Donesta® Phase III: Recruitment Completion of American Study and Additional Recruitment in the European Study

- **Successful recruitment of 1015 menopausal women for Donesta® Phase III US/Canada pivotal study**
- **Recruitment of additional patients for Donesta® Phase III Europe/Latam, mostly due to Covid-19, with a completion anticipated by H1 2022**
- **Primary efficacy data of both studies anticipated for end 2021**
- **Independent Data Safety Monitoring Board (DSMB) confirmed the safety profile of Donesta®**

Liege, Belgium, 21 September 2021 – 17:45 CEST – Mithra (Euronext Brussels: MITRA), a company dedicated to Women's Health, today announces the completion of recruitment of 1015 menopausal women in the "E4 Comfort" pivotal study[1] of Donesta® in the United States and Canada. Donesta® is a next generation orally-administrated estetrol-based hormone therapy product candidate for the relief of menopausal vasomotor symptoms (VMS).

Launched in late 2019, the Donesta® Phase III clinical program called "E4 Comfort" aims to recruit approximately 2,200 postmenopausal women (40-65 years) and includes 2 pivotal studies: one in North America (United States/Canada – C302); and a second spread over 14 countries in Europe, Latam and Russia (C301).

Both studies are worldwide randomized, multicenter, double-blind, placebo-controlled trials. The studies' primary objective is to measure the effect of treatment on frequency and severity of moderate to severe VMS (i.e. hot flushes), with different doses of estetrol (E4) (15mg and 20 mg), in menopausal women at 4 and 12 weeks of treatment. Secondary objectives include the evaluation of the effect of the treatment on a series of additional key efficacy and safety parameters.

Covid-19 impact

In the European study, the initial recruitment of 1288 women was also completed during summer 2021. After this completion, a thorough analysis of the number of drop-outs was performed which revealed a higher rate than expected. This higher rate was mainly related to patient's reticence to visit hospitals because of Covid-19 and amongst others to perform medical check-ups as recommended by the protocol. In order to mitigate the regulatory consequences of those study drop-outs, Mithra will recruit up to 300 additional non-hysterectomised women. Indeed, these additional data are necessary to address all regulatory requirements to obtain approval for use in non-hysterectomised women, which represents more than 70% of the market[2]. The recruitment of the European study should be completed in the first semester of 2022, which as consequence extends the duration of this second pivotal study.

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[1] For more information about the E4 Comfort Phase III Program, please visit the website of Clinicaltrials.gov by clicking here.

[2] National Health Interview Survey, 2018 data.

In the U.S. and Canadian study, the Covid-19 environment resulted in a slight shift in the recruitment timing (Q3 2021 instead of Q2 2021).

Efficacy topline results

Regarding the safety, the independent Data and Safety Monitoring Board (DSMB) completed its half-year safety assessment of the Phase III Clinical Program of Donesta®. The experts confirmed an expected pharmacological profile during the trial from initiation until the safety evaluation of 2,161 subjects treated and recommended to continue the studies without modification.

The primary efficacy data of both North American and European studies are on track for end of 2021. Depending on the evolution of the Covid-19 situation, study results and regulatory approvals, Mithra believes it could achieve marketing authorization for Donesta® in H1 2024 for the United States/Canada and in H2 2024 for Europe. In the meantime, as the abovementioned delay does not impact the potential of the product nor our business development strategy, Mithra is still in discussions with a range of companies and is determined to fully leverage the potential of its product candidate in menopause. The global menopause market currently stands at nearly USD 10 billion, which is expected to grow to approximately USD 17 billion by 2027[3].

Graham Dixon, CSO Mithra Women's Health, commented: *" In this very challenging Covid-19 context, we are pleased to see that all our actions taken to improve recruitment and mitigate the Covid-19 impact, allowed us to move forward with our Donesta® Phase III Clinical Program. The required additional data that will be generated in the European study extension will allow us to obtain an approval for use in non-hysterectomised women, representing 70% of our targeted market . We strongly believe in the promising potential of Donesta® as a next generation alternative addressing the unmet needs of menopausal women."*

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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 (Covid-19, neuroprotection…). 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

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",

[3] Market Research Future, 2020; IQVIA 2019

"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.