

Press Release

Aelis Farma announces positive results of a retrospective study suggesting that AEF0217 effects in people with Down syndrome translate into perceivable improvement in real life.

- **AEF0217 is Aelis Farma's first-in-class Signaling Specific inhibitor of the CB_1 receptor (CB_1-SSi), which has the potential to treat a broad spectrum of cognitive impairments.**
- **In this study, caregivers were asked to report changes in everyday adaptability observed in people with Down syndrome, who received AEF0217 or placebo during a previous randomized placebo-controlled Phase 1/2 trial.**
- **In participants receiving AEF0217, caregivers perceived meaningful and substantial improvements in daily living skills, independence, social interactions and communication that were not observed by caregivers of the placebo group.**
- **The consistency and amplitude of the positive effects observed in this study, rarely found in analysis of behavioral changes, suggest that AEF0217 has a visible and impactful effect on everyday life of people with Down syndrome.**
- **AEF0217 is being tested in a multinational Phase 2b clinical trial in people with Down syndrome. As planned, results are expected by the end of 2027.**

Bordeaux, France, November 6, 2026 – 07:30 AM CET – Aelis Farma (ISIN: FR0014007ZB4 – Ticker: AELIS), a clinical-stage biopharmaceutical company specializing in the development of treatments of diseases involving the CB_1 receptor, today announces positive results from AEF0217-001 clinical trial, an observational retrospective study conducted in the caregivers of people with Down syndrome who previously participated in a Phase 1/2 clinical trial with AEF0217.

In the Phase 1/2 study (AEF0217-102), a randomized, placebo-controlled clinical trial, 28 participants received either AEF0217 0.2 mg (n=18) or placebo (n=10) once daily for 28 days. As announced in November 2024, this study demonstrated that AEF0217 was well tolerated and significantly improved adaptive behaviors in daily living skills, socialization and communication, as measured by the Vineland Adaptive Behavior Scales, Second Edition (VABS-2).

The new retrospective study (AEF0217-001) was not designed to provide independent proof of efficacy but to investigate whether the improvements in adaptive behaviors previously observed in the Phase 1/2 trial using refined complex psychometric assessments, such as the VABS-2, resulted in changes in everyday life of people with Down syndrome perceivable by caregivers.

Caregivers (n=28) were invited to retrospectively answer an online questionnaire evaluating the changes they perceived in everyday adaptability of participants to the previous Phase 1/2 (AEF0217-102). Twenty-six caregivers consented to participate in the study, and 14 caregivers in the AEF0217 group and 8 in the placebo group answered most of the questions and could be fully analyzed (22 caregivers in total).

Given the small sample size and the categorical nature of the parameters studied, differences between groups were analyzed using the absolute standardized mean difference (ASMD) which is the most

appropriate statistical approach to evaluate the effect size of a treatment in these conditions [1]. ASMD evaluates the amplitude and meaningfulness of the differences between groups, ASMD values ≥0.2 indicate small but relevant differences, ASMD values ≥0.5 indicate robust meaningful difference and ASMD values ≥0.8 large substantial difference [2].

The results of this patient-centered retrospective study (AEF0217-001) show that the positive statistically significant effects of AEF0217, measured with sophisticated psychometric tests in a previous randomized Phase 1/2 trial (AEF0217-102), translated into perceivable impactful changes in daily living skills, autonomy, social interactions and communication of people with Down syndrome.

Perceived improvements in everyday functioning, autonomy, social interactions and communication

Global perception of AEF0217 effects

Compared with placebo (10%), a higher percentage (37.5%) of caregivers of participants treated with AEF0217 reported that the observed effects satisfied their expectations of a treatment for cognitive impairment of people with Down syndrome.

The perception of caregivers of the duration of the treatment effects also markedly differed between treatment groups. Caregivers in the AEF0217 groups (27%) perceived that the effects lasted well beyond the end of the treatment, whereas for all the caregivers in the placebo group effects declined shortly after treatment discontinuation.

Perceived improvements in specific behavioral domains

Specific assessments of different behavioral abilities were performed using 19 questions encompassing major areas (named subdomains) of daily living skills, independence, socialization, and communication. Improvements were evaluated by caregivers using an ordinal scale that ranged from 0 (no improvement) to 10 (marked improvement).

Relevant (ASMD> 0.2 n=5), meaningful (ASMD> 0.5, n=6) and substantial (ASMD > 0.8, n=5) differences favoring AEF0217 were identified in 16 of the 19 subdomains assessed (84%). No differences favoring placebo were observed. The highest proportion (81%) of the meaningful (5 out of 6) and substantial (4 out of 5) difference favoring AEF0217 were observed for abilities related to daily living skills, independence and sociability that are particularly important for the autonomy and social integration of people with Down syndrome.

Another difference between caregivers in the AEF0217 and placebo group was the extent of the improvement reported. Thus, for 8 of the 11 abilities showing meaningful or substantial differences, between 28 and 37% of the caregivers in the AEF0217 group reported marked improvements (score>5 in a scale from 0 to 10), whereas the same proportion of caregivers in the placebo groups reported no improvement at all (score=0).

The specific improvements observed were:

- **Daily living skills and independence:** Five of the eight subdomains of this area showed either meaningful (n=4) or substantial difference (n=1) favoring AEF0217. These subdomains concerned the ability to: 1. Manage personal needs (ASMD=0.82); 2. Carryout household tasks (ASMD=0.77); 3. Adapt to new situations (ASMD=0.59); 4. Manage responsibilities (ASMD=0.76); and 5. Navigate activities outside the home (ASMD=0.82).
- **Sociability:** All the subdomains of sociability (n=5) showed either relevant (n=1), meaningful (n=1) or substantial improvements (n=3) favoring AEF0217. These subdomains concerned the ability to: 1. Interact with others (ASMD=0.35); 2. Develop and maintain interpersonal relationships (ASMD=0.83); 3. Demonstrate empathy (ASMD= 0.76); 4. Participate in recreational activities with others (ASMD= 0.81); and 5. Adapt to new situations (ASMD=0.92).
- **Communication:** All the subdomains of communication (n=6) showed either relevant (n=4), meaningful (n=1) or substantial improvements (n=1) favoring AEF0217. The ability to read and understand text showed a meaningful improvement (ASMD=0.58) and the frequency of writing, the use of grammar and spelling had the highest substantial difference of the study (ASMD= 1.00). The four other subdomains showed smaller but relevant differences (ASMD>0.2) and concerned

the ability to: 1. Take part in a conversation (ASMD=0.37); 2. Listen more attentively and respond more appropriately (ASMD=0.24); 3. Understand better spoken and nonverbal information (ASMD=0.30); 4. Express verbally better needs, thoughts, and emotions (ASMD=0.42). These lower ASMDs were not due to smaller improvements in the AEF0217 group for these subdomains, but to the presence of some improvements in the placebo group. In fact, for most of the subdomains of the other abilities (daily living skill, independence and sociability) caregivers in the placebo groups reported no improvement at all. This observation suggests that the highest placebo effect is observed for the domain of communication.

In conclusion, the results of this retrospective study (AEF0217-101) provide convincing evidence suggesting that statistically significant improvements, measured by sophisticated psychometrics tests in a previous phase 1/2 with AEF0217 (AEF0217-102), translate into impactful improvements in the everyday life of people with Down syndrome that were clearly visible by their caregivers. The consistency and amplitude of the effects observed here, rarely found in studies measuring behavioral changes [(3)], strength the confidence in the positive impact that AEF0217 could have on the quality of life of people with Down syndrome.

Prof. Rafael de la Torre Fornell, Principal Investigator of the Phase 1/2 and observational studies, commented:

"The results of this observational study are particularly important because they suggest that the improvements induced by AEF0217, we previously measured with refined psychometric tools, are considered by the caregivers to positively impact on the daily lives of people with Down syndrome.

The consistency of these observations, in all the important abilities studied such as personal autonomy, social interactions and communication, is a particularly encouraging finding. Although this retrospective study was not designed to independently demonstrate efficacy, it provides a valuable additional patient-centered perspective on the potential relevance of the clinical improvements observed already after only four weeks of treatment with AEF0217.

We are now actively working on the ongoing Phase 2b study with AEF0217 that will further advance our understanding of its potential to improve the lives of people with Down syndrome and their families."

Pier Vincenzo Piazza, Co-founder and CEO of Aelis Farma, added:

"These encouraging new observations are another important step in our development program of AEF0217. Our central objective has always been to develop a treatment capable of making a tangible difference in the everyday lives of people with cognitive impairments, particularly in terms of autonomy, social interactions and communication. We have previously reported that AEF0217 statistically significantly improved the adaptive behaviors of people with Down syndrome, as measured by the reference psychometric test VABS-2. Seeing now that these effects of AEF0217 translate into improvements of everyday life that can be perceived by caregivers, strongly support our confidence in the positive impact that AEF0217 could have on the life of people with cognitive impairments.

We are now fully focused on the successful execution of an international Phase 2b study with AEF0217 in people with Down syndrome. The study is progressing according to plan with results expected by the end of 2027. This study represents a major milestone in our ambition to develop an innovative treatment addressing important unmet medical needs in the area of cognitive impairments."

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About AEF0217

AEF0217 is a first-in-class drug candidate developed by Aelis Farma for the treatment of a broad spectrum of cognitive impairments. It belongs to a novel pharmacological class discovered by the Company, the Signaling Specific inhibitors of the CB_1 receptor (CB_1-SSi).

AEF0217 selectively inhibits specific components of CB1 receptor intracellular signaling that seem associated with pathological states while preserving normal physiological functioning of the receptor, which predicts good tolerability and efficacy.

AEF0217 has shown in preclinical studies the ability to restore a broad spectrum of cognitive impairments associated with neurodevelopmental disorders, autism and aging.

The first clinical proof of concept of AEF0217 efficacy has been obtained in people with Down syndrome in a placebo controlled, multicentric, randomized Phase 1/2 clinical trial. As predicted, AEF0217 has also demonstrated very favorable safety and tolerability profile both in healthy volunteers and in people with Down syndrome.

AEF0217 ongoing Phase 2b clinical trials

Building on the positive safety and efficacy findings obtained so far with AEF0217, Aelis Farma is currently conducting an international, multicenter, randomized, double-blind, placebo-controlled Phase 2b clinical study with AEF0217 in people with Down syndrome.

The study is designed to further evaluate the safety and efficacy of AEF0217 and confirm its ability to improve adaptive behaviors and cognitive functions.

The trial plans to enroll 188 participants aged 16 to 32 years across clinical centers in France, Spain and Italy, with participants receiving placebo or one of three doses of AEF0217 (0.1, 0.2 and 0.6) once a day for six months.

In July 2026, following the first scheduled safety review, an Independent Data Monitoring Committee identified no safety concerns and recommended that the study continue without modification to the protocol.

The Phase 2b study continues to progress according to plan with clinical results expected by the end of 2027. These upcoming results will represent an important milestone in confirming the therapeutic potential of AEF0217 in people with Down syndrome and support the next stages (Phase 3 studies) of its clinical development.

This Phase 2b is part of the European ICOD (Improving Cognition in Down syndrome) project, supported by the European Union's Horizon 2020 research and innovation program (Grant Agreement No. 899986)

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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 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 consequently are predicted to be both safe and efficacious to treat many diseases of the brain and peripheral organs.

Aelis Farma currently has two first-in-class drug candidates. Clinical results obtained with both compounds have confirmed the safety and therapeutic efficacy of CB_1-SSi in humans. The first candidate, AEF0117, for the treatment of cannabis use disorder (CUD), has shown its ability to reduce cannabis use in two studies. The second candidate, AEF0217, for the treatment of cognitive impairments, showed a good safety profile and an improvement in adaptive behavior in young adults with Down syndrome in a Phase 1/2 study. On this basis, a Phase 2b study has started in Europe to confirm the efficacy and safety of AEF0217 in a larger

cohort of participants with Down syndrome. The Company also has a platform developing a portfolio of innovative CB_1-SSi for the treatment of other diseases involving the brain and peripheral organs. The new compounds share the same core mechanism of action but have distinct structures and functional effects enabling them to target different disease areas and ensuring that they are not substitutable for one another.

References:
1. Ferguson, C. J. (2009). An effect size primer: A guide for clinicians and researchers. Journal of Graduate Medical Education, 1(2), 301–304. doi.org
2. Cohen, J. (1988). Statistical power analysis for the behavioral sciences (2nd ed.). Lawrence Erlbaum Associates.
3. Hedges, L. V., & Olkin, I. (1985). Statistical methods for meta-analysis. Academic Press

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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 filed with the *Autorité des Marchés Financiers* on April 23, 2026, under number D.26-0284.

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.