Estetrol, the Next Generation of Hormone Therapy: Update on Clinical Development

Preliminary results of a Phase 2b dose-finding study in postmenopausal women (E4 Relief)

Rogerio A. Lobo[1], Maud Jost[2], Françoise Bruyère[2], Mélanie Taziaux[2], Lisa Walters[2], Ulysse Gaspard[3] and Jean-Michel Foidart[2,3], on behalf of the E4 Relief investigators

[1]Department of Obstetrics and Gynecology, Columbia University, New York, NY 10032, USA [2]Mithra Pharmaceuticals, 4000 Liège, Belgium [3]University of Liège, 4000 Liège, Belgium

Introduction

Estetrol (E4) is a Natural Estrogen with Selective action in Tissues (NEST). It acts as an estrogen agonist in bone, vagina, endometrium, brain, and cardiovascular system; with mixed agonist and antagonist estrogenic activity in the liver, and breast. In a preliminary study using E4 in postmenopausal women, 2 to 40 mg E4 once-daily improved vaginal cytology and vasomotor symptoms (VMS), and a dose-dependent estrogenic effect was observed on bone turnover markers, lipids and lipoproteins; with only a small effect on triglycerides and hemostatic variables.

Design and Primary Objectives

- E4 Relief was a prospective, multicenter, randomized, placebo-controlled, double-blinded, dose-finding study in both hysterectomized and non-hysterectomized postmenopausal women.
- The primary objective was to select the optimal effective oral dose of E4 for the treatment of VMS in post-menopausal women. Secondary objectives included the evaluation of safety, the effects of different doses of E4 on vulvar and vaginal atrophy (VVA; maturation index), bone biomarkers, and health-related quality of life.
- E4 Relief is registered with Clinicaltrials.gov NCT0283431.

Participants and Methods

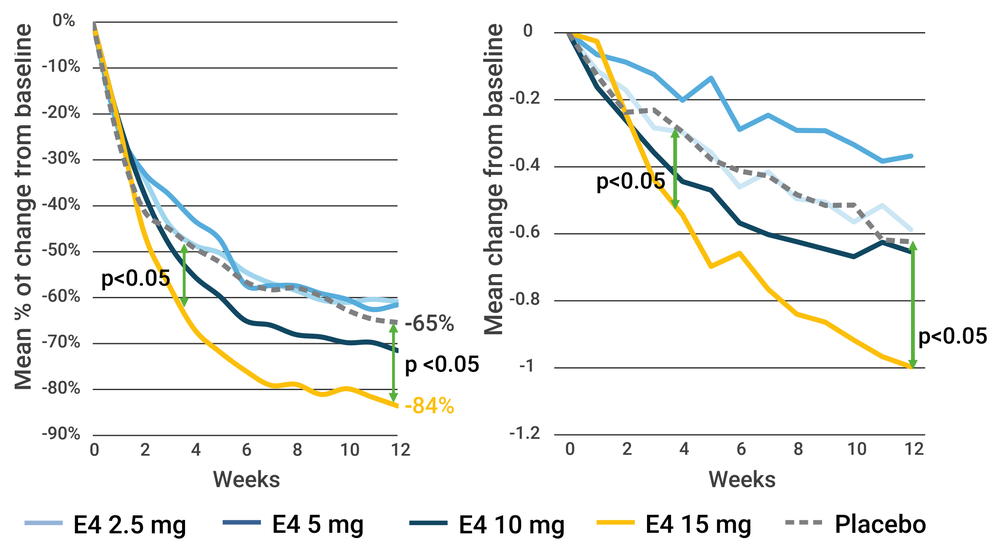
- E4 Relief was performed at designated centers in Belgium, Czech Republic, Ireland, Poland, and United Kingdom. In total, 257 postmenopausal women, aged 40–65 years, BMI 18-35 kg/m^2, ≥7 moderate to severe hot flushes (HF) per day, or ≥50 in the week preceding randomization, were included in the Intent-to-Treat analysis. For the non-hysterectomized women inclusion in the study was authorized only if transvaginal ultrasonography (TVUS) showed a bi-layer endometrial thickness ≤5 mm.
- E4 (2.5 mg, 5 mg, 10 mg, 15 mg), or placebo was administered orally, once-daily, for 12 consecutive weeks.
- After the treatment period, all non-hysterectomized subjects received 10 mg dydrogesterone once-daily, for 14 days.
- Efficacy was evaluated by recording changes in frequency and severity of VMS. Changes in maturation index, vulvar and vaginal atrophy (VVA) and bone health (C-terminal telopeptide (CTX-1)) were assessed as well.
- Health-related quality of life was assessed by scoring the Menopause Rating Scale (MRS).
- Safety included the evaluation of endometrial thickness in non-hysterectomized women, hemostatic and metabolic parameters, and recording of adverse events.

Conclusions

- E4 15 mg appears to be the minimal dose for effective treatment of VMS.
- All doses of E4 improved parameters of VVA.
- All doses of E4 reduced CTX-1, suggesting reduction in bone resorption.
- There were no apparent safety concerns. E4 was well tolerated.

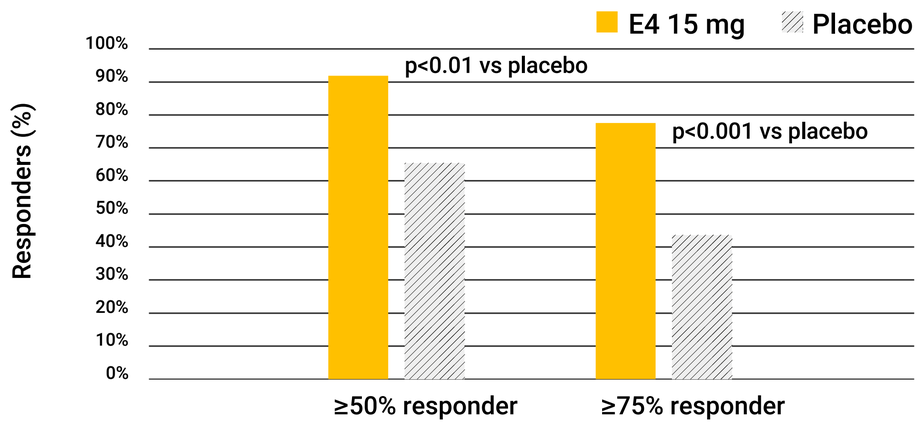
E4 15 mg reduced VMS frequency and severity

Figure 1: Mean change in weekly VMS frequency (left) and severity (right)



90% of women had a ≥50% VMS reduction, and almost 80% a ≥75% reduction

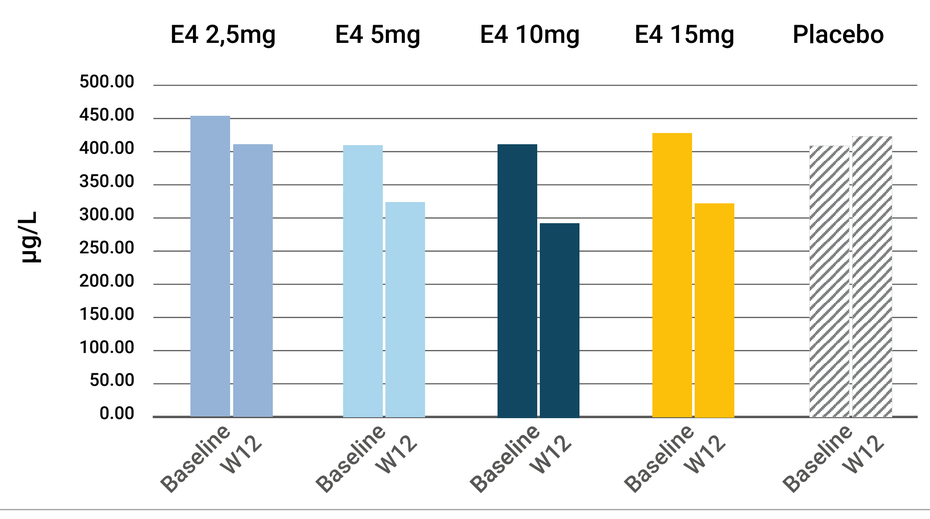
Figure 2: Responder analysis at week 12



Responders defined as ≥50% or ≥75% reduction in frequency of moderate-to-severe VMS from baseline to week 12.

E4 decreased bone resorption

Figure 3: CTX-1 serum concentrations at baseline and at Week 12



VVA & Maturation Index

- All E4 doses increased superficial cells and the vaginal maturation value.

Safety

- No endometrial hyperplasia was observed.
- Endometrial thickness returned to baseline after progestin therapy at 12 weeks.
- E4 15 mg had almost no effect on hemostasis parameters, and triglyceride plasma levels.
- E4 15 mg increased HDL cholesterol and glucose tolerance.
- Incidence of adverse events was low.

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Correspondence: M. Jost, Mithra Pharmaceuticals, Rue Saint Georges 5, 4000 Liège, Belgium. Tel: +32 4 349 2822. Fax: +32 4 349 2821. E-mail: mjost@mithra.com