Estetrol, the Next Generation of Hormone Therapy: Results of a Phase 2b Dose-finding Study in Postmenopausal Women (E4 Relief)

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Disclosures

• Mithra USA Advisory Board
• Did not participate in current clinical trials, but has assessed the analysed data
• Consultant: Mithra, AMAG, Pharmavite, Endoceutics
• Data presented are preliminary and not yet published in a peer reviewed journal
Currently used Estrogens are Aged Molecules

1929
Butenandt and Doisy discover the first estrogen (Estrone)

1930
Estriol

1936
Estradiol

1941
Conjugated Estrogens

1943
Ethinyloestradiol

No significant improvement for almost 80 years
Physiology of Estetrol (E4)

Estetrol (E4)

- Is produced by the fetal liver, crosses the placenta, is detected from the 9th week of gestation in maternal urine. Fetal plasma levels are 12 times higher than those of the mother.
- Circulates at high concentrations (up to 30 nM) in fetal plasma.
- Has a very long half-life (28–32 hours).
Estetrol (E4) is an estrogen with a distinctive profile of ERα activation.

E4 activates the nuclear ERα, but is an antagonist of the membrane ERα.

E4 is the first Natural Estrogen with Selective Action in Tissues (NEST).
Multicenter Dose-Finding, Randomized, Double-Blind, Placebo-Controlled Study to Select the Daily Oral Dose of E4 for the Treatment of Vasomotor Symptoms (VMS) in Post-Menopausal Women
**Disposition of Subjects**

- Clinical trial conducted in Europe (Belgium, UK, Ireland, Czech Republic and Poland)
- Mean age: $54.2 \pm 4.4$ years

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Placebo</th>
<th>2.5 mg</th>
<th>5 mg</th>
<th>10 mg</th>
<th>15 mg</th>
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<td>55</td>
<td>54</td>
<td>48</td>
<td>53</td>
<td>50</td>
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<tr>
<td><strong>Treated</strong></td>
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<td>55</td>
<td>53</td>
<td>47</td>
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<td><strong>Completers</strong></td>
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<td>11</td>
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Main Inclusion and Exclusion Criteria

- Written informed consent
- Postmenopausal women
- 40–65 years
- BMI 18–35 kg/m²
- ≥7 moderate to severe hot flushes per day, or ≥50 moderate to severe hot flushes in the week preceding randomization
- Not hysterectomized if transvaginal ultrasonography (TVUS) showed a bi-layer endometrial thickness ≤5 mm

- A history of malignancy, thromboembolism or coagulopathy, diabetes with poor glycemic control, and breast cancer
- Women with a uterus and history or presence of uterine cancer, endometrial hyperplasia, polyp or abnormal cervical smear
E4 15 mg reduced VMS frequency

Mean % of change from baseline

Weeks

E4 2.5 mg
E4 5 mg
E4 10 mg
E4 15 mg
Placebo

-90%
-80%
-70%
-60%
-50%
-40%
-30%
-20%
-10%
0%

-84%
-65%

p<0.05
E4 15 mg reduced VMS Severity

Mean change from baseline

Weeks

E4 2.5 mg
E4 5 mg
E4 10 mg
E4 15 mg
Placebo

Clinicaltrials.gov NCT0283431 | EudraCT 2015-004018-44

Data on file Mithra Pharmaceuticals
E4 15 mg reduced VMS frequency

≥50% response: p<0.01 vs placebo

≥75% response: p<0.001 vs placebo

Responders (%)
E4 increased the Vaginal Maturation Index

** p<0.001 vs placebo at Week 12

** p<0.001 vs placebo at Week 12

Clinicaltrials.gov NCT0283431 | EudraCT 2015-004018-44

Data on file Mithra Pharmaceuticals
E4 did not affect:

1. Any of the coagulation markers (prothrombin fragment 1 + 2, D-dimer, anti-thrombin, Protein-C, free Protein-S, Factor VIII, and free tissue factor pathway inhibitor).
2. The majority of the lipid and glucose metabolism parameters.

Treatment with E4 resulted in:

1. Small but potential beneficial changes in HDL-C and HbA1c values in the E4 10 mg and E4 15 mg groups.
2. Reduced CTX-1 and osteocalcin values, suggesting reduction in bone resorption.
3. A slight though significant increase in the baseline SHBG concentration in the E4 10 mg and E4 15 mg group, indicating that the E4 estrogenic effect was mild and dose dependent.
Safety

- No endometrial hyperplasia
- In 15 mg E4 group, the mean endometrial thickness increased from 2 to 6 mm and returned to baseline after progestin therapy
- Well tolerated
- No unexpected adverse events
Summary: Effects of E4

- All doses studied improved GSM/VVA
- 15 mg appears to be minimum effective dose for VMS
- The 15 mg E4 dose:
  - Positively influenced bone turnover
  - Did not increase triglyceride levels
  - Increased HDL-C
  - Improved glucose tolerance
  - Had no effects on coagulation parameters
- There were no apparent safety concerns, E4 was well tolerated
**E4 is the First NEST**

- **Native**
- **Estrogen with**
- **Selective Action in**

- Low risk of drug-drug interactions
- Low breast stimulation, pain, and low carcinogenic impact
- Low impact on triglyceride levels
- Neutral impact on markers of VTE risk

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Conclusion

- E4 is a promising natural estrogen for the treatment of postmenopausal women
- The selective tissue properties create a unique safety profile that should enhance the oral therapeutic utility of E4
Q&A
Backup
Low Risk of Drug-drug Interactions

**E4 does not interact with the CYP450 family**

*The risk of drug-drug interactions is low*

<table>
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<th>% inhibition of cytochrome P450 enzymes</th>
<th>CYP1A2</th>
<th>CYP2C9</th>
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<th>CYP2D6</th>
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<td>E4</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

*Visser M et al., Climacteric. 2008 1 (suppl 1):31-40*
Placebo Effects are expected in the Treatment of Hot Flushes

- In a meta-analysis of 85 menopause trials, significant differences were observed in placebo responses for hot flushes (Li 2017):
  - 5.8% – 71.8% at week 12 (n=8,302)
  - Age, BMI, number of HF at baseline, time since menopause, and route of administration were not related to a placebo response
  - Placebo response was higher in hormonal drug than non-hormonal drug trials
  - Placebo response increased over time and reached a plateau after week 12
- Variability depends on:
  - Type of disorder, severity of symptoms, heterogeneity of trial design, participant characteristics, subjective expectations of clinician and patient (Freeman 2015)
- In a phase 3 study of E4, factors that could lead to a higher than expected placebo effect should be controlled for