NFL Biosciences

NOVEMBER 2024

Letter to the shareholders

Dear Shareholders,

We continue our mission with determination, and it is important to emphasize that our commitment is essential: **we are fighting against smoking, a scourge responsible for more than 8 million deaths every year**, including 75,000 in France. Tobacco is the leading risk factor for cancer, involved in the development of **17 different types of cancer, particularly lung cancer** (80% of cases) **and bladder cancer** (40% of cases). One in five deaths from **heart disease** is related to smoking. According to the WHO, tobacco also has **severe environmental impacts**, including the destruction of 600 million trees and the emission of 84 million tons of CO_2 annually.

Currently, it is estimated that **780 million smokers worldwide wish to quit**, but only 4% succeed each year. **The last medication introduced to the market was in 2006**, 18 years ago. This situation highlights the urgent need for new smoking cessation solutions. Thanks to our drug candidate NFL-101, **we have the opportunity to play a key role by offering smokers an innovative aid: effective, timely yet lasting, and without side effects, to support them on their journey toward a smoke-free life**.

Supporting NFL Biosciences means investing in innovation, as well as in a public health mission and global environmental protection.

We are extremely proud of this dual mission that combines societal impact and economic performance. Addressing one of the major global public health challenges is at the heart of our commitment.

Through this letter, we wish to share with you **the next steps in the development of NFL-101, and the various options in our value creation strategy.**

Major breakthroughs in 2024

Since the beginning of the year, we have achieved two major milstones in the development of NFL-101: the study of the mechanism of action with the CEA, and the Phase 2 clinical study, CESTO II, conducted from 2023 to 2024 on 318 smokers.

✚ *MECHANISM OF ACTION STUDY*

The molecular imaging study conducted in collaboration with the French Alternative Energies and Atomic Energy Commission (CEA) revealed an innovative mechanism of action for NFL-101.

This mechanism likely involves neuro-immune communication that **restores normal brain activity in the thalamus,** a region involved in the craving to smoke. This effect is distinct from current treatments, which directly target nicotinic receptors.

The publication of the results in an international peer-reviewed scientific journal has provided new visibility for NFL-101, strengthening the scientific foundation supporting the efficacy and craving reduction subsequently observed in the CESTO II study.

The thalamus is the brain region most densely populated with nicotinic receptors. By restoring its normal activity, **NFL-101 could prove effective against the rapidly growing addiction to electronic cigarettes, especially among young people.**

Although often perceived as a way to quit smoking, electronic cigarettes can keep their users in a persistent dependency, which is hard to overcome, and they are not without health risks. This new indication, not addressed by current treatments, expands the therapeutic potential of NFL-101 to include e-cigarette cessation.

See the January 30, 2024, press release for detailed results.

✚ *CESTO II STUDY*

CESTO II is the first study to confirm the efficacy of NFL-101 compared to a placebo.

✓ **Efficacy:** statistical significance was achieved for continuous abstinence confirmed by urinary cotinine over the 4 weeks that correspond to the primary endpoint of the study. The relative improvement of 88% compared to placebo was maintained at 12 months.

Absolute and relative efficacy versus placebo compare favorably with current treatments. They show that NFL-101 has a place in the smoking cessation therapeutic offer.

✓ **Reduction of craving:** significant and lasting reductions in craving, particularly the compulsivity to smoke, were observed with NFL-101 compared to placebo.

Craving, the main factor in relapse during quit attempts, is poorly addressed by current smoking cessation options. NFL-101 has demonstrated its ability to reduce this overwhelming urge, combined with excellent tolerance and a short-time treatment. This makes it **a promising option for any smoker seeking to increase their chances of success**, whether or not they use other cessation methods simultaneously.

See the July 15, 2024, and October 8, 2024, press releases for detailed results.

→ *CALCULATION OF SAMPLE SIZE IN PHASE 3*

The efficacies observed in CESTO II suggest that a sample size of approximately 520 participants (260 per group) would be sufficient to validate the continuous abstinence criteria of the FDA (4 weeks) and the EMA (6 or 12 months), subject to regulatory approvals.

This protocol, based on a relatively small sample size treated on an outpatient basis, has been designed to optimize the use of resources while ensuring the robustness of the results

The next steps toward commercialization

Two essential elements must be validated before Phase 3: the development of production capacity and the validation of the clinical development plan.

+ STRENGTHENING RELATIONS WITH LABORATORIES AND RESEARCH AND FUNDING INSTITUTIONS

We are strengthening our relationships with laboratories that could become our future commercial partners, as well as with major research institutes that also provide funding. For a license purchase to become attractive to these potential partners, or to obtain substantial financial support for a clinical program, **we are focusing on reducing the perceived risks for these stakeholders by demonstrating the viability and robustness of our projects.**

An essential element in this approach is our ability to produce batches that meet the requirements for Phase 3 and potential commercialization. Furthermore, the validation of our clinical development plan for Phase 3 and its alignment with regulatory agencies' requirements **ensures that our approach is comprehensive and that all critical aspects have been rigorously taken into account.**

+ DEVELOPMENT OF PRODUCTION CAPACITY

We have established **new development and subcontracting agreements with international multi-site CDMOs** to meet the needs of Phase 3 clinical trials and large-scale commercialization.

Main steps for the industrialization of NFL-101:

1	2	3	4	5
Transfer manufacturing expertise to the new production sites.	Resize and optimize the manufacturing process.	Produce trial batches, then engineering batches.	Finalize the development and validation of quality control analytical methods.	Produce GMP batches

These initiatives support our partnership strategy by retaining responsibility for production, thereby maximizing value creation and facilitating partnerships with pharmaceutical companies that lack suitable production capabilities.

+ VALIDATION OF THE CLINICAL DEVELOPMENT PLAN

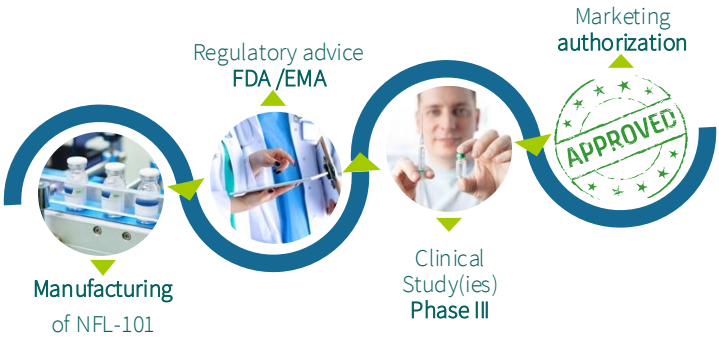
Approval from regulatory authorities for our clinical plan is a key step to optimize our chances of success. Currently, the development of smoking cessation drugs is guided by directives from the FDA and EMA.

These guidelines clarify essential aspects of clinical studies, such as the recognition of continuous abstinence as the primary criterion, biomarkers, and inclusion and exclusion criteria. The key points to discuss with regulatory agencies particularly include:

- The need for one or two Phase 3 studies must be clarified. In the United States, the FDA requires two studies, while in Europe, one may be sufficient.
- In Europe, an additional comparator arm may be required. In the United States, only the placebo is necessary.
- The duration of abstinence follow-up in Europe, whether 6 or 12 months, needs to be confirmed.
- In order to validate safety, the number of subjects exposed to NFL-101 before marketing authorization applications must be confirmed.
- In Europe, a decision will need to be made between a centralized procedure through the EMA or a national procedure with mutual recognition, depending on the advantages of each option.

We will be submitting a proposal to the agencies to carry out a study on 520 subjects in Europe before submitting a marketing authorization application in Europe, complemented in parallel by a second study in the United States for the American marketing authorization application.

Main steps for marketing authorization (MA):



A financing strategy to maximize value creation

+ OUR FINANCING OPTIONS

We aim to maximize value creation based on the progress and proven, as well as anticipated, potential of NFL-101.

Non-dilutive financing is our priority. We are in contact with key players such as Bpifrance, the EIC (European Innovation Council) in Europe, and, since the results of CESTO II, the NIDA (National Institute of Drug Abuse) in the United States.

License agreements reduce or eliminate the need for capital increases. However, they involve sharing future revenues with partners. The earlier these agreements are concluded in the development process, the higher the share of revenue ceded.

Capital increases dilute the stake of existing shareholders but allow the company to retain all future revenues. The more this option is used, the greater the dilutive effect on shareholders.

Non-dilutive financing is preferred, followed by finding the right balance between licensing agreements and capital increases to secure the best conditions for the success of our project.

We are moving towards a future where NFL-101 could become a cornerstone in the fight against smoking. **Driven by our commitment to innovation, scientific rigor, and societal impact, we approach the upcoming steps with confidence.** Through prudent financial management, we are convinced that our current efforts are laying the groundwork for our success, benefiting both our shareholders and society as a whole.

We warmly thank you for your support,

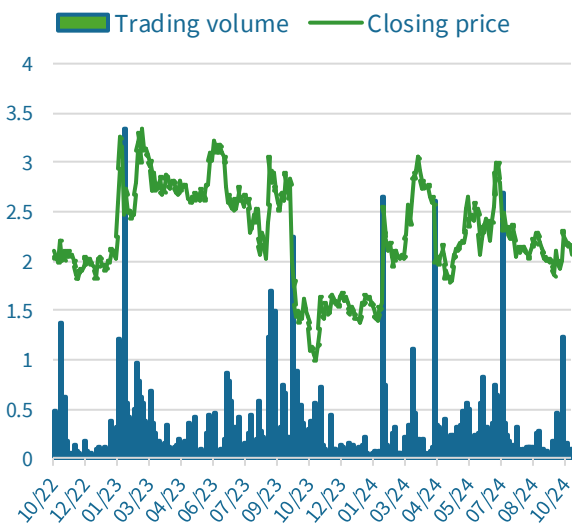
The management team of NFL Biosciences

Bruno Lafont
Chairman and CEO

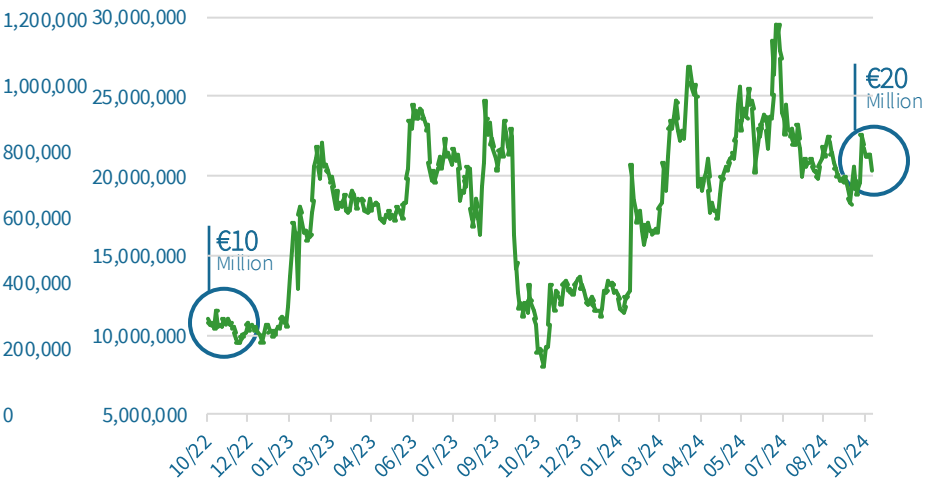
Ignacio Faus
Managing Director

Shareholder's datas

NFL Biosciences Stock Price Evolution



Market Capitalization Evolution of NFL Biosciences
over 2 Years, in Euros



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