Press release

Nature Medicine Publishes Discovery of New Pharmacological Class by Aelis Farma, Phase 2a Study of First Drug Candidate for Cannabis Use Disorder

- **Cannabis use disorder (CUD) affects over 14 million individuals in the US**
- **Despite the urgent need, there are no FDA-approved medications to treat CUD; behavioral treatments have shown limited benefit**
- **AEF0117 is the first of a new pharmacologic class, type 1 cannabinoid receptor signaling-specific inhibitors (CB_1-SSi), with a unique mechanism of action and greater safety and efficacy than prior generations of CB_1 inhibitors**
- **In a phase 2a clinical study in volunteers with CUD, AEF0117 produced statistically significant reductions in the positive subjective and reinforcing effects of smoked cannabis**

Bordeaux (France), June 8, 2023 – 5 p.m. CEST – Aelis Farma (ISIN: FR0014007ZB4 – Ticker: AELIS), a clinical-stage biopharmaceutical company focused on developing treatments for brain diseases, today announced publication of a series of studies describing a new pharmacological class, cannabinoid receptor 1 signaling-specific inhibitors (CB_1-SSi), and its first drug candidate, AEF0117, for the treatment of cannabis use disorder (CUD).

The report, "Signaling-specific inhibition of the CB_1 receptor for cannabis use disorder: phase 1 and phase 2a randomized trials," was published online by the journal Nature Medicine.

AEF0117 is the first compound that selectively inhibits the CB_1 receptor signaling pathway responsible for the addictive effects of cannabis, without interfering with the receptor's fundamental physiological and behavioral functions. This breakthrough approach differs from previous CB_1 receptor antagonists that, due to their broad blockade of all CB_1 receptor activity, caused significant adverse effects preventing their clinical use.

AEF0117, discovered and developed by Aelis Farma, is the first of the new pharmacologic class, CB_1-SSi, which is based on a natural brain mechanism that combats CB_1 receptor hyperactivity. This mechanism was discovered by the research group of Aelis Farma Chief Executive Officer Pier Vincenzo Piazza, MD, PhD, when he was the director of the Neurocentre Magendie of the French National Institute of Health and Medical Research (INSERM) in Bordeaux.[1] This unique mechanism of action enables CB_1-SSi to inhibit only the cellular signals involved in CUD – without disrupting the receptor's physiological activity. The CB_1-SSi class and AEF0117 represent a breakthrough in CB_1 pharmacology.

"This landmark article culminates more than a decade of research, from discovery of this natural brain mechanism to our proof-of-concept clinical trial," said **Dr. Piazza**. *"We are delighted to contribute to the field of neuropharmacology with a class of drugs never tested in humans before. Now, we at Aelis are sponsoring a large, placebo-controlled phase 2b study in collaboration with Columbia University Irving Medical Center, enrolling 330 participants with CUD to evaluate three dose levels of AEF0117 in treating cannabis addiction. Results should be available by mid-2024."*

Because of its unique mechanism of action, AEF0117 significantly reduced phase 2a study participants' self-reported ratings of the positive subjective effects of cannabis, the primary outcome measure, by a mean of 38% ($p<0.04$), while also reducing cannabis use as measured by self-administration ($p<0.05$), the key secondary endpoint. AEF0117 produced no treatment-related serious adverse events or treatment-emergent adverse

events distinct from placebo. These reductions in cannabis effects occurred without precipitating cannabis withdrawal, even for volunteers who smoked several grams of cannabis per day.

"No other medication has been shown to safely reduce the direct effects of smoked cannabis in daily cannabis smokers," said **Margaret (Meg) Haney**, PhD, supervisor of the phase 1 studies and principal investigator of the 2a proof-of-concept study, and Professor of Neurobiology in the Department of Psychiatry at Columbia University Irving Medical Center, where she is the Director of the Cannabis Research Laboratory and Co-Director of the Substance Use Research Center. *"These novel findings clearly suggest that AEF0117 may be an effective approach for patients seeking treatment for CUD."*

Aelis Farma thanks the volunteer study participants, Dr. Haney and her team at Columbia, the National Institute of Drug Abuse, and all the participating study centers and staff for their assistance.

About Cannabis Use Disorder

Cannabis use is widespread and often leads to CUD, the current definition of problematic cannabis use, which encompasses addiction.[2] CUD affects about 14.2 million individuals in the U.S,[3] and its prevalence is increasing worldwide.[4] Currently, CUD is treated using evidence-based behavioral treatments, which often have poor adherence and limited success.[5] No medications are approved by the FDA to treat CUD.

About AEF0117

AEF0117 is the first drug candidate of the new pharmacological class of CB_1-SSi, a rationally designed analog of pregnenolone, the naturally occurring steroid hormone that binds to a specific site on the CB_1 receptor. Pregnenolone and AEF0117 do not modify the binding of agonists to the CB_1 but only block certain signaling pathways activated by cannabinoid agonists, such as THC, on the CB_1. Through this selective mechanism of action, AEF0117 potently inhibits THC's behavioral effects without altering normal behavior. Unlike pregnenolone, AEF0117, is highly bioavailable when taken orally, exhibits favorable pharmacokinetic properties for once-daily administration, and is not converted into other steroids. AEF0117 has a 13,000-fold therapeutic index (i.e., the ratio between the toxic and active dose).

The clinical investigation of AEF0117 to date consists of two phase 1 safety studies (NCT03325595, NCT03443895) and one phase 2a proof-of-concept study (NCT03717272). The phase 1 single ascending dose and multiple ascending dose studies, performed in healthy volunteers, demonstrate that AEF0117 is safe, well tolerated and produces no behavioral changes relative to placebo. AEF0117 has favorable pharmacokinetic characteristics, allowing for once daily dosing, which facilitates medication compliance. The phase 2a study, conducted in 29 randomized participants with CUD who smoked cannabis daily (averaging 2-3 grams/day), demonstrated that AEF0117 significantly decreased both the positive subjective effects of cannabis (the main study endpoint) and the frequency of cannabis use (key secondary objective) without precipitating withdrawal, which has tended to limit the acceptability of inhibitors for addiction treatment.

The development of AEF0117 was made possible by a broad multinational collaboration with the Aelis Farma team. Several research groups of the Neurocentre Magendie of INSERM in Bordeaux contributed to the early preclinical development of AEF0117. The U.S. intramural program of the National Institute of Drug Abuse (NIDA) performed some of the preclinical experiments. Columbia University Irving Medical Center played a seminal role in the coordination and execution of the clinical studies. AEF0117 development has been supported by two NIDA grants, a first grant of $3.3 million and a second one of $4.5 million. AEF0117, is protected by a patent owned by INSERM and University of Bordeaux. Aelis Farma holds an exclusive worldwide license to AEF0117.

Development of AEF0117 as a treatment for cannabis addiction is currently ongoing. A phase 2b U.S. multi-center study, sponsored by Aelis Farma and coordinated by Professor Frances Levin of Columbia University, which will include 330 participants with CUD, is comparing the efficacy of three AEF0117 doses with placebo. Initial results are expected mid-2024. Aelis Farma and Columbia University are also conducting a complementary series of clinical pharmacokinetic studies and nonclinical regulatory studies to prepare AEF0117 for the Phase 3 program.

In summary, AEF0117 is the first drug candidate in the new pharmacological class of CB_1-SSi, which exhibits high specificity, signaling selectivity, and affinity for the CB_1 receptor at a distinct site from where cannabinoid agonists such as THC bind. Because of this selective molecular mechanism of action, AEF0117 potently inhibits the intoxicating effects produced by cannabis and reduces cannabis use without the behavioral side effects of the past generation of CB_1 receptor antagonists that prevented their use in humans. This profile suggests that AEF0117 has the potential to be a safe and novel treatment for CUD, supporting continued confirmatory investigations in phase 2b and phase 3 clinical trials.

About Nature Medicine

The description of AEF0117 development in *Nature Medicine* is unique as it describes the complete development of this new pharmacological class by Aelis Farma, including the chemical design and characterization of the signaling-specific inhibitors of the CB_1 receptor (CB_1-SSi) in collaboration with INSERM; the discovery and development of AEF0117 by Aelis Farma; as well as the clinical investigation with the contributions of Columbia University Irving Medical Center.

Nature Medicine is a monthly journal publishing original peer-reviewed research in all areas of medicine based on its originality, timeliness, interdisciplinary interest, and impact on improving human health. *Nature Medicine* also publishes commissioned content, including News, Reviews and Perspectives, aimed at contextualizing the latest advances in translational and clinical research to reach a wide audience of M.D. and Ph.D. readers. All editorial decisions are made by a team of full-time professional editors. Nature Medicine's 2-year Impact Factor (2021): 87.241

Collaboration with Indivior

Aelis Farma, in June 2021, signed an exclusive option license agreement with Indivior PLC ("Indivior"), a global pharmaceutical company working to help change patient's lives by developing medicines to treat substance use disorders and serious mental illnesses, for the development and commercialization of AEF0117 as a treatment for disorders related to excessive cannabis use. As part of this collaboration, Aelis Farma has received $30 million (option payment) and is eligible to receive, if the option is exercised by Indivior after the current phase 2b, a $100 million license fee (potentially by the end of 2024) and supplementary payments, up to $340 million, in development, regulatory and commercial milestones, as well as royalties in the mid-teen percentage range on global net sales. The option gives Indivior the right to assume all development and commercialization activities for AEF0117 upon successful completion of the phase 2b study. Phase 3 studies and commercialization would then be at Indivior's direction and expenses, while Aelis Farma funds and manages the current Phase 2b.

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 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. Thus CB_1-SSi have significant potential for the treatment of numerous brain diseases.

Aelis Farma is developing two first-in-class clinical-stage drug candidates: AEF0117 for the treatment of 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. The Company also has a portfolio of 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

Some information contained in this press release are forward-looking statements, not historical data. These forward-looking statements are based on current beliefs, expectations, and assumptions, including, but not limited to, assumptions about Aelis Farma's current and future strategy and the environment in which Aelis Farma operates. They involve known and unknown risks, uncertainties, and other factors, which may cause actual results, performance, or achievements, or industry results or other events, to differ materially from those described or implied by such forward-looking statements. These risks and uncertainties include those set out and described in detail in Chapter 3 "Risk Factors" of Aelis Farma's registration document approved by the *Autorité des Marchés* Financiers on January 14, 2022, under number I.22-003.

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.

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