Symptomatic Vulvar and Vaginal Atrophy (VVA). Relief was Achieved With Negligible to Very Low Systemic Absorption of Estradiol with TX-004HR (Estradiol Vaginal Inset): PK Comparison to Systemic and a Vaginal Estradiol

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Background
Greater than 60% of postmenopausal breast cancer patients report experiencing symptoms of vulvar and vaginal atrophy (VVA) including vaginal dryness and dyspareunia.1,2 VVA symptoms are reported as the most poorly addressed of their side effects while on adjuvant endocrine therapy including aromatase inhibitors.3

Methods
Bioavailability Studies

- TX-004HR PK was evaluated in two phase 1, randomized, single-dose, open-label, 2-way crossover studies (N=6 for each).
- TX-004HR 10 μg and 25 μg were compared with vaginal E2 tablet 10 μg and 25 μg (Vagifem®). Novo Nordisk, Plainsboro, NJ, respectively.

- Enrolled participants were healthy postmenopausal women aged 40 to 65 years with BMI 18.5 to 30.0 kg/m².

- Women sequentially received a single dose of TX-004HR and vaginal E2 tablet depending on each dosage level.

-TX-004HR PK was evaluated in two phase 1, randomized, single-dose, open-label, 2-way crossover studies of postmenopausal women (Table 1).

- Enrolled participants were healthy postmenopausal women aged 40 to 65 years with BMI 18.5 to 30.0 kg/m².

- Prior to dose on days 1 and 14.

- Baseline-adjusted mean plasma concentration versus time for E2 with TX-004HR (Estradiol Vaginal Insert): Oral Activella 10 μg.

- Phase 3 REJOICE Trial11: E2 PK parameters for TX-004HR compared with placebo are shown in Figure 2 and Table 3.

- TX-004HR 4 μg had no significant differences from placebo in E2 PK parameters.

- TX-004HR 10 μg was not different than placebo, with the exception of the Cmax that was higher than placebo on day 1.

- TX-004HR 25 μg was associated with higher Cmax and AUC0∞ versus placebo on days 1 and 14.

- E2 concentrations on day 84 were similar to baseline and placebo for the three doses.

- Estriol and estrone conjugate PK parameters with TX-004HR were similar to placebo across all doses (data not shown).

- TX-004HR may have up to 75-fold lower systemic E2 absorption than lower-dose oral E2 products in separate studies of postmenopausal women (Table 2).

- Figure 2: Baseline adjusted mean E2 concentration with TX-004HR over time

Results

Bioavailability Studies

- TX-004HR 10 μg and 25 μg resulted in statistically significantly lower E2 absorption PK parameters than with a vaginal E2 tablet at identical doses (Figure 1).

- TX-004HR had negligible to very low systemic absorption of E2

- TX-004HR had no significant differences from placebo in E2 PK parameters

- TX-004HR 10 μg was not different than placebo, with the exception of the Cmax that was higher than placebo on day 1.

- TX-004HR 25 μg was associated with higher Cmax and AUC0∞ versus placebo on days 1 and 14.

- E2 concentrations on day 84 were similar to baseline and placebo for the three doses.

- Estriol and estrone conjugate PK parameters with TX-004HR were similar to placebo across all doses (data not shown).

- TX-004HR may have up to 75-fold lower systemic E2 absorption than lower-dose oral E2 products in separate studies of postmenopausal women.

- Figure 2: Baseline adjusted mean E2 concentration with TX-004HR over time

Conclusions

- TX-004HR had negligible to very low systemic absorption of E2 with statistically significant improvements in VVA-associated, moderate to severe dyspareunia and vaginal dryness in a phase 3 study.

- In phase 1 studies, TX-004HR had lower systemic E2 absorption versus a commercially available vaginal E2 tablet (Vagifem®).

- While not directly compared with oral products in head-to-head studies,10,11 the PK profile of TX-004HR exhibited very low systemic E2 absorption consistent with vaginal administration.

- While TX-004HR has not been studied in women with a history of breast cancer, its PK profile, especially with the lowest 4 μg dose, suggests that further study in this patient population should be considered.

- Note: TX-004HR (TherapeuticsMD, Boca Raton, FL) has not been studied in women with known, suspected, or history of breast cancer.

- These women were excluded from these studies. Use in patients with known, suspected, or history of breast cancer is contraindicated in the current FDA-approved labeling for this class of products.

References


7. ACOG Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 139, April 2014. Available at: http://www.acog.org/Resources-And-Publications/Practice-Bulletins/Obstetrics/ACOG-Committee-on-Practice-Bulletins-Obstetrics-

8. Dr. Bernick serves on the speaker’s bureau for AMAG and Valeant. Drs. Bernick and Mirkin are employees of TherapeuticsMD with stock/stock options in the company. TherapeuticsMD sponsored TX-004HR studies and funded the medical writing assistance provided by Dominique Verlaan, PhD.

9. Dr. Mirkin is on the advisory boards for Amgen, Endo, and Eli Lilly and Co. Dr. Mirkin serves on the Speaker’s Bureau for Merck, and has received research support from Merck, Endo, and Amgen. Dr. Mirkin is an employee of TherapeuticsMD with equity ownership in the company. TherapeuticsMD sponsored TX-004HR studies and funded the medical writing assistance provided by Dominique Verlaan, PhD.

10. IMS 16th World Congress on Menopause, June 6-9, 2018 in Vancouver, Canada.