

THE EUROPEAN JOURNAL OF CONTRACEPTION AND REPRODUCTIVE HEALTH CARE PUBLISHES TWO SCIENTIFIC ARTICLES ABOUT E4 (ESTETROL) DINOX PHASE II STUDY: TWO OF THE MOST READ PAPERS BY THE SCIENTIFIC COMMUNITY

- Mithra Pharmaceuticals announces today the publication of two scientific articles based on the results of the E4 Dinox Phase II study of its estetrol-based product candidate Estelle®, a combined oral contraceptive composed of 15 mg Estetrol (E4) and 3 mg Drospirenone (DRSP).
- The articles concern the liver impact and the data on ovulation inhibition of E4 combinations.
- The published results are very interesting for the scientific community regarding the demonstration of the safe profile of Estetrol, which will be confirmed in the following study phases on the product candidates.

Liège, Belgium 26 August 2015 – Mithra Pharmaceuticals announces today that two articles have been published in the peer-reviewed European Journal of Contraception and Reproductive Health Care. The published results of the E4 Dinox Phase II study are particularly encouraging for the imminent launch of the Phase III study.

The first scientific article is entitled *Unique effects on hepatic function, lipid metabolism, bone and growth endocrine parameters of estetrol in combined oral contraceptives* and concerns the liver impact of E4 combinations.

The second scientific article is entitled *Inhibition of ovulation by administration of estetrol in combination with drospirenone or levonorgestrel: results of a phase II dose-finding pilot study* and concerns the data on ovulation inhibition by E4 combinations.

These articles are available on the European Journal of Contraception and Reproductive Health Care's website: <http://informahealthcare.com/journal/ejc> and are part of the most read articles by the scientific community.

About the article entitled *Unique effects on hepatic function, lipid metabolism, bone and growth endocrine parameters of estetrol in combined oral contraceptives*

Objectives: Estetrol (E4) is a natural estrogen produced by the human fetal liver. In combination with drospirenone (DRSP) or levonorgestrel (LNG), E4 blocks ovulation and has less effect on haemostatic biomarkers in comparison with ethinylestradiol (EE) combined with DRSP. This study evaluates the impact of several doses of E4/DRSP and E4/LNG on safety parameters such as liver function, lipid metabolism, bone markers and growth endocrine parameters.

Methods: This was a dose-finding, single-centre, controlled study performed in healthy women aged 18 to 35 years with a documented pre-treatment ovulatory cycle. Participants received 5 mg or 10 mg E4/3 mg DRSP; 5 mg, 10 mg or 20 mg E4/150 µg LNG; or 20 µg EE/3 mg DRSP as a comparator for

three consecutive cycles in a 24/4-day regimen. Changes from baseline to end of treatment in liver parameters, lipid metabolism, bone markers and growth endocrinology were evaluated.

Results: A total of 109 women were included in the study. Carrier proteins were minimally affected in the E4/DRSP and E4/LNG groups, in comparison with the EE/DRSP group, where a significant increase in sex hormone-binding globulin was observed. Similarly, minor effects on lipoproteins were observed in the E4 groups, and the effects on triglycerides elicited by the E4 groups were significantly lower than those in the EE/DRSP group. No imbalances in bone markers were observed in any groups. No alterations in insulin-like growth factor were observed in the E4 groups.

Conclusions: E4-containing combinations have a limited effect on liver function, lipid metabolism, and bone and growth endocrine parameters.

About the article entitled *Inhibition of ovulation by administration of estetrol in combination with drospirenone or levonorgestrel: results of a phase II dose-finding pilot study*

Objectives: The aim of the study was to evaluate the efficacy of different dosages of estetrol (E₄) combined with one of the progestins in suppressing the pituitary-ovarian axis and ovulation in healthy pre-menopausal women.

Methods: This was an open, parallel, phase II, dose-finding, pilot study performed in healthy women aged 18-35 years with a documented ovulatory cycle before treatment. For three consecutive cycles in a 24/4-day regimen, participants received 5 mg or 10 mg E₄/ 3 mg drospirenone (DRSP); 5 mg, 10 mg or 20 mg E₄/150 µg levonorgestrel; or 20 µg ethinylestradiol (EE)/3 mg DRSP as comparator. Pituitary-ovarian axis activity and the occurrence of ovulation were evaluated by monitoring follicular size, serum levels of follicle-stimulating hormone, luteinising hormone, estradiol and progesterone during treatment cycles 1 and 3. Endometrial thickness was evaluated throughout the trial, and the return of ovulation was evaluated after the last intake of medication.

Results: A total of 109 women were included in the trial. No ovulation occurred in any treatment group. Ovarian activity inhibition seemed proportional to the E₄: the highest suppression was observed in the 2 mg E₄ group and was very similar to that observed with EE/DRSP. Endometrial thickness was suppressed to the same extent in all groups. Post-treatment ovulation occurred in all participants between 17 and 21 days after the last active treatment. The study combinations were well tolerated and safe.

Conclusions: Combined with a progestin, E₄ adequately suppresses ovarian activity, particularly when given at a dosage above 10mg/day.

About the European Journal of Contraception and Reproductive Health Care

The European Journal of Contraception and Reproductive Health Care is the official journal of the European Society of Contraception and Reproductive Health. The Journal publishes six times per year original peer-reviewed research papers as well as review papers and other appropriate educational material and is indexed in Index Medicus/MEDLINE, EMBASE/Excerpta Medica and Chemical Abstracts.

About Mithra

Mithra Pharmaceuticals SA, founded in 1999 as a spin-off of the University of Liège by Mr. François Fornieri and Prof. dr. Jean-Michel Foidart, is a pharmaceutical company focused on women's health.

Mithra's mission is to support and assist women at every stage of their life, thereby improving their overall quality of life. As such the Company aims to become a worldwide leader in women's health by developing, manufacturing and commercialising proprietary, innovative and differentiated drugs and generic products in four therapeutic fields of women's health, fertility and contraception, menopause and osteoporosis, vaginal infections and cancers.

Mithra has a total headcount of approximately 85 staff members and is headquartered in Liège, Belgium. Further information can be found at: www.mithra.com

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