**PRESS RELEASE**
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# NFL BIOSCIENCES: CESTO II STUDY RESULTS

## NFL-101 for smoking cessation shows a comparable efficacy to Champix®, without its side effects
## Advancement to Phase 3 confirmed

**NFL BIOSCIENCES (Euronext Growth Paris – FR0014003XT0 – ALNFL), a biopharmaceutical company developing botanical drugs for the treatment of addictions, is announcing the results of its phase 2 clinical trial CESTO II for NFL-101, its smoking cessation drug candidate.**

**Dr. Yannick Plétan, pulmonologist, immunologist, pharmacologist and clinical development expert, strongly involved in the development of Champix®, member of NFL Biosciences' Board of Directors:**

*"The potential of NFL-101 as a smoking cessation treatment is confirmed and the fundamental objectives from this Phase 2 study have been achieved. CESTO II highlights an effect that compares favorably with current treatments, confirming an excellent safety profile and the and optimal dose, making it possible to advance the project to Phase 3".*

**Bruno Lafont, Managing Director and co-founder of NFL Biosciences:**

"*NFL-101 confirms its disruptive potential by equaling the efficacy of the best treatment currently available, with only two administrations, compared with two daily doses for 12 weeks, all without any side effects that could restrict its administration. The efficacy rates achieved mean that we can be confident about success in Phase 3.*

*Its unique mechanism of action, distinct from current treatments, as well as its one-off administration, would enable it to be used alone, or at the initiation of any treatment with nicotine substitutes or Champix®. NFL-101 would therefore have access to a considerable potential market, far greater than that of Champix, which had exceeded one billion dollars in annual sales, as Champix could not be taken with nicotine substitutes, targeting the same nicotine receptors in the brain.*

*Together with our partners, we have gained valuable expertise, while successfully managing this multicentric clinical study, in terms of the selection and supervision of the centers, as well as the management of the specific environment for addiction studies, where psychological factors are essential.*

*We thank all the participants in the CESTO II study, as well as the doctors and the hospital teams.".*

## CESTO II clinical trial conditions and objectives (recap)

NFL-101 is a nicotine-free tobacco extract derived from a subcutaneous desensitization treatment for tobacco allergies in tobacco factory workers. NFL-101 has already been tested in two clinical trials: a Phase 1 study - CESTO - confirmed its safety and a Phase 2a study - PRECESTO - confirmed its ability to significantly reduce smoking satisfaction in smokers who are not willing to quit. A study conducted with the French Alternative Energies and Atomic Energy Commission (CEA) in 2023 demonstrated a unique mechanism of action restoring normal brain activity in the region of the brain modified during a craving period[1]. **This mechanism of action is different from and complementary to current treatments**, which target nicotinic receptors in the brain, therefore competing directly with each other.

(1) Goutal S, Tran T, Leroy C, Benhamouda N, Leterrier S, Saba W, Lafont B, Tartour É, Roelens M, Tournier N. Brain Glucose Metabolism as a Readout of the Central Nervous System Impact of Cigarette Smoke Exposure and Withdrawal and the Effects of NFL-101, as an Immune-Based Drug Candidate for Smoking Cessation Therapy. ACS Chem Neurosci. 2024 Jul 3;15(13):2520-2531. doi: 10.1021/acschemneuro.4c00204. Epub 2024 Jun 14. PMID: 38875216.

Launched in December 2021, CESTO II is a multicentric, randomized, double blind and placebo controlled Phase 2 clinical trial, with three arms (dose 1, dose 2 and placebo), conducted with 318 smokers (106 per arm) willing to quit. The study was conducted in nine clinical centers in France with a 12-month follow-up period: the Clinical Investigation Centers (CIC) at CHU university hospital centers in Bordeaux, Clermont-Ferrand, Dijon, Lorient, Marseille, Montpellier, Poitiers and Rennes, as well as the Eurofins-Optimed research institute (Grenoble).

Dose 2 corresponded to double the amount of dose 1, with the latter presumed to be the optimum dose based on previous data. The main objectives were to select the best dose, assess the efficacy against placebo and confirm its safety. Two initial subcutaneous injections were administered one week apart, on days 1 (D1) and 8 (D8). The primary criterion was continued abstinence for four weeks from D15 to D43, while various secondary criteria measured continued abstinence from D15 for three months, six months, nine months and 12 months. Continued abstinence had to be validated with an exhaled CO test. Participants that were lost during the follow-up period were considered to have failed.

## NFL-101 for smoking cessation shows a comparable efficacy to Champix®, without its side effects

**The efficacy of the anticipated dose on continued abstinence for four weeks from D15 to D43 (28.7% dose 1 vs 17.8% Placebo, p = 0.06[2], thus a 60% relative improvement), even though it did not reach significance, is higher than the level for the nicotine replacement therapies and comparable to Champix®**, which is currently the most effective treatment, but with serious side effects. To better quantify the specific effect of NFL-101 and eliminate the impact of any concurrent use of nicotine replacement therapies, a post-hoc analysis was carried out. This reprocessed all of the data from the analysis of the primary criterion by considering any participant who reported using nicotine replacement therapies between D15 and D43 as a failure. **The results then show a larger difference between NFL-101 and placebo (26.9% dose 1 vs. 13.9% Placebo, p = 0.02, with a 95% relative improvement). This result, with its low p-value, confirms the efficacy of NFL-101 when compared to placebo.**

The demonstrated effect size paves the way for the transition to Phase 3, subject to regulatory approvals. **The number of subjects to be included in Phase 3 is in line with estimates made before the results of CESTO II were known.** In Phase 3, based on the same success rates, 275 subjects per group (for a total of 550 subjects) would enable statistical significance to be reached on measures of continued abstinence up to 12 months after the end of treatment. However, the number of subjects included in Phase 3 will probably have to be increased to take into account the requirements of health agencies to expose a sufficient number of participants to confirm the safety of the product, given that it will be widely administered. An NFL-101 exposure of around 500 people should be proposed to the authorities. This increase in the number of subjects to be included will also make it easier to achieve statistical significance. **Marketing authorization (MA) could then be granted.**

By **demonstrating a clinically relevant effect size**, **CESTO II also made it possible to select the optimal dose**, which is the primary goal of a Phase 2 study, despite the fact that **one clinical center contributed to a significant increase in the placebo effect**. This center, which has a tobacco addiction unit, adopted a comprehensive approach to participant care, including effective psychological support, sometimes combined with the prescription of nicotine replacement therapies. The majority of the successes observed in the placebo group came from this center.

Doubling the dose (dose 2) does not provide any additional efficacy, which confirms that the anticipated dose 1 is justified as the optimal dose.

(2) A p-value of 0.06 means that there is a 6% chance of obtaining an equally or more extreme difference if there is actually no difference between the two groups. P-values depend on the percentages to be compared and the sample size. With constant percentages, the larger the sample size, the lower the p-value. For example, with a sample size of 120 subjects per group, the comparison of 28.7% to 17.8% gives a p-value that is strictly less than 0.05.

| | CESTO II | | EAGLES | | |
|---|---|---|---|---|---|
| | NFL-101 Dose 1 | Placebo | Nicotine replacements | Champix® (Varenicline) | Placebo |
| For 4 weeks[3] | **28.7%** | 17.8% | 23.4% | 33.5% | 12.5% |
| 3 months after the end of the treatment | **21.3%** | 12.9% | 15.7% | 21.8% | 9.4% |
| 12 months after the end of the treatment | **15.7%** | 9.9% | Follow-up stopped three months after the end of the treatments | | |

The EAGLES study, the benchmark for nicotine addiction research, measured the rates of continued abstinence for the main smoking cessation products up to three months after the end of the treatments. An indirect comparison with this study shows that, over equivalent periods following the end of treatments, **the efficacy of NFL-101 exceeds that of nicotine replacement therapies and is comparable to Champix®**. Moreover, the efficacy of NFL-101 one year after stopping treatment is equivalent to that of nicotine replacement therapies just three months after stopping treatment.

**The two doses were very well tolerated.** No serious adverse events were observed in relation to them. Transient adverse effects, of mild to moderate intensity, in less than 10% of cases primarily concern pain and reactions at the injection sites, as well as headaches. No adverse effects commonly associated with Champix®, such as insomnia, abnormal dreams and thoughts, nausea, other gastrointestinal issues or depressive events, were observed.

A detailed analysis of a number of exploratory criteria will be carried out when the final analysis report is received, and the complete results will be submitted for publication in an international peer-reviewed journal and presented at scientific conferences.

## Advancement to Phase 3 confirmed

The development of the Phase 3 batch manufacturing program, representative of future commercial batches, was launched at the start of 2024. These steps include the optimization of NFL-101 manufacturing before Phase 3.

NFL-101 represents a major innovation for smokers who are struggling to quit, offering a different and complementary approach to current treatments, without any significant adverse effects. Its occasional administration facilitates its adoption and offers new hope. The next steps will aim to confirm its efficacy and safety across a large number of smokers.

*About NFL Biosciences*

NFL Biosciences is a biopharmaceutical company based in the Montpellier area which develops botanical drug candidates for the treatment of addictions. NFL Biosciences' ambition is to bring new, natural, safer and more effective therapeutic solutions to the entire world population, including low- and middle-income countries. Its most advanced product, called NFL-101, is a standardized, nicotine free tobacco leaf extract protected by two patent families. NFL Biosciences intends to offer smokers who want 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 disorder.

The shares of NFL Biosciences are listed on Euronext Growth Paris (FR0014003XT0 – ALNFL). Find out more at www.nflbiosciences.com

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(3) The efficacy levels of nicotine replacement therapies and Champix® are measured while participants are still undergoing treatments