Press release

NFL Biosciences releases new results on NFL-101 and reaffirms its personalized approach to smoking cessation

- **Identification of a biomarker predictive of efficacy, enabling a personalized approach to smoking cessation with NFL-101**
- **In the target population, efficacy approximately 30% higher than that of Champix® (based on results from the EAGLES study)**
- **Target population carrying the biomarker represents 57% of patients, opening significant market potential**
- **Statistically significant results versus placebo, confirming the clinical potential of NFL-101 in the target population**
- **NFL-101 with biomarker opens new development and partnership opportunities for NFL Biosciences' tobacco franchise**
- **Validation of the strategy announced in January 2026 aimed at achieving superior and differentiated efficacy levels in smoking cessation**

Webinar in French for shareholders
Tuesday, June 2, 2026, at 3:00 p.m.
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Montpellier, France, June 1, 2026 – at 5:45 pm CEST – NFL BIOSCIENCES (Euronext Growth Paris – FR0014003XT0 – ALNFL), a biopharmaceutical company developing innovative botanical drugs for the treatment of addictions, today presents the results of efficacy analyses conducted in a target population defined by a predictive biomarker associated with NFL-101, a drug candidate for smoking cessation.

Bruno Lafont, Chief Executive Officer and co-founder of NFL Biosciences, states: *"These results represent an important validation of the strategy announced by NFL Biosciences last January, which aims to achieve higher efficacy levels in smoking cessation, whether through a personalized medicine approach or through the development of new products with innovative mechanisms of action. NFL Biosciences warmly thanks Professor Eric Tartour's team at the Georges Pompidou European Hospital for its collaboration in conducting the biomarker assays."*

A modern approach to identifying predictive biomarkers

These additional analyses were conducted using data from the Phase 2 CESTO2 clinical study. They demonstrate that the efficacy of NFL-101 is associated with patients' specific IgG1 levels prior to treatment administration — these levels being required to be below 200 ng/mL. This identification is not the result of an undifferentiated exploratory search: it derives directly from NFL-101's immunomodulatory mechanism of action (MOA) (see press release dated May 25, 2025), giving it strong biological robustness.

This approach — post-hoc identification driven by the MOA, followed by prospective pre-specified confirmation in the next study — is the current and recognized pathway behind successful personalized medicine developments, particularly in oncology. NFL Biosciences is following this strategy by integrating "biomarker positive" status as an inclusion criterion in the protocol of the next clinical study.

A validated biomarker

The four validation criteria detailed by NFL Biosciences in its May 11, 2026 press release have been fully met.

The efficacy of NFL-101 is significantly higher in the target population of patients carrying the biomarker, while the response to placebo remains comparable between patients who do and do not carry the biomarker, ruling out any treatment-independent effect. In the population of patients who do not carry the biomarker, NFL-101 does not perform better than placebo, confirming that the benefit is indeed concentrated in the targeted patients. Finally, the biomarker is directly linked to the immunomodulatory mechanism of action of NFL-101—it logically follows from it, which gives it a recognized biological robustness in personalized medicine approaches.

Efficacy Results in Different Patient Populations

Samples from 306 of the 318 enrolled patients were available for analysis. Among them, 57.2% met the biomarker definition of an IgG1 level below 200 ng/mL, representing a substantial target population and market potential.

The table below presents the results for Dose 1 across all endpoints. Green cells indicate statistically significant results *($p < 0.05$)*.

Biomarker : IgG1 < 200 ng/mL				
Population	**Continuous abstinence 4 weeks (exhaled CO)**	**Continuous abstinence 4 weeks (cotinine)**	**Continuous abstinence 12 months (exhaled CO)**	**Continuous abstinence 12 months (cotinine)**
General population (100%)				
NFL-101 (n=108)	28.7 %	24.1 %	15.7 %	13.0 %
Placebo (n=101)	17.8 %	12.9 %	9.9 %	6.9 %
Relative risk (RR)	1.61	1.87	1.59	1.88
p-value	*0.063*	***0.038***	*0.208*	*0.147*
Target population (57%) (biomarker-positive)				
NFL-101 (n=61)	36.1%	29.5%	21.3%	16.4%
Placebo (n=58)	19.0%	12.1%	10.3%	6.9%
RR	1.90	2.44	2.06	2.38
p-value	*0.033*	*0.016*	*0.096*	*0.101*
other population (43%) (non-carrier of the biomarker)				
NFL-101 (n=45)	20.0%	17.8%	8.9%	8.9%
Placebo (n=40)	17.5%	15.0%	10.0%	7.5%

In the target population carrying the biomarker, treatment efficacy was substantially enhanced across all endpoints over a 4-week period (the measurement period for the primary endpoint of CESTO2). Statistical significance *($p < 0.05$)* was achieved for the 4-week period for both exhaled CO and urinary cotinine *($p = 0.033$ and 0.016)*, despite the reduced sample size. Patients who did not carry the biomarker showed a negligible effect, and the placebo response remained stable across subpopulations, confirming that the observed improvement indeed reflects a treatment effect and not a variation in the placebo response.

At 12 months, the trend remains favorable for NFL-101 in the target population carrying the biomarker (2.06- and 2.38-fold higher than placebo, respectively, as confirmed by CO or cotinine), p-values are lower than those obtained in the general population, although statistical significance is not reached *($p = 0.096$ and 0.101)*, which is an expected result, as the CESTO2 study was not powered to demonstrate a difference on this endpoint. Prospective confirmation in the upcoming study, with enriched recruitment of patients with the biomarker and sample sizes calculated accordingly, will allow for a conclusion on this endpoint. The same improvements, across all observation periods, were observed for the second dose tested.

The complete results will be submitted for presentation at scientific conferences and for publication in a peer-reviewed international journal.

Impact on Sample Size in Phase 3

The efficiency gains observed in the biomarker-positive target population, along with the increased margin of difference compared to placebo relative to the general population, are expected to significantly reduce the number of subjects required to demonstrate a statistically significant difference in clinical trials, which could represent a significant operational and financial advantage. Assuming a Phase 3 study conducted exclusively in the biomarker-positive population, the required sample size could be reduced by approximately half, with an estimated need of around 450 participants, compared to approximately 1,000 in the general population.

The exact terms of this optimization will, however, depend on discussions with regulatory agencies, particularly regarding expectations for prospective confirmation of the biomarker, the criteria selected for its use in the clinical protocol, as well as the number and design of the future Phase 3 study or studies.

Comparison with reference treatments (EAGLES study)

The EAGLES study is the reference study in tobacco addiction. An indirect comparison with this study is presented below for illustrative purposes and subject to the limitations inherent to cross-study comparisons.

Indirect comparison CESTO2 vs. EAGLES (continuous abstinence, exhaled CO)

Period	CESTO2 General Population NFL-101	CESTO2 Target Population (with biomarker) NFL-101	EAGLES Nicotine Replacement Therapy	EAGLES Champix (varenicline)
During 4 weeks	28.7 %	**36.1 %**	23.4 %	33.5 %
3 months after end of treatment	21.3 %	**27.9 %**	15.7 %	21.8 %
12 months after end of treatment	15.7 %	**21.3 %**	Not measured	Not measured

The most reliable comparison is the one measured 3 months after the end of treatment: over this period, NFL-101 efficacy in the target population reached 27.9%, approximately 30% higher than Champix efficacy (21.8%) in EAGLES. Champix is administered over 12 weeks; the 4 weeks of continuous abstinence reported in EAGLES are measured while patients are still receiving treatment. These contextual elements reinforce the relevance up to 3-month post-treatment comparison.

This efficacy advantage is complemented by a favorable safety profile: NFL-101 did not show any of the characteristic adverse events associated with Champix — notably nausea and abnormal dreams — and requires only two administrations one week apart, compared with twice-daily dosing over 12 weeks for Champix.

Market outlook

Although use of the biomarker targets a specific population of smokers, this group nevertheless represented 57% of participants analyzed in CESTO2, constituting a substantial potential market. The Company believes that the higher efficacy level achieved could significantly enhance treatment attractiveness among smokers seeking rapid and long-lasting cessation and enable NFL-101 to gain market share against existing solutions while expanding the overall treated smoking cessation market.

"The identification of a predictive biomarker introduces a new paradigm of personalized medicine to the field of smoking cessation. Prospective validation of this approach could represent a major breakthrough, making it possible for the first time to tailor treatment to patients' biological profiles and to bring about a lasting transformation in the management of tobacco addiction," states **Prof. Scott Lukas, Director of the McLean Imaging Center and the Behavioral Psychopharmacology Research Laboratory at McLean Hospital (United States).**

Outlook and next steps

The results released today mark a significant milestone for NFL Biosciences in defining its clinical development strategy for smoking cessation.

As announced by the Company on May 11, 2026, the decision to continue developing NFL-101 in the target population of patients carrying the biomarker was based on three criteria: the magnitude of the increase in effect size, the level of absolute efficacy relative to standard-of-care treatments, and the size of the target population. As these three criteria have been met, NFL Biosciences confirms the continued development of NFL-101 with the specific IgG1 biomarker as a pre-specified inclusion criterion in upcoming clinical studies.

The exact terms of the Phase 3 development will be defined in consultation with regulatory agencies as well as with potential partners interested in the program. Several development strategies remain open, including targeted development of NFL-101 in the biomarker-positive population, parallel development of NFL-101 and NFL-102, or separate agreements depending on partners' interest in each program.

The results obtained with NFL-101 also serve as an internal benchmark for evaluating the performance of NFL-102 in the TONIC study and for prioritizing development efforts within the Company's portfolio. With a 36.1% sustained abstinence rate at 4 weeks in the target population—representing approximately 57% of the smokers analyzed—NFL-101 establishes a baseline level of efficacy for evaluating the results of NFL-102 in the TONIC study.

Partnership attractiveness

NFL Biosciences intends to maintain maximum flexibility in the commercialization of its assets. The Company favors an open approach that may include comprehensive licensing or co-development partnerships covering both NFL-101 and NFL-102, as well as separate agreements based on partners' strategic interests, geographic regions, or targeted indications.

In this context, the results published today for NFL-101 represent a pivotal milestone for the entire therapeutic franchise developed by the Company. By removing one of the traditional barriers to licensing decisions in the field of addiction—uncertainty regarding clinical efficacy—they reinforce the credibility of NFL Biosciences' scientific approach based on tobacco extracts.

In the target population, the superior efficacy of NFL-101 is clearly demonstrated, with a favorable comparison to Champix. Combined with a predictive biomarker protected by a patent application, this drug profile enhances the appeal of NFL-101 as well as the entire portfolio to potential industrial partners.

About NFL Biosciences: www.nflbiosciences.com

NFL Biosciences is a biopharmaceutical company based in the Montpellier region (France) developing botanical drug candidates for the treatment of addictions. NFL Biosciences' ambition is to provide new natural therapeutic solutions that are safer and more effective for people worldwide, including in low- and middle-income countries. NFL-101 and NFL-102 are standardized tobacco leaf extracts protected by five patent families. NFL Biosciences aims to offer smokers who wish to quit a natural, safe, easy-to-administer and personalized alternative. NFL Biosciences is also developing NFL-301, a natural drug candidate intended to reduce alcohol consumption and has a drug development program targeting cannabis use disorders.

NFL Biosciences shares are listed on Euronext Growth Paris (FR0014003XT0 - ALNFL).

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