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E4Relief: a phase 2b study with Estetrol (E4), the next generation hormone therapy for menopausal symptoms

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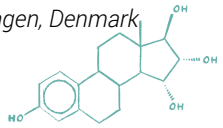

Introduction: Estetrol (E4) is a native fetal human estrogen. Its selective action in tissues differs from that of SERMs. E4Relief was a multicenter, randomized, placebo-controlled, double-blind, dose-finding study in postmenopausal women to identify the minimum effective E4 dose in decreasing the frequency and severity of hot flushes (HF). Secondary endpoints were the effects on genitourinary symptoms, quality of life along with the effect of E4 on lipid and glucose metabolism, hemostasis, and bone laboratory parameters.

Methods: Postmenopausal women were eligible when presenting ≥7 moderate to severe HF per day, or ≥50 per week. In total, 257 women received 2.5; 5; 10; 15 mg E4, or placebo, once-daily, for 12 weeks. Endometrial thickness, absence of hyperplasia, and bleeding control were the key safety parameters for women with an intact uterus.

Results: At week 12, HF frequency and severity were significantly decreased in 15 mg E4 vs placebo users (HF frequency: -82% vs -65%, $p<0.05$; HF severity:-44% vs -28%, $p=0.057$). In the 15 mg E4 group, 90% had ≥50% reduction in HF, and almost 80% a ≥75% reduction ($p<0.01$, 15 mg E4 vs placebo). Genitourinary symptoms also decreased with most doses, with significant effects on vaginal dryness ($p<0.05$) and pain linked with intercourse ($p<0.01$). A dose related increase was observed in the vaginal maturation value ($p<0.0001$), along with a small decrease in osteocalcin) and larger decrease in CTX-1, suggesting a net positive effect on bone formation). Endometrial thickness returned to baseline after progestin use post E4 treatment. No endometrial hyperplasia was observed. Triglyceride levels and hemostasis variables did not show significant changes from baseline at all E4 doses. A small statistically significant, but non-clinically meaningful change of free protein S and ETP-based nAPCsr were observed at the highest E4 dose. There was an increase in HDL cholesterol and glucose tolerance improved. There were no unexpected adverse events.

Conclusion: 15 mg E4 was found to be the minimum effective dose for the treatment of vasomotor symptoms. E4 appears to be a promising next generation oral hormonal treatment to address the full spectrum of postmenopausal symptoms, with a considerably lower impact on hemostasis variables and triglycerides. This may potentially result in a reduced risk of thrombosis. Phase 3 clinical studies of E4 15 and 20 mg are currently being planned in Europe, Russia, Latin America, USA, and Canada.