



## MITHRA ANNOUNCES FURTHER POSITIVE PHASE IIB DONESTA® EFFICACY AND SAFETY DATA

- Further analysis of the *E4 Relief* dose-finding study shows a statistically significant reduction in the severity of VMS (hot flushes) at the optimal minimum dose (15 mg E4)
- Data reinforce the previously announced positive Phase IIB Donesta® results, demonstrating a meaningful and statistically significant reduction in the frequency of VMS
- Encouraging cardiovascular safety profile further confirmed by hemostatic, glucose and lipid markers
- Data will be presented at the International Menopause Society Conference on 8 June 2018

Liège, Belgium, 30 May 2018, 16:06 CET – Mithra (Euronext Brussels: MITRA), a company specialized in Women's Health, today announces further positive topline data 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. 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. As previously reported in April 2018, the study successfully concluded that 15 mg of E4 was the optimal oral minimum dose for effective treatment of VMS.

Further analysis has demonstrated that 15 mg of E4 resulted in a reduction of over 40% in the severity of moderate to severe VMS when compared to baseline. The mean change in VMS severity was statistically significant compared to placebo at Week 4 ( $p < 0.05$ ) and at Week 12 ( $p < 0.05$ ). As previously announced in April 2018, the 15 mg E4 dose cohort demonstrated a statistically significant reduction of over 80% versus baseline in the frequency of moderate to severe VMS when compared to placebo ( $p < 0.05$  at 12 weeks), with both frequency and severity of VMS the key efficacy endpoints of the study.

The safety parameters continue to be encouraging, with additional data demonstrating a lower bone turnover versus placebo<sup>1</sup>. Also, in line with previously published research on E4, the clean overall safety profile of Donesta® has been reconfirmed with regard to the hemostatic parameters (including

---

<sup>1</sup> As measured by a decrease in both the CTX-1 and osteocalcin markers with E4 use vs placebo. The effect is most pronounced for the 15 mg dose (near-significant for CTX-1 and significant at  $p < 0.05$  for osteocalcin).

pro-coagulant and anticoagulants factors) and the plasma levels of SHBG<sup>2</sup>, a marker of hepatic estrogenicity. Moreover, for the 15 mg dose, a clear and significant improvement in the metabolism of glucose<sup>3</sup> and lipids<sup>4</sup> has been shown versus placebo ( $p < 0.05$ ), with only a very slight increase in triglyceride levels. These factors contribute to the promising cardiovascular safety profile of Donesta.

The company plans to present more information and background on the results of the Donesta<sup>®</sup> study at upcoming conferences, including at 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<sup>5</sup>. Thanks to the unique profile and mode of action of the native estrogen E4, Donesta<sup>®</sup> has the potential to effectively treat VMS while offering an improved safety profile, hence addressing the unmet medical need in menopause<sup>6,7,8</sup>.

**François Fornieri, CEO of Mithra, commented:** *“These additional data demonstrate a significant reduction in the severity of hot flushes in post-menopausal women, further reinforcing Donesta<sup>®</sup>'s potential as an efficacious, novel treatment for menopausal symptoms. Together with the previously announced reduction in the frequency of hot flushes, Donesta<sup>®</sup> could offer a truly novel and differentiated therapy for women experiencing some of the most troublesome symptoms of menopause. The encouraging safety profile demonstrated in the E4 Relief Phase II study has also been augmented by the most recent analysis. While further research is needed, for a number of important parameters, the results indicate a lower impact on a number of hemostatic and metabolic factors when compared to currently commercialized HT treatments.*

*“The data have been discussed with a key opinion leader board in Europe in a very productive meeting. The KOL board are very supportive of the results, and are keen to progress Donesta<sup>®</sup> into Phase III. Initial discussions around the design of a Phase III have been initiated with KOL input. We look forward to presenting more details at the International Menopause Society conference in June and to further discussions with our KOLs and the regulatory agencies.”*

---

<sup>2</sup> Sex-hormone binding globulin

<sup>3</sup> As shown by the significant decrease in Hb1A1C (glycated haemoglobin), measured primarily to indicate the three-month average plasma glucose concentration.

<sup>4</sup> 15 mg E4 significantly increases cholesterol-HDL levels ( $p < 0.05$ ).

<sup>5</sup> Transparency Market Research 2017

<sup>6</sup> 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).

<sup>7</sup> 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.

<sup>8</sup> 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.

### About the *E4 Relief Donesta*<sup>®</sup> Phase II study

Donesta<sup>®</sup> is a next generation orally-administered hormone therapy based on E4 for vasomotor menopausal symptoms (VMS). In May 2016, Donesta<sup>®</sup> 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 whom 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.

### For more information, please contact:

#### Investor Relations

**Sofie Van Gijssel, IRO & VP of Strategy**

+32 485 19 14 15

[investorrelations@mithra.com](mailto:investorrelations@mithra.com)

[svangijssel@mithra.com](mailto:svangijssel@mithra.com)

#### Press

**Consilium Strategic Communication**

Jonathan Birt, Philippa Gardner, Hendrik Thys

[mithra@consilium-comms.com](mailto:mithra@consilium-comms.com)

+44 2 037 095 700

### 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<sup>®</sup>, and a next generation hormone therapy, Donesta<sup>®</sup>- 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](http://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.*

To subscribe to Mithra's newsletter, visit [investors.mithra.com](https://investors.mithra.com)