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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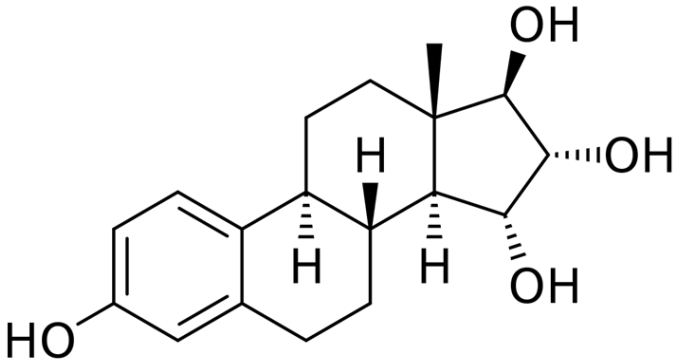
Disclosures

- 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 ERα in several tissues incl. breast[6]
  - Antagonistic to E2 on the breast[7]
  - Not considered as a SERM[8,9]



Estetrol (E4)

E2: estradiol |ER: estrogen receptor |
SERM: selective estrogen receptor modulator

[1]Hagen et al. Acta Endocrinol 1965 | [2]Heikkilä J. Steroid Biochem. 1971 | [3]Arnal et al. Physiol Rev 2017 | [4]Foidart et al. ISGE Series 2019 | [5]Abot et al. EMBO Mol Med 2014 | [6]Gérard et al. Expert Rev Clin Pharmacol 2022 | [7]Gérard et al. J Endocrinol 2015 | [8]Foidart et al. J Endocr Soc 2019 | [9]Douxfils et al. Thrombosis Research 2022

Estetrol (E4) - continued

- Unique pharmacokinetic and metabolic profile
  - No specific binding to SHBG[10]
  - Not metabolized to E3, E2 or E1[11]
  - CYP enzymes do not play a major role[12]
  - Low risk for drug-drug interactions[13,14] Poster Presentation M. Taziaux
  - Limited impact on the liver incl. triglycerides, SHBG, angiotensinogen and hemostasis markers[15-17]
- Combined with drospirenone, E4 15 mg is recently marketed as an oral contraceptive

E1: estrone | E2: estradiol | E3: estriol | SHBG: steroid hormone-binding globulin

[10]Hammond et al. Climacteric 2008 | [11]Coelingh Bennink et al. Climacteric 2008 | [12]Apter et al. ESC abstract book 2022| [13]Foidart et al. Menopause 2022 (in press)| [14]Visser et al. Climacteric 2008 | [15]Douxfils et al. Contraception 2021| [16]Klipping et al. Contraception 2021 | [17]Douxfils et al. Climacteric (under revision)

Estetrol (E4) in menopause

- 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

NCT04209543 and NCT04090957

[1]Gaspard et al. Menopause 2020 | [2]Gaspard et al. Menopause (under revision) | [3]Douxfils et al. Climacteric (under revision)

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

Primary objective

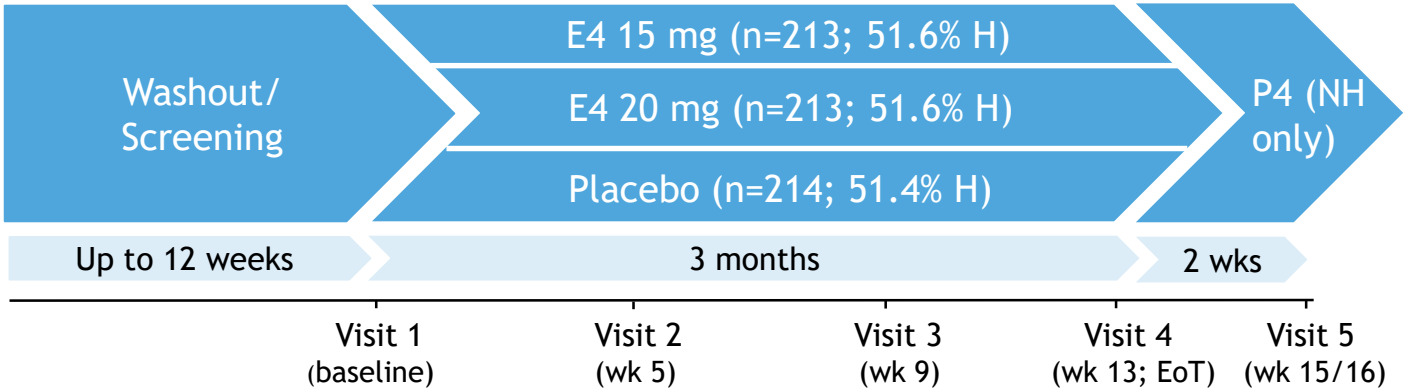
Evaluate efficacy and safety of E4 15 and 20 mg for the treatment of moderate to severe VMS in postmenopausal women

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



EoT: end of treatment | H: hysterectomized | NH: non-hysterectomized | P4: progesterone

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

Main **inclusion** criteria

- Hysterectomized (H) or non-hysterectomized* (NH) postmenopausal women
- Aged 40-65 years
- BMI 18.0-38.0 kg/m^2
- ≥7 moderate to severe hot flushes daily
  or
  ≥50 in the week before randomization

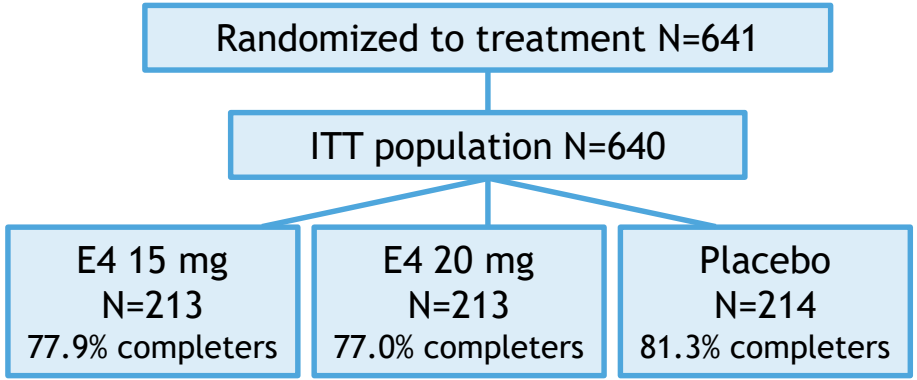
Main **exclusion** criteria

- 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

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

BMI: body mass index| DBP: diastolic blood pressure | H: hysterectomized | NH: non-hysterectomized | SBP: systolic blood pressure | TVUS: transvaginal ultrasound

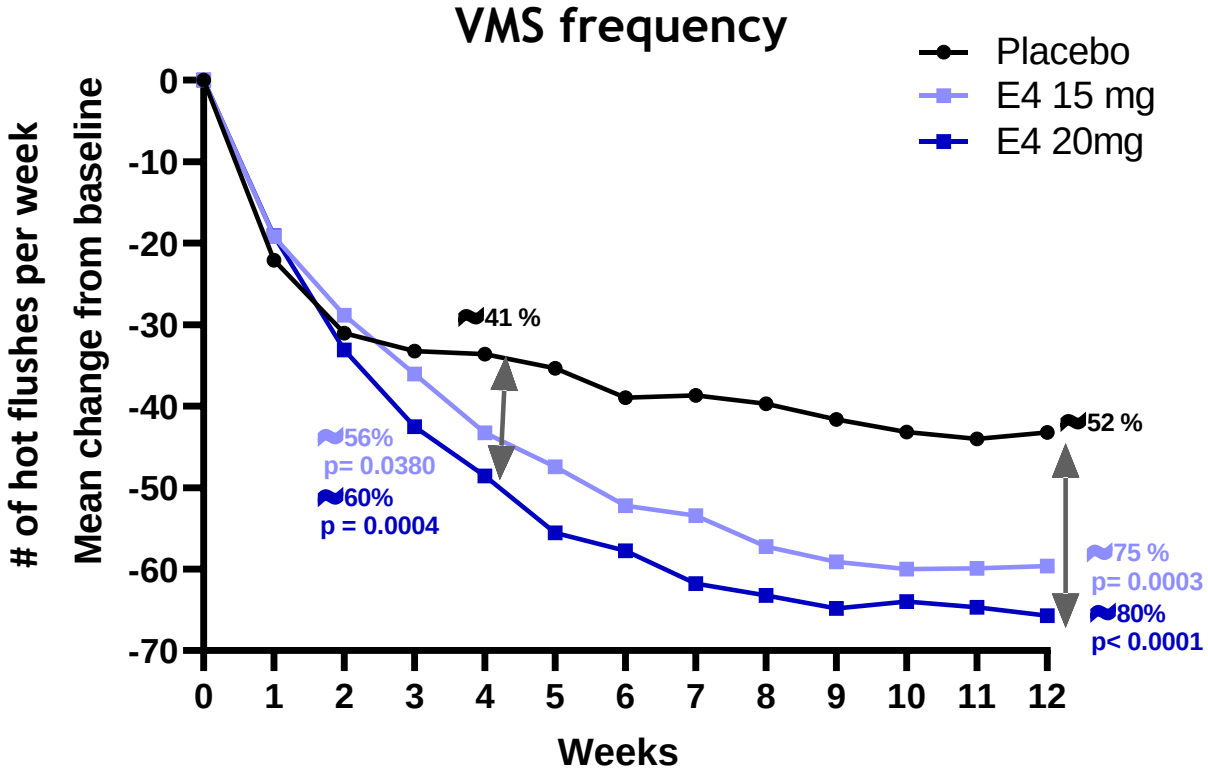
E4Comfort I: Randomized, double-blind, placebo-controlled, multicenter Phase 3 trial



	Total population (N=640)
Age, mean (SD), years	53.9 (4.9)
BMI, mean (SD), kg/m^2	27.5 (4.4)
Hysterectomized, n (%)	330 (51.6)

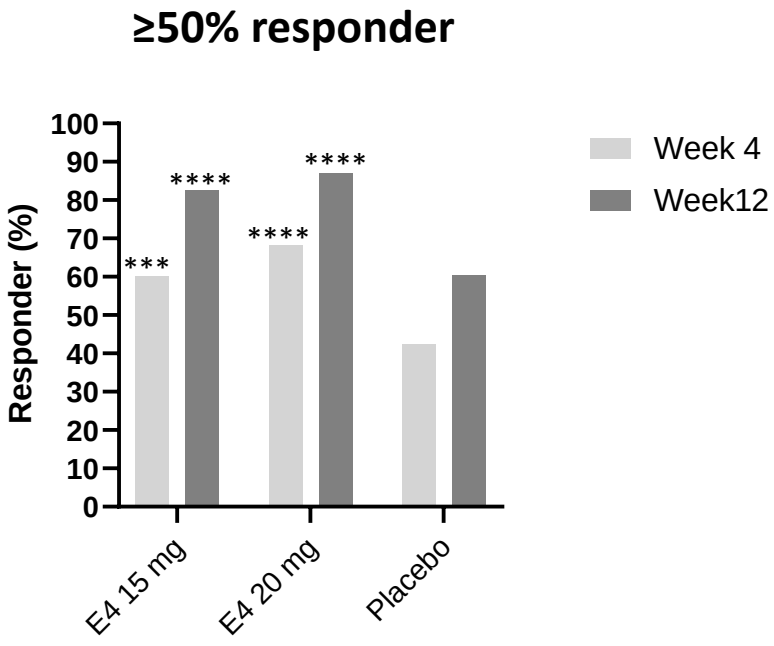
BMI: body mass index | ITT: intention-to-treat | N: total number of subjects | n: number of hysterectomized subjects

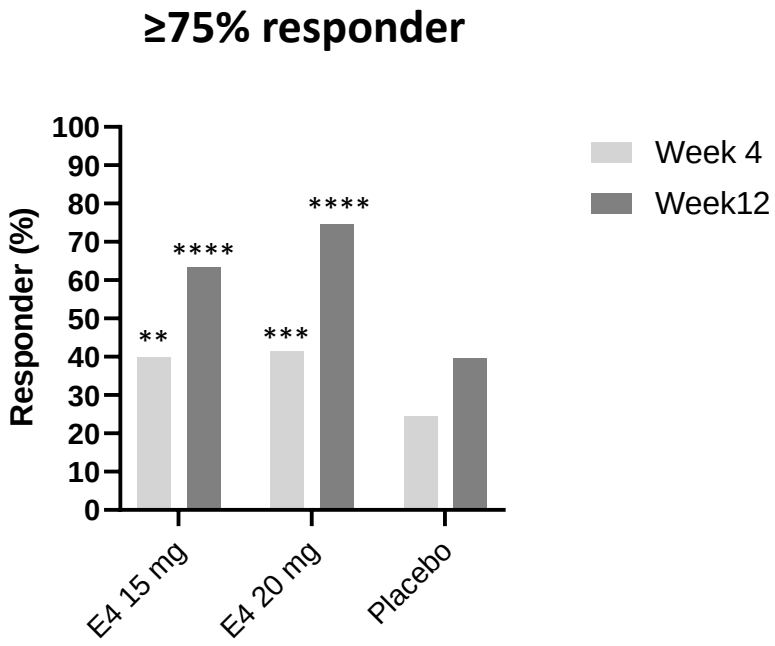
E4 significantly decreased the frequency of moderate to severe VMS



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)

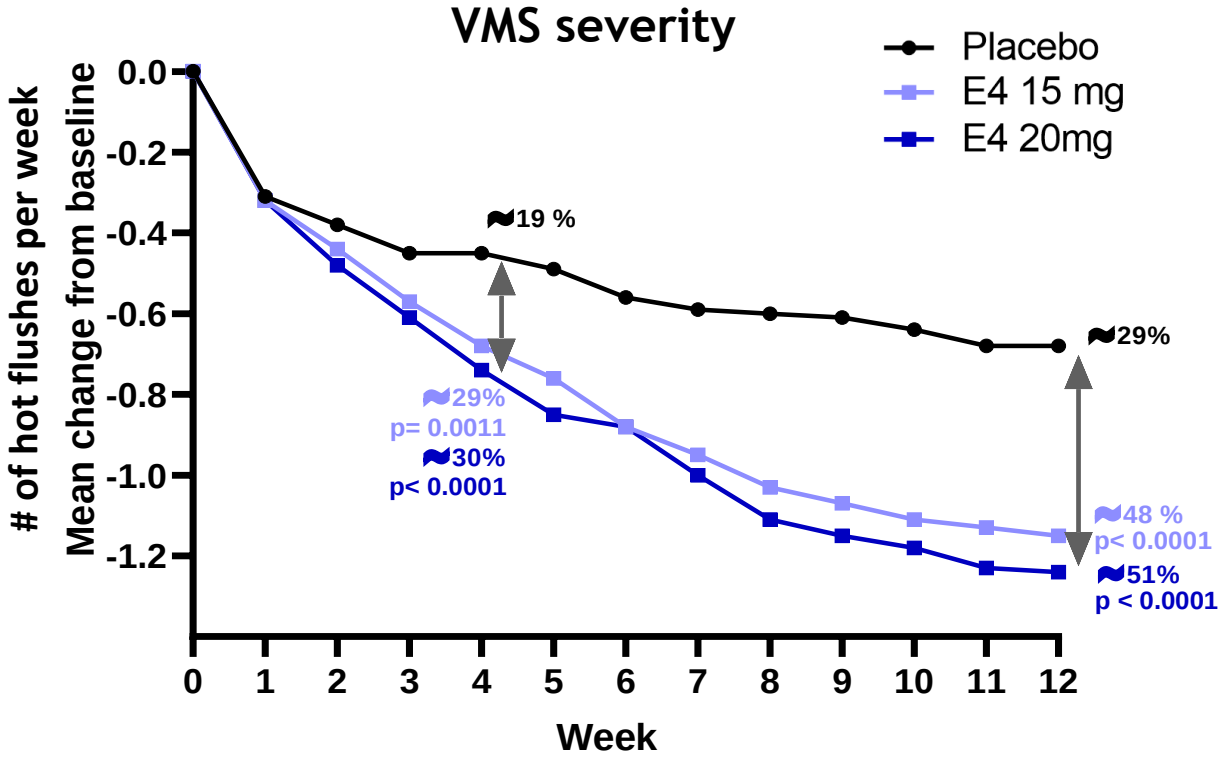
Significantly more women had ≥50% or ≥75% reduction in VMS frequency with E4 than placebo





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)

Summary of efficacy

- 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]

E4: estetrol | HRT: hormone replacement therapy | VMS: vasomotor symptoms

[1]MacLennan et al. The Cochrane Library 2009

Drug-related Treatment Emergent Adverse Events

(reported in ≥2% of total population)

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

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

*Includes vaginal bleeding and spotting

N: total number of subjects | n: total number of subjects with event | TEAEs: treatment emergent adverse events

Summary of safety

- 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

CV: cardiovascular | CVA: cerebral vascular accident | MI: myocardial infarction | NH: non-hysterectomized | P4: progesterone | SAEs: serious adverse events | TEAEs: treatment emergent adverse events | TIA: transient ischaemic attack | VTE: venous thromboembolism

Phase 3 program (E4Comfort trials)

Study number	Primary study objectives	Population	E4 doses
E4Comfort I EU/LATAM/US/Can	• To assess the **efficacy of E4 15 & 20 mg vs placebo** on **VMS** relief (12 weeks duration) • To evaluate the **endometrial impact of E4 20 mg + Progesterone 100 mg** (1 year duration)	• 600 PM women for efficacy • 600 PM women for endometrial safety	E4 15 mg E4 20 mg
E4Comfort II US/Can	• To assess the **efficacy of E4 15 & 20 mg vs placebo** on **VMS** relief (12 weeks duration + 9 months FU) • To evaluate the **general and endometrial safety of 15 & 20 mg E4** (1 year duration)	• 600 PM women for efficacy • 400 PM women for safety	E4 15 mg E4 20 mg

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

Q&A