Press release

NFL Biosciences presents its 2024 annual results and provides an update on its clinical program

- Significant advances for NFL-101, *first-in-class* treatment for smoking cessation: phase 2 efficacy validated and demonstration of innovative mechanism of action with CEA

- Active discussions with regulatory authorities to prepare the NFL-101 Phase 3 study, to be conducted in two parts to allow for the announcement of initial efficacy results and derisking the second part

- First efficacy results to be announced within 12 months of the start of initial inclusions

- NFL Biosciences will prioritize a partner or non-dilutive financing to fund the first part of the Phase 3 study, with a maximum budget of €5m

- Low cash burn ensuring financial visibility until early Q4 2025

Montpellier, France, April 11, 2025, at 17:45 CEST - NFL BIOSCIENCES (Euronext Growth Paris - FR0014003XT0 - ALFNL), a biopharmaceutical company developing innovative botanical medicines for the treatment of addiction, today announced its financial results for the year ended December 31, 2024, approved by the Board of Directors on April 10, 2025, and provided an update on its clinical advances during the year.

Bruno LAFONT, Chairman and CEO, said: *"In 2024 and early 2025, NFL Biosciences achieved decisive milestones in the development of its lead drug candidate, NFL-101. We obtained particularly solid clinical and preclinical results, confirmed the efficacy of our anti-smoking treatment, secured its safety to unprecedented levels, and made progress in our industrial strategy. Building on these advances, we are implementing a structured clinical development strategy, that we are currently validating with the regulatory agencies. The objective is to launch a two-part Phase 3 trial as soon as possible. We are in active discussions with potential partners and non-dilutive funding sources to fund the first part of this Phase 3 study, with a maximum budget of €5 million, mainly aimed at quickly generating initial efficacy results. The clinical centers involved in the first part would continue recruitment for the second, thus ensuring both operational and methodological continuity, we could then initiate the second part of phase 3 rapidly after the communication of these initial results."*

Update on clinical advances

NFL-101, a *first-in-class* treatment for smoking cessation: Phase 2 efficacy results obtained

NFL-101 is a tobacco extract derived from a subcutaneous desensitization treatment for tobacco allergy to tobacco factory workers. Preclinical studies demonstrated the safety of NFL-101, which lead regulatory authorities to authorize its use in human clinical trials. The Phase 1 (CESTO) and Phase 2a (PRECESTO) trials corroborated the safety of NFL-101 and provided the first data measuring its efficacy in a controlled environment.

Demonstration of NFL-101's innovative mechanism of action with CEA and scientific publication

NFL Biosciences and the French Alternative Energies and Atomic Energy Commission (CEA) presented the results of their study investigating the mechanism of action of NFL-101 in a mouse model. The study highlighted a disruptive mechanism of action, demonstrating NFL-101's ability to reduce the urge to smoke ("craving") by restoring normal brain activity in the brain region associated with craving. It also showed a targeted and specific action, with no impact on brain activation in mice not exposed to tobacco.

These results were presented in June and November 2024 at the Albatros and Société Francophone de Tabacologie (SFT) congresses, France's two most important annual events in the fields of treatment of addictology and tabacology in France.

The study was also published in the peer-reviewed international scientific journal, ACS Chemical Neuroscience. The scientific article entitled *"Brain glucose metabolism as a readout of the CNS impact of cigarette smoke exposure, withdrawal, and the effects of NFL-101, as an immune-based drug candidate for smoking cessation therapy"* was co-authored by scientists from CEA, CNRS, Inserm, BioMaps, Université Paris-Saclay, Université Paris Cité, PARCC, APHP Immunology Department, Hôpital Européen Georges Pompidou, Hôpital Necker and by NFL Biosciences.

Link to article: https://pubs.acs.org/doi/10.1021/acschemneuro.4c00204

Validation of NFL-101 efficacy in the phase 2 CESTO II trial

The Phase 2b, multicenter, randomized, double-blind CESTO II trial included three arms (dose 1, dose 2 and placebo) and enrolled 318 smokers (106 per arm) who wished to quit smoking. The study confirmed the efficacy of dose 1, with a continuous abstinence rate of 24.1% versus 12.9% for placebo ($p = 0.038 < 0.05$), representing a relative improvement of 87%. This efficacy was measured over the primary endpoint period, from day 15 to day 43. Continued abstinence was confirmed by urinary cotinine measurement, considered the strictest and most specific biomarker. These results validate NFL-101's potential as a smoking cessation treatment and pave the way for its progression into Phase 3. CESTO II showed efficacy that exceeds nicotine substitutes and compares favourably with Champix®[1], a drug known for serious side effects and requiring twice-daily administration for 12 weeks, compared to just two administrations of NFL-101.

In addition, NFL-101 confirmed its excellent safety profile: both doses of NFL-101 were very well tolerated, with no serious adverse events and, in less than 10% of cases, transient side effects of mild or moderate intensity.

In Phase 3, the 4-week continuous abstinence period—confirmed by urinary cotinine—is recognized by the FDA as a valid primary efficacy endpoint for marketing authorization.

[1] *Comparison with the results of the EAGLES study, the gold standard in tobacco research, which measured continuous abstinence rates for the main smoking cessation products for up to 3 months after the end of treatment, and confirmed abstinence by measuring exhaled CO.*

The CESTO II trial has thus demonstrated that, even with a limited number of patients, NFL-101 is able to meet the efficacy criteria required for FDA registration. This considerably increases the chances of success in Phase 3 with larger numbers of patients. These would enable efficacy to be demonstrated by achieving statistical significance for longer periods of continuous abstinence, in line with the requirements of the European Medicines Agency (EMA) or European national agencies. These larger numbers are needed to expose enough subjects to NFL-101 and thus confirm its safety prior to marketing authorization applications.

Validation of NFL -101 industrialization in preparation for GMP batch production

Thanks to subcontracting agreements with international CDMOs, Fareva for the manufacture of the active ingredient and Synerlab Group for the manufacture of doses, NFL Biosciences now has the production capacity for phase 3 and the marketing of NFL-101 for smoking cessation. The key milestones in the industrialization of NFL-101 have thus been validated, enabling the preparation of GMP (Good Manufacturing Practice) batches. This milestone confirms the transition from a manufacturing capacity of a few thousand doses per year to several million, strengthening the attractiveness of NFL-101 to pharmaceutical companies interested in licensing deals, as well as to non-dilutive financing organizations.

Post-closing events

Positive results from a complementary program confirm NFL-101's excellent safety profile

To strengthen its regulatory file, support NFL-101's late-stage clinical development and meet the expectations of potential industrial partners, NFL Biosciences conducted an extended toxicity program. This program aimed to evaluate the administration of higher doses of NFL-101, through daily injections as opposed to the weekly administrations used in the previous program conducted before the start of clinical trials. It also included genotoxicity and mutagenicity tests, carried out at the maximum authorized doses. The toxicity study evaluated daily subcutaneous administration of increasing doses of NFL-101 in Sprague Dawley rats for 14 days. The maximum cumulative dose tested was 630 times higher than the cumulative dose evaluated in humans and showed no signs of systemic or local toxicity.

Results from the immunological analysis of phase 2 CESTO II study confirming NFL-101's efficacy

A secondary objective of the Phase 2 CESTO II study was to investigate a possible association between anti-tobacco IgG induction and continued smoking abstinence, to provide additional biological evidence supporting the behavioral observations based on abstinence measurements. Since continuous abstinence had already been confirmed using urinary cotinine as a biomarker, the increase in IgG served as a distinct immunological marker reflecting the specific biological response triggered by treatment. Immunogenicity tests, now available at several times, enabled this analysis and confirmed a dose-dependent increase in anti-tobacco IgG levels - an effect not observed in the placebo group - indicating that NFL-101 has an intrinsic immunogenic effect. When comparing anti-tobacco IgG levels over time between continuously abstinent and non-abstinent subjects, statistically significant differences ($p<0.05$) were observed, with higher IgG levels among continuously abstinent individuals, regardless of the dose of NFL-101 received. These results suggest a correlation between the increase in anti-tobacco IgG following NFL-101 administration and sustained abstinence. This association reinforces the evidence that the superior efficacy observed in terms of continuous abstinence is indeed attributable to NFL-101 administration. These findings mark the completion of the CESTO II study and have been incorporated into the upcoming publication.

NFL-301, designed to combat excessive alcohol consumption

Since 2022, NFL-301 is subject to a co-development agreement with Athena Pharmaceutiques, a leading French player for the development and production of oral drugs, to develop a prolonged-release form of Kudzu plant extracts in micro-granules form. NFL Biosciences aims to develop the first oral delivery drug based on kudzu extracts to tackle excessive alcohol consumption.

A first patent application was filed in July 2023 in the United States. In mid-December 2023, NFL Biosciences submitted a pre-IND application with the FDA in the United States with aim of formalizing the NFL-301 development program, covering manufacturing methods, quality control, preclinical data and clinical trials. The FDA issued its response to this in May 2024. Following the meeting with 17 FDA experts and the FDA report, NFL Biosciences now has a development plan for NFL-301, in line with FDA's expectations. To benefit from the "botanical drug candidate", the Kudzu extract from which NFL-301 is developed must comply with the guidelines for this type of drug[2]. The formulation remained will need to be presented to the FDA prior to clinical trial approval. This status will considerably streamline the preclinical program, particularly prior to Phase 1.

Governance

NFL Biosciences has strengthened its operational team with the recruitment of a Head of Development and Manufacturing, Lara Babich, to oversee the implementation and management of the NFL-101 manufacturing chain for Phase 3 batches, equivalent to commercial batches. She is helping to deploy an organization capable of managing the change of scale (from production of a few thousand doses to millions) from suppliers to CDMOs, and the GMP (Good Manufacturing Practice) manufacturing process.

The Chairman and Chief Executive Officer and the Managing Director have exchanged their roles within the governance structure to pave the way for Phase 3 and registration of its priority drug candidate for smoking cessation, NFL-101. Bruno Lafont, formerly Managing Director, has been appointed Chairman and Chief Executive Officer, and Ignacio Faus has been appointed Managing Director.

Accelerated clinical development of NFL-101 in 2025 and outlook

In 2025, NFL Biosciences will devote all its human and financial resources to its main program, NFL-101 in smoking cessation.

NFL Biosciences has recently submitted scientific opinions to health authorities in Europe and the UK and plans to submit one in the USA soon. These submissions are the culmination of in-depth work on manufacturing, preclinical and clinical studies, with the aim of presenting a coherent and comprehensive development program. Once the files have been analyzed, meetings will be organized by the relevant authorities. Their feedback will enable us to validate the development strategy implemented to date, and to specify the regulatory pathway to be followed with a view to future marketing authorizations.

On the clinical front, NFL Biosciences is presenting a randomized, double-blind, placebo-controlled Phase 3 protocol involving around 1,100 participants, structured in two successive stages. This two-part Phase 3 design offers several advantages: it enables us to rapidly obtain exploitable results thanks to the anticipated analysis of the first part and the methodological and operational continuity between the two parts; it facilitates confirmation of efficacy with statistical power control, while reinforcing the evaluation of safety by exposing a larger number of participants to the treatment. This approach also has the advantage of incorporating an intermediate value-creation milestone, likely to maximize the company's value and generate an attractive return for its shareholders.

[2] *https://www.fda.gov/regulatory-information/search-fda-guidance-documents/botanical-drug- development-guidance-industry*

First efficacy results obtained 12 months after the start of enrolment

The first part of the study would include 300 participants recruited from clinical centers in Europe. A partial unblinding would take place on day 43 after the start of treatment, to assess efficacy on the primary endpoint recognized by the FDA: 4 weeks of continuous abstinence between day 15 and day 43. Participants would then remain followed until the end of the study, without knowing which treatment they had received.

The results obtained on day 43 of the last participant included would be communicated to the market within 12 months of the start of inclusions and subject to national authorizations.

The second part, carried out on a larger sample, would aim to confirm effectiveness over the long term. The clinical centers that participated in the first part would be retained and supplemented by new sites, to absorb the increase in numbers, while maintaining methodological and operational continuity.

This two-part organization would allow us to rapidly obtain initial results of efficacy and would derisk phase 3 as a whole.

Confirmation of efficacy with statistical power control

Recruitment for the second part of the study would start soon after the first results were obtained, following the partial unblinding on day 43 of the last participant included in the first part, so that there would be some continuity in enrolment.

The second part would include around 800 participants and would be extended to the United States. Its aim would be confirming the efficacy of the treatment with a size consistent with the expectations of health authorities for a large target population, while controlling statistical power to validate continuous abstinence in both the short and medium term. Based on the results of CESTO II, a total of around 400 participants per arm would represent a good compromise: sufficient to obtain statistically robust results, while maintaining a level of power appropriate to the evaluation of efficacy.

Confirmation of safety at the end of the study

The total number of participants exposed to NFL-101 in both parts of the study would provide sufficient numbers to robustly assess the safety of the treatment, in particular to detect any rare adverse events. This is the advantage of structuring the study in two parts: increasing the number of exposed subjects with statistical power control, in the efficacy analysis. This approach also meets the expectations of health authorities, who require large-scale exposure when the treatment is intended for a large target population.

Intermediate value creation milestone

To finance its clinical program, NFL Biosciences has several options: conclude an agreement with a pharmaceutical company, proceed with a capital increase, or find non-dilutive financing. Advanced discussions are underway with several laboratories, and the possibility of signing a partnership agreement before the start of Phase 3 is being actively studied. However, the company will only enter such discussions if the proposed conditions are deemed sufficiently value-creating for its shareholders.

In the event of no satisfactory agreement being finalized in time, completion of the first part would represent a strategic step. It would rapidly provide initial efficacy results and derisking the study as a whole, while reducing the uncertainties linked to operational execution and compliance with the timetable. The estimated cost of this first part is a maximum of 5 million euros. The ability to continue quickly with the second part, as part of a program validated by the regulatory authorities as leading to

marketing authorizations, should then constitute a decisive level for materializing a partnership under the best possible conditions.

Financing

At present, NFL Biosciences has a cash horizon until the beginning of Q4 2025. Aware of the stakes involved in pursuing its development, the Company continues to optimize its resources and to actively explore complementary financing solutions.

NFL Biosciences is continuing discussions with pharmaceutical companies and partners for potential licensing agreements for the NFL-101 phase 3 study.

2024 financial results

The 2024 financial statements, drawn up in accordance with French accounting standards, were approved by the Board of Directors at its meeting on April 10, 2025. They have been audited by the statutory auditors, and the annual report will be made available to the public on Monday April 14 after the close of trading.

Parent company financial statements in euros	December 31, 2024 *(12 months)*	December 31, 2023 *(12 months)*
Net revenues	-	-
Total operating income	46	200,011
EBIT	(2,790,091)	(4,230,422)
Financial income	73,842	118,554
Non-recurring income	-	-
Income tax	(635,410)	(366,393)
Net income	**(2,080,839)**	**(3,745,476)**
Shareholders' equity	976,431	349,945
Conditional advances	1,190,000	1,190,977
Intangible assets (patents)	145,286	141,041
Liabilities	1,443,418	2,429,706
of which financial liabilities	40,975	62,174
of which operating liabilities	1,402,443	2,367,532
of which prepaid income		
Cash and cash equivalents	1,913,523	2,338,044
Balance sheet total	**3,609,849**	**3,970,628**

NFL BIOSCIENCES recorded no net revenue in 2024. As a reminder, in 2023 net revenues amounted to 200k€, corresponding to a grant obtained as part of the France 2030 program on the PRECESTO program carried out in the year ended December 31, 2023. The Company has not generated any sales in the past two years.

EBIT amounted to (2,790) k€ versus (4,230) k€ in 2023. This 1,440 k€ improvement in EBIT is due to the Company's R&D expenditure, in particular the clinical costs of the CESTO II study over 12 months in 2023 and over the first 4 months in 2024. In the 2nd half of 2024, the Company incurred R&D expenses mainly on additional analyses of the results of the phase 2b CESTO2 study and on the industrial organization project for the manufacture of future doses of NFL-101.

Net financial income amounted to €74k in 2024, compared with €119k in 2023, and corresponds to the return on cash surpluses in capital-guaranteed investments.

The research tax credit (CIR) recognized in 2024 amounts to 635 k€, compared with 366 k€ in 2023.

In 2024, net income came to (2,080) k€ compared with (3,745) k€ in 2023.

At December 31, 2024, the Company's cash position set at €1.9 million, compared with €2.3 million at December 31, 2023. As the Company's financial visibility extends to the beginning of the 4th quarter of 2025, the going concern statement was adopted by the Board of Directors, which approved the financial statements for the year 2024.

Total debt at December 31, 2024, amounts to 1,443 k€, including 41 k€ of medium-term financial debt with the Company's main bank 1,402 k€ of operating debt compared with a total of 2,430 k€ in 2023. Repayable advances for a total of 1,190 k€ correspond to two installments of two recoverable advances from the BPI received in 2023, scheduled for repayment in quarterly installments starting in December 2025.

Lastly, the Annual General Meeting of Shareholders, initially scheduled for June 25, 2025, will be held on May 21, 2025.

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 Paris (FR0014003XT0 - ALNFL).

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