MITHRA ANNOUNCES POSITIVE DONESTA® PHASE IIB STUDY ACHIEVING PRIMARY OBJECTIVE AND CONFIRMING PROMISING SAFETY PROFILE

- ***E4 Relief*** **dose-finding study identifies 15 mg E4 as the optimal minimum dose for effective treatment of VMS (hot flushes)**
- **15 mg E4 demonstrated a meaningful reduction of over 80% in VMS versus baseline, and a statistically significant reduction compared to placebo**
- **Safety profile consistent with previous E4 studies confirming Donesta®'s promising hemostatic and lipid profile, as well as an improved quality of life**
- **Data strongly support further development of Donesta® as a unique next-generation hormone therapy**

Liège, Belgium, 19 April 2018 – 7:30 AM – Mithra (Euronext Brussels: MITRA), a company specialized in Women's Health, today announces positive topline results from the *E4 Relief* Phase II study of Donesta® for the treatment of Vasomotor Symptoms (VMS), and in particular hot flushes relief, in post-menopausal women, with the study achieving its primary and key secondary objectives. Donesta® is Mithra's next-generation hormone therapy (HT) candidate with oral administration of Estetrol (E4).

The aim of the *E4 Relief* study was to establish the optimal minimum dose of E4 for the treatment of VMS. The study included 257 women receiving at least one active or placebo dose (Intent to Treat population, ITT). Four different dose levels of E4 (2.5 mg, 5 mg, 10 mg and 15 mg) were tested compared to placebo in this double-blinded study.

The study successfully concluded that 15 mg of E4 was the optimal oral minimum dose for effective treatment of VMS. This dose cohort demonstrates a reduction of over 80% in the frequency of moderate to severe VMS when compared to baseline. Importantly, the effect was statistically significant compared to placebo at Week 12 ($p < 0.05$)[1], with improvements over placebo seen as early as Week 2 and a trend towards significance observed at Week 4 ($p=0.056$)[2]. The combined weighted score of frequency and severity of VMS also indicates a clear effect for the 15 mg dose.

A number of key secondary endpoints were also achieved. First, over the different doses, and in a dose-dependent way, there is a significant improvement of the vaginal maturation index versus placebo (reaching $p < 0.001$ for the 15 mg dose), which indicates a positive effect on vulvo-vaginal atrophy (VVA or vaginal dryness). Since VVA is one of the most bothersome and frequent symptoms

[1] The placebo group reported a reduction of approximately 60% in the frequency of moderate to severe VMS at Week 12. Note that a high placebo effect is well-documented in VMS studies. This is often attributed to the increased doctor/patient focus, amongst other factors. The Cochrane meta-analysis of menopausal studies shows an overall placebo effect of 58%, and a 78% effect for HT treatments (Maclennan A.H. et al., 2009. *Cochrane Database Syst Rev*)

[2] Data based on the ITT and considering the imputation of drop-outs (Last Observation Carry Forward or LOCF analysis). Over 200 subjects received an active dose or placebo for the full treatment period of 12 weeks.

of (post)menopause, this is an important result. Secondly, the Menopause Rating Scale (MRS) also points to an overall improvement in quality of life, with the strongest effect for the 15 mg dose.

Furthermore, the study confirms Donesta®'s clean overall safety profile with regard to the hemostatic and metabolic factors, indicating a minimal impact on the different parameters measured, consistent with previous studies of E4[3,4]. As expected, with the minimal effective dose at 15 mg, the addition of a progestin will be needed to curb endometrial proliferation for non-hysterectomized women.

In conclusion, top-line results show that 15 mg E4 is highly efficacious for relieving some of the most bothersome and frequent symptoms of menopause, while offering a promising safety profile. This highlights the potential of Donesta® as a unique next-generation hormone therapy and provides a solid foundation for the next stage of clinical development.

The company plans to present more detailed results of the Donesta® study at upcoming conferences, including a the IMS International Menopause Society conference in Vancouver (June 6-9).

The global menopause market currently stands at USD 8.6 billion and is expected to grow to approximately USD 16 billion by 2025, driven by growing awareness for Women's Health issues, the unmet medical need in menopause, and the aging population, in addition to market expansion with the introduction of new treatment options that provide a safer alternative to currently available therapies[5]. Given these top-line results, Donesta® has the potential to address this unmet medical need.

Valerie Gordenne, CSO and Maud Jost, Project Director E4 programs of Mithra, commented: "*We are very pleased with the top-line results obtained: we defined a minimal effective dose of E4 for the treatment of VMS, and we are excited to see a statistically significant reduction in the frequency of hot flushes at Week 12 already at this stage of clinical development. Moreover, the clean safety profile observed has the potential to set Donesta® apart from current hormonal treatments in menopause. We look forward to discussing the results with the agencies and our KOLs to define next steps for the further development of Donesta®."*

François Fornieri, CEO of Mithra, commented: *"The significant reduction in the incidence of hot flushes in post-menopausal women demonstrates that Donesta® may be an efficacious, novel treatment for menopausal symptoms. With these results in hand, we filed a patent application to further strengthen and extend our existing E4 IP portfolio. Moreover, we are very encouraged by the beneficial safety profile emerging from the study, and in particular the confirmation of the favourable hemostatic profile of E4.*

Given the exceptional results, we will explore the various options to rapidly advance the development and maximize the value of Donesta® in the very large, and fast growing, menopause market. If approved, Donesta® could offer a true novel and differentiated therapy with an improved benefit/risk profile for women globally confronted with the range of menopausal symptoms."

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[3] Kluft et al, 2017, *Contraception*, 95_140-147

[4] Mawet et al, 2015, *Eur J Contracep Reprod Health Care*, 20(6):463-75

[5] Transparency Market Research 2017

About the *E4 Relief* Donesta® Phase II study

Donesta® is a next generation orally administered hormone therapy based on E4 for vasomotor symptoms (VMS). In May 2016, Donesta® entered into a European Phase II dose-ranging study, *E4 Relief* (MIT-Do0001-C201) in 257 women aged 40-65 in the Czech Republic, Poland, Belgium, Ireland and the UK, 200 of which completed a treatment period of 12 weeks. Four doses of E4 (2.5 mg, 5 mg, 10 mg and 15 mg) compared to placebo were tested to establish the minimum effective dose. For non-hysterectomized women, E4 therapy is followed by a progestin therapy (Dydrogesterone 10 mg) for 2 weeks as a protective measure to curb any endometrial growth.

The primary endpoint is an evaluation of the changes in frequency and severity of moderate to severe VMS (vasomotor symptoms or hot flushes). Secondary outcomes include: (1) evaluation of the effects of different doses on vulvovaginal atrophy, on vaginal maturation index and on vaginal pH; (2) evaluation of additional secondary endpoints, including bone parameters, lipid & glucose metabolism, hemostatic laboratory variables, PK and women satisfaction; (3) a safety assessment, with most importantly a measurement by transvaginal ultrasonography of the change in endometrial thickness at each study visit.

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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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