Mithra announces promising topline safety results from Donesta® Phase 3 Study in North America

- **Phase 3 North American Study topline safety results support overall good safety profile of Donesta®, Mithra's next generation Estetrol (E4)-based product candidate for menopause, as consistently demonstrated in previous E4 studies.**
- **Topline safety results were demonstrated for the treatment of post-menopausal women aged 40-65 years with moderate to severe vasomotor symptoms with key secondary endpoints achieved, including E4's beneficial effect on cholesterol profile and on bone turnover biomarkers. These highlights will be presented during the webcast dedicated to Mithra's 2022 full year results.**
- **These results will support the filing with U.S. regulatory agency anticipated by end of H1 2023 for a market authorization in H1 2024, whereas primary safety data are anticipated in H1 2024 for Europe with a market authorization in H1 2025.**
- **Full dataset analysis is still in progress.**

Liege, Belgium, 3 March 2023 – 19:00 CET – Mithra (Euronext Brussels: MITRA), a company dedicated to Women's Health, today announced positive topline safety results from the Phase 3 Donesta® pivotal E4 COMFORT clinical trial in the United States and Canada aiming at evaluating the efficacy and safety of Donesta® for the treatment of Vasomotor Symptoms (VMS) in post-menopausal women. Donesta® is Mithra's next generation orally-administered Estetrol (E4)-based hormone therapy product candidate.

The Phase 3 Clinical Program carried out in 2,550 postmenopausal women[1] (40-65 years) includes two pivotal studies: one in North America (C302) and a second in 14 countries in Europe, Latin America and Russia (C301). Both trials are randomized, multicentre, double-blind, placebo-controlled trials. Early 2022, Mithra announced the topline efficacy results of both trials, which demonstrated a meaningful reduction in VMS from baseline and compared to placebo with all co-primary efficacy endpoints statistically (all $p<0.05$) met[2].

Topline safety results

Previous E4 studies have demonstrated the overall's safety profile of Estetrol. Whereas the full dataset analysis is still in progress, these topline safety results not only confirm Donesta®'s safety profile in the treatment of VMS, but also delineate further E4's unique benefit/risk profile for postmenopausal women.

[1] Considering recruitment extension of the C301 endometrial safety study

[2] Mithra's press release, 14/04/2022

In the C302 trial, safety data were captured up to 12 months of treatment either with the 15 mg and 20 mg E4 doses compared to placebo (efficacy part) or open-label with the 20 mg E4 dose (safety part). These topline safety results, evaluated general safety and secondary endpoints such as health-related quality of life, treatment satisfaction, lipid and glucose metabolism and endometrial safety in hysterectomized and non-hysterectomized women.

Key secondary endpoints

Among the highlights of these results, the study confirmed previous clinical and biochemical evidence with minimal changes in hemostasis parameters and hepatic markers, E4's positive influence on bone turnover markers and beneficial effect on cholesterol profile. These results contribute to showcase the unique profile of E4.

At a daily dose of 15 mg or 20 mg, Donesta® was well tolerated in hysterectomized women. In non-hysterectomized women, as expected for an estrogen administered alone, endometrial proliferation was observed and confirmed the need of adding a progestogen to curb related events in this population. Therefore, once the estrogen was first administrated and followed with the administration of progesterone, endometrial thickening was, partially to completely, reversed within a two-week treatment. Most of the treatment emergent adverse events were mild or moderate in intensity.

Webcast

On Tuesday March 7th at 09:00 CET, highlights of these results will be presented during the live webcast for 2022 financial and operating results.

The live webcast can be accessed on the Mithra investor's section or by clicking here. A replay will be available shortly after the close of the call.

Update on European study (C301)

The European study C301 is still ongoing with primary safety data anticipated for H1 2024. Barring any unforeseen event, Mithra confirms its ambition to achieve marketing authorization for Donesta® in H1 2024 for the United States and in H1 2025 for Europe. A marketing authorization that was initially anticipated in Q4 2024 and moved to H1 2025 owing to a slow recruitment.

Graham Dixon, CSO Mithra Women's Health, commented: *"These safety results show Donesta®'s complete profile to safely and effectively treat menopausal symptoms. At the beginning of 2024, the European study (C301) should reinforce the unique safety profile of E4, supporting further the fantastic therapeutic potential of this molecule. After having successfully signed the licence agreement with Gedeon Richter for the commercialization of Donesta® in Europe, these topline safety results will support the upcoming regulatory filing process and bring us closer to a marketing authorization in North America."*

****

For more information, please contact:

Benoît Mathieu (IRO) : +32 473 35 80 18 – investorrelations@mithra.com

About E4 Comfort Phase 3 Program

Donesta® Phase 3 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

ESTELLE® and DONESTA® are registered trademarks 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.