Demographics and the Placebo Response in the REPLENISH Trial: A Study of Vasomotor Symptoms

Ginger D Constantine, MD[1]; Shelli Graham, PhD[2]; Brian Bernick, MD[2]; and David F Archer, MD[3]

[1]EndoRheum Consultants, LLC, Malvern, PA
[2]TherapeuticsMD, Boca Raton, FL
[3]Clinical Research Center, Eastern Virginia Medical School, Norfolk, VA

Disclosures

- **Consultant:** TherapeuticsMD as well as other pharmaceutical companies
- **Stock options:** TherapeuticsMD

Disclaimer

- TX-001HR is an investigational drug and its safety or effectiveness has not been established

Placebo Response

- Placebo response in vasomotor symptom (VMS) studies is known to be high[1-4]
  - 17% to 61% reduction from baseline in VMS frequency[1-4]
  - Pooled analysis of 10 trials showed that 27% to 52% of women taking placebo had a ≥50% reduction in hot flush frequency[3]
- The REPLENISH trial had a large placebo response rate (55%)
  - Placebo response rates were evaluated by subgroups
    - BMI, age, and race
    - Only race had a significant effect on the placebo response rate

1. Lobo RA, et al. *Fertil Steril.* 2009;92:1025-1038. **2.** MacLennan AH, et al. *Cochrane Database Syst Rev.* 2004:CD002978. **3.** Loprinzi CL, et al. *J Clin Oncol.* 2009:27:2831-2837. **4.** Gabapentin NDA 225-506. Available at https://www.citizen.org/sites/default/files/2099.pdf. Accessed on 20 Sep 2017.

Presentation Objectives

- To evaluate in the REPLENISH trial by race
  - Placebo response rates
  - Frequency of VMS
  - MENQOL vasomotor domain

MENQOL: menopause-specific quality of life questionnaire.

The REPLENISH Trial

- Phase 3, randomized, double-blind, placebo-controlled, multicenter, trial of TX-001HR in postmenopausal women with an intact uterus
  - Women with ≥7/day or ≥50 moderate-to-severe hot flushes at baseline were enrolled in a 12-week VMS substudy
  - In the substudy, women were randomized to 4 daily oral 17β-estradiol (E2)/ progesterone (P4) doses or placebo

Treatment Groups
• 1 mg E2/100 mg P4 • 0.5 mg E2/100 mg P4 • 0.5 mg E2/50 mg P4 • 0.25 mg E2/50 mg P4 • Placebo

Study Endpoints

- Four co-primary efficacy endpoints were changes in moderate-to-severe VMS frequency and severity with TX-001HR versus placebo at weeks 4 and 12
  - Women completed daily diaries for hot flush frequency and severity
- Prespecified secondary endpoints were responder analyses and MENQOL questionnaire at 12 weeks
  - Responders had a change in VMS frequency of ≥50% or ≥75% from baseline
  - MENQOL consists of 29 items (symptoms) grouped in 4 domains (vasomotor, psychosocial, physical, and sexual)
    - Symptoms were rated using a 7-item Likert scale ranging from “Not at all bothered” to “Extremely bothered”
- Subgroup analysis of efficacy was performed by demographics including race

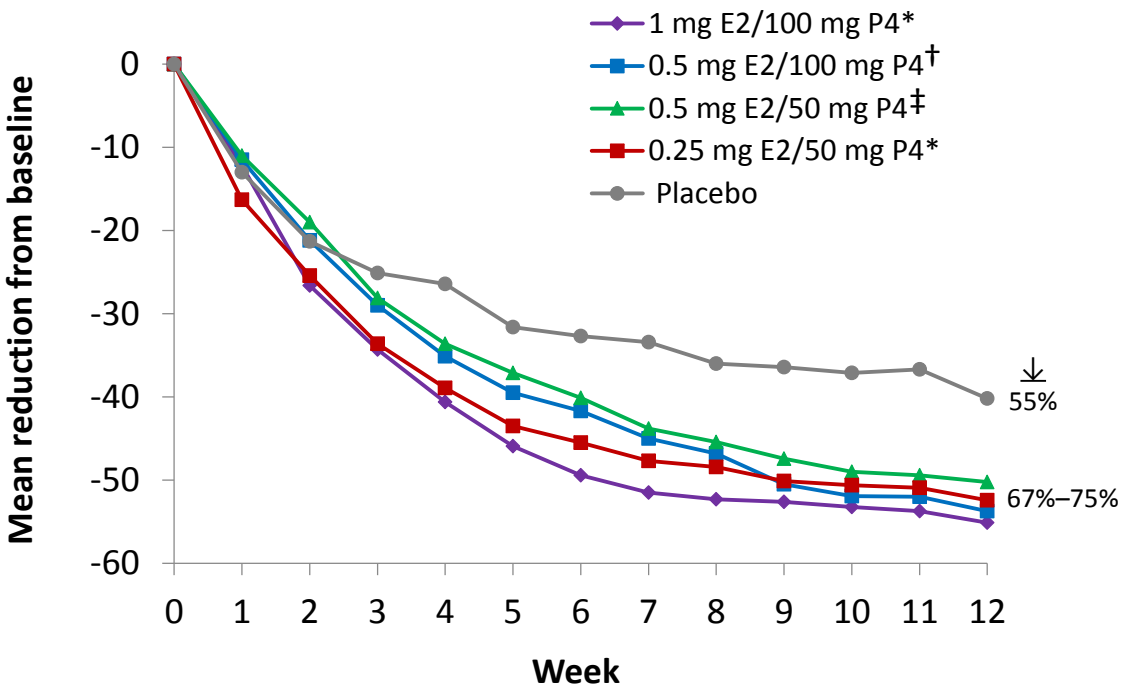
Study Demographics by Race

- Mean age was similar
- More African-American vs White women
  - Had BMI ≥30 kg/m^2
  - Were current smokers
- Higher percentage of African Americans were in REPLENISH than in US female population aged 45-64 years[1]
  - 31% vs 12%
  - Higher than other VMS clinical trials[2-4]

		White	African American
N (%)		486 (67)	225 (31)
Age, y	Mean (SD) Range	54.9 (4.4) 41–65	54.1 (4.3) 40–65
BMI, kg/m^2	Mean (SD) Range	26.1 (4.0) 14.0–34.2	27.9 (3.7) 18.0–34.5
BMI Category, %	<25 25 to <30 30+	41.4 39.9 18.7	23.1 44.4 32.4
Smoking, %	Never Former Current	56.2 24.9 18.9	44.0 21.8 34.2

1. U.S. Census Bureau, Current Population Survey, Annual Social and Economic Supplement, 2010. Table 1. Available at https://www.census.gov/data/tables/2010/demo/race/ppl-bc10.html. Accessed 09Feb2018. **2.** Santoro N, et al. *Menopause* 2017;24:238-246. **3.** Archer DF, et al. *J Womens Health* 2016;25:1102-1111. **4.** Archer DF, et al. *Menopause* 2012;19:622-629.

Reductions in Weekly VMS Frequency



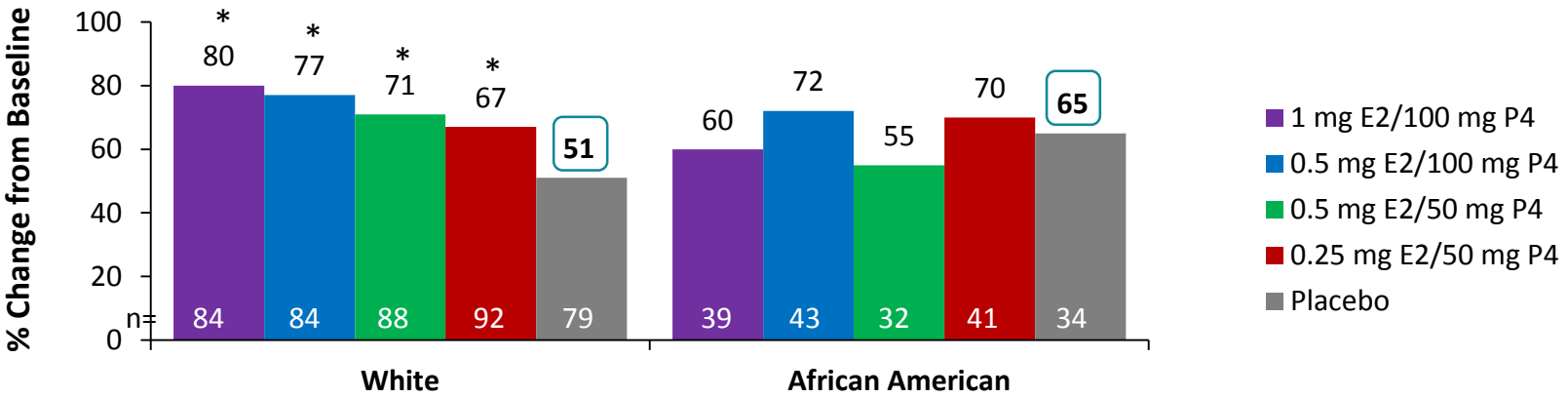
- Treatment with E2/P4 significantly reduced the frequency of VMS compared with placebo
- Women treated with placebo had a 55% reduction of VMS from baseline at 12 weeks

P<0.05 from *Weeks 3–12; †Weeks 4–12; ‡Weeks 6-12 vs placebo.

↓: Percent change from baseline at 12 weeks

Percent Change in Weekly VMS Frequency

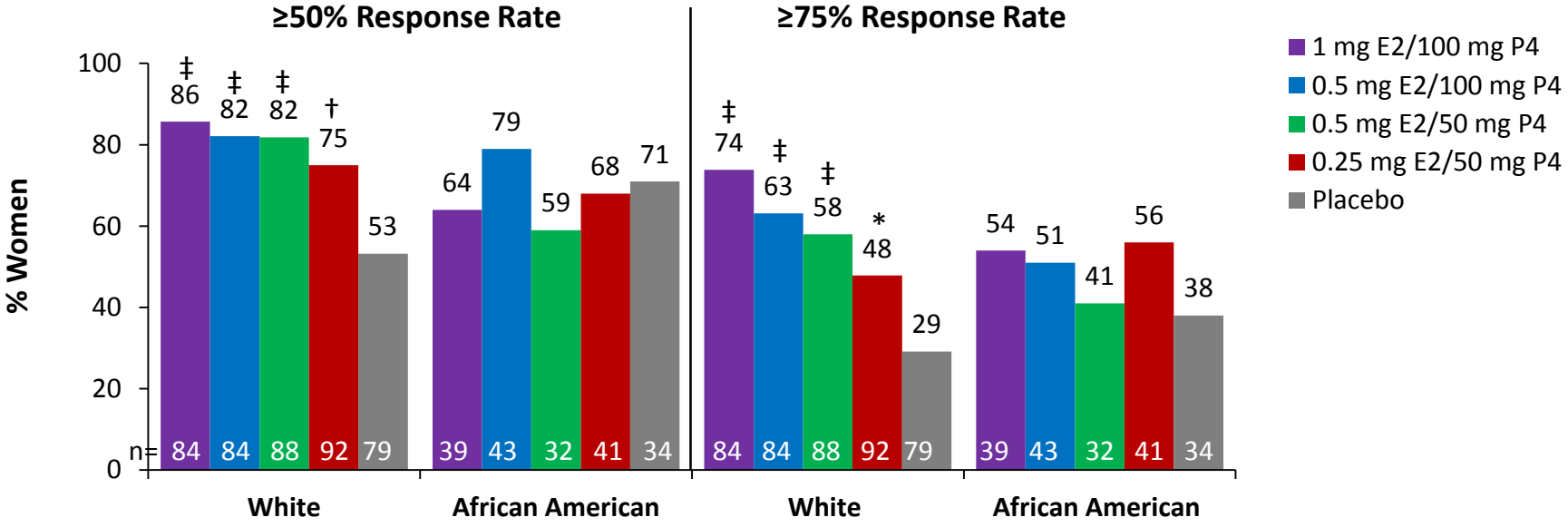
- VMS frequency improvements at 12 weeks were observed in significantly more White women treated with E2/P4 doses than with placebo
  - But not in African-American women, due to the high placebo response
- Placebo response rate was significantly different between White and African-American women (*P*=0.049)



**P*<0.001 vs placebo.

Response Rate at 12 Weeks

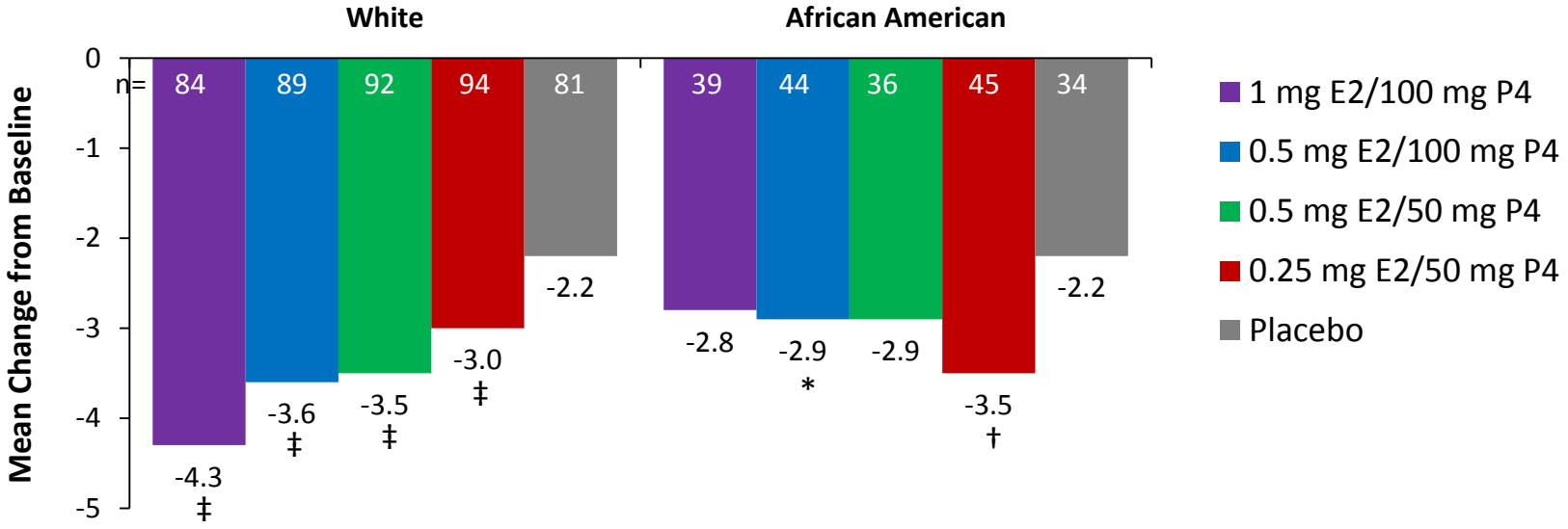
- Significant differences in responders were observed for all E2/P4 doses compared with placebo in White women but not African-American women



*P<0.05; †P<0.01; ‡P<0.001 vs placebo.
Responders were women with a change in VMS frequency of ≥50% and ≥75% from baseline.

MENQOL Vasomotor Domain Score by Race

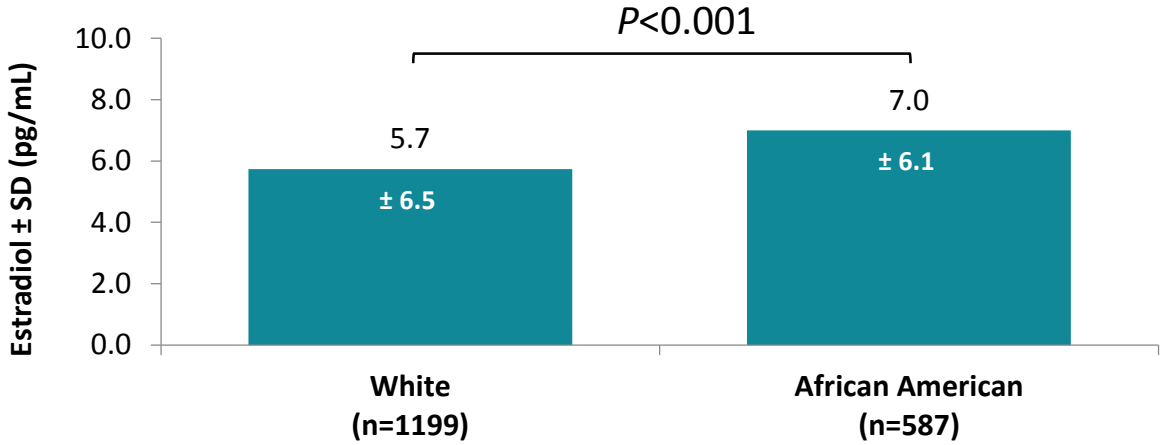
- Significant differences in MENQOL vasomotor domain at 12 weeks were observed for E2/P4 doses vs placebo in White women but not for all doses in African-American women



*P<0.05; †P<0.01; ‡P<0.001 vs placebo.

Baseline Estradiol Levels by Race

- Baseline serum estradiol levels* were significantly higher in African-American women than White women

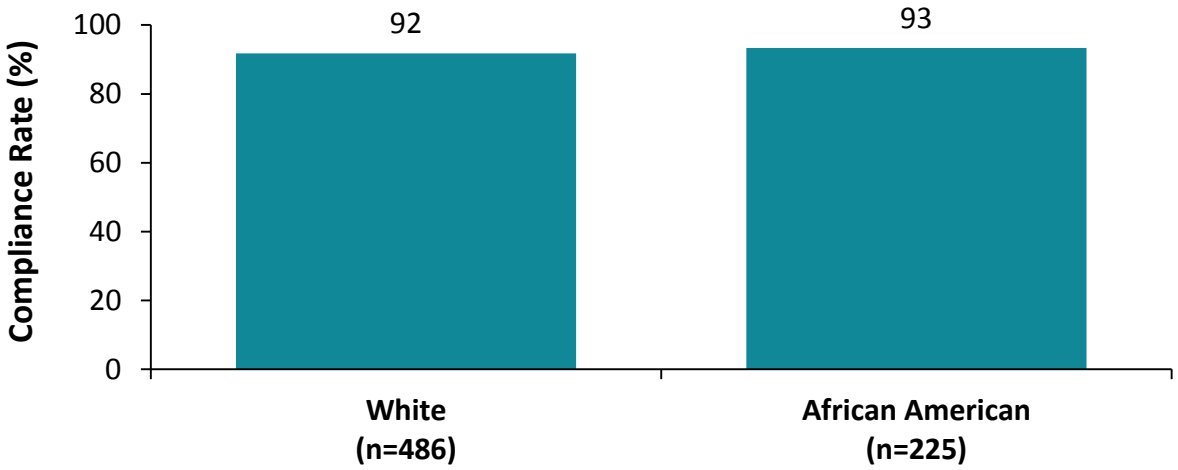


- Baseline weekly VMS frequencies were similar between White and African-American women (74 vs 75)

*In total study population.
SD: standard deviation.

Compliance Rates by Race

- Self-report of compliance rates at week 12 were similar between White and African-American women



Compliance was defined as the number of capsules taken between Study Day 1 and 84 (364) divided by the number of capsules expected 168 (728) for the respective treatment period, regardless of whether subject completed or discontinued study.

Conclusions

- Large placebo responses for frequency of VMS were more commonly observed in African-American women in the REPLENISH trial
- Significant differences in responder rates and the MENQOL vasomotor domain were observed for all E2/P4 doses vs placebo in White women but not in African-American women
  - Likely due to the high placebo response
  - Improvement was lower in African-American women
  - Significant differences in baseline serum estradiol levels but not compliance rates at 12 weeks
- Understanding factors that contribute to placebo responses is important in designing and assessing the efficacy of medications in clinical trials