Nonsmokers May Benefit from Lower Doses of an Oral 17β-Estradiol/Progesterone Capsule – Data from the REPLENISH Trial

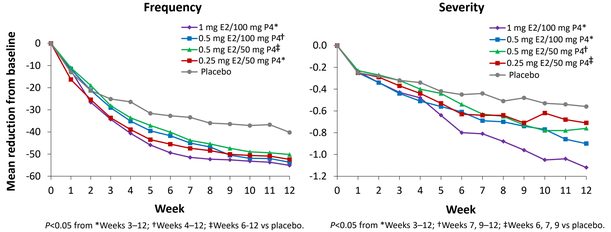
Ginger Constantine, MD[1]; Nanette Santoro, MD[2]; Shelli Graham, PhD[3]; Brian Bernick, MD[3]; Sebastian Mirkin, MD[3]

[1]EndoRheum Consultants, LLC, Malvern, PA; [2]Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Aurora, CO; [3]TherapeuticsMD, Boca Raton, FL

Introduction

- Smoking has been reported to alter exogenous estradiol metabolism[1-3] and reduce the effectiveness of hormone therapy (HT) in postmenopausal women[2,3]
  - Differences in smoking rates among clinical trial populations may also contribute to differences in effects of HT observed across the trials[2]
- The REPLENISH trial (NCT01942668) was a 12-month, phase 3, randomized, placebo-controlled trial that evaluated 4 doses of TX-001HR (17β-estradiol and progesterone [E2/P4]) for the treatment of menopausal, moderate to severe vasomotor symptoms (VMS) in women with a uterus; detailed results are published in Lobo et al (2018)[4]
  - The 1 mg E2/100 mg P4 dose was approved by the FDA as Bijuva® (TherapeuticsMD, Boca Raton, FL) in October 2018
  - Statistically significant improvements in the frequency and severity of moderate to severe VMS were observed with the two highest doses of E2/P4 evaluated (1/100 and 0.5/100) (**Figure 1**)[4]
  - 0.5 mg of E2 was the lowest oral dose that showed efficacy (reductions in frequency and severity) for VMS treatment
- The high percentage of smokers in this trial (24%) allowed for an analysis of the impact of smoking on estrogen levels and E2/P4 efficacy

Figure 1. Weekly improvement in frequency and severity of moderate to severe hot flushes[4]



P<0.05 from *Weeks 3–12; †Weeks 4–12; ‡Weeks 6-12 vs placebo. *P*<0.05 from *Weeks 3–12; †Weeks 7, 9–12; ‡Weeks 6, 7, 9 vs placebo.

Objective

To determine the impact of smoking on E2/P4 treatment efficacy and systemic hormone levels in the REPLENISH trial

Methods

REPLENISH Study Design

- Women with moderate to severe hot flushes (≥7/day or ≥50/week) were included in a VMS substudy and were randomized 1:1:1:1:1 to daily E2/P4 (mg/mg) of 1/100, 0.5/100, 0.5/50, or 0.25/50, or placebo for 12 months; women with less severe VMS were randomized 1:1:1:1 to the active E2/P4 doses only[4]
- Eligible women were between the ages of 40 and 65 years, postmenopausal, and seeking treatment or relief for VMS associated with menopause[4]
  - Women who reported smoking ≥15 cigarettes per day or any electronic cigarettes were to be excluded
- Women completed a daily VMS diary by recording number and severity of hot flushes up to week 12
- The safety population included those who took ≥1 capsule of study treatment
- The modified intent-to-treat (MITT)-VMS population (primary efficacy population) included women in the VMS substudy who took ≥1 dose of study treatment, had ≥5 days of baseline VMS diary data, and had ≥4 days of VMS diary data for one on-treatment week
- Current smokers were defined as those reporting smoking <15 cigarettes/day; nonsmokers were never or past smokers

Efficacy Measurements

- Mean change from baseline for VMS frequency and severity and ≥50% and ≥75% reductions in VMS frequency (responder analysis) were calculated at weeks 4 and 12 for E2/P4 vs placebo and analyzed by smoking status in the MITT-VMS population

Hormone Level Measurements

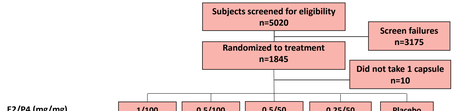
- Hormone levels were measured at baseline and 9-16 hours after treatment dose at weeks 4 and 12, and months 6, 9, and 12
- Estradiol and estrone concentrations were measured using validated gas chromatography-tandem mass spectroscopy (GC-MS/MS) assays
- Median estradiol and estrone levels of nonsmokers were compared with smokers in the safety population using a two-sample median test

Results

Study Disposition and Demographics

- A total of 1845 women were randomized; 1835 were in the safety population; 1275 completed 52 treatment weeks (**Figure 2**)
- Of the 726 in the MITT-VMS population, 647 (89%) completed the 12-week efficacy VMS substudy
  - Overall, 24% of women (174/726) were current smokers in the MITT-VMS population
  - The 0.5/100 group had the highest proportion of smokers (26.2%)

Figure 2. Patient disposition in the REPLENISH trial



E2/P4 (mg/mg)	1/100	0.5/100	0.5/50	0.25/50	Placebo
Population, n (%)					
Safety	415	424	421	424	151
Completed at 52 weeks	284 (68.4)	305 (71.9)	312 (74.1)	281 (66.3)	93 (61.6)
Smokers	90 (21.7)	111 (26.2)	90 (21.4)	101 (23.8)	39 (25.8)
MITT-VMS	141	149	147	154	135
Completed at 12 weeks	125 (88.7)	135 (90.6)	130 (88.4)	139 (90.3)	118 (87.4)
Smokers	28 (19.9)	39 (26.2)	34 (23.1)	39 (25.3)	34 (25.2)

Effects of Smoking in VMS Frequency and Severity

- All E2/P4 doses significantly reduced the weekly frequency and severity of moderate to severe VMS in nonsmokers from baseline to weeks 4 and 12 versus placebo, except for 0.5/50 at week 4 for severity (**Figure 3**)
- Smokers in any of the E2/P4 groups did not have significant improvements in their weekly frequency or severity compared with smokers in the placebo group at any timepoints (**Figure 3**)
- Significantly more nonsmokers had ≥50% and ≥75% reductions in VMS frequency with E2/P4 vs placebo at week 4 (except 0.5/50 at ≥75% level) and week 12 (**Figure 4**)
  - Proportions of smokers who responded to treatment were not different from placebo

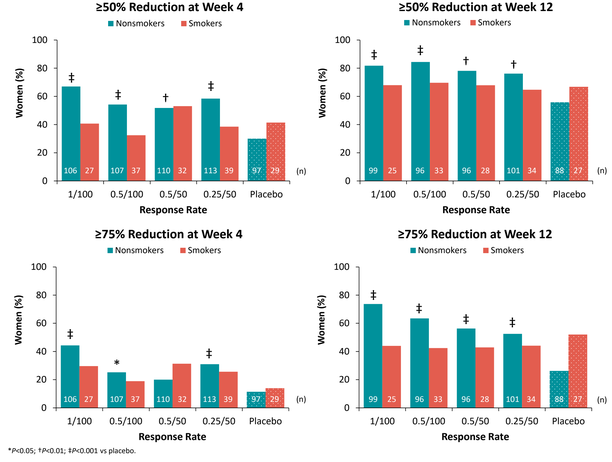
Effects of Smoking on Estradiol and Estrone Levels

- Median estradiol (range, 3.8–4.7 pg/mL) and estrone (range, 19.5–22.3 pg/mL) levels at baseline were similar between current smokers and nonsmokers in any group
- Significant differences between smokers and nonsmokers were observed at all timepoints for estradiol (**Figure 5**) levels with E2/P4 doses but not with placebo (data not shown)
  - Similar results were observed for estrone levels (data not shown)
  - Smokers versus nonsmokers treated with E2/P4 had reductions of 22%–38% in median estradiol levels and of 25%–42% in median estrone levels at week 12

Figure 3. Mean change from baseline in weekly VMS frequency and severity at weeks 4 and 12

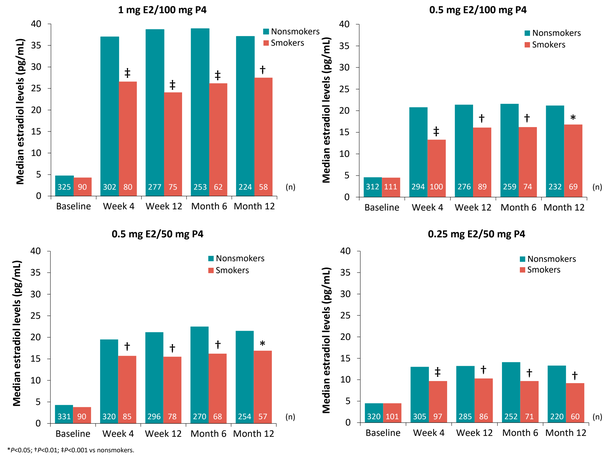
*P<0.05; †P<0.01; ‡P<0.001 vs placebo.

Figure 4. Responder analysis: ≥50% and ≥75% reductions in VMS frequency at weeks 4 and 12



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

Figure 5. Median Estradiol levels by E2/P4 in nonsmokers versus smokers



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

Conclusions

- Results from this large randomized, placebo-controlled trial demonstrated a significant impact of current smoking on efficacy and estradiol and estrone concentrations
  - Efficacy in reducing the frequency and severity of VMS was greater in nonsmokers than smokers compared with placebo
  - Response to treatment was greater in nonsmokers than smokers compared with placebo
  - A greater placebo response was observed in smokers than in nonsmokers
  - Estradiol and estrone were significantly reduced in smokers versus nonsmokers
- The effect of smoking (<15 cigarettes/day) was notable in this trial given
  - The large percentage of smokers (24%) compared with the smoking rate of the general population
  - Low doses, as were tested in REPLENISH, provide less estrogen substrate for hepatic metabolism, most likely leading to lower systemic concentrations of estrogen
- Nonsmokers desiring treatment of menopausal, moderate to severe VMS may benefit from lower E2 doses than smokers

References

1. Jensen J, et al. *N Engl J Med*. 1985;313:973-975. **2.** Tansavatdi K, et al. *Minerva Ginecologica*. 2004;56:105-114. **3.** Ruan X, et al. *Climacteric*. 2015;18:38-46. **4.** Lobo RA, et al. *Obstet Gynecol*. 2018;132:161-170.

Disclosures

- GC consults to multiple pharmaceutical companies including but not limited to TherapeuticsMD and has stock options from TherapeuticsMD. NS has served on the advisory board for Astellas/Ogeda and Menogenix with stock option in Menogenix. SG, BB, and SM are employees of TherapeuticsMD with stock/stock options. BB is also a Board member of TherapeuticsMD.
- TherapeuticsMD sponsored the study and supported the medical writing assistance provided by Dominique Verlaan, PhD (Precise Publications, LLC).

2019 Annual Meeting of the North American Menopause Society • September 25-28 • Chicago, IL