Press release

Aelis Farma announces positive results of non-clinical studies required by regulatory agencies to enter its first CB_1-SSi, AEF0117, in phase 3 clinical trial for the treatment of cannabis use disorder

- **Positive results of *in vivo* toxicology studies in which AEF0117 shows a favorable therapeutic index >13,000 time the active dose:**
  - ✓ **Chronic oral toxicity studies (6 months in rats and 9 months in dog) allowing for unrestricted chronic treatment in humans.**
  - ✓ **Reproductive toxicology studies showing that AEF0117 does not modify embryonic and embryofetal development.**
  - ✓ **Juvenile tox studies permitting the administration of AEF0117 in adolescent, an important target population in cannabis use disorder (CUD).**
  - ✓ **Positive results of phototoxicity studies showing that AEF0117 does not sensibilize to sunlight.**
- **Finalization of the drug substance and drug product late-stage developments allowing its administration in Phase 3 clinical trials.**
- **Completion of environmental risks assessment indicating that AEF0117 does not pose any risk for the environment.**
- **These non-clinical developments confirm the positive feedback from an independent safety committee (DSMB) on the first 115 patients of the phase 2b of AEF0117 in CUD (end of recruitment Q4 2023) that has confirmed the good tolerability of AEF0117 in people with CUD.**

Bordeaux, November 7, 2023 – 6:30 pm CET – Aelis Farma (ISIN: FR0014007ZB4 – Ticker: AELIS), a clinical-stage biopharmaceutical company specializing in the development of treatments for brain disorders, today announces that it has successfully completed all the regulatory non-clinical studies necessary to enter in phase 3 clinical trials AEF0117, the Company's most advanced signaling specific inhibitor of the CB_1 receptor of the endocannabinoid system. AEF0117 is currently tested in a large phase 2b study in people with cannabis use disorder (CUD). CUD is the current definition of cannabis abuse and dependence in the DSM5, the reference diagnostic manual for psychiatric diseases. Recruitment is on track and results are expected in Q2 2024. Thanks to the successful completion of the non-clinical development ahead of schedule, AEF0117 will be prepared to enter pivotal phase 3 clinical trials for CUD upon successful completion of the present phase 2b clinical study and regulatory clearance of the phase 3 protocol.

Pier Vincenzo Piazza, CEO of Aelis Farma, said: *"We are very pleased with the successful end of this campaign of non-clinical studies which shows three important things. First, AEF0117 confirms its safety profile with a safe dose 13,000 times higher than the active dose, which means that no side effects of AEF0117 have been identified in animals. Second, AEF0117 will be ready to enter phase 3 clinical studies after the completion of the current phase 2b in cannabis use disorder, optimizing the pathway to market. Third, Aelis Farma delivers on its promises, in this case ahead of time, highlighting our ability to perform complex clinical and non-clinical programs in parallel. I would like to take this occasion to thank the Aelis team for this great achievement".*

The favorable safety profile of CB_1-SSi resolves a bottleneck in CB_1 pharmacology and opens the way to several markets with strong medical needs

CB_1-inhibitors, a main objective for drug development upended by safety concerns

Developing CB_1 antagonists has been a major goal for the pharmaceutical industry with most of the main players engaged in this endeavor. Indeed, due to its important and diverse physiological roles, CB_1 receptors could be a gateway to addressing several peripheral and central nervous system diseases with significant medical needs. For example, for the periphery: metabolic, fibrotic and skin diseases and for the brain: addiction, cognitive impairments, psychosis and autism spectrum disorders. Unfortunately, the first generation of CB_1 antagonists had unacceptable behavioral side effects and poor therapeutic index often inferior to 10 which led either to their withdrawal from the market (Sanofi, rimonabant) or to the suspension of their developments (e.g. Pfizer, Merck).

To circumvent this problem, some companies have developed periphery restricted CB_1 antagonists, i.e. drugs that work like rimonabant but do not access the brain, such as the compound developed by Inversago, recently acquired by Novo Nordisk. While these drugs are likely safer than the previous generation of CB_1-antagonists, they only target peripheral diseases, and cannot be used for brain disorders.

Aelis Farma's CB_1-SSi allow to address safely the entire spectrum of CB_1-related diseases as they reproduce a natural mechanism used by the brain to control the hyperactivity of the CB_1

CB_1-SSi are not antagonists, which block all the activity of the receptor, but they are able to selectively inhibit only some functional outputs (signalings) of the CB_1. Their name, Signaling Specific inhibitors (SSi), stems from this characteristic. In particular, CB_1-SSi seem able to selectively inhibit the signaling of the receptor linked to pathological states while preserving normal physiological activities. This characteristic confers them their very favorable safety profile. A striking aspect of their action is that they do not modify behavior per se, in animals or in humans, but are able to potently reverse the hyperactivation of the CB_1 induced by cannabis (AEF0117, Nature Medicine[1]) or restore certain impaired cognitive functions (AEF0217).

CB_1-SSi can have this disease specific effect because instead of having an artificial mechanism of action like antagonists, they copy a natural inhibitory mechanism that the brain uses to control a hyperactivity of the CB_1. This mechanism, discovered by the CEO of Aelis Farma, Dr. Pier Vincenzo Piazza, has been fine-tuned by evolution and is mediated by the hormone pregnenolone. Pregnenolone can inhibit CB_1 activity in this signaling specific manner countering the overactive receptor while preserving its normal basal functioning (Science paper[2]). Unfortunately, pregnenolone cannot be used as a therapeutic drug. It has very low oral absorption, a very short half-life because is rapidly transformed in several active steroids (progesterone, testosterone etc..) that can potentially induce serious side effects. CB_1-SSi are new molecular entities that reproduce the signaling inhibition of the CB_1 by pregnenolone, but are well absorbed, stable and not transformed in steroids.

Aelis Farma is developing a differentiated pipeline of CB_1-SSi which will allow to access a large spectrum of CB_1-dependent diseases.

Aelis Farma pipeline overview

AEF0117 is the first CB_1-SSi developed by Aelis Farma, designed to counteract the effects of THC (Δ9-tetrahydrocannabinol), the active ingredient of cannabis. The company has a second CB_1-SSi at the clinical stage, AEF0217, designed to treat cognitive disorders by opposing the effects of an excess of endocannabinoids production by the brain. Both compounds have a favorable safety profile and no effect on normal behavior per se. Aelis Farma, using its proprietary screening platform, has also identified new families of CB_1 compounds, chemically and functionally differentiated from the first two, but sharing the core mechanism of action.

[1] Signaling-specific inhibition of the CB_1 receptor for cannabis use disorder: phase 1 and phase 2a randomized trials; Nature Medicine; 29; pages 1487–1499 (2023); June 8, 2023

[2] Pregnenolone Can Protect the Brain from Cannabis Intoxication; Science; Vol 343, Issue 6166; pp. 94-98; January 3, 2014

The development of AEF0117, for the treatment of cannabis use disorder is progressing according to plan.

AEF0117 is currently in a phase 2b study conducted in 11 clinical centers in the US and coordinated by Pr. Frances Levin (Columbia University, New York). The study, that aims to enroll up to 330 patients, progresses according to plan with recruitment expected to be finalized by Q4 2023. The first results should be available in Q2 2024.

To ensure a smooth transition of AEF0117 to the phase 3 study after a positive phase 2b, Aelis Farma initiated, in parallel with the phase 2b clinical studies, a series of toxicology studies required by the regulatory authorities. These confirmed the very favorable therapeutic index >13,000 time the active dose. Importantly, chronic oral toxicity studies (6 months in rats and 9 months in dog) allow AEF0117 to be used as unrestricted chronic treatment in humans and juvenile toxicity studies enable its administration in adolescents, an important target population in CUD. Furthermore, the reproductive toxicology studies show that AEF0117 does not modify embryonic and embryofetal development. Finally, Aelis Farma has successfully completed environmental risk assessments, indicating that AEF0117 poses no risk to the environment, as well as phototoxicity study, showing that AEF0117 does not sensitize to sunlight. The favorable safety profile observed in these non-clinical studies confirm the positive feedback from an independent safety committee (DSMB) on the first 115 patients of the phase 2b that has confirmed the good tolerability of AEF0117 in cannabis addicts.

AEF0117 development is supported by Indivior, a leading pharmaceutical company in the treatment of addiction

For the development and commercialization of AEF0117 for disorders due to excessive cannabis use, Aelis Farma has an exclusive option-license agreement with Indivior PLC, a leading pharmaceutical company in the treatment of addiction. As part of this agreement, Aelis Farma has received already $30 million (option payment). If Indivior exercises the license option at the end of the phase 2b (H2 2024), Aelis Farma will receive a $100 million license fee and up to $340 million in additional payments contingent on the achievement of development, regulatory and commercial milestones as well as, royalties on net sales of AEF0117 ranging between 12% and 20%. Following the exercise of the option, all development, registration, and commercialization costs of AEF0117 will be borne by Indivior.

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About AELIS FARMA

Founded in Bordeaux in 2013, Aelis Farma is a biopharmaceutical company that is developing a new class of drugs, the Signaling-Specific inhibitors of the CB_1 receptor of the endocannabinoid system (CB_1-SSi). CB_1-SSi have been developed by Aelis Farma based on the discovery of a natural brain defense mechanism made by the team led by Dr. Pier Vincenzo Piazza, the Company's CEO, when he was director of Neurocentre Magendie of the INSERM in Bordeaux. By mimicking this natural mechanism, CB_1-SSi appear to selectively inhibit the disease-related activity of the CB_1 receptor without disrupting its normal physiological activity. CB_1-SSi have consequently the potential to provide new treatments for several brain diseases.
Aelis Farma is currently developing two first-in-class clinical-stage drug candidates: AEF0117 for the treatment of cannabis use disorder (CUD), currently being tested in a phase 2b study in the United States; and AEF0217 for cognitive disorders, including those of Down Syndrome (Trisomy 21), currently in a phase 1/2 study in Spain in people with Down syndrome. The Company also has a portfolio of new innovative CB_1-SSi for the treatment of other disorders associated with a dysregulation of the activity of the CB_1 receptor.
Aelis Farma draws on the talents of more than 20 highly qualified employees.
For more information, visit **www.aelisfarma.com** and follow us on **LinkedIn** and **Twitter**.

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Forward-looking statements

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These forward-looking statements are made only as of the date of this press release and Aelis Farma expressly disclaims any obligation or undertaking to release any updates or corrections to the forward-looking statements included in this press release to reflect any change in expectations or events, conditions, or circumstances on which any such forward-looking statement is based. Forward-looking information and statements are not guarantees of future performance and are subject to various risks and uncertainties, many of which are difficult to predict and generally beyond Aelis Farma's control. Actual results could differ materially from those described in, or implied or projected by, forward-looking information and statements.