MITHRA ANNOUNCES LAST SUBJECT COMPLETES DONESTA® PHASE II STUDY

- **Donesta® Phase II study on track to yield top line data late Q1 2018**
- **260 women recruited in total, of which over 200 have completed at least 12 weeks of treatment as part of the Phase II study**
- **12-week data generated for an additional 15% of study subjects in order to improve robustness of analysis**

Liège, Belgium, 25 January 2018 – Mithra (Euronext Brussels: MITRA), a company specialized in Women's Health, today announces that the last subject completed the *E4 Relief* Phase II study of Donesta®, Mithra's next-generation hormone therapy (HT) candidate with oral administration of Estetrol (E4) for Vasomotor Menopausal Symptoms (VMS) relief. Top-line data remain on track to be available late in the first quarter of 2018.

The *E4 Relief* dose-finding study includes centres in the Czech Republic, Poland, Belgium, Ireland and the UK, with subjects receiving an active dose or placebo for a treatment period of 12 weeks. In total four dose levels of Donesta® (2.5 mg, 5 mg, 10 mg and 15 mg) are being tested compared to placebo in this double-blinded study. The primary objective of the Phase II clinical trial is to identify the oral daily minimum dose of Donesta® required to effectively treat VMS, or hot flushes, in post-menopausal women. Secondary outcomes include an evaluation of other menopausal symptoms such as vulvo-vaginal atrophy (VVA), or vaginal dryness, lipid and glucose metabolism as well as bone metabolism markers. The study will also analyze key safety issues including endometrial thickness.

Research shows that current HT-based treatments may increase the risk of breast cancer and venous thromboembolic events (VTE) such as blood clots[1,2]. Thanks to the unique profile and mode of action of the native estrogen E4, Donesta® has the potential to effectively treat VMS while offering an improved safety profile, hence addressing the unmet medical need in menopause[3,4,5].

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[1] Roehm E. A reappraisal of Women's Health Initiative Estrogen-Alone Trial: long-term outcomes in women 50-59 years of age. *Obstet Gynecol Int* 2015; 2015:713295.

[2] Baber RJ, et al. 2016 IMS Recommendations on women's midlife health and menopause hormone therapy. *Climacteric* 2016; 19:109–150.

[3] Coelingh Bennink H, et al. Pharmacodynamic effects of the fetal estrogen estetrol in postmenopausal women: results from a multiple-rising-dose study. *Menopause* 2017 (Vol. 24:6)

[4] Gerard C, et al. Combined estrogenic and anti-estrogenic properties of estetrol on breast cancer may provide a safe therapeutic window for the treatment of menopausal symptoms. *Oncotarget* 2015; 6:17621–17636.

[5] Abot A, et al. The uterine and vascular actions of estetrol delineate a distinctive profile of estrogen receptor modulation, uncoupling nuclear and membrane activation. *EMBO Molecular Medicine* 2014 6 1328–1346.

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.[6]

François Fornieri, CEO of Mithra, commented: *"With today's news, we can reconfirm the time line towards top line results at the end of Q1 2018. We are looking forward to the results, which have the potential to corroborate earlier studies indicating that Donesta® may be an efficacious novel treatment for menopausal symptoms with an improved benefit/risk profile for women. If approved, Donesta® could represent an important differentiated therapy in the very large, and rapidly growing, menopause market."*

About the *E4 Relief* Donesta® Phase II study

Donesta® is a next generation orally administered hormone therapy based on E4 for vasomotor menopausal symptoms (VMS). In May 2016, Donesta® entered into a European Phase II dose-ranging study, *E4 Relief* (MIT-Do0001-C201) in 260 women aged 40-65 in the Czech Republic, Poland, Belgium, Ireland and the UK, for a treatment period of 12 weeks. Four doses of Donesta® (2.5 mg, 5 mg, 10 mg and 15 mg) compared to placebo are being 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 sypmtoms 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.

Mithra has contracted Synteract HCR as CRO for the *E4 Relief* study.

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[6] Transparency Market Research 2017

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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