Mithra Announces Positive Top-line Results of Estelle® Phase III Oral Contraceptive Study in U.S/Canada

- **Primary efficacy endpoint indicates excellent contraceptive efficacy, with a Pearl Index (PI) of 2.41[1] per 100 women, in line with expectations**
- **Key secondary endpoints achieved, including excellent bleeding profile, cycle control, quality of life and safety and tolerability**
- **Data in line with previously announced Phase III trial in EU / Russia confirming Estelle's® outstanding profile as a novel, next-generation combined oral contraceptive**
- **Filing with U.S. and EU regulatory agencies anticipated by year end**

Liège, Belgium, 30 January 2019, 07:00 CET – Mithra (Euronext Brussels: MITRA), a company dedicated to Women's Health, today announced that its Phase III Estelle® study conducted in the United States and Canada successfully met its primary efficacy endpoint. Efficacy is well in line with expectations, similar to a recently FDA approved combined hormonal contraceptive (Annovera™ PI 2.98 [95% Confidence Interval 2.13-4.06]) per 100 woman-years of use[2]) and to Lo-Loestrin®[3] (PI 2.92 [95% Confidence Interval 1.94-4.21]), one of the best-selling Combined Oral Contraceptives (COC) in the United States with USD 527.7 million sales in 2018 (15% yoy growth)[4]. Estelle® is Mithra's COC candidate, composed of Estetrol (E4) 15 mg and drospirenone (DRSP) 3 mg.

The safety profile is supported by the unique Mode of Action of E4, which is a native estrogen with selective action in tissues. Two earlier Phase II studies conducted by Mithra confirmed E4 has a minimal impact on liver cells and metabolic pathways, including on the coagulation parameters[5] resulting in an overall beneficial hemostatic profile. These coagulation parameters are effected more negatively by Ethinyl-Estradiol (EE), present in most oral contraceptives, making Estelle® a promising new contraceptive solution for women with a unique benefit/risk profile.

Mitchell Creinin, Director of Family Planning at the University of California, Davis commented: *"I am excited about the introduction of a truly new estrogen into the field of hormonal contraception. This novel product has great potential based on Phase 2 data which shows less effects on liver metabolism, lipids, and the coagulation profile as compared to contraceptives using ethinyl estradiol. The overall efficacy, safety and excellent cycle control demonstrated in the Phase 3 studies confirms that Estelle® offers a truly innovative, next-generation oral contraceptive option*."

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[1] European definition
[2] Registered trademark of Therapeutics MD
[3] Registered trademark of Allergan Plc
[4] Allergan plc 2018 full year earnings release
[5] Kluft C et al., Contraception 2017; 95(2):140-7
https://investors.mithra.com/wp-content/uploads/2018/03/2018-03-08-Hemostasis-ISGE-en-final.pdf

François Fornieri, CEO Mithra Women's Health, commented: *"We are very pleased with the outcome of the U.S. / Canadian top-line results, which complete the Phase 3 program and clearly demonstrate that Estelle® is a novel, 'next generation' oral contraceptive option for women. We are delighted to be one step closer to bringing Estelle® to the U.S. market ($5.53 billion[6]). We believe it has the potential to support healthcare providers and women in their choice of a predictable and effective contraceptive respecting women's wellbeing and lifestyle with the greatest sense of safety."*

The study assessed the efficacy, cycle control, general safety and acceptability of Estelle® in healthy women aged 16-50 years and involved subject participation for 12 months (13 cycles, 1 cycle = 28 days). Women with a Body Mass index (BMI) up to 35.0 kg/m² were included in the study. The primary endpoint was contraceptive efficacy measured by the number of on-treatment pregnancies per 100 women per 12 months of exposure among the women aged 16-35 years old at study entry. Results showed a Pearl Index (PI) of 2.41 (95% confidence interval 1.73-3.88) during 13,979 at risk cycles, in the absence of other contraceptive methods.

Amongst women aged 16-50 years old at study entry, results showed a PI of 2.30 (95% confidence interval 1.67-3.64) during 15,797 cycles, with in the absence of other contraceptive methods. The PI corresponds to a 98% efficacy rate over one year of use, in line with the efficacy goals of the study.

Cycle control and bleeding profile, which are essential to women's adherance, showed an excellent regular bleeding pattern similar to patterns seen with oral contraceptives containing EE[7]. Safety, acceptability and general well-being of the subjects (measured by two questionnaires) were also analyzed. Results from the MDQ (menstrual distress questionnaire) and QoL (quality of life) questionnaire showed that Estelle® is well tolerated by women, while their overall quality of life is maintained. There were no lipid and metabolic changes. These results reinforce the safety profile of Estelle®.

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6 IQVIA Market Analysis, January 2019

7 Marr, J., C. Gerlinger, and M. Kunz, A historical cycle control comparison of two drospirenone-containing combined oral contraceptives: ethinylestradiol 30 mug/drospirenone 3 mg administered in a 21/7 regimen versus ethinylestradiol 20 mug/drospirenone 3 mg administered in a 24/4 regimen. Eur J Obstet Gynecol Reprod Biol, 2012. 162(1): p. 91-5.

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 next-generation hormone therapy Donesta® - are built on Mithra's unique native 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 CDMO. Mithra was founded in 1999 as a spin-off from the University of Liège by Mr. François Fornieri and Prof. Dr. Jean-Michel Foidart. Mithra 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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