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

LBFRI-11

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Background

- Vaginal, low-dose estrogens are recognized as safe and effective treatment options for women with moderate-to-severe symptoms of VVA[1,2]
- 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 2-3 times lower than with an approved low-dose vaginal estradiol tablet at identical doses ($AUC_{0\text{-}24}$ $P<0.0001$ for both doses; C_{max} $P=0.0194$ for 10 µg and $P<0.0001$ for 25 µg)[4]

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 (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 their most bothersome symptom (MBS) as moderate-to-severe dyspareunia
  - Body mass index ≤38 kg/m^2
  - Anticipated sexual activity (with vaginal penetration) during the trial period
- Main exclusion criteria included use of oral estrogen-, progestin-, androgen-, or SERM-containing drug products within 8 weeks

Study Endpoints

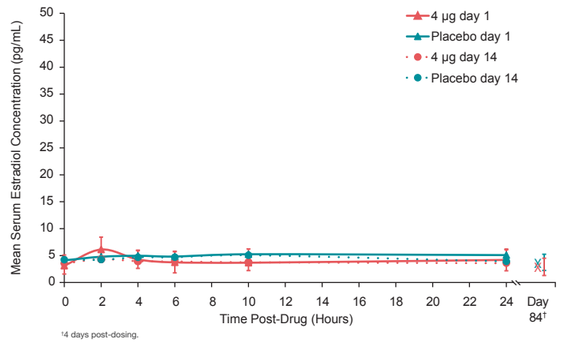
- For PK, serum was sampled pre-dose and at 2, 4, 6, 10, and 24 h post-dose on days 1 and 14, and once 4 days following the last insertion of TX-004HR (at approximately day 84), for E2, estrone (E1), and estrone conjugates (E1Cs)

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_{max}, maximum serum concentration, days 1 and 14
  - C_{min}, minimum serum concentration, day 14
  - t_{max}, apparent time of maximum serum concentration, by inspection of timed measurements on days 1 and 14
  - $AUC_{0\text{-}24}$, area under the serum concentration versus time curve, days 1 and 14
  - C_{avg}, average serum concentration, day 14
  - R, accumulation ratio, day 14/day 1, for AUC and C_{max}
- 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)



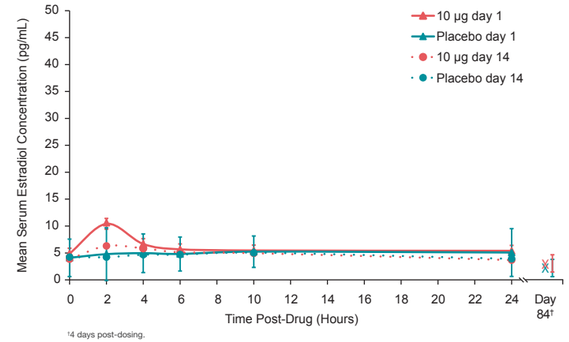
†4 days post-dosing.

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

		AUC (h*pg/mL)	C_{avg} (pg/mL)	C_{max} (pg/mL)
Day 1	4 µg	91.7 (37.9)	3.9 (1.5)	6.5 (2.1)
	Placebo	116.6 (77.3)	4.9 (3.2)	6.6 (4.9)
	P-value*	0.2292	0.2670	0.9586
Day 14	4 µg	87.2 (42.8)	3.6 (1.78)	4.8 (2.3)
	Placebo	104.2 (66.4)	4.3 (2.8)	5.5 (3.4)
	P-value*	0.3829	0.3829	0.5174

*Treatment vs placebo.

Figure 2. Unadjusted Mean Serum Estradiol Concentrations TX-004HR 10 µg (n=19) vs Placebo (n=17)



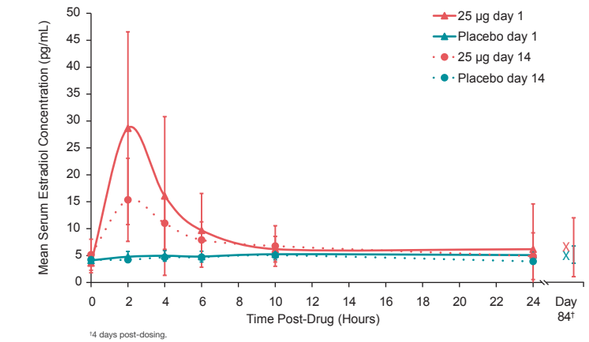
†4 days post-dosing.

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

		AUC (h*pg/mL)	C_{avg} (pg/mL)	C_{max} (pg/mL)
Day 1	10 µg	138.2 (75.2)	5.8 (3.1)	10.9 (5.0)
	Placebo	116.6 (77.3)	4.9 (3.2)	6.6 (4.9)
	P-value*	0.4028	0.4028	0.0116
Day 14	10 µg	110.1 (54.6)	4.6 (2.3)	7.3 (2.4)
	Placebo	104.2 (66.4)	4.3 (2.8)	5.5 (3.4)
	P-value*	0.7724	0.7724	0.0702

*Treatment vs placebo.

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



†4 days post-dosing.

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

		AUC (h*pg/mL)	C_{avg} (pg/mL)	C_{max} (pg/mL)
Day 1	25 µg	217.4 (99.0)	9.1 (4.1)	29.8 (17.5)
	Placebo	116.6 (77.3)	4.9 (3.2)	6.6 (4.9)
	P-value*	0.0021	0.0021	<0.0001
Day 14	25 µg	171.6 (80.14)	7.1 (3.3)	15.7 (7.6)
	Placebo	104.2 (66.4)	4.3 (2.8)	5.5 (3.4)
	P-value*	0.0108	0.0108	<0.0001

*Treatment vs placebo.

Patient Disposition and Demographics

- The substudy randomized 72 women at 11 centers
- Participants had a mean age of 59 years and a mean BMI of 28 kg/m^2; the majority (94%) were white

PK Parameters

Estradiol

- 4 µg TX-004HR showed no statistical differences from placebo in baseline-adjusted and unadjusted E2 area under the concentration-time curve (AUC), average concentration (C_{avg}), and peak concentration (C_{max}; Table 1)
- At the 10 µg dose (Table 2), C_{max} values were slightly higher than placebo on day 1, but were not significantly different from placebo on day 14
- At the 25 ug dose, there were minor increases in the PK parameters (Table 3), but all were within the normal postmenopausal range (i.e., ≤19 pg/mL[5]) by day 14
- Concentration versus time curves show similar E2 concentrations 24 hours post-dosing between all TX-004HR doses and placebo at days 1 and 14 (Figures 1-3)
- There was no accumulation at day 84, and levels were similar to placebo

Estrone and Estrone Conjugates

- 4 µg TX-004HR E1 C_{max} was significantly lower than placebo at days 1 and 14, as was C_{avg} on day 1. PK parameters for E1Cs with 4 µg did not differ from placebo (Table 4).
- No differences from placebo were observed for 10 µg or 25 µg TX-004HR in any E1 or E1Cs PK parameters (Table 4)

Efficacy Endpoints (Main Study)

- All doses of TX004-HR versus placebo at week 12
  - Demonstrated significant improvement in all 4 co-primary clinical endpoints (Table 5) despite the lack of systemic absorption
  - Showed efficacy for symptoms of vaginal dryness ($P<0.01$ for all doses) and irritation ($P\leq0.05$ for all doses)

Table 4. Unadjusted E1 and E1C Parameters with TX-004HR vs Placebo

		Day 1			Day 14		
		AUC (h*pg/mL)	C_{avg} (pg/mL)	C_{max} (pg/mL)	AUC (h*pg/mL)	C_{avg} (pg/mL)	C_{max} (pg/mL)
Estrone	4 µg	290.2 (123.7)	13.0 (4.7)*	15.7 (6.1)*	326.6 (114.1)	13.6 (4.8)	16.0 (5.5)*
	10 µg	462.7 (195.6)	19.3 (8.2)	23.5 (9.9)	464.1 (243.9)	19.3 (10.2)	23.9 (13.5)
	25 µg	419.1 (147.9)	17.5 (6.2)	21.9 (7.7)	428.7 (161.7)	17.9 (6.7)	22.4 (8.9)
	Placebo	467.9 (278.8)	19.5 (11.6)	25.7 (18.4)	426.8 (180.7)	17.8 (7.5)	22.8 (10.9)
Estrone Conjugates	4 µg	5077 (3798.4)	215.9 (154.8)	273.1 (196.4)	5172.9 (3382.9)	215.5 (141.0)	289.0 (183.8)
	10 µg	5931.9 (4210.0)	247.2 (175.4)	329.4 (226.6)	8978.0 (9811.2)	374.1 (408.8)	511.7 (568.8)
	25 µg	9126.0 (9186.4)	380.3 (382.8)	542.1 (475.5)	9930.2 (11712.0)	413.8 (488.0)	579.5 (610.1)
	Placebo	5637.9 (3151.5)	244.6 (128.1)	309.8 (146.1)	6275.2 (3397.5)	261.5 (141.6)	343.6 (182.2)

TX-004HR lower than placebo ($P<0.05$).

Table 5. Efficacy (LS Mean Change From Baseline [SE] to Week 12) With TX-004HR at 12 Weeks in the MITT Population (n=747)

	% Superficial cells	% Parabasal cells	Vaginal pH	Dyspareunia (Score)
4 µg (n=186)	17.5 (1.5)†	-40.6 (1.8)†	-1.3 (0.1)†	-1.5 (0.1)*
10 µg (n=188)	16.7 (1.5)†	-44.1 (1.8)†	-1.4 (0.1)†	-1.7 (0.1)†
25 µg (n=186)	23.2 (1.5)†	-45.6 (1.7)†	-1.3 (0.1)†	-1.7 (0.1)†
Placebo (n=187)	5.6 (1.5)	-6.7 (1.8)	-0.3 (0.1)	-1.3 (0.1)

*$P=0.0149$; †$P<0.0001$ vs placebo.

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_{max} on day 1 (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[5] 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)
- This PK substudy in conjunction with the efficacy results of the main study demonstrate that TX-004HR provided local benefits of E2 without an increase in systemic exposure

References

1. North American Menopause Society. *Menopause.* 2013;20:888-902.
2. The American College of Obstetricians and Gynecologists Committee on Gynecologic Practice. *Obstet Gynecol.* 2016;127(3):e93-96.
3. Pickar J, et al. *Climacteric.* 2016;19(2):181-187.
4. Ulrich L, et al. *Climacteric.* 2010;13:228-237.

Disclosures

DA serves as consultant to Shionogi Inc., Agile Therapeutics, AbbVie, Bayer Healthcare, CHEMO, Endoceutics, HRA Pharma, and TEVA, and serves on the Speakers' Bureau for Agile Therapeutics. GC, HK, and PM consult to pharmaceutical companies including but not limited to TherapeuticsMD. BB, SG, and SM are employees of TherapeuticsMD. TherapeuticsMD sponsored the study and supported the medical writing assistance provided by Jolene Mason, PhD (Precise Publications, LLC).

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