Efficacy and Safety of Estetrol (E4), a Promising New Treatment for Menopausal Vasomotor Symptoms: Results of a randomized, double-blind, placebo-controlled Phase 3 trial

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Disclosures

- Member of Mithra Advisory Board and Pharmavite Advisory Board
- This clinical study was sponsored by Estetra SRL, an affiliate company of Mithra Pharmaceuticals
Estetrol (E4)

- Native estrogen produced by the human fetal liver\(^1,\)\(^2\)
- Tissue-selective with unique mode of action\(^3-^5\)
  - Limited activity on membrane ER\(\alpha\) in several tissues incl. breast\(^6\)
  - Antagonistic to E2 on the breast\(^7\)
  - Not considered as a SERM\(^8,^9\)

Unique pharmacokinetic and metabolic profile

- No specific binding to SHBG\(^\text{10}\)
- Not metabolized to E3, E2 or E1\(^\text{11}\)
- CYP enzymes do not play a major role\(^\text{12}\)
- Low risk for drug-drug interactions\(^\text{13,14}\)
- Limited impact on the liver incl. triglycerides, SHBG, angiotensinogen and hemostasis markers\(^\text{15-17}\)

Combined with drospirenone, E4 15 mg is recently marketed as an oral contraceptive

Phase 2 Clinical data showed that E4 is effective in alleviating vasomotor symptoms (VMS), genitourinary symptoms, and quality of life, with a favorable safety profile in postmenopausal women\(^1-3\).

Phase 3 Clinical Program with 2,300 postmenopausal women includes 2 pivotal trials:
- E4Comfort I: 14 countries in Europe, Latin America and North America (US/Canada)
- E4Comfort II: North America (US/Canada)

Here, we present top line efficacy results from the E4Comfort I trial on the use of E4 for treatment of moderate to severe VMS in postmenopausal women.
Primary objective
Evaluate efficacy and safety of E4 15 and 20 mg for the treatment of moderate to severe VMS in postmenopausal women

Co-primary endpoints
- Mean change from baseline vs placebo for moderate to severe VMS frequency and severity at week 4 and 12 (based on daily diary reports)

Secondary endpoints
- VMS frequency responder analysis
- Safety assessed up to 12 weeks of treatment with E4 alone or placebo

E4Comfort I: Randomized, double-blind, placebo-controlled, multicenter Phase 3 trial

Washout/Screening
E4 15 mg (n=213; 51.6% H)
E4 20 mg (n=213; 51.6% H)
Placebo (n=214; 51.4% H)
P4 (NH only)

Visit 1 (baseline) Visit 2 (wk 5) Visit 3 (wk 9) Visit 4 (wk 13; EoT) Visit 5 (wk 15/16)
Up to 12 weeks 3 months 2 wks

EoT: end of treatment | H: hysterectomized | NH: non-hysterectomized | P4: progesterone
**Main inclusion criteria**
- Hysterectomized (H) or non-hysterectomized* (NH) postmenopausal women
- Aged 40-65 years
- BMI 18.0-38.0 kg/m²
- ≥7 moderate to severe hot flushes daily or ≥50 in the week before randomization

*For NH subjects: uterus with bi-layer endometrial thickness ≤4 mm on TVUS

**Main exclusion criteria**
- History of malignancy, thromboembolism or coagulopathy, diabetes with poor glycemic control, and breast cancer
- NH women: history or presence of uterine cancer, endometrial hyperplasia, polyp or abnormal cervical smear
- SBP >130 mmHg, DBP >80 mmHg
E4Comfort I: Randomized, double-blind, placebo-controlled, multicenter Phase 3 trial

Randomized to treatment N=641

ITT population N=640

E4 15 mg
N=213
77.9% completers

E4 20 mg
N=213
77.0% completers

Placebo
N=214
81.3% completers

Total population (N=640)

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>53.9 (4.9)</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>27.5 (4.4)</td>
</tr>
<tr>
<td>Hysterectomized, n (%)</td>
<td>330 (51.6)</td>
</tr>
</tbody>
</table>

BMI: body mass index | ITT: intention-to-treat | N: total number of subjects | n: number of hysterectomized subjects
E4 significantly decreased the frequency of moderate to severe VMS

Statistical analysis via Mixed Model for Repeated Measures on change from Baseline to Week 4 and Week 12 for weekly Frequency of moderate to severe VMS; intent-to-treat (ITT) population; p-values between E4 treatments and placebo on the change from Baseline versus placebo (difference of LS means)
Significantly more women had ≥50% or ≥75% reduction in VMS frequency with E4 than placebo

Proportion of subjects with 50% or 75% reduction from baseline in the weekly frequency of moderate to severe VMS over time; Efficacy Study Part- Intent-to-treat (ITT) population; * : p-value < 0.05; ** : p-value < 0.01 ; *** : p-value < 0.001; **** : p-value < 0.0001 compared to placebo
E4 significantly decreased the severity of moderate to severe VMS

Statistical analysis via Mixed Model for Repeated Measures on change from Baseline to Week 4 and Week 12 for weekly Severity of moderate to severe VMS by FDA method; intent-to-treat (ITT) population; p-values between E4 treatments and placebo on the change from Baseline versus placebo (difference of LS means)
Both E4 dosages (15 and 20 mg) demonstrated a statistically significant difference compared to placebo on the VMS frequency and severity at weeks 4 and 12, with a more pronounced effect at week 12.

Significantly more women had ≥50% or ≥75% reduction in their moderate-to-severe VMS frequency with E4 15 mg or E4 20 mg than with placebo.

Observed placebo response is in line with previously reported placebo effects in HRT trials.¹
## Drug-related Treatment Emergent Adverse Events

(Reported in ≥2% of total population)

<table>
<thead>
<tr>
<th>TEAEs</th>
<th>E4 15 mg (N=213)</th>
<th>E4 20 mg (N=213)</th>
<th>Placebo (N=214)</th>
<th>Total (N=640)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Headache, n (%)</strong></td>
<td>14 (6.6)</td>
<td>10 (4.7)</td>
<td>12 (5.6)</td>
<td>36 (5.6)</td>
</tr>
<tr>
<td><strong>Breast pain, n (%)</strong></td>
<td>17 (8.0)</td>
<td>23 (10.8)</td>
<td>2 (0.9)</td>
<td>42 (6.6)</td>
</tr>
<tr>
<td><strong>Breast tenderness, n (%)</strong></td>
<td>9 (4.2)</td>
<td>12 (5.6)</td>
<td>0</td>
<td>21 (3.3)</td>
</tr>
<tr>
<td><strong>Nipple pain, n (%)</strong></td>
<td>5 (2.3)</td>
<td>8 (3.8)</td>
<td>1 (0.5)</td>
<td>14 (2.2)</td>
</tr>
<tr>
<td><strong>Nausea, n (%)</strong></td>
<td>5 (2.3)</td>
<td>8 (3.8)</td>
<td>1 (0.5)</td>
<td>14 (2.2)</td>
</tr>
<tr>
<td><strong>Vaginal discharge, n (%)</strong></td>
<td>6 (2.8)</td>
<td>6 (2.8)</td>
<td>1 (0.5)</td>
<td>13 (2.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endometrium-related TEAEs in non-hysterectomized women only</th>
<th>E4 15 mg (N=103)</th>
<th>E4 20 mg (N=103)</th>
<th>Placebo (N=104)</th>
<th>Total (N=310)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em><em>Vaginal haemorrhage</em>, n (%)</em>*</td>
<td>49 (47.6)</td>
<td>61 (59.2)</td>
<td>11 (10.6)</td>
<td>121 (39.0)</td>
</tr>
<tr>
<td><strong>Endometrial disorder, n (%)</strong></td>
<td>46 (44.7)</td>
<td>42 (40.8)</td>
<td>4 (3.8)</td>
<td>92 (29.7)</td>
</tr>
<tr>
<td><strong>Endometrial thickening, n (%)</strong></td>
<td>9 (8.7)</td>
<td>13 (12.6)</td>
<td>0</td>
<td>22 (7.1)</td>
</tr>
<tr>
<td><strong>Endometrial hyperplasia, n (%)</strong></td>
<td>3 (2.9)</td>
<td>5 (4.9)</td>
<td>0</td>
<td>8 (2.6)</td>
</tr>
</tbody>
</table>

*Includes vaginal bleeding and spotting

N: total number of subjects | n: total number of subjects with event | TEAEs: treatment emergent adverse events
Most TEAEs occurred in the reproductive system and breast, and were mild or moderate in severity.

Majority of related SAEs included endometrial events of special interest (disordered proliferative endometrium (n=7 [1.1%]), hyperplasia without atypia (n=5 [0.8%])

Endometrial data up to 3 months confirmed the estrogenic profile of E4 on the endometrium and confirmed the need of progestin administration in NH women.

- Mean endometrial thickening returned to the level <4 mm after treatment with P4 200 mg for 2 weeks.

- No major CV or thrombotic events (VTE/MI/CVA/TIA) were reported. One TEAE of superficial thrombophlebitis occurred in placebo arm.
# Phase 3 program (E4Comfort trials)

<table>
<thead>
<tr>
<th>Study number</th>
<th>Primary study objectives</th>
<th>Population</th>
<th>E4 doses</th>
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<tr>
<td>E4Comfort I</td>
<td>• To assess the <strong>efficacy of E4 15 &amp; 20 mg vs placebo</strong> on VMS relief (12 weeks duration)</td>
<td>• 600 PM women for efficacy</td>
<td>E4 15 mg</td>
</tr>
<tr>
<td>EU/LATAM/US/Can</td>
<td>• To assess the <strong>endometrial impact of E4 20 mg + Progesterone 100 mg</strong> (1 year duration)</td>
<td>• 600 PM women for endometrial safety</td>
<td>E4 20 mg</td>
</tr>
<tr>
<td></td>
<td>• To evaluate the <strong>endometrial impact of E4 20 mg + Progesterone 100 mg</strong> (1 year duration)</td>
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<tr>
<td>E4Comfort II</td>
<td>• To assess the <strong>efficacy of E4 15 &amp; 20 mg vs placebo</strong> on VMS relief (12 weeks duration + 9 months FU)</td>
<td>• 600 PM women for efficacy</td>
<td>E4 15 mg</td>
</tr>
<tr>
<td>US/Can</td>
<td>• To assess the <strong>general and endometrial safety of 15 &amp; 20 mg E4</strong> (1 year duration)</td>
<td>• 400 PM women for safety</td>
<td>E4 20 mg</td>
</tr>
<tr>
<td></td>
<td>• To evaluate the <strong>general and endometrial safety of 15 &amp; 20 mg E4</strong> (1 year duration)</td>
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E4: Estetrol | FU: follow-up | PM: postmenopausal | VMS: vasomotor symptoms

NCT04209543 and NCT04090957
Conclusions

- E4 treatment is **effective** at decreasing vasomotor symptoms in postmenopausal women
- Current data suggests a **favorable safety profile** of E4

These data suggest that E4 will offer a **novel treatment option** for symptomatic postmenopausal women