



MITHRA PRESENTS POSITIVE HEMOSTASIS RESULTS AT ISGE CONFERENCE

- **Analysis across a range of parameters points to limited hemostatic impact for Estelle[®], at least comparable to EE/LNG (Melleva[®]) and much lower than benchmark EE/DRSP (Yaz[®])**
- **Results corroborate earlier findings and further delineate unique safety profile of Estelle[®]**

Liège, Belgium, March 08, 2018 – Mithra (Euronext Brussels: MITRA), a company specialized in Women's Health, today presents more details of its Phase II hemostasis study of Estelle[®], Mithra's combined oral contraceptive (COC) candidate based on 15 mg E4 (Estetrol) and 3 mg DRSP (drospirenone). The data were presented at the occasion of the Gynaecological Endocrinology Conference (ISGE) in Florence.¹

The hemostasis study is a substudy running in parallel with the ongoing Phase III pivotal trials for Estelle[®] in EU/Russia and the US/Canada, the results of which are expected in Q3 2018 and Q1 2019, respectively. The aim of the current study is to analyze a series of parameters that are widely accepted as surrogate markers of coagulation (blood clotting) and fibrinolysis (breakdown of clots). Hence, these markers may help determine the risk profile of a novel COC for deep venous thrombosis (DVT) and pulmonary embolism, which are well-documented side effects of certain commonly prescribed contraceptive pills.

Hemostatic data were analyzed for 98 subjects divided over three treatment groups: 15 mg E4/3 mg DRSP (Estelle[®]), 30 mcg EE/150 mcg LNG (Melleva[®]), and 20 mcg EE/3 mg DRSP (Yaz[®]). The inclusion of the LNG (levonogestrel) comparator is required by the regulatory agencies, as a 'second generation' contraceptive option which is shown to have a limited impact on hemostasis parameters². Mithra elected to include Yaz[®] as an additional comparative arm, given the well-documented elevated DVT risk for current DRSP-based COCs relative to LNG-based products.³ Especially since Estelle[®] also contains DRSP, a direct comparison with Yaz[®] is of great interest. Moreover, with EUR 1.2bn, the Yaz[®] family still is the best-selling contraceptive pill in value⁴, and Estelle[®]'s benchmark for commercialization.

The ISGE presentation focuses on hemostasis parameters that are pro- and anti-coagulant factors across the three treatment arms⁵. Below graph illustrates that the mean changes of hemostasis parameters with EE/LNG and EE/DRSP follow trends reported in literature, with a less pronounced effect for EE/LNG than for EE/DRSP. Importantly, for a number of key parameters under analysis, the effects of E4/DRSP are comparable to those of EE/LNG, and in some cases even better. Overall,

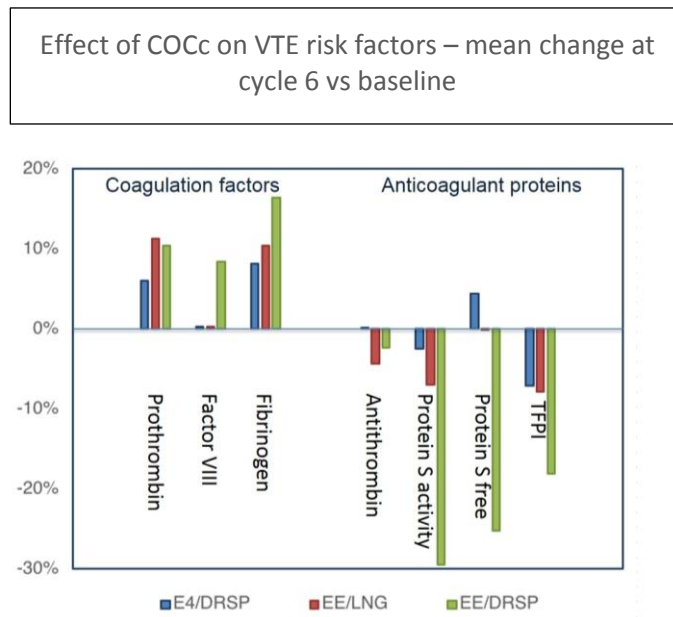
¹ <http://isge2018.isgesociety.com/>.

² Lidegard et al 2011. *BMJ* 2011;343:d6423

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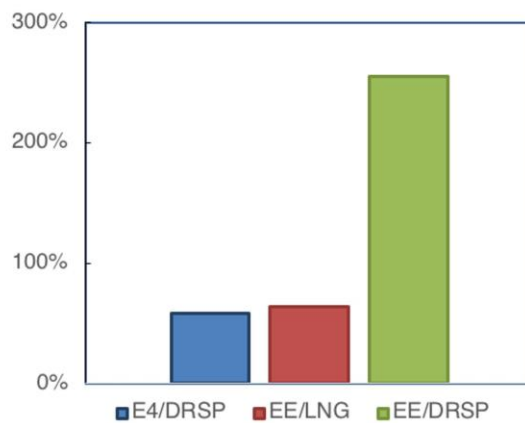
⁴ IMS Health Q3 2017

E4/DRSP shows a lower increase in coagulation factors as well as a lower decrease in coagulation inhibitors (anticoagulant proteins) than the comparators. Hence, E4/DRSP has a lower impact on these hemostatic parameters.



Another important factor closely watched by clinicians and KOLs is the change in SHBG (sex-hormone binding globulin), a protein whose synthesis is highly sensitive to oestrogens and androgens. Below graph indicates the reduced impact of Estelle® on SHBG levels, in line with results of previous studies⁶, confirming E4’s minimal impact on the liver proteins, including hemostasis proteins:

Change of Sex Hormone Binding Globulin (SHBG)
Cycle 6 - Baseline (%)



In conclusion, the hemostasis data point to minimal changes in markers of coagulation and fibrinolysis, even when compared to an LNG-based COC. Moreover, whereas Estelle® also is a DRSP-based pill, the results indicate that the combination with E4 does not lead to the higher hemostatic impact found with Yaz®. Hence, Estelle® has the potential to be a ‘fifth generation pill’, combining the quality of life offered by DRSP with a safer hemostatic profile.

⁶ See e.g. Klufft C et al., *Contraception*. 2016, for the SHBG results of the Phase IIa Estelle® study.

François Fornieri, CEO of Mithra, commented: *“We are very pleased with the impressive results of our hemostasis study. The differentiation of Estelle® versus our benchmark Yaz® as well as an LNG-based comparator highlights the unique safety profile of our product candidate. With our Phase III trials in Europe/Russia and US/Canada well underway, the hemostasis results are of great importance to the regulatory bodies but also to our current and prospective commercialization partners: they corroborate earlier findings that Estelle® offers the potential of a true ‘next generation’ contraceptive option for women.”*

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About Estelle®

Estelle® is Mithra’s novel oral contraceptive product candidate composed of 15 mg Estetrol (E4), its unique native estrogen, and 3 mg DRSP. Currently, pivotal Phase III Estelle® trials (*E4 Freedom*) are ongoing in Europe and Russia as well as in the US and Canada, with top line results expected in Q3 2018 and Q1 2019, respectively. The *E4 Freedom* studies are open-label single arm trials to assess the safety and efficacy of Estelle® in over 1,550 participants in Europe/Russia and approximately 2,000 participants in the US/Canada, over a period of 13 cycles.

About Mithra

Mithra (Euronext: MITRA) is dedicated to providing innovation and choice in women's health, with a particular focus on fertility, contraception and menopause. Mithra's goal is to develop new and improved products that meet women's needs for better safety and convenience. Its two lead development candidates - a fifth generation oral contraceptive, Estelle®, and a next generation hormone therapy, Donesta®- are built on Mithra's unique natural estrogen platform, E4 (Estetrol). Mithra also develops, manufactures and markets complex therapeutics and offers partners a complete spectrum of research, development and specialist manufacturing at its Mithra CDMO. Mithra was founded in 1999 as a spin-off of the University of Liège by Mr. François Fornieri and Prof. Dr. Jean-Michel Foidart and is headquartered in Liège, Belgium. Further information can be found at: www.mithra.com

Important information

The contents of this announcement include statements that are, or may be deemed to be, "forward-looking statements". These forward-looking statements can be identified by the use of forward-looking terminology, including the words "believes", "estimates," "anticipates", "expects", "intends", "may", "will", "plans", "continue", "ongoing", "potential", "predict", "project", "target", "seek" or "should", and include statements the Company makes concerning the intended results of its strategy. By their nature, forward-looking statements involve risks and uncertainties and readers are cautioned that any such forward-looking statements are not guarantees of future performance. The Company's actual results may differ materially from those predicted by the forward-looking statements. The Company undertakes no obligation to publicly update or revise forward-looking statements, except as may be required by law.

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