Press Release

Aelis Farma obtains regulatory approval of the Phase 2B trial with AEF0217 in people with Down syndrome

- **AEF0217 is a first-in-class CB_1 receptor Signalling Specific inhibitor (CB_1-SSi) developed as a potential first pharmacological treatment for impairments in adaptive behaviours and cognition in neurodevelopmental disorders, a major unmet medical need.**
- **Regulatory approvals have been obtained via the EU Clinical Trials Information System (CTIS) and from the relevant national competent authorities and ethics committees in France, Italy and Spain for a multinational Phase 2B dose-finding trial in 188 participants with Down syndrome aged 16 to 32 years.**
- **The Phase 2B trial (AEF0217-201) is designed to confirm and extend the positive Phase 1/2 data with AEF0217, which showed a very favourable safety and pharmacokinetic profile, and statistically significant improvements in adaptive behaviours and brain activity in young adults with Down syndrome.**
- **Recruitment is expected to start speedily, last-participant-last-visit is anticipated in Q1 2027 and preliminary results should be available around mid-2027.**
- **The company has implemented several measures that extend its cash runway up to beginning of 2028 included and will pursue a further extension of its financial visibility.**

Bordeaux, France, December 2, 2025 – 07:00 am CET – Aelis Farma (ISIN: FR0014007ZB4 – Ticker: AELIS), a clinical-stage biopharmaceutical company specializing in the development of treatments for brain and peripheral diseases involving the CB_1 receptor, today announces that it has received the approvals from the European Medical Agency (EMA) and from the competent authorities and ethics committees in France, Italy and Spain of the protocol of the Phase 2B clinical study of AEF0217 for the treatment of adaptive behaviours and cognitive impairments in people with Down syndrome (Trisomy 21). Authorizations were granted via the EU Clinical Trials Information System (CTIS) under Regulation (EU) No 536/2014 and by the relevant competent authorities and ethics committees in France, Italy and Spain.

People with Down syndrome frequently present lifelong impairments in adaptive behaviour and cognition for which no pharmacological treatment is currently approved. Standard care is limited to educational, behavioural, and supportive interventions, which often remain insufficient to allow these individuals to reach their full potential in terms of autonomy and quality of life.

Literature suggests that people with Down syndrome present a hyperactivity of the cannabinoid type-1 (CB_1) receptor. Selectively inhibiting this receptor improve cognitive performance and neurobiological activities in genetic animal models of several neurodevelopmental conditions, including Fragile X, Phelan-McDermid and Down syndrome.

AEF0217 belongs to a new class of inhibitors of the CB_1 receptor developed by Aelis Farma, the Signaling Specific inhibitors (CB_1-SSi). CB_1-SSi and AEF0217 have the unique ability to inhibit only certain components of CB_1 activity. This molecular signalling selectivity generates the first CB_1 inhibitors ("first-in-class") showing beneficial pharmacodynamic and therapeutic effects while lacking the adverse effects that caused the arrest of the development of the CB_1 inhibitors of the previous generation, the CB_1 antagonists, which inhibit the entire activity of the CB_1 receptor.

AEF0217 has already been evaluated in a Phase 1/2 randomized, double-blind, placebo-controlled study in 29 young adults (aged 18 to 35 years) with Down syndrome recruited in two centres in Spain. In this trial, participants were treated for four weeks with AEF0217 at 0.2 mg/day. The positive results of this study were communicated in November 2024. The study showed a very favourable safety and pharmacokinetic profile. In addition, after only four weeks of treatment, AEF0217 induced a statistically significant improvement in key adaptative behaviours, as measured by the Vineland Adaptive Behaviour Scales (VABS), such as the ability to communicate, to take care of oneself and to develop social interactions, paralleled with an improvement in brain activity.

The newly approved international multicenter Phase 2B study ("AEF0217-201") is designed to confirm and extend these promising results in a larger population and over a longer treatment duration. This randomized, double-blind, placebo-controlled, parallel-group clinical trial will enrol 188 participants with Down syndrome aged 16 to 32 years across 10 specialised clinical centres in France, Italy and Spain (five in France, three in Italy and two in Spain). Eligible participants will be randomised into four groups receiving once-daily oral treatment with one of three doses of AEF0217 (0.1 mg, 0.2 mg or 0.6 mg) or placebo for 24 weeks, with a subsequent eight-week follow-up period.

The primary objective of the trial is to demonstrate that AEF0217 administered once daily for 24 weeks can induce an improvement in adaptive behaviours compared to placebo, using normalized raw scores of the nine subdomains of the Vineland Adaptive Behaviour Scales, Third Edition (VABS 3), as the primary endpoint. It is noteworthy that improvements in adaptative behaviours measured by the VABS were observed in the previous Phase 1/2 study and, are considered by regulatory authorities as the key endpoint to be used to obtain market approval. Secondary efficacy objectives will evaluate if AEF0217 improves: 1. the main domains of cognition (fluid and crystallised[1]); 2. quality of life; 3. sleep efficiency. Efficacy assessments will be performed at baseline and at Weeks 4, 12, 24 (end of treatment) and 32 (end of the follow-up). Safety will be closely monitored throughout the study period, and an independent data monitoring committee (IDMC) will perform an interim safety analysis after at least 40 participants have completed 12 weeks of treatment. Recruitment of participants should begin in the coming weeks. Last-patient-last-visit is currently anticipated in the first quarter of 2027, with preliminary results expected around mid-2027.

To be able to fully execute this ambitious international trial and pursue the development of its broader CB_1-SSi pipeline, Aelis Farma has implemented a set of operational and cost-optimisation measures over the past months. As a result, the Company now estimates that its cash runway extends to beginning of 2028 included, which encompasses the planned conduct of the AEF0217-201 trial until its data read-out. The Company will continue to explore additional options, including non-dilutive funding, partnerships and further prioritisation, with the objective of extending its financial visibility beyond early 2028.

Pr. Rafael de la Torre Fornell, the principal investigator and global coordinator of the study, comments: "*After the exciting positive results of the previous Phase 1/2 trial,* m*y teams in Barcelona and our colleagues in Spain, France and Italy are thrilled to launch this landmark Phase 2B study. It represents the culmination of several months of meticulous preparation, including meetings and discussions with people with Down syndrome and their families. At present, there is no approved*

[1] Fluid cognition endpoint: change sensitive score of the NIH Toolbox Cognitive Battery for Intellectual Disabilities (NIH TCB for ID).
Crystallised cognition endpoint: Verbal Comprehension Index (VCI) of the Wechsler Intelligence Scale for Children, Fifth Edition (WISC V).

pharmacological therapy for the adaptive behaviours and cognitive disorders associated with Down syndrome. Consequently, demonstrating benefits with AEF0217 in this large study would push boundaries of knowledge in the field and could potentially change the lives of this population in dire need of a treatment for their impairments in adaptive behaviours and cognitive abilities."

Pier Vincenzo Piazza, CEO of Aelis Farma, concludes: *"I am truly delighted with the launch of this Phase 2B study with AEF0217, which represents a significant milestone in the advancement of our program. This is a very innovative cutting-edge trial that uses new types of analyses and measurements specifically adapted to Down syndrome that we have developed with our partners. We are really pleased that the EMA and the national ethics committees have accepted all the proposed innovations. These innovations have been based on the positive results of the Phase 1/2 study with AEF0217, which has shown improvements in several important dimensions of adaptive behaviours and brain activity. This new Phase 2B aims to confirm these benefits on a larger scale and pave the way for the design of Phase 3 trials. I would like to also congratulate the entire Aelis Farma team and the investigators at the participating centres for their commitment and excellence and sincerely thank the many families of people with Down syndrome for their interest and input on how to design a trial best adapted to people with Down syndrome and their caregivers."*

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About AEF0217 and the clinical program for the treatment of adaptive behaviours and cognitive disorders in Down syndrome: the European ICOD project

AEF0217 is Aelis Farma's second clinical-stage drug candidate. It belongs to a new class of drugs discovered by the company, the Signaling Specific inhibitors of the CB_1 receptor of the endocannabinoid system (CB_1-SSi). Hyperactivity of the CB_1 is involved in many brain and peripheral disorders. AEF0217, like the other CB_1-SSi, is able to inhibit only certain components of CB_1 activity. This molecular selectivity generates the first CB_1 inhibitors that show beneficial pharmacodynamic and therapeutic effects but lack the side effects characterizing the CB_1 inhibitors of the previous generation, the CB_1 antagonists that block the entire activity of the CB_1 receptor.

AEF0217 is developed as a new approach for the treatment of cognitive impairments, a group of brain disorders which seem to involve the CB_1 receptor. The first indication targeted by AEF0217 is the impairment in adaptive behaviour and cognition associated with Down syndrome.

The clinical development of AEF0217 so far comprises a Phase 1 programme in healthy volunteers including three independent studies, the recently completed Phase 1/2 study in people with Down syndrome and the current Phase 2B study in people with Down syndrome. These trials are part of the European H2020 ICOD project (Improving COgnition in Down syndrome, Grant Agreement ID 899986). The ICOD project received €6 million of fundings from the European Commission and involves partners in Spain, France and Italy.

About the AEF0217-201 Phase 2B trial

The AEF0217-201 trial ("A randomized, double-blind, placebo-controlled, parallel-group, multicentre, Phase 2B trial to assess the efficacy, safety, and tolerability of AEF0217 for 24 weeks in adults and older adolescents with Down syndrome") is sponsored by Aelis Farma. It is designed to evaluate the efficacy, safety and tolerability of AEF0217 administered once-daily for 24 weeks, followed by an eight-week follow-up period, in 188 participants with Down syndrome aged 16 to 32 years, with mild to moderate intellectual disability and sufficient communication abilities to participate in the trial procedures. The study will be conducted at 10 specialised expert centres in three European countries (five in France, three in Italy and two in Spain) and is carried out in accordance with the Declaration of Helsinki and ICH-GCP guidelines. Participants will be randomised in a 1:1:1:1 ratio to receive one of three oral doses of AEF0217 (0.1 mg, 0.2 mg or 0.6 mg) or placebo once daily.

The primary efficacy endpoint is the change from baseline to Week 24 in adaptive behaviours, assessed using normalized raw scores across the nine subdomains of the Vineland Adaptive Behaviour Scales, Third Edition (VABS-3), which capture communication, daily living skills and socialisation abilities. Adaptive behaviours measured by the Vineland scale are recognised by regulatory authorities as a clinically

meaningful endpoint that can support potential registration in this indication. Key secondary endpoints include measures of fluid and crystallised cognition (NIH Toolbox Cognitive Battery for Intellectual Disabilities and WISC-V), quality of life (Peds-QL) and sleep efficiency (PSQI), as well as a clinician-rated functional assessment specific to Down syndrome. Safety will be monitored throughout the study through clinical evaluations, vital signs, ECGs, laboratory parameters and psychiatric assessments, and an Independent Data Monitoring Committee (IDMC) will conduct an interim safety review after at least 40 participants have completed 12 weeks of treatment. The trial has been authorised under the EU Clinical Trials Regulation (EU) No 536/2014 (EU CT number: 2025-521013-10-00).

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 regulatory mechanism of CB_1 hyperactivity made by the team led by Dr Pier Vincenzo Piazza, the Company's CEO, when he was the director of the Neurocentre Magendie of 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 safe treatments for several brain and peripheral organ diseases.

Aelis Farma currently has two first-in-class clinical-stage drug candidates. AEF0117 for the treatment of cannabis use disorders (CUD), that has shown to be able to decrease cannabis use across two studies. AEF0217 for cognitive disorders, which has shown in a Phase 1/2 to be safe and able to improve adaptive behaviour in young adults with Down syndrome (Trisomy 21). The clinical results obtained with these 2 compounds have confirmed the safety and therapeutic activity of CB_1-SSi in humans. 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, including diseases involving peripheral organs, such as obesity and related metabolic conditions. The different drugs developed by the company belong to the same general pharmacological class, the CB_1-SSi, but have distinct functional effects allowing to target different types of dysregulations of the CB_1 receptor and guaranteeing that the different compounds are not substitutable one with the others.

Aelis Farma draws on the talents of more than 20 highly qualified employees.

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Forward-looking statements

Some information contained in this press release is 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, 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 Universal Registration Document approved by the Autorité des Marchés Financiers on April 28, 2025, under number R. 25-0314s.

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 forwardlooking 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.