Press release

NFL Biosciences significantly raises its efficacy targets for smoking cessation

- **In-depth understanding of the mechanism of action of its drug candidates based on new data**
- **Enhanced clinical development strategy based on these advances, targeting clinical efficiencies superior to those of current treatments**
- **Identification of a novel mechanism of action in smoking cessation, paving the way for continued clinical development of NFL-101 targeting a subpopulation of smokers with an increased response potential**
- **Introduction of NFL-102, a drug candidate with an extended mechanism of action, intended for the general smoking population to achieve superior efficacy compared to standard treatments across the entire population**
- **NFL-101 acts primarily on neuroinflammation, while NFL-102 targets the central mechanisms of smoking cessation by modulating key signaling pathways, in particular CREB, recognized as a major regulator of tobacco addiction**
- **Unchanged projected clinical development timelines and reduced costs for confirmatory studies**
- **Active search for strategic partners for Phase 3 financing**
- **Extension of intellectual property rights with a new patent application extending protection until 2047 and expanding to other addictions beyond tobacco and nicotine**

Montpellier, France, January 26, 2026 – 5:45pm CET – **NFL Biosciences SA (Euronext Growth Paris – FR0014003XT0 – ALNFL)**, a biopharmaceutical company developing innovative botanical drugs for the treatment of addiction, announces today that it is significantly raising the efficacy targets for its drug candidates in smoking cessation.

Bruno Lafont, CEO and Co-founder of NFL Biosciences: *"This in-depth understanding of the mechanism of action of tobacco extracts as smoking cessation treatments now enables the company to deploy a more ambitious strategy, targeting higher levels of efficacy, secured by NFL-101, which only needs to confirm its efficacy in a subpopulation specifically selected for its better response, while NFL-102 is based on a composition with an extended mechanism of action designed to enhance efficacy across the entire smoking population."*

1) Evidence of a novel mechanism of action in smoking cessation

Smoking induces lasting immune changes. Subcutaneous administration of tobacco extracts reactivates this pre-existing immune memory in smokers and induces a transient innate immune signal associated with the normalization of brain biomarkers affected by smoking cessation.

Previous preclinical and clinical studies, conducted in collaboration with the Georges Pompidou European Hospital (HEGP), had shown that the injection of tobacco extracts reactivated an immune memory associated with smoking, inducing an innate immune response, and that this activation was correlated with prolonged smoking abstinence (see press release dated March 24, 2025).

In addition, preclinical work conducted by the French Alternative Energies and Atomic Energy Commission (CEA) had shown a normalization of activity in certain regions of the brain after administration of tobacco extracts to mice that had previously been exposed to tobacco and then placed in a withdrawal situation (see press releases dated January 30, 2024, and May 5, 2025).

The objective was now to identify the molecular mechanisms responsible for modulating brain activity, known biomarkers of smoking, to elucidate a complete mechanism of action, in line with the expectations of regulatory agencies and potential pharmaceutical partners.

<u>Study of the effect of smoking cessation on brain biomarkers:</u>

The CEA conducted a proteomic analysis of mice brains that had been exposed to tobacco for four weeks and then placed in withdrawal conditions for 16 days after receiving a placebo or tobacco extracts. Samples were taken from the prefrontal cortex and thalamus at the end of the study, on day 16. The thalamus is rich in nicotinic receptors, while the prefrontal cortex plays a key role in controlling behavior by exerting top-down inhibitory regulation on reward circuits; its alteration by chronic smoking compromises this control, reducing the ability to resist cravings and promoting relapses.

Two extracts were studied: NFL-101 and NFL-102. NFL-102 contains the same components as NFL-101 but also other components from tobacco leaves and has successfully passed the same preclinical toxicity studies as NFL-101.

NFL-101 reduces the expression of several markers of neuroinflammation, particularly cytokines and growth factors involved in smoking-related inflammation ($p < 0.001$ to $p < 0.0001$).

NFL-102 normalizes signaling pathways that are overactive during smoking cessation, significantly lowering CREB ($p < 0.001$), NF-κB ($p < 0.05$), and JNK ($p < 0.001$), as well as smoking-associated astrogliosis, with a significant decrease in GFAP ($p < 0.01$), and decreases the expression of pro-inflammatory cytokines ($p < 0.01$ to $p < 0.0001$).

Nicolas Tournier, Pharmacologist, Radiopharmacist, and Director of the Pharmacological Neuroimaging Team at the CEA, states: *"Smoking cessation often fails because the brain remains permanently marked by tobacco. Our results suggest that there is a persistent neuroimmune context and lasting changes in neural signaling, particularly in the prefrontal cortex, which could contribute to weakened impulse control and increase the risk of relapse. During withdrawal, several signaling pathways remain abnormally active: CREB, known for its central role in the development of tobacco addiction through the reorganization of neural circuits; JNK, involved in the cellular and behavioral stress response; and NF-κB, a major player in neuroinflammation. Added to this is astrogliosis, i.e., the chronic activation of astrocytes, the most abundant cells in the brain, which contributes to cerebral disorders associated with craving. NFL-101 reduces neuroinflammation and NFL-102 modulates these markers and attenuates the neuroimmune and neuronal imprint of smoking, which goes beyond simply controlling the effects of withdrawal*."

Find the mechanistic differences between NFL-102 and current smoking cessation treatments in the appendix to the press release.

2) **Differentiating characteristics associated with response to NFL-101 treatment**

Additional exploration analyses conducted on a sample of CESTO2 participants indicate that participants with certain characteristics have significantly higher sustained abstinence rates than those observed in the overall study population.

These preliminary results, based on analyses of a sample of around 60 participants, will need to be refined by analyzing the characteristics of all CESTO2 study participants. The data currently available suggest an **efficacy of between 35% and 60% in a subpopulation representing approximately one-third of the general population**.

As a reminder, the efficacy in terms of continuous abstinence for 4 weeks, confirmed by urinary cotinine testing, was 24.1% in the general population, significantly higher than that of a placebo and comparable to current treatments.

3) Respective positioning of NFL-101 and NFL-102

The development of **NFL-101 and NFL-102 covers two complementary aspects of smoking cessation**: controlling active inflammation during withdrawal in targeted smokers and normalizing overactive signaling pathways during smoking cessation and reducing astrogliosis in the general smoking population.

The two candidates are designed to be potentially sequential in the event of failure of the first treatment. The order of prescription could depend on the validation of the predictive biomarker associated with NFL-101 and the level of clinical efficacy demonstrated by NFL-102 in the general population.

4) A reinforced clinical development strategy based on recent results

For the record, in its initial plan, the company had planned to continue the clinical development of NFL-101 through a two-part Phase 3 study: a first part aimed at confirming the efficacy observed in the CESTO2 Phase 2 study, followed by a second part aimed at validating efficacy in the general population, with approximately 900 participants and a 12-month follow-up period.

Considering the recently obtained results, the company is now implementing a reinforced and more efficient clinical development strategy based on two complementary drug candidates, NFL-101 and NFL-102, with no impact on the overall development timeline.

NFL-101: development targeted at a high-response subpopulation

NFL-101 aims to reduce functional inflammation induced by smoking and has already demonstrated its clinical efficacy in the CESTO2 Phase 2 study.
The comprehensive analysis of the discriminating characteristics of all participants in this study, expected in the coming months, will confirm both the superior level of efficacy observed and the size of the targeted subpopulation.

The identified predictive biomarker will then be validated for use in Phase 3 for participant selection.

Given the expected higher efficacy in this target population, the initial two-part Phase 3 design is no longer necessary. The development of NFL-101 would proceed directly to a pivotal Phase 3 study, with a significantly reduced number of participants compared to the initial plan in the general population, automatically leading to a substantial reduction in development costs.

NFL-102: a development for the general population with an expanded mechanism of action

NFL-102 is intended for the general smoking population. Its enriched composition and more comprehensive mechanism of action aim to normalize the signaling pathways that are overactivated during smoking cessation and reduce astrogliosis, with expected efficacy superior to that of NFL-101 in the general population.

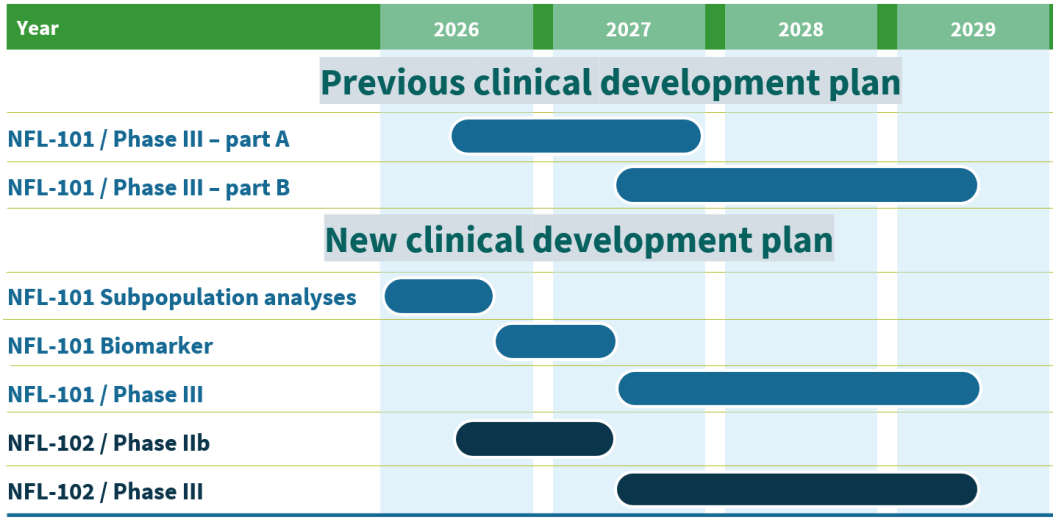
NFL-102 has been successfully evaluated in the same preclinical studies as NFL-101, at doses up to 600 times the clinical dose, with conclusive genotoxicity and mutagenicity data.

The company plans to file a Phase 2b clinical trial application in mid-2026, aiming to demonstrate efficacy, select the dose, and confirm safety.

This dose selection study would be conducted in France at around ten clinical centers and would include 450 participants randomized in a double-blind, placebo-controlled trial. Four doses would be evaluated, with 100 participants for three of them and for the placebo, and 50 participants for a minimum expected dose with no effect. Two treatment administrations are planned on days 1 and 8. The primary endpoint will be continuous abstinence for 4 weeks, measured between day 15 and day 43 and confirmed by urinary cotinine testing. The visit on day 43 will be the last visit of the study. An independent Data and Safety Monitoring Board (DSMB) will review safety data after the first 30 participants have been enrolled to authorize further enrollment.

The follow-up period, limited to 43 days, will reduce costs per participant and facilitate recruitment, with an **overall budget estimated to be slightly lower than that of the first part of the Phase 3 trial initially planned with NFL-101**.

At the end of this Phase 2b, the company could launch a **pivotal Phase 3 study**, the number of participants in which will depend on the results obtained but should be **significantly less than 900**, which would also allow for a **substantial reduction** in clinical development costs.



Support from a strategic partner will be preferred for the financing of phases 3.

5) Extension of intellectual property rights until 2047

The composition of NFL-102 was the subject of a new patent application filed in January 2026, extending intellectual property protection until 2047 and broadening its scope to other addictions beyond tobacco and nicotine, including alcohol, psychostimulants, opioids, and cannabinoids. This extension is based on the central role of the CREB signaling pathway in the neurobiological mechanisms common to these addictions, particularly the processes of neuroadaptation, tolerance, dependence, and craving maintenance.

The company is **prepared to file an additional patent application** relating to the subpopulation and biomarker predictive of NFL-101 efficacy following confirmation by the full analysis of CESTO2 study participants.

About NFL Biosciences: www.nflbiosciences.com

NFL Biosciences is a biopharmaceutical company based in the Montpellier region of France, developing plant-based drug candidates for the treatment of addictions. NFL Biosciences' ambition is to bring new, safer and more effective natural therapeutic solutions to the entire world population, including low- and middle-income countries. Its most advanced product, NFL-101, is a standardized tobacco leaf extract protected by three patent families. NFL Biosciences intends to offer smokers wishing to quit a natural, safe, easy-to-administer and personalized alternative. NFL Biosciences is also developing NFL-301, a natural drug candidate for the reduction of alcohol consumption and has a drug development project for the treatment of cannabis use disorders.

NFL Biosciences shares are listed on Euronext Growth Paris (FR0014003XT0 - ALNFL). The company is qualified as an "Innovative Company" eligible for FCPI investment. More information on www.nflbiosciences.com

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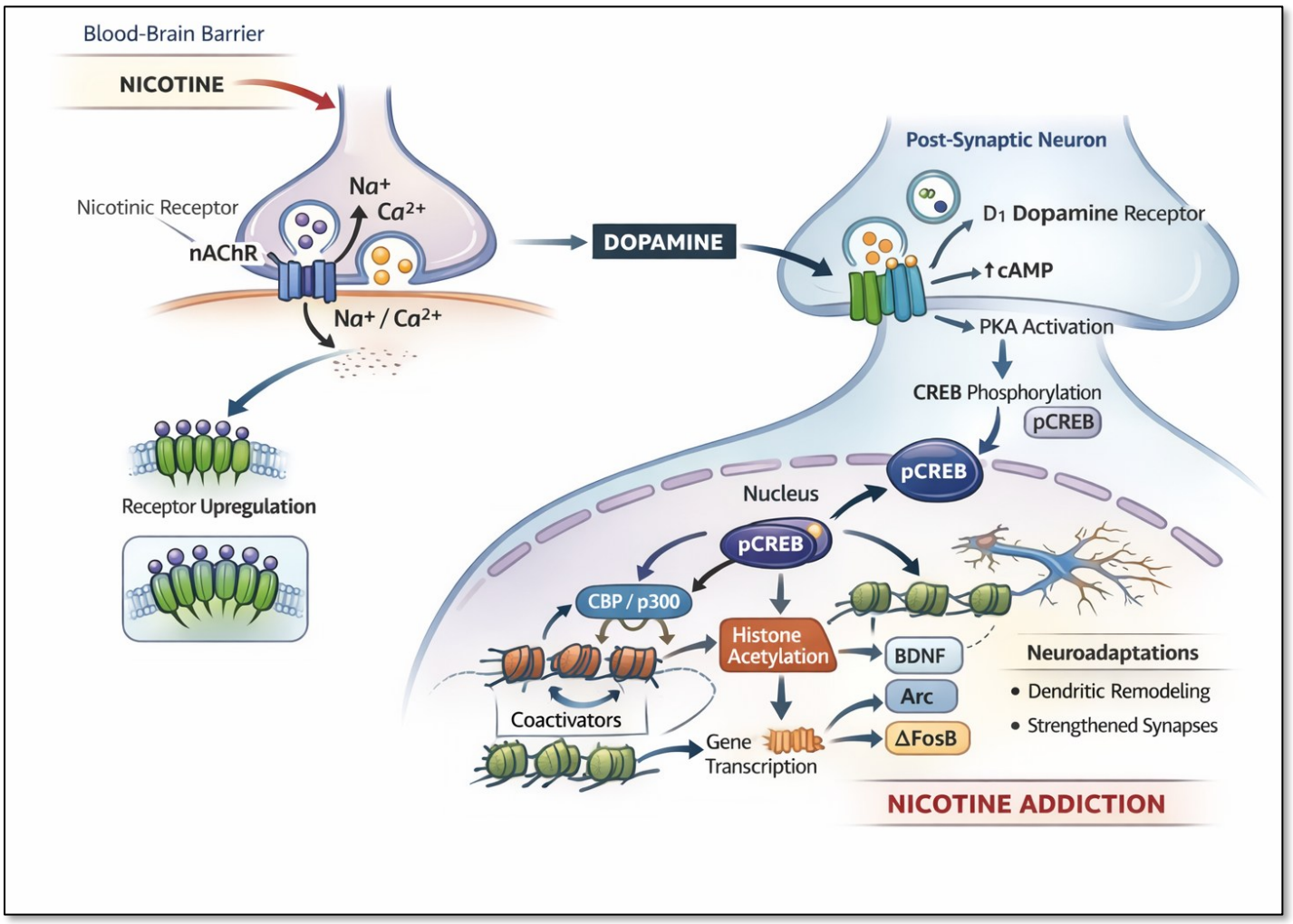
APPENDIX

Mechanistic differences between NFL-102 and current smoking cessation treatments:

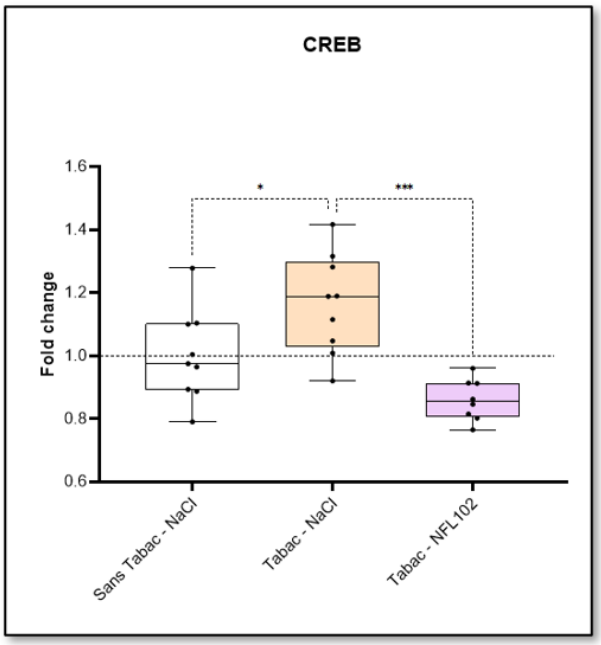
Current smoking cessation treatments (nicotine replacement therapies, varenicline, cytisine) act primarily on nicotinic receptors to alleviate withdrawal symptoms associated with nicotine cessation. While they provide temporary relief from withdrawal, they do not directly address the lasting changes in neural signaling and neuroplasticity induced by tobacco addiction, which persist after cessation and contribute significantly to the risk of relapse.

Conversely, NFL-102 acts downstream of nicotinic receptors, modulating signaling pathways that are permanently altered by smoking. NFL-102 significantly reduces CREB activity, which current scientific research identifies as a major regulator of tobacco addiction, involved in maladaptive neuroplasticity and the reorganization of neural circuits underlying addictive behaviors.

Nicotine activates nicotinic receptors (nAChR), inducing dopamine release and activation of the cAMP/PKA/CREB pathway in postsynaptic neurons. CREB phosphorylation leads to epigenetic and transcriptional changes responsible for lasting neuroadaptations, contributing to the development and maintenance of nicotine addiction.



Results of the proteomic study on CREB:



CREB in the prefrontal cortex

Consequence of tobacco exposure:
The group of mice exposed to tobacco and given a placebo expressed significantly more CREB than the group not exposed to tobacco and given a placebo ($p < 0.05$).

Correction by NFL-102:
The group of mice exposed to tobacco and given NFL-102 expressed significantly less CREB than the group exposed to tobacco and given a placebo ($p < 0.001$).

Controlled normalization:
There is no significant difference in CREB expression between the group not exposed to tobacco and given a placebo and the group exposed to tobacco and NFL-102.

By targeting CREB as a key mechanistic node, NFL-102 differs from current treatments in its approach to correcting the neural circuits involved in relapse, beyond simply controlling withdrawal symptoms.