Incidence of Abnormal Mammograms with Oral, Combined 17β-Estradiol and Progesterone Capsules

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Introduction

- Hormone therapy (HT) containing synthetic progestogen has been associated with an increased incidence of abnormal mammograms and breast cancer[1-3]
- In the Women's Health Initiative (WHI), the percentage of women with abnormal mammograms was significantly greater among women taking conjugated equine estrogens plus medroxyprogesterone acetate for 1 year than among women taking placebo (9.4% vs 5.4%, $P<0.001$)[1]
- Abnormal mammograms are associated with additional breast procedures (e.g. biopsies, additional mammograms) and women's anxiety[4,5]
- The REPLENISH study (NCT01942668) is a 12-month, phase 3, randomized, double-blind, placebo-controlled, multicenter trial evaluating TX-001HR (TherapeuticsMD, Boca Raton, FL) for the treatment of menopausal, moderate-to-severe vasomotor symptoms (VMS) in women with a uterus[6]
  - TX-001HR is an investigational combination of 17β-estradiol (E2) plus progesterone (P4) in a single, oral softgel capsule
  - To date, no HT formulation combining natural E2 and P4 has been approved by any regulatory agency

Objective

- To determine the proportion of women with abnormal mammograms after taking TX-001HR versus placebo for 1 year in the REPLENISH study

Methods

- REPLENISH was a phase 3, randomized, double-blind, placebo-controlled, multicenter trial
- Healthy menopausal women were randomized to a daily dose of TX-001HR: 1.0 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; or placebo
- Mammograms were
  - Performed at screening or within 6 months prior to the first dose and at study end (year 1 or early termination)
  - Read locally
  - Assessed using the universal classification system, Breast Imaging and Reporting and Database System (BI-RADS; **Table 1**)[7]
- Women had to have a BI-RADS of 1 or 2 to be enrolled; BI-RADS 0 (incomplete) was not acceptable
- Abnormal mammograms were considered BI-RADS scores of 3 (short-term interval follow up suggested) or 4 (suspicious abnormality)
- The proportion of women in each BI-RADS score category was determined at screening and at the end of the study

Results

- 1835 women took one study dose (safety population); 1831 mammograms were analyzed at screening and 1340 at study end (**Table 2**)
- At screening, 1821 (99.5%) women had a normal mammogram (BI-RADS 1 or 2); 8 (0.4%) had BI-RADS 3 or 4; and 2 (0.1%) had BI-RADS 0 (**Table 2**)
- Two women were enrolled with a BI-RADS score of 0, 6 with a score of 3, and 2 with a score of 4 at screening
  - For the BI-RADS 0 scores, 1 woman's mammogram was considered normal by the investigator at screening, and later was normal at study end (BI-RADS 2; benign); the other woman was lost to follow up
  - Two women had a BI-RADS score of 4 at screening, but were included since no evidence of malignancy was observed prior to randomization. One woman discontinued treatment due to uterine fibroids, while the other had subsequent normal (BI-RADS 2) mammograms (1 unscheduled at ~4 months from randomization and another at study end)
- After 1 year of TX-001HR /placebo use, 1292 (96.4%) had normal mammograms and 39 (2.9%) had final abnormal mammograms (**Table 2**)
- Similar rates of abnormal mammograms (BI-RADS 3 and 4) were observed between all TX-001HR doses and placebo (**Figure 1**)
- A total of 6 women who took TX-001HR had breast cancer (incidence 6/1684 = 0.36%: 2 [0.5%] with 1.0 mg/100 mg, 2 [0.5%] with 0.5 mg/100 mg, 1 [0.2%] with 0.5 mg/50 mg, 1 [0.2%] with 0.25 mg/50 mg, and 0% with placebo)
- Five of the 12 women with a BI-RADS score of 4 at study end were diagnosed with breast cancer. The remaining 7 women underwent additional evaluation with no malignancy found

Table 1. BI-RADS Score Description and Management Recommendations[4]

BI-RADS Score	Description	Management Recommendations
0	Incomplete	May require additional imaging
1	Negative	Routine screening recommended
2	Benign	Routine screening recommended
3	Probably benign	Short-term (6-month) follow up or continued surveillance
4	Suspicious for malignancy	Tissue diagnosis
5	Highly suggestive of malignancy	Tissue diagnosis
6	Known biopsy-proven malignancy	Surgical excision when clinically appropriate

BI-RADS, Breast Imaging and Reporting and Database System

Figure 1. Incidence of Abnormal Mammograms at Study End

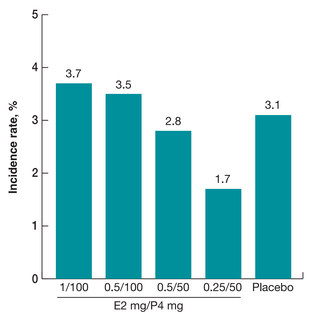

Table 2. BI-RADS Classification of Mammograms at Screening and at Study End

Parameter	Estradiol / Progesterone				Placebo
	1 mg / 100 mg	0.5 mg / 100 mg	0.5 mg / 50 mg	0.25 mg / 50 mg	
Randomized	415	424	421	424	151
Screening, n	415	422	421	422	151
BI-RADS, n (%)					
0	0	0	1 (0.2)	1 (0.2)	0
1	193 (46.5)	214 (50.7)	202 (48.0)	213 (50.5)	66 (43.7)
2	221 (53.3)	208 (49.3)	215 (51.1)	205 (48.6)	84 (55.6)
3/4 (abnormal)	1 (0.2)	0	3 (0.7)	3 (0.7)	1 (0.7)
Study End, n	300	314	325	303	98
BI-RADS, n (%)					
0	2 (0.7)	2 (0.6)	1 (0.3)	4 (1.3)	0
1	129 (43.0)	149 (47.5)	151 (46.5)	152 (50.2)	51 (52.0)
2	158 (52.7)	152 (48.4)	164 (50.5)	142 (46.9)	44 (44.9)
3/4 (abnormal)	11 (3.7)	11 (3.5)	9 (2.8)	5 (1.7)	3 (3.1)

Conclusions

- A low incidence of abnormal mammograms was observed among menopausal women taking any dose of the novel, oral, E2/P4 combination (TX-001HR) in the REPLENISH study, which is consistent with: 1) that of placebo reported here; 2) that of placebo reported in WHI (5.4%);[1] and 3) the incidence of abnormal results in screening mammograms in the US (5%-6%)[8]
  - This is in contrast to an increased incidence of abnormal mammograms with HT containing synthetic progestogen[1]
- In addition, the breast cancer incidence reported here with TX-001HR (0.36%) is consistent with that of the Surveillance, Epidemiology, and End Results (SEER) data (0.29%) for women 40 to 64 years of age[9]
- TX-0001HR, if approved, may offer an alternative VMS treatment option to the unregulated and unapproved compounded HT used by millions of postmenopausal women

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Disclosures

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