

RETHINKING THE TREATMENT OF NICOTINE ADDICTION

From the clinical development of NFL-101 to the emergence of NFL-102: **a refocused strategy based on efficacy, personalization and preparation for the next clinical phases**

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EDITORIAL

Bruno Lafont,
Chief Executive Officer and co-founder of NFL Biosciences

Ladies and Gentlemen, dear shareholders,

NFL Biosciences' latest announcements mark an important step in the structuring of our strategy in smoking cessation. The new results from the Phase 2 CESTO II study confirm the potential of NFL-101 within a personalized medicine approach, based on the identification of a predictive biomarker consistent with its immunomodulatory mechanism of action.

This biomarker, based on baseline levels of NFL-101-specific IgG1, makes it possible to identify a target population representing approximately 57% of the patients analyzed. In this population, the efficacy of NFL-101 is significantly enhanced, and the difference versus placebo is greater, with statistically significant results versus placebo at 4 weeks, the period corresponding to the primary endpoint of the CESTO II study. These data validate the strategy announced at the beginning of the year, aimed at achieving higher and more differentiated levels of efficacy in smoking cessation.

The value of this approach is twofold. From a clinical perspective, it could enable better selection of the patients most likely to benefit from the treatment. From a development perspective, it opens the way to optimizing future Phase 3 studies, with potentially reduced patient numbers and a clearer asset profile for both regulatory agencies and industrial partners.

These results also strengthen the attractiveness of NFL-101 from a partnership perspective. By combining enhanced efficacy in a significant target population, a predictive biomarker protected by a patent application, a simple administration regimen and a favorable tolerability profile, NFL-101 has a strongly differentiated positioning in an area where medical needs remain significant.

Our roadmap is clear: to continue developing NFL-101 in the population of patients carrying the biomarker, while evaluating NFL-102 in the general population of smokers. NFL-102 is a drug candidate developed for smoking cessation with an approach complementary to that of NFL-101, intended to address a broader population of smokers. The next data will make it possible to determine the priority program for Phase 3, with the objective of selecting the asset with the strongest clinical, industrial and partnership potential.

In this shareholders' letter, we also wish to answer the main questions you have addressed to us following these announcements. Transparency, education and dialogue with our shareholders remain essential at this new stage of development.

I would like to thank our teams, our scientific partners and our shareholders for their trust. Our ambition remains unchanged: to develop innovative, natural and differentiated solutions in addictions, for the benefit of patients and long-term value creation.

Bruno Lafont

Our mission

Rethinking and improving the treatment of addictions with safe, natural and effective botanical drugs, giving patients the means to overcome them and lead healthier lives.

A paradigm shift in the understanding and treatment of nicotine addiction

Nicotine addiction is no longer viewed solely as a temporary imbalance in the brain, but as a chronic condition that durably modifies certain neural circuits. Over time, nicotine alters the mechanisms associated with pleasure, stress and habits.

It also acts on the brain's support cells, which can maintain this state of dependence. This approach helps explain why the risk of relapse remains high, even after smoking cessation.

Current treatments mainly relieve withdrawal symptoms; **research aims to go further, helping the brain restore more stable functioning and reduce relapses.**

Our two drug candidates

in smoking cessation

NFL-101

Botanical drug candidate composed of tobacco leaf proteins, developed for smoking cessation. **Its mechanism of action is based on immune and neuroimmune modulation rather than on nicotinic receptors.** Clinical data suggest that it **promotes abstinence by stimulating anti-tobacco immune responses, reducing neuroinflammation and restoring certain brain functions altered by chronic smoking.**

NFL-102

Drug candidate designed to reduce vulnerability to relapse after smoking cessation. **It acts on neurobiological pathways involved in the persistence of addiction, neuroplasticity and cellular stress.** Preclinical data suggest that it could help **restore the flexibility of neural circuits linked to motivation and reward**, beyond simply relieving acute withdrawal symptoms.

What are the differences between NFL-102 and NFL-101?

NFL-102 contains the components of NFL-101, with an expanded composition enriched with additional compounds derived from tobacco leaves. While NFL-101 primarily targets immune and neuroinflammatory mechanisms, NFL-102 more broadly targets the molecular mechanisms involved in the persistence and chronicity of nicotine addiction.

Watch the video on NFL-102's mechanism of action

Clinical advances and next steps

NFL-101

Additional analyses from the Phase 2 CESTO II study made it possible to identify a patient subpopulation, referred to as **BM+**, defined by baseline NFL-101-specific IgG1 levels below 200 ng/mL. This population represents approximately 57% of the participants analyzed and shows an enhanced response to treatment. In this population, **NFL-101 achieved a 4-week continuous abstinence rate of 36.1% versus 19.0% for placebo, with statistical significance reached using both confirmation methods.**

This advance opens up an important clinical perspective for NFL-101: **its development could now follow a personalized medicine approach**, with the specific IgG1 biomarker used as an inclusion criterion in the next clinical study.

This strategy aims to:

- select the patients most likely to respond to treatment,
- improve the efficacy levels observed,
- potentially reduce the number of subjects required in future studies.

NFL-102

NFL-102 is being developed as a drug candidate enriched with certain compounds and featuring an extended mechanism of action. Unlike NFL-101, **NFL-102 targets the general population of smokers.** Its clinical development is based on the **Phase 2 TONIC study, designed to confirm its safety, assess its efficacy and select the optimal dose.** NFL-102 therefore represents a second development path, potentially broader in terms of target population, provided its clinical results are confirmed.

Our clinical pipeline in smoking cessation

Our clinical development strategy

NFL Biosciences' clinical strategy will consist in comparing the potential of the two programs before Phase 3. The results obtained with NFL-101 in the BM+ population represent a **strategic benchmark**: if NFL-102 reaches or exceeds this level of efficacy in the general population in the TONIC study, it could be prioritized for advancement into Phase 3. Conversely, NFL-101 in the BM+ population would become the priority program. This approach enables NFL Biosciences to maintain two complementary clinical options, while directing its resources toward the candidate with the strongest medical, industrial and partnership potential.

FAQ

What do the new results on NFL-101 show?

NFL Biosciences presented new efficacy analyses from the Phase 2 CESTO II study. These analyses identify a target population of patients carrying a biomarker defined by baseline NFL-101-specific IgG1 levels below 200 ng/mL before treatment. This population represents 57.2% of the patients analyzed.

In this target population, NFL-101 showed enhanced efficacy versus placebo. In other words, compared with the general population, efficacy in the target population is higher, the effect size versus placebo is greater, and statistical significance versus placebo is reached over the 4-week period corresponding to the primary endpoint, using both confirmation methods: urinary cotinine and exhaled CO. These results support the continued development of NFL-101 in a personalized medicine approach, which will need to be prospectively confirmed in the next clinical study.

What is the target population carrying the biomarker?

The target population corresponds to patients whose baseline NFL-101-specific anti-IgG1 level is below 200 ng/mL before treatment. In CESTO II, 306 of the 318 patients were analyzed, and 57.2% of them presented this profile.

These patients have an immunological profile that is more receptive to the action of NFL-101. Conversely, patients not carrying the biomarker have a less receptive immunological profile. Efficacy in these patients was found to be comparable to that of placebo.

What are IgG1 and specific IgG1?

IgG1 are a subclass of antibodies associated with acquired immune responses and immunological memory. NFL-101-specific anti-IgG1 reflect the immune memory developed over time through chronic exposure to tobacco.

As NFL-101 is composed of tobacco leaf protein extracts, these antibodies indicate prior recognition of these antigens by the immune system. Their baseline level therefore provides information on the patient's pre-existing immune status with regard to tobacco antigens.

What does the IgG1 < 200 ng/mL threshold mean?

The 200 ng/mL threshold corresponds to the concentration used to distinguish patients carrying the biomarker from those not carrying it. "ng/mL" means nanograms per milliliter, a concentration unit used to measure antibody quantities in a biological sample.

Patients with low NFL-101-specific IgG1 levels retain immune receptivity that allows NFL-101 to act fully. Conversely, patients with higher levels are thought to already have an established or more tolerogenic immune response, associated with lower receptivity to the treatment.

How should the 4-week and 12-month results be interpreted?

When the protocol was designed, the number of patients to be included was calculated based on efficacy assumptions for 4-week continuous abstinence. This 4-week abstinence period was defined as the study's primary endpoint, meaning the endpoint on which statistical significance had to be demonstrated for the study to be considered successful. The other continuous abstinence measures, up to 12 months, are secondary endpoints designed to document the persistence of the treatment effect. As the number of patients to be included was not defined based on these endpoints, statistical significance was not expected for them.

For the 4-week and 12-month endpoints, compared with the general population, efficacy in the target population is higher and the difference versus placebo is greater. In addition, for the 4-week endpoint, statistical significance versus placebo is reached using both validation criteria, urinary cotinine and exhaled CO.

Does the absence of statistical significance at 12 months call the results into question?

No.

CESTO II was designed to demonstrate efficacy on 4-week continuous abstinence, which was the protocol's primary endpoint. Continuous abstinence at 12 months was a secondary endpoint. The number of patients, calculated for the primary endpoint, was not sufficient to demonstrate a statistically significant difference at 12 months, as continuous abstinence naturally decreases over time.

For the 12-month endpoint, compared with the general population, efficacy in the target population is higher and the difference versus placebo is greater. Ultimately, an efficacy rate of 21.3% at 12 months and a 2.4-fold efficacy ratio versus placebo are excellent results, demonstrating the value of selecting this target population.

Why is this referred to as a post-hoc analysis?

It is referred to as a post-hoc analysis because the biomarker was not predefined in the initial CESTO II protocol. NFL-101-specific IgG1 levels were analyzed as part of the work to better understand NFL-101's mechanism of action, and the 200 ng/mL threshold was identified based on the study data.

This does not make the analysis irrelevant. It simply means that the biomarker was identified during an exploratory and biological understanding phase. To become a fully robust tool in clinical development, it will need to be prospectively confirmed in a future study, with a threshold and use defined in advance.

What does prospective confirmation of the biomarker mean?

Prospective confirmation means testing the biomarker in a new study designed from the outset to use it. In practical terms, the specific IgG1 threshold and biomarker carrier status would be defined before patient inclusion and analysis.

NFL Biosciences plans to integrate patient biomarker carrier status as an inclusion criterion in the protocol of the next NFL-101 clinical study. This step is important because it must confirm that the relationship observed in CESTO II can be reproduced in a pre-specified study.

Has the biomarker already been validated?

The four evaluation criteria are met in the available analyses: enhanced efficacy in biomarker-carrying patients, comparable placebo response between subpopulations, limited effect in non-biomarker-carrying patients, and biological consistency with the mechanism of action.

However, regulatory validation of a biomarker requires prospective confirmation. The most precise wording is therefore that the biomarker is supported by coherent and promising data from CESTO II, and that its prospective confirmation is planned in the next clinical study.

Why compare NFL-101 with Champix if the comparison is indirect?

NFL Biosciences presents the comparison with the EAGLES study as an indirect comparison, intended to provide positioning evidence. It does not constitute a direct comparative study between NFL-101 and Champix.

This comparison nevertheless makes it possible to position the results observed with NFL-101 against published reference treatments. NFL Biosciences notably emphasizes the comparison at 3 months after the end of treatment, a period considered more relevant in the context of very different administration regimens. This interpretation should remain cautious and does not replace a direct comparative study.

What is the difference between the general population and the target population?

The general population refers to all smokers included or targeted by a study without prior selection based on a biomarker. The target population refers to patients carrying the biomarker, i.e. those whose baseline NFL-101-specific IgG1 level is below 200 ng/mL before treatment.

In CESTO II, NFL-101's efficacy is higher and the difference versus placebo is greater in this target population than in the general population. This observation has led NFL Biosciences to consider developing NFL-101 through a personalized medicine approach.

Is NFL-101 being replaced by NFL-102?

NFL-102 does not replace NFL-101. The two drug candidates are being developed in parallel with different positioning: NFL-101 in a personalized medicine approach, focused on the biomarker-carrying target population; and NFL-102 in the general population of smokers, with an expanded mechanism of action. The two products have complementary positioning and different mechanisms of action.

The development priority for advancement into Phase 3 will depend on efficacy results, regulatory discussions, discussions with potential partners and, where applicable, resource allocation.

What is the difference between NFL-101 and NFL-102?

NFL-101 is a tobacco leaf protein extract designed to act primarily on immunological and neuroinflammatory mechanisms. Its development is now being considered in a target population carrying a predictive efficacy biomarker.

NFL-102 contains the components of NFL-101 as well as additional compounds derived from tobacco leaves. It targets an expanded mechanism of action, notably involving signaling pathways implicated in the deeper mechanisms of addiction, and is being developed for the general population of smokers.

What is the role of the TONIC study?

TONIC is the planned Phase 2 study designed to evaluate NFL-102 in the general population of smokers. Its objectives are to confirm safety, assess efficacy and select the optimal dose of NFL-102. The study is expected to include 450 participants randomized in a double-blind, placebo-controlled design, in France, across approximately ten clinical centers. The planned primary endpoint is 4-week continuous abstinence, confirmed by urinary cotinine, with a final visit at day 43. A product safety assessment will be carried out by an independent committee after the first 40 patients.

When could Phase 3 start?

The objective is to advance at least one of the two candidates into Phase 3 by 2027–2028. For NFL-101, the next step is to engage with regulatory agencies on the biomarker and the clinical design of the Phase 3 study. For NFL-102, the priority is the manufacturing of the clinical batch, the submission of the TONIC study application and the availability of the study results.

The effective start of a Phase 3 study will therefore depend on regulatory feedback, the results of TONIC, the prioritization decision between the programs and financing or partnership conditions.

How could the next clinical phases be financed?

NFL Biosciences will prioritize financing Phase 3 studies with pharmaceutical partners, through licensing agreements, co-development agreements or other possible formats.

Self-financing would be an alternative scenario, requiring the Company to raise additional resources when financing Phase 3.

Where do discussions with potential industrial partners stand?

The Company is in discussions with several potential partners, with possible formats including global agreements or agreements by geographic region. These discussions remain confidential for the time being. The NFL-101 results in the biomarker-defined population have not yet been presented.

There is no firm timetable for concluding a partnership. The timing and terms of any potential agreement will need to be assessed in light of the interests of the Company and its shareholders.

What is the role of McLean Hospital?

McLean Hospital has a twofold role: first, McLean is conducting additional work on the mechanism of action; second, Prof. Scott Lukas plays a key scientific opinion leader role, particularly in supporting the value of the results, publications and conference presentations.

What does the biomarker patent application change?

The patent application aims to protect the use of the predictive biomarker associated with NFL-101, in particular the use of specific IgG1 to identify a population of patients more likely to respond to treatment. It also covers the potential development of a test to identify patients carrying the biomarker.

This patent application strengthens NFL Biosciences' intellectual property around smoking cessation. The Company now holds five patent families in smoking cessation based on tobacco leaf extracts.

How could the biomarker test work in practice?

The process would be based on a blood sample taken before treatment. The physician would prescribe a test measuring NFL-101-specific IgG1. If the result is below 200 ng/mL, the patient would be considered biomarker-positive and potentially eligible for NFL-101.

This type of test could be performed in a community or hospital laboratory. Treatment with NFL-101 is based on two subcutaneous injections administered one week apart, on Day 1 and Day 8. This pathway remains linked to clinical development and will need to be confirmed as part of the next regulatory steps.

What are the main points to be confirmed?

The results presented strengthen the development strategy for NFL-101 and provide a solid basis for Phase 3 preparation. Discussions with regulatory agencies will focus on the prospective validation of the biomarker, as well as on the inclusion population and the sizing of the study.

Other elements also remain to be clarified: the relative development trajectory between NFL-101 and NFL-102, which will depend on the results of the TONIC study, the financing conditions for Phase 3 studies, and the potential conclusion of agreements with industrial partners. These elements are not weaknesses to be concealed; they correspond to the normal next steps in biotech clinical development.

SHAREHOLDER INFORMATION

OUR FINANCING OPTIONS

Our priority remains to **finance the development of NFL-101 and NFL-102 while limiting shareholder dilution.**

Since 2025, NFL Biosciences has strengthened its financial visibility through several financings: **€3.0 million raised in May 2025, €1.2 million in non-dilutive financing obtained in July 2025, then, in 2026, a €500k Bpifrance loan and €2.6 million in bond financing.** Cash position therefore stood at **€3.9 million as of April 15, 2026**, providing visibility until the **third quarter of 2027**.

We continue to prioritize **non-dilutive financing** whenever accessible. In parallel, **licensing agreements or industrial partnerships** remain a strategic option to finance the next clinical phases, particularly Phase 3 studies, while reducing reliance on capital increases.

Finally, the optimization of our clinical strategy, with **NFL-101 targeted at a more responsive subpopulation and NFL-102 intended for the general population**, could reduce the cost of confirmatory studies and improve the financing conditions for development.

Our objective is clear: **to find the right balance between non-dilutive financing, partnerships and potential market financing, to maximize value creation for shareholders.**

STOCK MARKET INFORMATION

ALNFL EURONEXT GROWTH · ELIGIBLE PEA PME · bpifrance Entreprise Innovante

ISIN code: **FR0014003XT0**

Ticker symbol: **ALNFL**

2026 FINANCIAL CALENDAR

- General Meeting: June 17
- Half-year results: October 27

Dear shareholders, cast your vote for the June 17, 2026 General Meeting

OUR SOCIAL MEDIA

CONTACTS

NEWCAP
Investor Relations / Media Relations
Mathilde Bohin / Jérémy Digel
Tel.: 01 44 71 94 94
E-mail : nfl@newcap.eu

NFL BIOSCIENCES
Bruno Lafont
Tél.: 04 11 93 76 67
E-mail: info@nflbiosciences.com