)** | **E4 15 mg (n=48)a** | **Placebo (n=54)** | **Total (n=255)** |
|  |  | n | % | n | % | n | % | n | % | n | % | n | % |
| **Dysuria** |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| Baseline | None | 46 | 86.8 | 42 | 89.4 | 45 | 84.9 | 37 | 77.1 | 43 | 78.2 | 213 | 83.2 |
| Mild | 5 | 9.4 | 3 | 6.4 | 4 | 7.5 | 8 | 16.7 | 8 | 14.5 | 28 | 10.9 |
| Moderate | 1 | 1.9 | 1 | 2.1 | 4 | 7.5 | 3 | 6.3 | 4 | 7.3 | 13 | 5.1 |
| Severe | 1 | 1.9 | 1 | 2.1 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0.8 |
| End of treatment | None | 51 | 96.2 | 45 | 95.7 | 50 | 94.3 | 39 | 81.3 | 48 | 87.3 | 233 | 91 |
| Mild | 2 | 3.8 | 2 | 4.3 | 3 | 5.7 | 5 | 10.4 | 5 | 9.1 | 17 | 6.6 |
| Moderate | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 8.3 | 1 | 1.8 | 5 | 2 |
| Severe | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1.8 | 1 | 0.4 |
| **Vaginal Pain Associated with Sexual Activityb** |  |  |  |  |  |  |  |  |  |  |  |
| Baseline | None | 30 | 56.6 | 20 | 42.6 | 31 | 58.5 | 26 | 54.2 | 28 | 50.9 | 135 | 52.9 |
| Mild | 16 | 30.2 | 12 | 25.5 | 15 | 28.3 | 12 | 25.0 | 6 | 10.9 | 61 | 23.9 |
| Moderate | 6 | 11.3 | 9 | 19.1 | 6 | 11.3 | 8 | 16.7 | 13 | 23.6 | 42 | 16.5 |
| Severe | 1 | 1.9 | 6 | 12.8 | 1 | 1.9 | 2 | 4.2 | 7 | 12.7 | 17 | 6.7 |
| End of treatment | None | 41 | 77.4 | 32 | 68.1 | 45 | 84.9 | 37 | 77.1 | 33 | 60.0 | 188 | 73.4 |
| Mild | 8 | 15.1 | 9 | 19.1 | 8 | 15.1 | 9 | 18.8 | 8 | 14.5 | 42 | 16.4 |
| Moderate | 2 | 3.8 | 5 | 10.6 | 0 | 0 | 2 | 4.2 | 10 | 18.2 | 19 | 7.4 |
| Severe | 2 | 3.8 | 1 | 2.1 | 0 | 0 | 0 | 0 | 4 | 7.3 | 7 | 2.7 |

E4, estetrol.

The percentage participants in each severity category (none, mild, moderate, and severe) in each E4 group was compared to the change in the placebo group using logistic regression. None of the differences were significant (*P* > 0.05).

a One participant was randomized to E4 15 mg but temporarily took E4 2.5 mg and was excluded from the analysis. One participant was randomized to E4 2.5 mg and temporarily took E4 10 mg, but was included in the 2.5 mg group for the analysis.

b One participant did not complete the item for vaginal pain associated with sexual activity.