Evaluation of Systemic Effects of a Vaginal Estradiol Softgel Capsule Insert (TX-004HR) in Menopausal Women with Moderate to Severe Dyspareunia

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Disclosures

- **Advisory board member**: AMAG, Palatin Technologies, and Valeant
- **Consultant**: TherapeuticsMD
- **Speaker's bureau**: Valeant

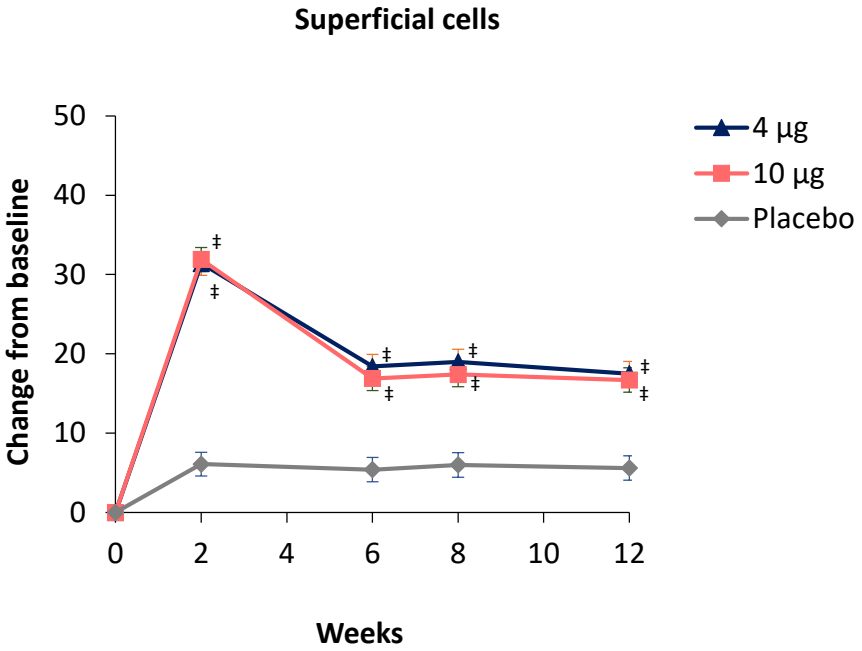
Background

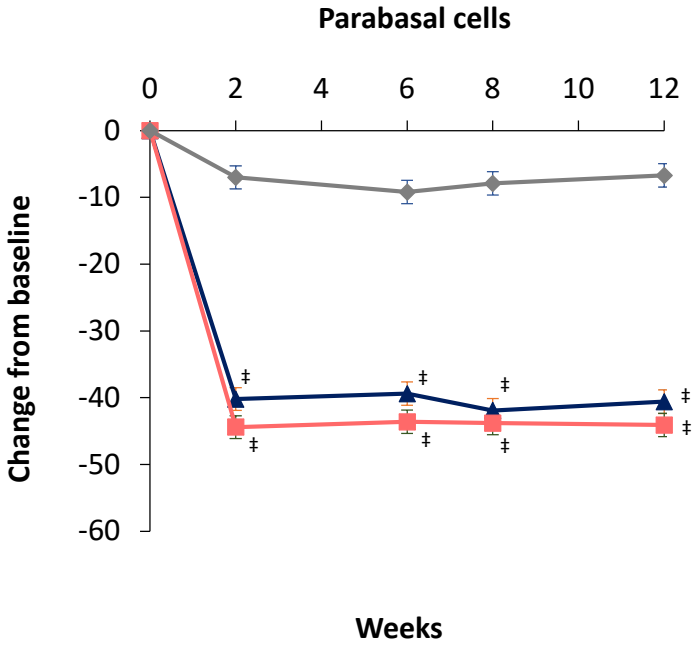
- Up to 69% of postmenopausal women show clinical signs of vulvar and vaginal atrophy (VVA),[1] with ~50% reporting symptoms[2,3]
  - VVA can be persistent and can reduce quality of life[4,5]
- TX-004HR (IMVEXXY™ [4-µg and 10-µg doses]) are low-dose, softgel vaginal inserts of solubilized 17β-estradiol (E2) recently approved (May 2018) in the US to treat moderate to severe dyspareunia due to menopause[6,7]
- One goal of vaginal estrogen therapies is to minimize systemic absorption and potentially reduce related side effects[8]
- Pharmacokinetic data for TX-004HR show mean systemic E2 absorption with 4 µg and 10 µg to be similar to placebo and baseline, and generally within the postmenopausal range[9]

1. Gass M, et al. Menopause. 2011;18:1160-1171. **2.** Santoro N and Komi J. J Sex Med. 2009;6:2133-2142. **3.** Simon J, et al. Menopause. 2013;20:1043-1048. **4.** Dennerstein L, et al. Obstet Gynecol. 2000;93:351-358. **5.** Nappi R and Kokot-Kierepa M. Maturitas. 2010;67:233-238. **6.** Imvexxy Prescribing Information. TherapeuticsMD. **7.** Constantine G, et al. *Menopause* 2017;24:409-416. **8.** NAMS. *Menopause*. 2007;14:357-369. **9.** Archer DF, et al. *Menopause*. 2017;24:510-516.

REJOICE Trial: Co-Primary Efficacy Endpoints

- TX-004HR significantly improved vaginal cells[1,2]



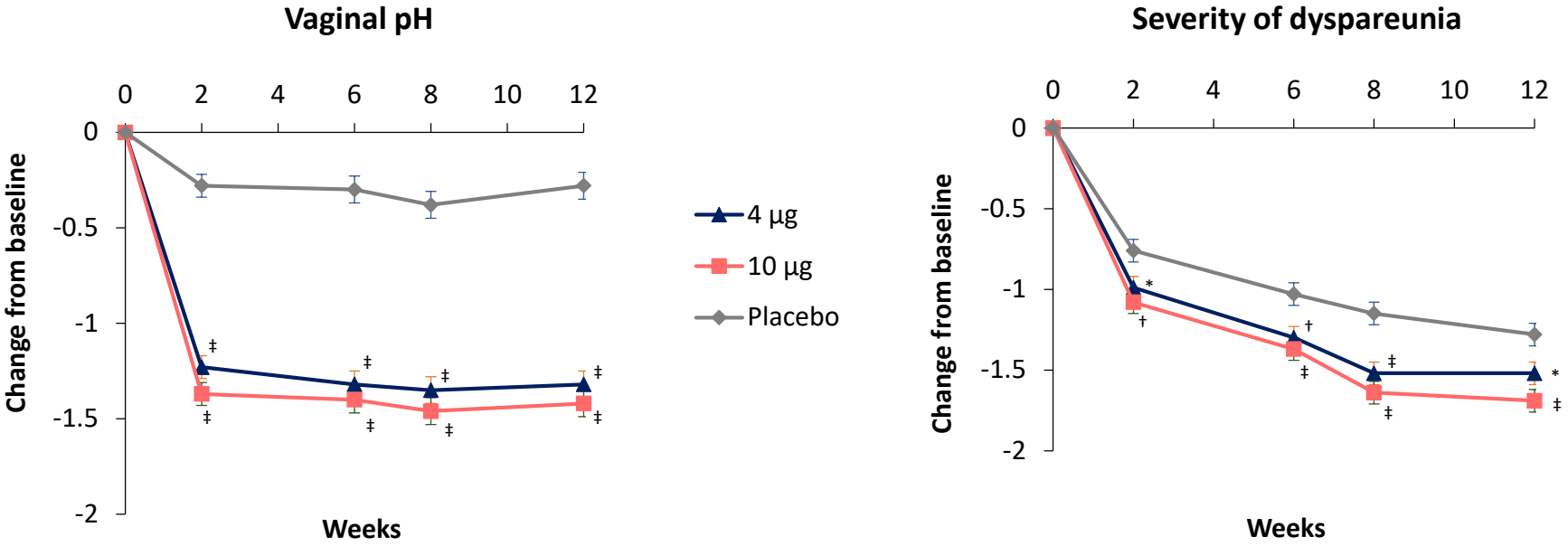


‡*P*<0.001 for TX-004HR vs placebo.

1. Constantine G, et al. *Menopause* 2017;24:409-416. **2.** Simon JA, et al. *Maturitas*. 2017;99:51-58.

REJOICE Trial: Co-Primary Efficacy Endpoints

- TX-004HR significantly improved vaginal pH and dyspareunia severity[1,2]

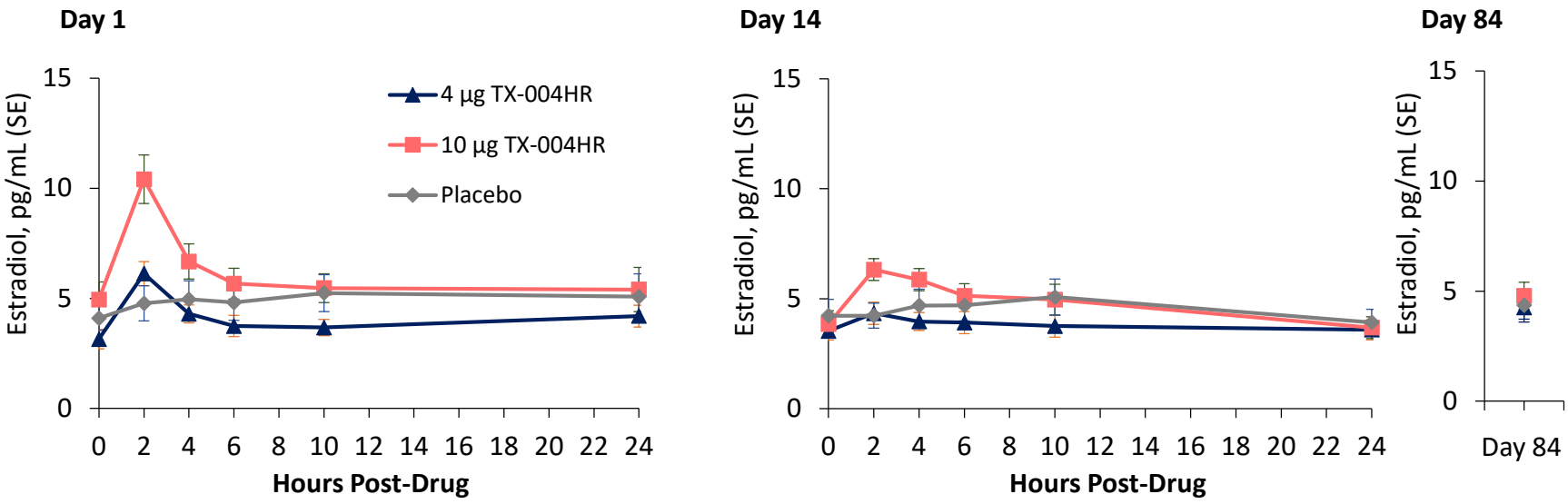


*P<0.05, †P<0.01; ‡P<0.001 for TX-004HR vs placebo.

1. Constantine G, et al. *Menopause* 2017;24:409-416. **2.** Simon JA, et al. *Maturitas*. 2017;99:51-58.

REJOICE Trial: Serum Estradiol Levels

- E2 absorption with 4 µg and 10 µg of TX-004HR was similar to placebo and baseline, and generally within the postmenopausal range



Archer DF, et al. *Menopause.* 2017;24:510-516.

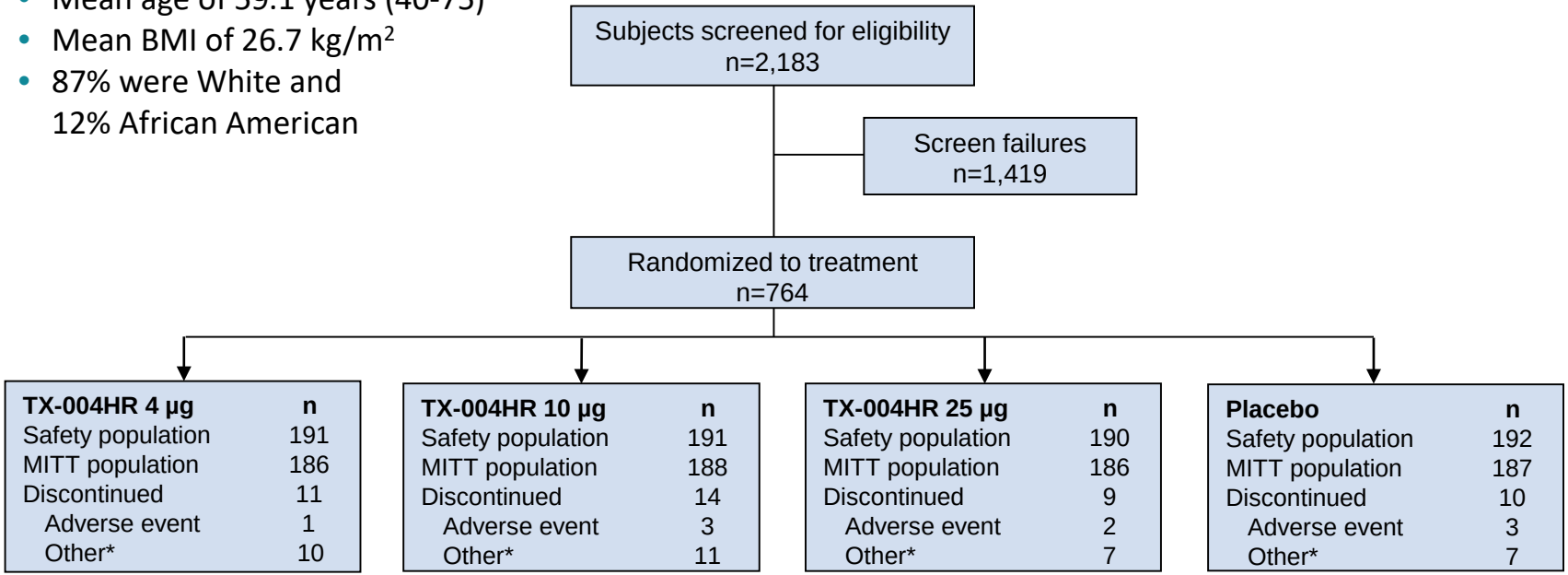
Objective and Design

- **Objective:** This report summarizes the effects of TX-004HR on clinical outcomes (in the REJOICE trial) that may be influenced by systemic E2 absorption
- **Design:** REJOICE was a randomized, double-blind, placebo-controlled, multicenter, phase 3 trial of TX-004HR 4 µg, 10 µg, and 25 µg
  - Self-administered vaginally (1x daily for 2 weeks; 2x weekly for 10 weeks)
  - TEAEs of special interest were collected and summarized here (e.g., cardiovascular and breast events)
  - 12-lead ECGs and breast exams were performed at baseline and week 12
  - SHBG was measured at baseline and weeks 2 & 12 in a subset of women (n=72)

ECG: electrocardiograms; SHBG: serum sex hormone binding globulin.
Constantine G, et al. *Menopause* 2017;24:409-416.

REJOICE Trial: Disposition and Demographics

- 94% completed at 12 wks
- Mean age of 59.1 years (40-75)
- Mean BMI of 26.7 kg/m^2
- 87% were White and
  12% African American



TX-004HR 4 µg	n
Safety population	191
MITT population	186
Discontinued	11
Adverse event	1
Other*	10

TX-004HR 10 µg	n
Safety population	191
MITT population	188
Discontinued	14
Adverse event	3
Other*	11

TX-004HR 25 µg	n
Safety population	190
MITT population	186
Discontinued	9
Adverse event	2
Other*	7

Placebo	n
Safety population	192
MITT population	187
Discontinued	10
Adverse event	3
Other*	7

*Other included Investigator decision, lack of efficacy, lost to follow up, protocol violation, and withdrew consent.

Constantine G, et al. *Menopause* 2017;24:409-416.

Overall Safety

- No clinically significant differences in AEs were observed between treatment and placebo groups

Treatment-related TEAE ≥3% of any treatment arm	4 µg (n=191)	10 µg (n=191)	Placebo (n=192)
Headache	7 (3.7)	5 (2.6)	6 (3.1)
Vaginal discharge	5 (2.6)	6 (3.1)	12 (6.3)
Vulvovaginal pruritus	2 (1.0)	3 (1.6)	8 (4.2)

- No signal of estrogenic stimulation of the endometrium
  - No cases of endometrial hyperplasia or malignancies were reported
- No treatment-related serious AEs or deaths were reported
- All doses of TX-004HR were well tolerated

TEAE: treatment-emergent adverse event.
Constantine G, et al. *Menopause* 2017;24:409-416.

Cardiovascular-related TEAEs

- Five cardiovascular TEAEs were reported; all were considered mild
- Only the 2 cases of palpitations were considered possibly related to treatment
- No CHD, VTE or other thrombotic episodes were reported

Cardiovascular TEAEs	4 µg (n=191)	10 µg (n=191)	Placebo (n=192)
Total	3	1	1
Complete heart block	0	0	0
Atrioventricular block first degree	1 (0.5)*	0	0
Palpitations	1 (0.5)	0	1 (0.5)
Sinus bradycardia	1 (0.5)*	0	0
Sinus node dysfunction	0	1 (0.5)	0

*reported by the same individual

CHD: coronary heart disease; TEAE: treatment-emergent adverse event; VTE: venous thromboembolism.

Cardiovascular Outcomes

- **ECG findings**: No treatment-related, clinically significant adverse ECG changes
- **Blood pressure**
  - 2 women (4 µg group) had mild incident hypertension
    - One was considered possibly related to treatment
  - 3 women (n=1 each; 4 µg, 10 µg, placebo) had mild blood pressure increases
    - One was considered not treatment related (10 µg)
    - Two were considered possibly related
- **Chemistry-related TEAEs**
  - 2 women (n=1 for 4 µg, n=1 for 10 µg) had incident hypercholesterolemia
  - 3 women (n=1 for 10 µg, n=2 for placebo) had triglycerides increases

ECG: electrocardiogram; TEAE: treatment-emergent adverse event.

Breast-related TEAEs

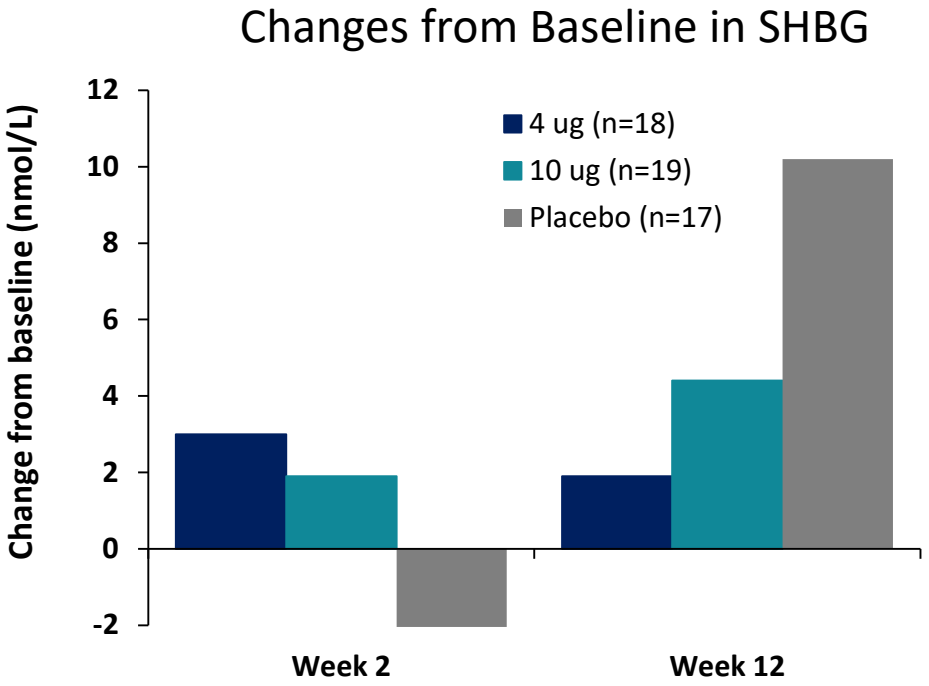
- Seven breast-related TEAEs were reported
  - All but two were considered as possibly or probably related to treatment
  - 6 were in the placebo group
  - Breast tenderness was reported in 1 case taking 10-µg dose
- No other clinically significant breast events were reported

Breast TEAEs	4 µg (n=191)	10 µg (n=191)	Placebo (n=192)
Total	0	1	6
Breast discomfort	0	0	1 (0.5)
Breast mass (benign breast nodule)	0	0	1 (0.5)*
Breast pain	0	0	2 (1)
Breast tenderness	0	1 (0.5)	0
Fibrocystic breast disease	0	0	2 (1)*

*not considered related to treatment.

Sex Hormone Binding Globulin (SHBG)

- Changes with TX-004HR were comparable to changes with placebo
- No dose-related pattern was apparent



Conclusions

- No clinically meaningful differences in TEAEs or treatment-related TEAEs of special interest were observed between TX-004HR and placebo
  - Cardiovascular or thrombotic events, blood pressure, cholesterol or triglycerides levels
  - Breast-related events
- No evidence of estrogen-related clinical outcomes such as an increase in serum SHBG suggesting significant systemic absorption
- No evidence of systemic effects of the E2 vaginal insert TX-004HR was observed in the 12-week REJOICE trial
- These safety data in conjunction with the improved moderate to severe dyspareunia efficacy data and minimal E2 absorption support a local effect of the TX-004HR E2 vaginal insert