Mithra Announces Positive Top-Line Results from Donesta® Phase 3 Studies in Menopausal Women

- **Donesta®, Mithra's next generation estetrol (E4)-based hormone therapy product candidate, demonstrated a meaningful reduction in vasomotor symptoms from baseline and compared to placebo**
- **Positive efficacy data strongly move forward the Clinical Program, recently extended with 3 additional studies to further broaden the scope of Donesta® as a global alternative for millions of menopausal women**
- **Donesta® safety profile confirmed by end-year independent Data Safety Monitoring Board (DSMB), which recommended to continue the Phase III Clinical Program as planned**
- **Primary safety results anticipated for end 2022 in the United States/Canada and for end H1 2023 in Europe. On track to target marketing authorization in 2024**
- **Webcast today at 09:00 am CET to present results**

Liege, Belgium, 14 January 2022 – 07:30 CET – Mithra (Euronext Brussels: MITRA), a company dedicated to Women's Health, today announces positive efficacy top-line results from Donesta® Phase 3 pivotal "E4 Comfort" clinical trials for the treatment of Vasomotor Symptoms (VMS) in post-menopausal women. Donesta® is Mithra's next generation orally-administrated estetrol (E4)-based hormone therapy product candidate.

Launched in late 2019, the Phase 3 Clinical Program carried out in 2,300 postmenopausal women (40-65 years) includes 2 pivotal studies: one in North America (C302); and a second in 14 countries in Europe, Latam and Russia (C301). Both studies are worldwide randomized, multicentre, double-blind, placebo-controlled trials. This Phase 3 Program aims to measure the treatment effects of vasomotor symptoms' frequency and severity at 15mg and 20 mg doses of E4, especially for hot flushes. The co-primary efficacy endpoints are the mean change from baseline in the frequency and severity of moderate to severe VMS at week 4 and week 12 compared to placebo.

Both studies demonstrated a meaningful reduction in VMS frequency and severity from baseline and compared to placebo. At week 12, the results showed a reduction up to 80% in the frequency of hot flushes when compared to baseline. Regarding the severity, this reduction was up to 56% compared to baseline. All co-primary efficacy endpoints were statistically (all $p<0.01$) met in both studies, except for a borderline non-significant result for the severity criteria at week 4 in the C302 study, which reached and exceeded statistical significance by week 5 ($p<0.01$). Both studies also showed that the number and severity of hot flushes continued to decrease week after week until the end of the study, i. e. 3 months of treatment. Secondary endpoints evaluated at 3 months in the C301 study suggest a very positive impact of Donesta® on the quality of life (hot flushes, mood swings, anxiety, sleep, joint pain, skin & hair quality, libido,…) as measured by validated patient-reported outcome questionnaire. For C302 study, results for secondary endpoints at 3 and 12 months are expected end 2022.

Graham Dixon, CSO Mithra Women's Health, commented: *"These positive top-line results demonstrate that Donesta® reduces significantly the frequency and severity of hot flushes and therefore strongly improves the daily quality of life of menopausal women. Menopause lasts for an average of 7 years and requires a safe long-term treatment that can act both on the main symptoms strongly impacting women's private and professional lives, and offer an advantageous benefit/risk profile. These first Phase 3 positive data allow us to pursue with confidence our clinical and regulatory activities. We look forward to receiving the safety data by the end of this year, as well as additional data on all secondary endpoints related to quality of life. Today, we are even more convinced that Donesta® can be a game-changer, offering a global solution to address the unmet needs of menopausal women."*

Clinical Program moving forward

The Donesta® Phase III Clinical Program is still ongoing with patients completing a treatment duration for 52 weeks. Regarding the safety, the independent Data and Safety Monitoring Board (DSMB) completed its last 2021 safety assessment of the Phase 3 Clinical Program of Donesta®. Experts confirmed an expected pharmacological profile during the trial from initiation until the safety evaluation of 2213 subjects treated and recommended to carry on the studies without modification. The primary safety data are anticipated at the end 2022 for the American study and for end H1 2023 for the European study. Depending on the evolution of the Covid-19 situation, study results and regulatory authorizations, Mithra believes it could achieve marketing authorization for Donesta® in H1 2024 for the United States and in H2 2024 for Europe.

Convinced of the potential of Donesta® on other major estrogen deficiency symptoms, Mithra also decided late 2021 to broaden the scope of its Clinical Program with three additional studies on the effect of E4 on vulvovaginal atrophy, skin and hair quality. These studies will be launched in 2022, depending on regulatory agency feedback.

As presented during Mithra's Investor Day held in November 2021[1], a quantitative market research program surveying over 1000 prescribers and women confirmed a large unmet medical need in the menopause market. One in two women currently do not seek medical treatment because of their safety concerns of current hormonal treatment. The research confirmed that women suffer from bothersome symptoms beyond VMS and highlighted the significant opportunity for a novel, safe hormone therapy to treat menopausal symptoms beyond VMS. The global menopause market is currently worth nearly USD 10 billion and is expected to reach around USD 17 billion by 2027[2].

Leon Van Rompay, CEO Mithra Women's Health, commented: *" **2021 was** an incredible year marked by the worldwide launch of our first estetrol product and 2022 is starting off in another great way with these positive efficacy results, which confirm the strong potential of Donesta® as an innovative hormone therapy targeting several major menopausal symptoms. We clearly believe that the unique profile of Donesta® could provide relief for millions of menopausal women in their daily struggle against the negative effects of estrogen loss during menopause."*

****

[1] Investor Day webcast 29/11/2021
[2] Market Research Future, 2020; IQVIA 2019

Webcast

Mithra will host a webcast today at 09:00 CET to further discuss Donesta® top-line results. This live webcast can be accessed on the Company's website (Investor Relations section) or by clicking here. A replay will also be available via this same link shortly after the end of the conference.

For more information, please contact:

Benoît Mathieu (IRO) : +32 473 35 80 18 - investorrelations@mithra.com
Maud Vanderthommen (Press) : +32 473 58 61 04 – press@mithra.com

About E4 Comfort Phase 3 Program

*Donesta® phase III Clinical Program "E4 Comfort" carried out on 2,300 postmenopausal women (40-65 years) includes 2 pivotal studies: one in America (*NCT04090957*-C302); and a second spread over 14 countries in Europe, Russia and America (*NCT04209543 *-C301). Both studies are worldwide randomized, multicenter, double-blind, placebo-controlled trials.*

Each studies is composed of an efficacy and a safety part. The efficacy part in each studies is designed to evaluate the frequency and severity of vasomotor symptoms (VMS) in both hysterectomized and non-hysterectomized postmenopausal participants after treatment with two doses of E4 (15 mg or 20 mg) or placebo for 12 consecutive weeks. For endometrial protection, all non-hysterectomized subjects will receive treatment with 200 mg progesterone (P4) once daily for 14 consecutive days, after completion of the E4/placebo treatment.

The safety part of the C302 study is designed to evaluate the general safety and secondary endpoints (health-related quality of life, treatment satisfaction, hemostasis, lipid and glucose metabolism, breast density and endometrial safety) in hysterectomized and non-hysterectomize women after treatment with E4 20 mg for one year. The safety part of the C301 study is designed to evaluate the endometrial safety of E4 20 mg in combination with continuous administration of 100 mg P4 in non-hysterectomized women for one year.

About Mithra

Mithra (Euronext: MITRA) is a Belgian biotech company dedicated to transforming Women's Health by offering new choices through innovation, with a particular focus on contraception and menopause. Mithra's goal is to develop products offering better efficacy, safety and convenience, meeting women's needs throughout their life span. Mithra explores the potential of the unique native estrogen estetrol in a wide range of applications in women health and beyond. After having successfully launched the first estetrol-based product in 2021, the contraceptive pill Estelle®, Mithra is now focusing on its second product Donesta®, the next-generation hormone therapy. Mithra also develops and manufactures complex therapeutics in the areas of contraception, menopause and hormone-dependent cancers. It offers partners a complete spectrum of research, development and specialist manufacturing at its technological platform Mithra CDMO. Active in more than 100 countries around the world, Mithra has an approximate headcount of 300 staff members and is headquartered in Liège, Belgium. www.mithra.com

Donesta® is a registered trademark of Mithra Pharmaceuticals or one of its affiliates.

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.