PRESS RELEASE

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NFL BIOSCIENCES: EFFICACY VALIDATED THROUGH UPDATED ANALYSES FROM CESTO II FOR SMOKING CESSATION. SIGNIFICANT REDUCTION IN CRAVING. STRONG COMMERCIAL POTENTIAL CONFIRMED.

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

Bruno Lafont, Chief Operating Officer and co-founder of NFL Biosciences: *"The results of the urinary cotinine measurements have made it possible to confirm continuous abstinence with a perfectly rigorous approach. Statistical significance is achieved for continuous abstinence confirmed over the four-week period, which corresponds to the study's primary criterion. This result demonstrates the efficacy of NFL-101 administered on its own and indicates that even with a small sample size, NFL-101 meets the efficacy criterion required for FDA registration.*

This efficacy is considered to be linked to the significant reductions in craving and specifically the compulsivity to smoke. Craving is the main cause of relapses when attempting to stop and is not well mitigated by the current smoking cessation drugs.

The ability of NFL-101 to reduce craving, combined with its excellent tolerance levels, confirms its greater commercial potential than Champix®, which had annual sales of over one billion dollars. NFL-101 could therefore be offered to all smokers that want to increase their chances of success, whether or not they are using other smoking cessation treatments simultaneously".

Efficacy results

With the efficacy results published in July 2024, continuous abstinence was confirmed based on exhaled CO. Exhaled CO is a simple and quick method, but it is not specific and its short half-life and potential interferences mean that it is a less reliable biomarker than cotinine. **The urinary cotinine measurements obtained since then through High-Performance Liquid Chromatography (HPLC) have enabled a perfectly rigorous confirmation of continuous abstinence.**

For reference, the period for measuring continuous abstinence for **the primary criterion is four weeks**, from D15 to D43, while secondary criteria measure continuous abstinence from D15 to 12 months. **Continuous abstinence over four weeks is significantly higher with NFL-101 than with the placebo.**

CESTO II STUDY
Continuous abstinence confirmed with cotinine

	NFL-101 Dose 1	Placebo	P-value	Relative improvement
For 4 weeks	**24.1%**	**12.9%**	**0.038**	**87%**
3 months after the end of the treatment	18.5%	10.9%	0.121	70%
12 months after the end of the treatment	13.0%	6.9%	0.147	88%

In Phase 3, this four-week period of continuous abstinence, confirmed by measuring urinary cotinine, is recognized as a valid efficacy criterion by the Food and Drug Administration (FDA) with a view to obtaining a marketing authorization.

The CESTO II study has therefore demonstrated that, even with a small sample size, NFL-101 is able to meet the efficacy criterion required for FDA registration. This considerably increases the chances of success in Phase 3 with larger sample sizes. They would make it possible to demonstrate its efficacy by achieving statistical significance for longer periods of continuous abstinence, in accordance with the requirements of the European Medicines Agency (EMA) or national agencies in Europe. These larger sample sizes are required in order to expose a sufficient number of subjects to NFL-101 and confirm its safety before submitting the marketing authorization applications.

NFL-101 reduces craving and specifically the compulsivity to smoke

The French Tobacco Craving Questionnaire - 12 items (FTCQ-12)[1], an approved version of the Tobacco Craving Questionnaire, was used throughout the study (D1, D8, D15, D43, M3, M6, M9 and M12). The FTCQ-12 makes it possible to measure craving and its various components: “emotionality”, “expectancy”, “compulsivity” and “purposefulness”.

- The “emotionality” factor measures a person’s perception of the capacity of cigarettes to improve their emotional or mental state, such as reducing fatigue or depression, or improving mental clarity and control.
- The “expectancy” factor measures a person’s expectations or anticipations in relation to the smoking experience, assessing whether they expect smoking to be pleasant or unpleasant, as well as their desire or intention to smoke when an opportunity arises.
- The “compulsivity” factor measures the degree of control or urgency that a person feels in relation to smoking, including the difficulty of resisting the temptation to smoke, the willingness to do anything to obtain a cigarette, and the inability to control their consumption.
- The “purposefulness” factor measures a person’s inclination to smoke depending on the occasion, assessing their ability to resist or ignore the opportunity to smoke when it arises.

Craving is significantly reduced in the dose 1 group versus the placebo group between D15 and M12 (with p-values ranging from 0.001 to 0.05 during the various assessments and minimal between D15 and D43).

This reduction in craving is linked primarily to **a significant decrease in the “compulsivity” component between D8 and M12** (with p-values ranging from 0.0001 to 0.05 at the various visits and minimal between D15 and M3). The “emotionality” component is also reduced on D15 and D29 ($p < 0.05$). No significant difference is observed for the other two components: “expectancy” and “purposefulness”.[2]

The full, updated results will be submitted for publication in an international peer-reviewed journal and presented at scientific conferences.

NFL-101’s strong commercial potential

NFL-101 therefore presents itself as a short-term treatment that would sustainably reduce craving. NFL-101 could therefore limit relapses, as craving is the main cause of failure when attempting to stop. Moreover, craving is reduced only slightly by the current treatments.

These observations confirm the strong commercial potential of NFL-101, which could be prescribed to any smoker who is trying to stop, whether or not they are using other smoking cessation treatments simultaneously. NFL-101 would therefore not be in competition with the current treatments. On the contrary, smokers using the other smoking cessation treatments would have every interest in also using NFL-101 to increase their chances of success.

In France, in 2022, approximately 2.6 million smokers reportedly used nicotine patches to quit smoking (source: OFDT). If only a quarter of these smokers chose to increase their chances of success by also using NFL-101, this

(1) Berlin I, Singleton EG, Heishman SJ. Validity of the 12-item French version of the Tobacco Craving Questionnaire in treatment-seeking smokers. Nicotine Tob Res. 2010 May;12(5):500-7. doi: 10.1093/ntr/ntq039. Epub 2010 Mar 24. PMID: 20335281; PMCID: PMC2902858.
(2) The statistical treatment using the ANOVA model involved analyzing, based on the data observed, at each visit, the differences between the two groups for changes in relation to the baseline scores. The significant reductions in craving and its “compulsivity” and “emotionality” factors were also confirmed by more advanced statistical analyses using the Mixed Model for Repeated Measures (MMRM).

would represent over 600,000 potential patients. Considering that **between 20 and 30 million people worldwide use nicotine substitutes each year**, the commercial potential represented by smokers using other cessation treatments and looking to further increase their chances of success is considerable.

This unique characteristic on the market for smoking cessation drugs, i.e. the ability to be administered to any smoker wishing to quit, regardless of whether they are using another treatment, represents a major asset. It offers considerable commercial potential **by expanding the potential base of patients likely to adopt NFL-101**.

CESTO II clinical trial conditions and objectives (recap)

NFL-101 is a nicotine-free tobacco extract that 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 looking to quit. A study conducted with the French Alternative Energies and Atomic Energy Commission (CEA) in 2023 highlighted a unique mechanism of action restoring normal brain activity in the region of the brain modified during a craving period[3]. This mechanism of action is different from current treatments, which all target nicotinic receptors in the brain and therefore compete with each other.

Launched in December 2021, CESTO II is a multicentric, randomized and double blind Phase 2b clinical trial, with three arms (dose 1, dose 2 and placebo), conducted with 318 smokers (106 per arm) looking to quit. The study was conducted in nine clinical centers in France with a 12-month follow-up period. 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 the 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 continuous abstinence for four weeks from D15 to D43, while various secondary criteria measured continuous abstinence from D15 and up to 12 months.

The first results were published on July 15, 2024 based on the data available.

Principles of biomarker confirmation for continued abstinence

In a smoking cessation study, periods of continuous abstinence are assessed based on participants' reports (claiming not to have smoked any cigarettes since the previous visit), confirmed with a biomarker. This biomarker may involve measuring either the level of exhaled CO (with a confirmation limit for smoking abstinence ≤ 10 ppm) or the level of cotinine, while the most reliable method is to measure urinary cotinine using HPLC (with a confirmation limit for smoking abstinence < 0.05 µg/mL).

Carbon monoxide (CO) is traditionally used as a marker for tobacco exposure. However, it is not specific to this exposure: its levels are influenced by the environment, and particularly air pollution, as well as the subject's respiratory condition, or analytical interferences. Its short half-life, of 2 to 5 hours, only makes it possible to assess tobacco exposure for the few hours prior to the measurement. The CO in exhaled air is measured directly by the clinical centers; this is an easy, low-cost method and the results are available immediately. This method also offers the possibility to compare continuous abstinence rates with those from the EAGLES study, considered to be the benchmark for tobacco research. The EAGLES study measured continuous abstinence rates, confirmed by measuring the levels of exhaled CO, for the main smoking cessation treatments up to three months after completing treatments in over 8,000 smokers.

On the other hand, cotinine is a sensitive and specific biomarker for exposure to tobacco smoke. It quantifies the degree of nicotine absorption over the previous two days. Its measurement with HPLC requires the involvement of a specialist clinical laboratory and this approach is more complex, time-consuming and expensive. **Measuring urinary cotinine with HPLC offers a more reliable, precise and specific biomarker than measuring exhaled CO.** The confirmation of continued abstinence by measuring exhaled CO tends to give higher results than when the confirmation is based on measuring the level of urinary cotinine using HPLC.

The two biomarkers are recognized by the regulatory agencies in Europe (EMA) and The United-States (FDA), making it possible to choose either of them to confirm periods of continuous abstinence. However, **in phase 3 and for NFL-101, the agencies are expected to prioritize the strictest biomarker, i.e. cotinine**.

(3) 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.

NFL-101 represents a major innovation for all smokers, offering a different approach to current treatments, without any significant adverse effects. Its short-term administration facilitates its adoption and offers new hope for smoking cessation. 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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