Blockbuster Potential in Perimenopause with new E4 Candidate and Acceleration of Donesta Phase III Program

- **Potential for new perimenopause product candidate PeriNesta launch as early as 2023, with an estimated market opportunity of at least 18 million patients annually in the US and key EU markets[1]**
- **Donesta® phase III E4 monotherapy patient recruitment anticipated to start in Q3 2019 pending approvals , potential market authorisation by end 2023**
- **Ongoing global patent filings could protect Donesta® and PeriNesta IP estate until 2039**

Liège, Belgium, 07 January 2019 – 6:00 CET – Mithra (Euronext Brussels: MITRA), a company dedicated to Women's Health, today announces the further expansion of its Estetrol (E4)-based programs with a decision to target the underserved perimenopausal market, which affects women between reproductive age and post-menopausal age. The Company believes this additional indication for a product with a comparable formulation to E4 15mg/DRSP 3mg represents a major new market opportunity that requires only limited additional investment.

The Company also announced plans to accelerate preparations for its proposed Phase III E4 monotherapy study of Donesta® in menopause. Mithra has appointed leading specialist Contract Research Organization (CRO) ICON Plc (NASDAQ: ILCR) to manage the study and recruitment is expected to begin in the second half of 2019, pending approvals.

François Fornieri, CEO of Mithra Women's Health, commented: *"Mithra's move into the perimenopausal market presents a major additional market opportunity. PeriNesta has the potential to be the first product to offer women experiencing perimenopause an improved benefit/risk contraceptive solution and address the challenge of hot flushes. We are also making rapid progress with our planned phase III development of Donesta® for women in menopause and look forward to discussing our progress with potential commercial partners. With our focus on contraception, menopause and perimenopause, Mithra has the potential to provide the right therapeutic option for women throughout their female lifecycle."*

PeriNesta product candidate: potential blockbuster opportunity for E4 in perimenopause

Mithra will pursue regulatory approval for PeriNesta with a comparable formulation to E4 15mg/DRSP 3mg. The PeriNesta product candidate will specifically target relief of hot flushes, or vasomotor symptoms (VMS), while providing effective contraception for women who are starting to exit reproductive stage and are transitioning into postmenopause. Part of reproductive aging, this intermediate phase between reproductive age and postmenopausal age is known as perimenopause[2].

[1] IQVIA , 2019 market analysis (US, France, UK, Germany)

Women in perimenopause can often experience VMS, which can significantly affect their quality of life.

Perimenopause begins approximately three years prior to menopause and ends one year after the final menstrual period. Perimenopause is characterized by persistent irregular menstrual cycles, extreme fluctuations in hormonal levels, frequent anovulation and the appearance of VMS[2]. A significant number of women also experience sleep disorders, depressive symptoms, such as mood swings, irritability, and poor concentration[3]. The addressable market is estimated to be at least 18 million patients annually in the US and key EU markets (France, UK, Germany)[1].

To date there is currently no approved product that provides both contraceptive efficacy and VMS relief. PeriNesta has the potential to be the first officially- approved product brought to market that addresses the unmet need of women in perimenopause who require an improved benefit/risk contraceptive solution that simultaneously addresses the burden of VMS.

Mithra has filed an additional global patent application based on the existing data generated in previous clinical studies. If granted, the patent will strengthen and extend the existing E4 intellectual property estate in menopause and perimenopause until 2039.

The Company intends to conduct a safety study with a comparable formulation to E4 15 mg/DRSP 3 mg in women aged around 50 years of age affected by VMS. Mithra is confident the study cost should not exceed EUR 20 million as the Company will be leveraging existing clinical data. Pending regulatory agency approval, Mithra should be in a position to target market authorization in 2023.

Prof. Jean-Michel Foidart, MD, Perpetual Secretary of the Royal Academy of Medicine of Belgium, commented: *"The risk of venous thrombo embolism increases with age among users of combined oral contraceptives so the need for an effective contraceptive control that will show a safer profile while reducing the frequency and severity of hot flushes is an important medical need for clinicians and patients. This PeriNesta program represents therefore an attractive perspective for the medical community."*

Christophe Maréchal, CFO of Mithra Women's Health, commented*: "As previously communicated, Mithra continues to have a strong cash position with the capacity to maximize the potential of its lead products and pipeline. At the end of June 2018, the Company had a cash position of EUR 85.8 million which was further reinforced with an additional EUR 20 million payment from the divestment of Mithra's Belux generic portfolio and EUR 35 million from the LSA signed with Gedeon Richter. The PeriNesta trial expenses are expected to be moderate overall and will be limited in 2019 and mainly incurred from 2020 onwards. By the time these development expenses will become more material, Mithra should be in an excellent position to conclude partnering agreements including for this new perimenopausal product candidate with downpayments which will further cover the trial expenses. We will continue to uphold our track record of tightly controlling expenditure and managing resources carefully."*

Donesta® program update: moving rapidly into phase III with strengthened capabilities

In April 2018 Mithra announced positive results from the E4 Relief Phase II study for its next-generation hormone therapy product candidate, Donesta® for the treatment of Vasomotor Symptoms (VMS) in post-menopausal women. The dose-finding study successfully achieved its primary efficacy

2 Climacteric. 2012 Apr;15(2):105-14. doi: 10.3109/13697137.2011.650656. Epub 2012 Feb 16

3 Bosworth et al., 2001

objective demonstrating a meaningful and statistically significant reduction in the frequency of VMS while confirming the clean safety profile.

Following these positive results, Mithra is accelerating plans for the pivotal phase III E4 monotherapy study to bring Donesta® to market to help address unmet medical needs in menopause as quickly as possible. The global menopause market is valued at c. USD 8.6 billion and is expected to grow to approximately USD 16 billion by 2025[4].

To unlock this full commercial potential as soon as possible, Mithra has reinforced its internal management capabilities and appointed a series of expert scientific development partners and commercial advisors.

Patient recruitment for the phase III E4 monotherapy is anticipated to start in H2 2019 pending approvals, with a potential market authorization anticipated by the end of 2023. The study will be a worldwide randomized, partly double-blind placebo controlled, multicentered phase III trial and will assess the efficacy and safety of E4 for the treatment of moderate to severe VMS in post-menopausal women.

The study's primary objective is to measure the effect of treatment with 10 mg E4, 15 mg E4 or 20 mg E4 compared to placebo on the frequency and severity of moderate to severe VMS in post-menopausal women at 4 and 12 weeks. Secondary objectives include the evaluation of the effect of the treatment on a series of additional key efficacy and safety parameters. The study design comprises five arms. The overall study duration is 12 months and may last up to 19 months, factoring in the patient washout, screening and run-in periods.

The indicated cost of the phase III program is in line with trials designed with placebo or active drug comparators[5]. Mithra has a strong cash position to finance the trial independently and accelerate the development of Donesta® to realize the full commercial potential of the product for its commercial partners.

Mithra will partner with ICON Plc (NASDAQ: ILCR) for the management of the pivotal phase III study. ICON is a leading global clinical research organization with extensive experience in studies concerning the treatment of VMS. ICON has a strong track record of delivery, with >85% of trials completing within or ahead of the contracted milestones.

Mithra will in addition also work with LBR, an expert US-based clinical and regulatory consulting services company with a strong track record in women's health clinical study project management. LBR recently completed the successful management of two major women's health phase III clinical studies in the USA which supported FDA approval of two drugs.

In order to further strengthen the Company's strategic and operational leadership, recruitment is currently underway for a Chief Medical Officer. Mithra is also in the process of recruiting a medical advisor and four clinical research study leaders, associates and support staff to help ensure the study is executed to the best standards, on time and budget.

Mithra remains committed to collaborate with commercial partners for its menopause program worldwide and has appointed Rothschild & Co Global Advisory Services to organize a structured partner search process with a view to accelerate the commercial licensing in menopause and perimenopause for US and major EU markets.

****

[4] Transparency Market Research 2017

[5] https://www.ncbi.nlm.nih.gov/pubmed/30264133

For more information, please contact:

Investor Relations & Press

François Fornieri (CEO): +32 4 349 28 22
Jean-Manuel Fontaine (PRO): +32 (0)476 96 54 59
investorrelations@mithra.com

Consilium Strategic Communications
Susan Stuart, Olivia Manser, Melissa Gardiner
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® 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.

To subscribe to Mithra's mailing list,
please visit investors.mithra.com