Mithra Launches a Research Programme on Estetrol's Effect in Covid-19 Treatment

- **Women are more likely than men to be spared by Covid-19, with less severe infections and lower mortality rates**
- **Protective role of estrogen against human coronaviruses already demonstrated during the SARS infection, and currently being tested in the U.S. among hospitalized patients**
- **Mithra plans to develop a research program to study Estetrol (E4) mechanism of action in the treatment of Covid-19.**

Liège, Belgium, 25 May 2020 - 7:30 CEST - Mithra (Euronext Brussels: MITRA), a company dedicated to Women's Health, today announces its intention to launch a Phase II study program to assess the potential beneficial effect of Estetrol (E4) on Covid-19 infection. E4 is a naturally occurring estrogen produced by the liver of the human fetus, passing in maternal blood at relatively high levels during pregnancy.

Male-female immune differences

Recent epidemiological studies in China, Italy and the United States indicate that Covid-19 affects more men than women and more severely. Italy has suffered four times as many male deaths as female deaths[1]. In the United States, twice as many men as women die from Covid-19. One explanation for this gender disparity is believed to be biological differences in the immune system.

Estrogen's protective effect

This immuno-sexual difference was already observed with other infectious diseases caused by human coronaviruses, such as Severe Acute Respiratory Syndrome (SARS). An American study showed that male mice infected with the SARS virus developed more frequent, more severe and often more fatal infections than female mice[2]. In addition, removal of the ovaries or administration of anti-estrogens in females aggravated infection and increased fatalities, demonstrating the protective role played by estrogen. Estrogen acts on a protein known as Angiotensin Converting Enzyme 2 (ACE2) and enables its expression to be reduced. This ACE2 protein specifically serves as a gateway for certain coronaviruses (such as the one that causes Covid-19) to enter human cells.

"It would be very interesting to investigate further the effect of estrogen, in particular Estetrol, on the immune response of patients affected by Covid-19," comments Jean-Louis Vincent, Professor of Intensive Care at the Belgian University ULB and intensive care physician at the Erasmus University Hospital in Brussels. *"Pregnant women, naturally under increased influence of estrogens, are relatively unaffected* and

[1] Andrea Remuzzi, Giuseppe Remuzzi, COVID-19 and Italy: what next?, The Lancet, 13 Mars 2020, https://doi.org/10.1016/S0140-6736(20)30627-9

[2] Channappanavar et al., Sex-Based Differences in Susceptibility to Severe Acute Respiratory Syndrome Coronavirus Infection, The Journal of Immunology, April 2017, 198: 4046–4053.

this is strikingly different from *H1N1 flu virus. Furthermore, administering estrogen to patients over a short period of time would not pose any major safety concerns and would be of limited cost."*

Estetrol's unique profile

"*Studies are currently underway at two US hospitals to see if hormones can have an impact on the disease, especially in men*," says Mitchell Creinin, Professor of Gynecology at UC Davis University, *California. "Estetrol has unique properties and a profile of activity that is distinct from that of classical estrogens. It would therefore be interesting to explore its effect on Covid-19 and assess its impact on the blood vessels of infected patients, especially as the virus induces strokes among young patients*."

"Men and women react differently to viral respiratory infections, due to different responses of innate immune cells," adds Professor Jean-Michel Foidart, Permanent Secretary of the Royal Academy of Medicine of Belgium. *"Similarly, changes in estrogen levels in women at puberty, during pregnancy and menopause are associated with changes in their natural immunity. It is therefore considered useful to ascertain the favourable impact of natural human estrogen such as Estetrol, which has a higher safety profile than other classical estrogens. In Belgium, the death rate of women is lower than that of men up to the age of 74. This beneficial gender effect disappears in the 75-84 age group, before reversing after the age of 85. This is consistent with the hypothesis of the protective role of estrogens in women during their hormonal cycle and even up to 15-20 years after the natural menopause"."*

Following epidemiological and clinical data, Mithra has decided to launch a research program on the potential beneficial impact of Estetrol in the treatment of Covid-19. The protocol for this program is currently being developed in consultation with various international experts active in Covid-19 research. This Phase II study should be conducted in late 2020 on both male and female patients infected with the virus.

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Professor Jean-Michel Foidart, Perpetual Secretary of the Royal Academy of Medicine of Belgium, available for interview on request.

About Estetrol (E4)

*E4 is a natural estrogen produced by the human fetus, which passes into maternal blood during pregnancy. Thanks to its favorable pharmacodynamic and pharmacokinetic profile, E4 potentially represents a major breakthrough in various therapeutic fields like contraception and menopause. Potential benefits of E4 include a f*avorable VTE risk profile, lower breast pain and lower carcinogenic potential in the presence of E2, favorable drug-drug interaction profile, minimal increase of triglycerides, good user acceptability, body weight control, excellent cycle control, improved spotting and general well-being.[3] Its safety margin and tolerability also present an opportunity to investigate its use in other areas of Women's

[3] Kluft C et al., Contraception. 2016.; Gerard C et al., Oncotarget. 2015;6(19):17621-36.; Viss- er M et al., Horm Mol Biol Clin Invest. 2012;9:95-103.; Visser M et al., Climactic. 2008;11 Suppl 1:64-8.; Mawet M et al., Eur. J. Contracept. Reprod. Healthcare 2015:1-13.; Apter D. et al., Eur. J. Contracept. Reprod. Healthcare 2017;22:4 ; Apter D. et al., Contraception. 2016;94(4):366-73

Health such as oncology (hormonal cancers), emergency contraception and osteoporosis, as well as in indications that go beyond the sector of Women's Health such as neuroprotection and wound healing.

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. Its three lead development candidates are built on Mithra's unique native estrogen platform, Estetrol (E4): Estelle®, a new era in oral contraception, PeriNesta®, the first complete oral treatment for perimenopause and 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 250 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", "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.