TX-004HR Vaginal Estradiol Effectively Treats Vulvar and Vaginal Atrophy (VVA) With Negligible to Low Systemic Absorption

Background

- Vaginal, low-dose estrogens are recognized as safe and effective treatment options for women with moderate-to-severe symptoms of VVA.

- TX-004HR (TherapeuticsMD, Inc., Boca Raton, FL) is an investigational, applicator-free, low-dose, vaginal softgel capsule containing solubilized 17β-estradiol, with a new lower effective dose (4 µg). It is designed to provide rapid and sustained efficacy and improved user experience for the treatment of menopausal VVA, with negligible systemic absorption.

- Phase 1 studies showed that systemic estrogen concentrations with 10 µg and 25 µg TX-004HR were 2.5 times lower than with an approved low-dose vaginal estradiol tablet at identical doses (AUC<sub>0-24</sub>, P<0.001 for both doses; C<sub>max</sub>, P<0.0194 for 10 µg and P<0.001 for 25 µg).

Objectives

- To determine whether VVA efficacy can be achieved with negligible systemic absorption as measured by pharmacokinetics (PK) of a vaginal estradiol capsule in postmenopausal women with moderate-to-severe dyspareunia.

Methods

Study Design

- A PK substudy was part of a large, multicenter, double-blind, randomized, placebo-controlled phase 3 trial evaluating the efficacy and safety of TX-004HR at 4 µg, 10 µg, and 25 µg compared with placebo for treating postmenopausal moderate-to-severe dyspareunia (see companion poster to be presented Saturday, April 2, 2016).

- Treatments were administered vaginally once daily for 2 weeks and then twice weekly for 10 weeks.

Study Participants

- Postmenopausal women (40-75 years) were included if they had:
  - VVA, defined as ≥5% superficial cells on vaginal cytological smear; vaginal pH ≤5.0
  - Self-identified as their most bothersome symptom (MEB) as moderate-to-severe dyspareunia
  - Body mass index ≤38 kg/m<sup>2</sup>
  - Anticipated sexual activity (with vaginal penetration) during the trial period

Study Endpoints

- Main exclusion criteria included use of oral estrogen, progesteron, androgens, or SERM-containing drug products within 8 weeks

Study Participants

- Participants had a mean age of 59 years and a mean BMI of 28 kg/m<sup>2</sup>

Analyses

- Estradiol, estrone, and estrone conjugates were measured in serum samples by validated GC/MS methods.

- The following PK parameters were determined using algorithms composed in SAS:
  - C<sub>max</sub>: maximum serum concentration, day 1 and 14
  - C<sub>avg</sub>: average serum concentration, maximum concentration, by inspection of timed measurements on days 1 and 14
  - AUC<sub>0-24</sub>: area under the concentration-time curve
  - CL<sub>sys</sub>: systemic clearance
  - V<sub>sys</sub>: systemic volume of distribution
  - R, accumulation ratio, day 14/day 1, for AUC and C<sub>max</sub>

- Pairwise comparisons were performed for each of the parameters using paired t-tests with pooled variance for each dose of TX-004HR versus placebo on days 1 and 14.

Results

- Figure 1. Unadjusted Mean Serum Estradiol Concentrations TX-004HR 4 µg (n=18) vs Placebo (n=17)

- Table 1. Unadjusted Estradiol Parameters With 4 µg TX-004HR vs Placebo (mean [SD])

- Figure 2. Unadjusted Mean Serum Estradiol Concentrations TX-004HR 10 µg (n=18) vs Placebo (n=17)

- Table 2. Unadjusted Estradiol Parameters With 10 µg TX-004HR vs Placebo (mean [SD])

- Figure 3. Unadjusted Mean Serum Estradiol Concentrations TX-004HR 25 µg (n=18) vs Placebo (n=17)

- Table 3. Unadjusted Estradiol Parameters With 25 µg TX-004HR vs Placebo (mean [SD])

Conclusions

- Vaginal TX-004HR resulted in negligible to very low systemic absorption of E2:
  - 4 µg TX-004HR was similar to placebo for E2 PK parameters at day 1 and day 14, and showed no drug accumulation post therapy.
  - 10 µg TX-004HR was similar to placebo for all E2 parameters except C<sub>avg</sub> on day 14 (mean 10.9 pg/mL vs 6.6 pg/mL for placebo). All PK parameters were not different from placebo at day 14; there was no drug accumulation post therapy.
  - While there were minor increases in the E2 PK parameters with 25 µg TX-004HR, concentrations remained within the normal postmenopausal range by day 14.
  - There was no evidence of accumulation or increased levels at day 84.

- All doses of TX-004HR improved the signs and symptoms of VVA in the overall study (see companion poster Saturday, April 2).

- The PK substudy in combination with the efficacy results of the main study demonstrate that TX-004HR provided local benefits of E2 without an increase in systemic exposure.

References


Disclosures

DA serves as consultant to Shionogi Inc., Agila Therapeutics, Abbot, Alzex Pharmaceuticals, Amgen, and TherapeuticsMD, Inc. BS serves on the Speaker’s Bureau for Agile Therapeutics. SC, VH, and MB consult to pharmaceutical companies including but not limited to TherapeuticsMD, BB, SG, and SM are employees of TherapeuticsMD. AG gratefully acknowledges and acknowledges the medical writing assistance provided by Jolene Mason, PhD (Pricewater Publicity, LLC).