



Corporate Presentation

March 2026

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Developing Addiction Treatments Through a Pipeline of Biological Drugs Derived from Botanical Sources

	DISEASE	MOA	PRECLINICAL	PHASE I	PHASE II	PHASE III	COMMENTS
Programs							
NFL 101 + biomarker Tobacco leaf extract	Smoking Cessation						To be developed on a sub-population
NFL 102 Tobacco leaf extract Comprehensive MOA	Smoking Cessation			Planned study			Targeting the general population
NFL-301 Extract of the kudzu plant Co-development with 	Excessive Alcohol Consumption						
NFL-201 Tobacco/cannabis mix extract	Cannabis Use Disorder						



Tobacco Leaf Extracts

First in class drug candidates for smoking cessation



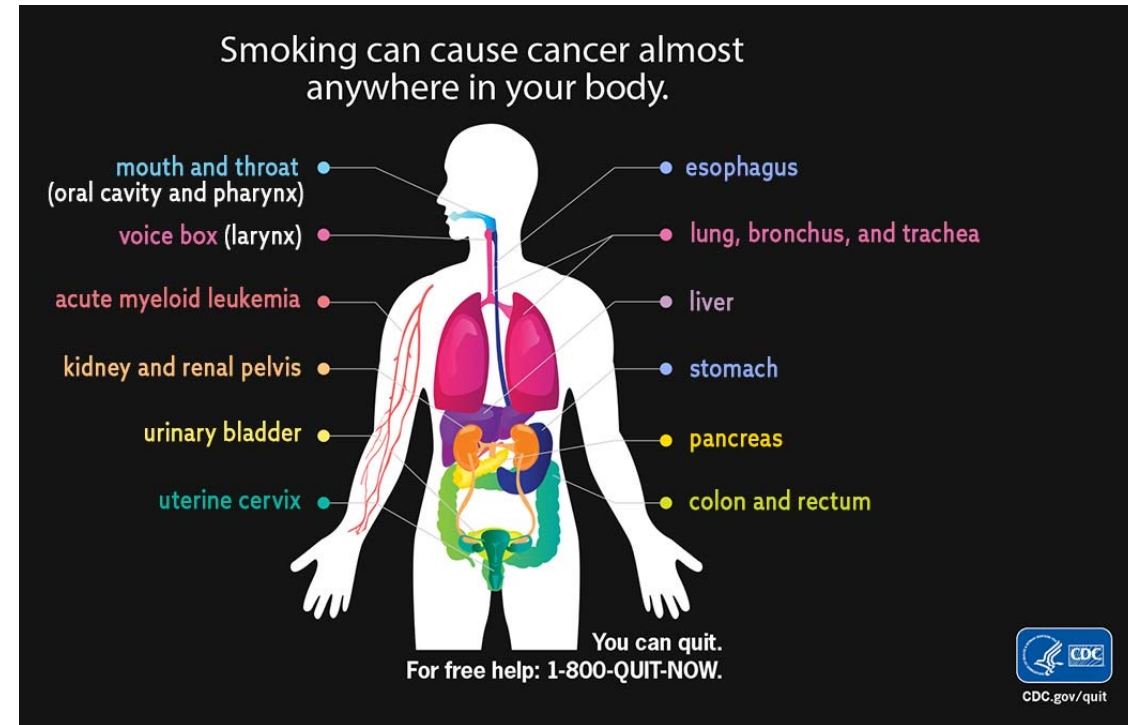
Smoking Kills More Than 10 Million People Every Year

- There are still **780 million smokers worldwide** who want to quit
- **In the US** (32.8 million smokers):

70%
Say that
they want
to quit

50%
Try each
year to do it

4%
Succeed



Tobacco Has a Major Environmental Impact



- **80 million tonnes of CO2** released each year from production and consumption of tobacco
- **200,000 hectares of land** each year cleared for tobacco agriculture
- **>7,000 chemicals in tobacco smoke**, at least 70 cause cancer
- **4.5 trillion of discarded cigarette butts** pollute the environment every year
- **2 million tonnes** of packaging waste
- **22 billion tonnes of water** every year used in tobacco production
- **3.7 litres of water used to make one cigarette**

Currently Available Treatments Exhibit Low Efficacy & Compliance Rates

Nicotine Replacement Therapy (NRT)



Patches



Chewing Gum

- **Targeting** Nicotine acetylcholine receptor
- **Low efficacy** (16%; 3 months after end of treatment)
- Low compliance (30%)
- **Adherence required for 12 weeks (1 patch per day)**

Varenicline (Chantix® / Chantix®)



- **Targeting** Nicotine acetylcholine receptor
- **Low efficacy** (22%; 3 months after end of treatment)
- Low compliance (38%)
- **Adherence required for 12+ weeks (2 pills per day)**

Cytisine (Tabex®)



- **Targeting** Nicotine acetylcholine receptor
- Comparable to varenicline
- **Adherence required for 6 or 12+ weeks (3 pills per day)**
- Used in Eastern Europe for 40 years. A modified version, **cytisinicline**, in Phase III in the USA

- **Improper dosing regimens contribute to poor adherence**
- **All available commercial treatments work through the same mechanism of action (MoA)**
- **Comparable efficacy to Champix®, superior safety**
- **Craving is the main relapse factor**

Tobacco Leaf Extracts for Smoking Cessation...

Two extracts developed for **smoking cessation** by NFL Biosciences: **NFL-101** and **NFL-102**

NFL-101 has demonstrated its efficacy compared to a placebo in a phase 2 study

NFL-102 contains the same components as NFL-101, as well as additional constituents derived from tobacco leaves, and has successfully completed the **same preclinical toxicity studies as NFL-101**

Two subcutaneous injections one week apart

No side effects

Unique Mechanism of Action (MOA)



Preliminary Results on the MOA of Tobacco Leaf Extracts Showing Some Restoration of the Normal Brain Activity

ACS Chemical
Neuroscience

pubs.acs.org/chemneuro

Research Article

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

Sébastien Goutal, Thi Tran, Claire Leroy, Nadine Benhamouda, Sarah Leterrier, Wadad Saba, Bruno Lafont, Éric Tartour, Marie Roelens, and Nicolas Tournier*

Cite This: <https://doi.org/10.1021/acschemneuro.4c00204>

Read Online

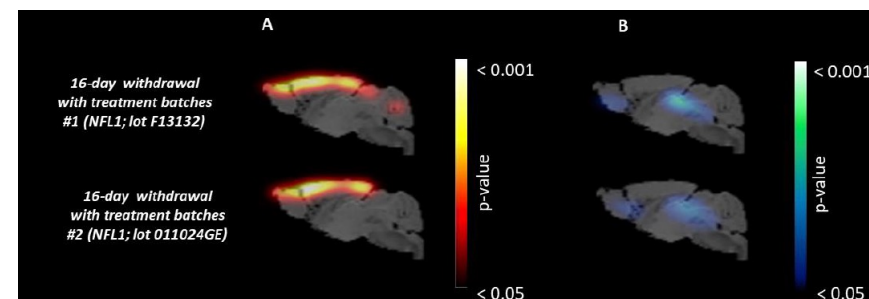
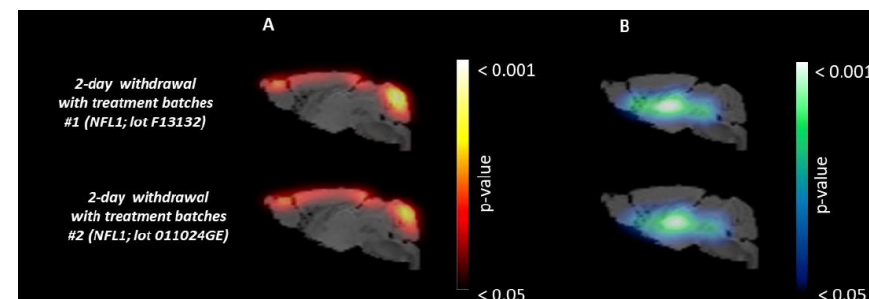
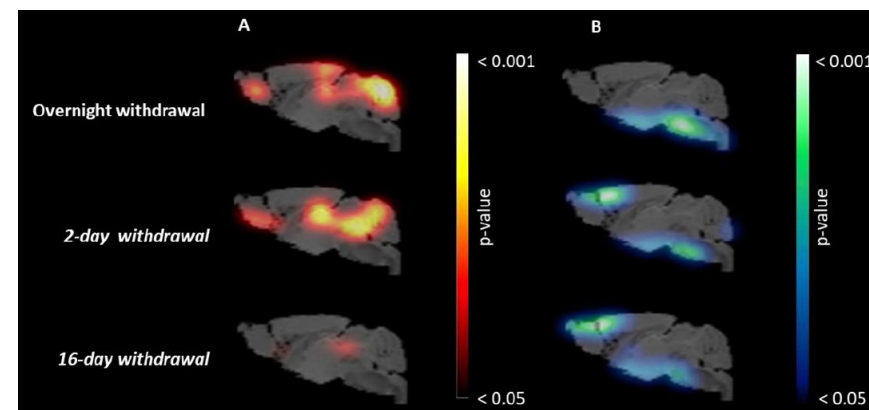
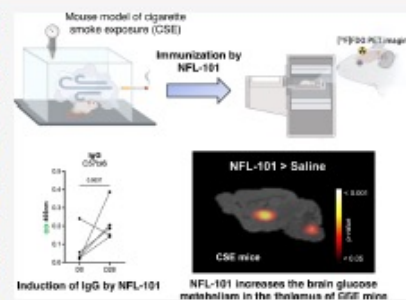
ACCESS |

Metrics & More

Article Recommendations

ABSTRACT: Neuroimaging biomarkers are needed to investigate the impact of smoking withdrawal on brain function. NFL-101 is a denicotinized aqueous extract of tobacco leaves currently investigated as an immune-based smoking cessation therapy in humans. However, the immune response to NFL-101 and its ability to induce significant changes in brain function remain to be demonstrated. Brain glucose metabolism was investigated using [^{18}F]fluoro-deoxy-glucose ([^{18}F]FDG) PET imaging in a mouse model of cigarette smoke exposure (CSE, 4-week whole-body inhalation, twice daily). Compared with control animals, the relative uptake of [^{18}F]FDG in CSE mice was decreased in the thalamus and brain stem ($p < 0.001$, $n = 14$ per group) and increased in the hippocampus, cortex, cerebellum, and olfactory bulb ($p < 0.001$). NFL-101 induced a humoral immune response (specific IgGs) in mice and activated human natural-killer lymphocytes in vitro. In CSE mice, but not in control mice, single-dose NFL-101 significantly increased [^{18}F]FDG uptake in the thalamus ($p < 0.01$), thus restoring normal brain glucose metabolism after 2-day withdrawal in this nicotinic receptor-rich region. In tobacco research, [^{18}F]FDG PET imaging provides a quantitative method to evaluate changes in the brain function associated with the withdrawal phase. This method also showed the CNS effects of NFL-101, with translational perspectives for future clinical evaluation in smokers.

KEYWORDS: cigarette smoke, neuroimaging, neuro-immunopharmacology, nicotine, positron emission tomography, substance use disorder, tobacco, smoking cessation therapy



Complementary Results on the Mechanism of Action of Tobacco Extracts

CEA conducted a proteomic analysis using brains from mice previously exposed or not exposed to tobacco for 4 weeks, followed by a 16-day withdrawal period after administration of either a placebo or tobacco extracts. Samples were collected from the prefrontal cortex and the thalamus at the end of the study, on day 16

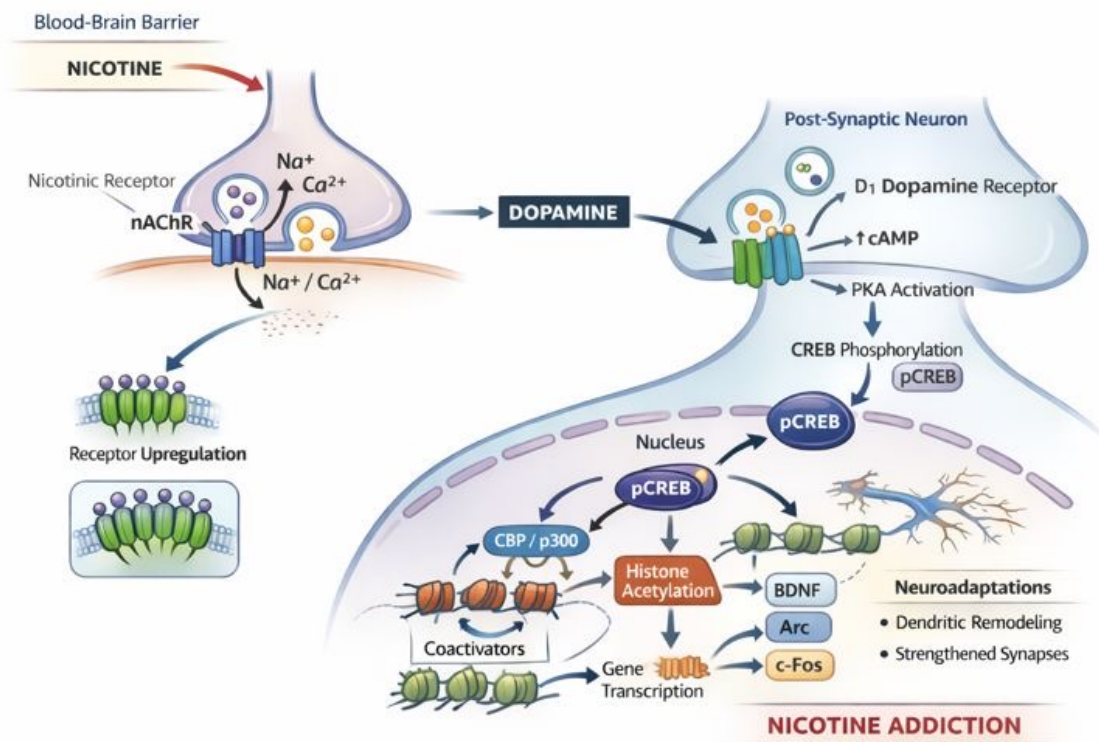
The **thalamus is rich in nicotinic receptors**, whereas the **prefrontal cortex plays a key role in behavioural control by exerting inhibitory top-down regulation over reward circuits**. Its impairment by chronic smoking compromises this control, reducing the ability to resist craving and promoting relapse

Two extracts were studied: NFL-101 and NFL-102

- **NFL-101 reduces the expression of several neuroinflammatory markers**, including cytokines and growth factors involved in smoking-related inflammation ($p < 0.001$ to $p < 0.0001$)
- **NFL-102 normalizes signalling pathways that are overactivated during smoking cessation** by significantly reducing **CREB** ($p < 0.001$), **NF- κ B** ($p < 0.05$), and **JNK** ($p < 0.001$), as well as smoking-associated **astrogliosis**, with a significant decrease in **GFAP** ($p < 0.01$), and reduces the expression of **pro-inflammatory cytokines** ($p < 0.01$ to $p < 0.0001$)

CREB Links Dopaminergic Signalling to Long-Term Addiction

CREB does not trigger addiction but stabilizes it by converting transient dopaminergic signals into long-lasting transcriptional and synaptic adaptations that anchor dependence and promote relapse.



CREB

(transcription factor regulating gene expression)

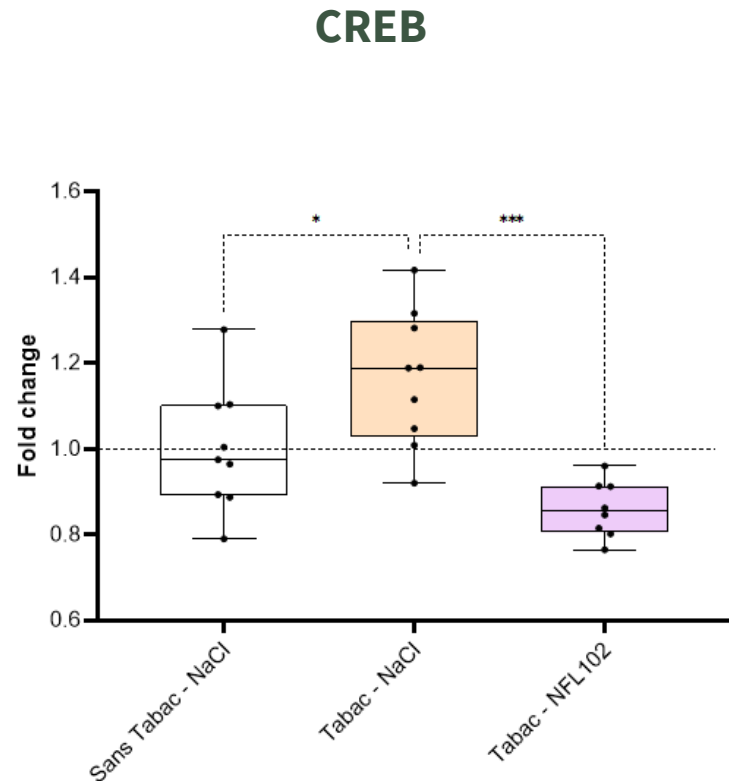
Signalling:

Nicotine → nAChR → Increased Calcium → Increased Dopamine/cAMP → PKA activation → CREB phosphorylation (pCREB)

Target Genes:

pCREB activates the transcription of genes such as *BDNF*, *Arc* or *fos-B*, leading to long-lasting modifications in the structure of neurons

NFL-102, Therapy Modulating CREB Activity



Proteomic analysis of mice previously exposed or not to tobacco for 4 weeks, then subjected to a 16-day withdrawal period after receiving placebo or NFL-102. Samples were collected from the prefrontal cortex on day 16.

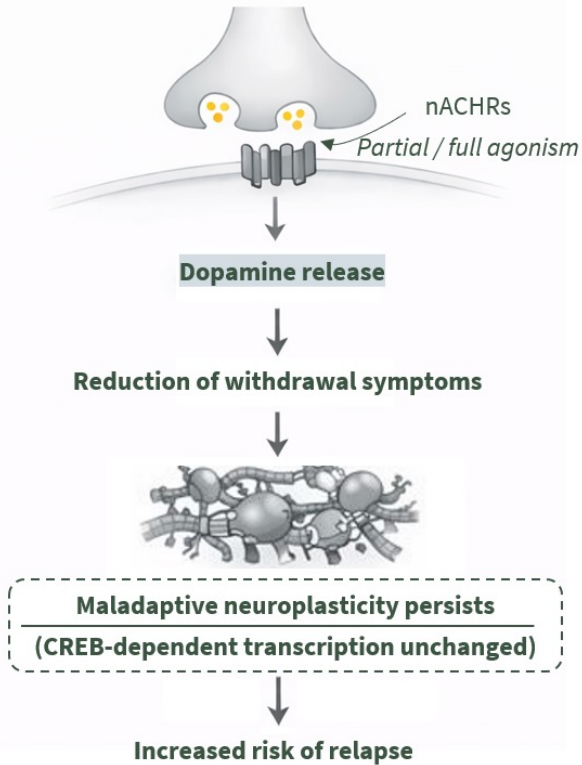
The **prefrontal cortex** plays a key role in behavioural control by exerting inhibitory top-down regulation over reward circuits; its alteration by chronic tobacco exposure compromises this control, reducing the ability to resist **craving** and promoting **relapse**

- As a result of **tobacco exposure**: the group of mice exposed to tobacco and treated with placebo exhibited significantly **higher CREB expression** than the non-exposed placebo-treated group ($p < 0.05$)
- Normalization mediated by NFL-102: the group of tobacco-exposed mice treated with **NFL-102 exhibited significantly lower CREB expression** than the tobacco-exposed placebo-treated group ($p < 0.001$)
- **Controlled normalization**: no significant difference in CREB expression was observed between the non-exposed placebo-treated group and the tobacco-exposed group treated with NFL-102

Mechanistic Differences Among Smoking Cessation Therapies

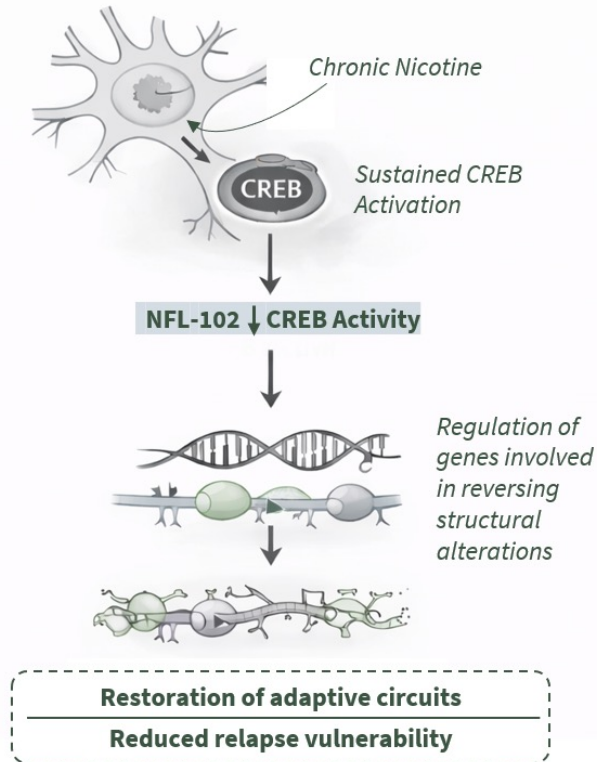
Nicotinic Receptor-Targeted Therapies

Nicotine replacement, Varenicline, Cytisine



CREB-Targeted Therapy

NFL-102



From receptor-level symptom management to circuit-level neuroplasticity correction

Current smoking cessation therapies (nicotine replacement therapies, varenicline, cytisine) primarily act at the level of **nicotinic receptors** to alleviate withdrawal symptoms associated with nicotine discontinuation. While they provide **transient relief during cessation**, they **do not directly address the long-lasting alterations in neuronal signalling and neuroplasticity induced by tobacco addiction, which persist after cessation and substantially contribute to relapse risk**.

In contrast, **NFL-102 acts downstream of nicotinic receptors** by modulating signalling pathways that remain durably altered by chronic tobacco exposure. In particular, **NFL-102 significantly reduces CREB activity, a central regulator of maladaptive neuroplasticity and the reorganization of neural circuits** involved in addiction. This modulation is accompanied by normalization of stress- and neuroinflammation-related pathways associated with withdrawal, as well as attenuation of the neuro-immune imprint left by tobacco exposure. By targeting CREB as a key mechanistic node, NFL-102 differs from current therapies by aiming to **correct the neural circuits underlying relapse vulnerability, beyond the mere control of withdrawal symptoms**.

Tobacco Leaf Extracts: a Game-Changing MoA Unlike Any Competitors

Adherence



Neuro-immune communication leading to :

- reduction in functional inflammation induced by smoking (NFL-101)
- normalisation of signalling pathways, reduction in astrogliosis and pro-inflammatory cytokines (NFL-102)



Targeting
nicotinic
receptors

Innovative MoA

Scientific Advices

Meetings between May/October 2025

3 EU national authorities

Germany : Bfarm



Belgium : FAMHP



Netherlands : MEB



The UK

MHRA



The US

FDA



Main outcomes:

- Tobacco leaf extracts are biological drugs derived from botanical sources ✓
- Further understand the mechanism of action (MOA) ✓
- Further describe the product composition ✓
- Urinary cotinine for continuous abstinence (CA) confirmation validated ✓
- One Phase 3 in Europe ($\alpha < 0,01$) and primary endpoint 12-month CA
- An additional Phase 3 for the US, primary endpoint 4-week CA and secondary endpoint 6-month CA



NFL-101

The first tobacco leaf extract developed



Phase 1 and 2a Demonstrated an Excellent Safety Profile and Promising Efficacy

CESTO, Phase 1 (NCT02521701)

- Open label, two doses (100 and 200 µg of tobacco proteins)
- 24 smokers
- Safety was confirmed, absence of side effects
- Specific action on the immune system
- All subjects described a reduction in satisfaction with cigarettes and a reduction in the desire to smoke

PRECESTO, Phase 2a (NCT06091826)

- Randomized, double blind, placebo controlled
- 34 smokers not willing to quit
- Cross-over design with 2 periods of 28 days: NFL-101 or placebo administered on D1 of each period
- Primary objective: NFL-101 significantly reduces smoking satisfaction (assessed by the mCEQ questionnaire)

CESTO II : Phase 2b Randomized Clinical Trial

AIM : Test the efficacy and safety of NFL-101 vs. Placebo and select a dose

STUDY DESIGN

- Double-blind RCT
- Multicentric
- 3 arm trial: Placebo, Dose 1 (100µg) and Dose 2 (200µg)
- 2 mandatory injections (D1 and D8)
- 12-month follow-up

N = 318

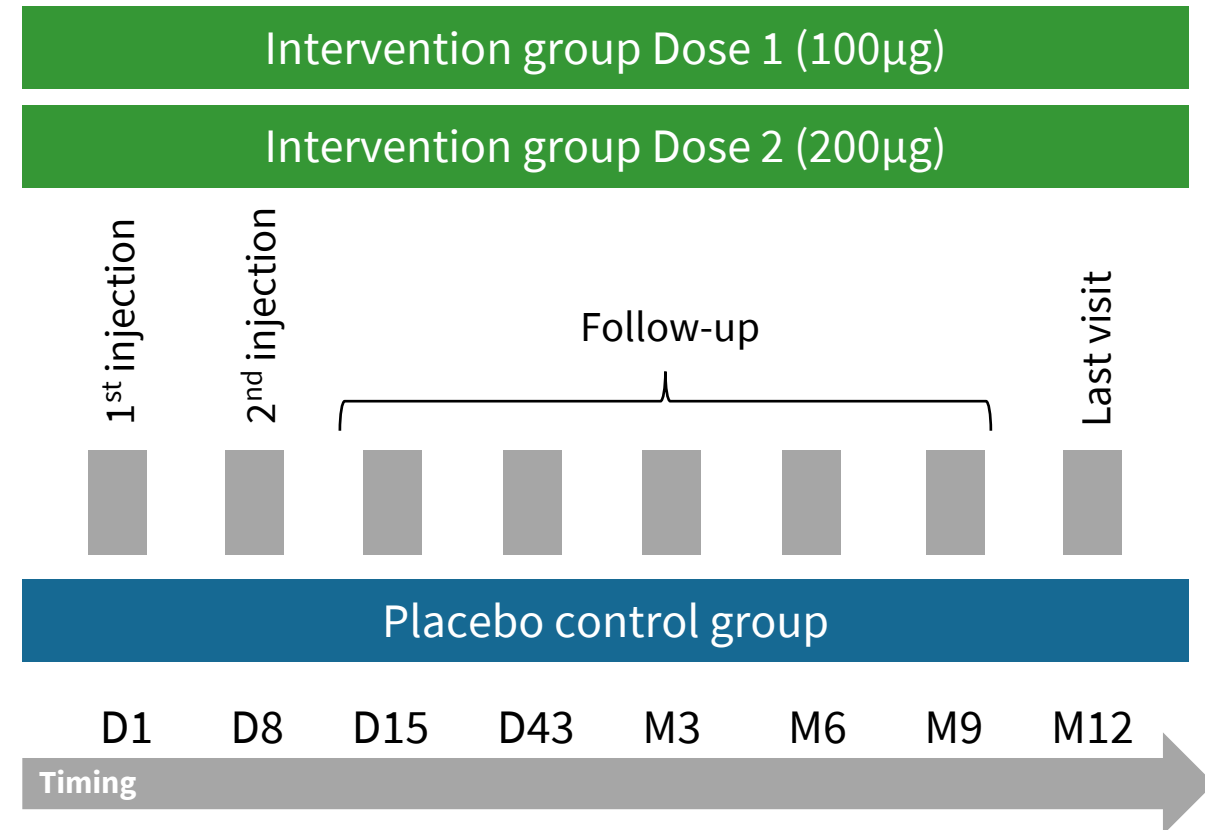
OUTCOME

Primary endpoint: Biochemically verified 4-week continuous abstinence from D15 to D43

Secondary endpoints: Biochemically verified 3, 6, 9 and 12-month continuous abstinence from D15

Safety: Adverse events, serious adverse events

Analysis: All subjects who received at least one administration were included. Those lost during the follow-up were considered as having resumed smoking

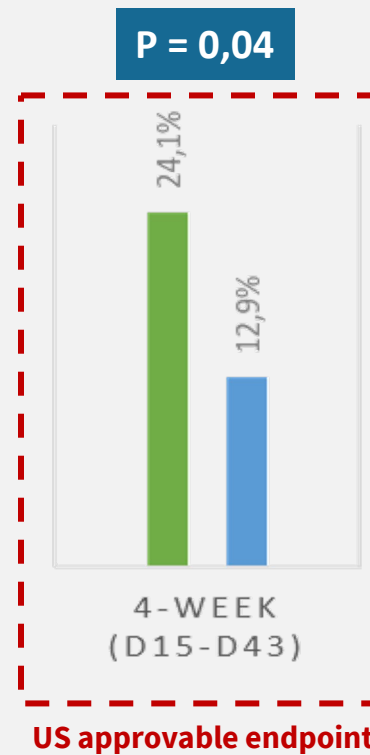


CESTO II (Phase 2b) Results Pave the Way for Phase III Clinical Studies

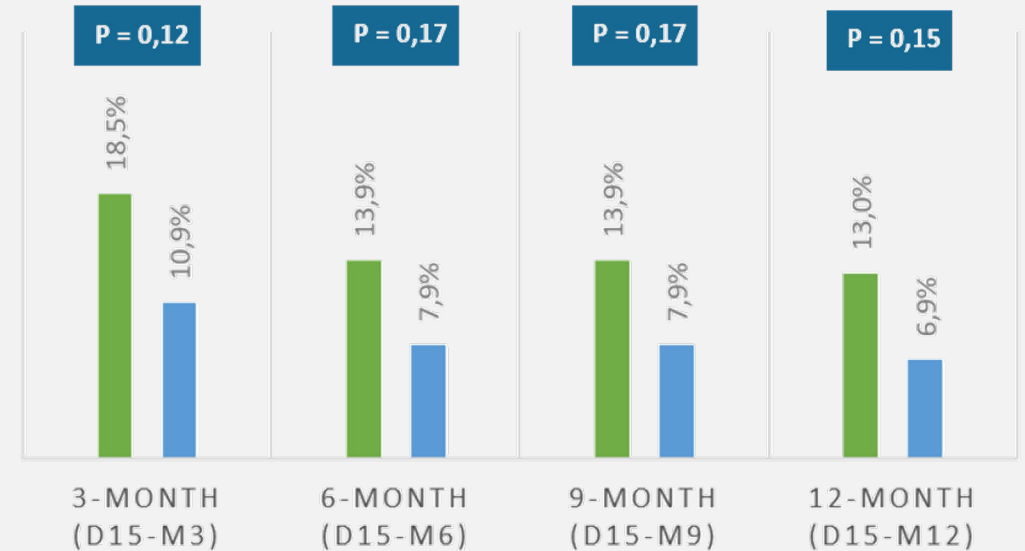
- **Biomarker Validation:** HPLC urinary cotinine – most trusted abstinence biomarker, detecting smoking exposure over 3 days vs a few hours for exhaled CO
- **Efficacy:** NFL-101 demonstrates statistically significant efficacy vs placebo ($p=0.04$)
- **Odds Ratio (OR):** Consistent effect of NFL-101 in proportion to placebo over 12-months, $OR = 1.88$
- **Dose Selection:** Doubling the dose (Dose 2) showed no additional efficacy, confirming Dose 1 as optimal

CONTINUOUS ABSTINENCE (HPLC URINARY COTININE VALIDATED)

Primary endpoint period



Secondary endpoint periods



In Phase 3, the sample size will be calculated to achieve statistical significance over a 12-month period

CESTO II Confirmed an Excellent Safety Profile

Excellent safety profile:

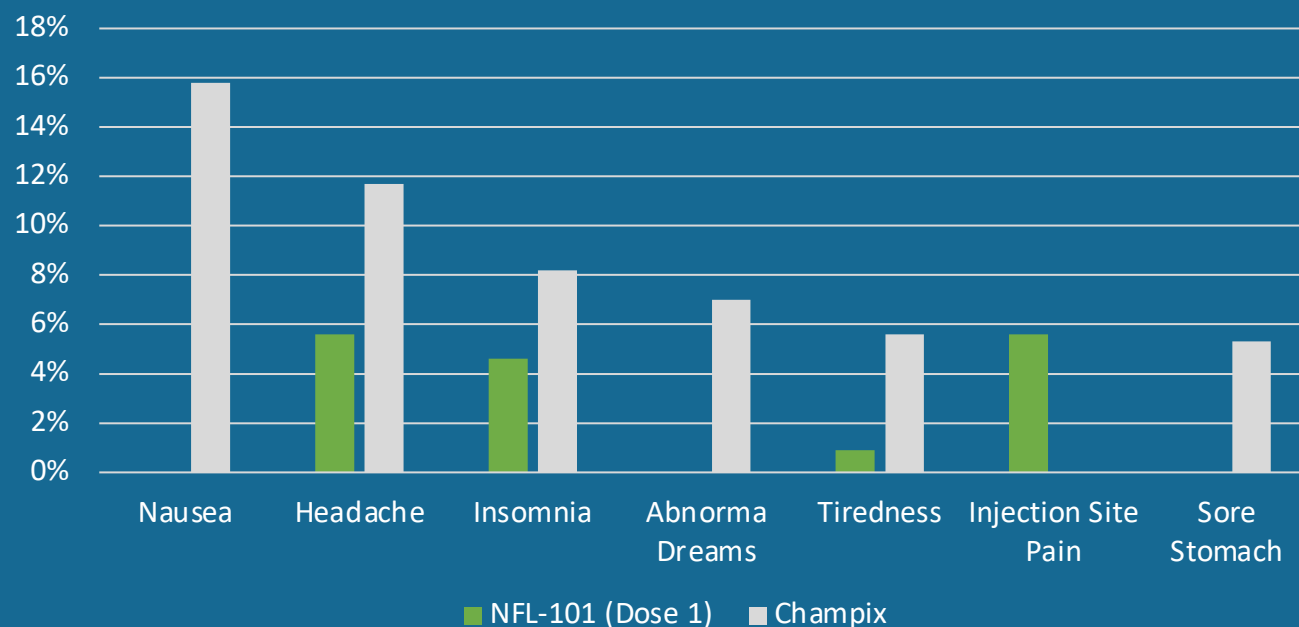
- Very good tolerance of the two doses
- No serious adverse events observed
- Transient adverse effects, of mild to moderate intensity, in less than 10% of cases primarily concern pain and reactions at the injection sites, as well as headaches

Much better when compared to Chantix:

- NFL-101 did not show any of the common side effects associated with Champix®, such as insomnia, nausea, or depressive events, reducing the compliance issues often seen with Champix

COMPARISON WITH CHANTIX/CHAMPIX®

Adverse events (>5% subjects)



Publication of CESTO2 Results

The screenshot shows the PubMed interface. At the top is the NIH National Library of Medicine header with a 'Log in' button. Below is the PubMed logo and a search bar with a 'Search' button. The search results section displays the title 'Efficacy and Safety of NFL-101 as a Smoking Cessation Therapy: A Randomized Phase II Clinical Trial CESTO2' and the authors: Claire Lafay-Chebassier¹, Pierre-Olivier Girodet², Fabrice Laine³, Jean-Sébastien Allain⁴, Gisele Pickering⁵, Mathilde Latreille⁶, Anastasia Demina⁷, Hugues Chevassus⁸, Isabelle Ingrand⁹, Eric Tartour¹⁰, Nadine Benhamouda¹⁰, Marie-Laure Fraisse¹¹, Liliya Chamitava¹², Yannick Plétan¹¹, Julie Balland¹³, Yves Donazzolo⁶, Bruno Lafont¹¹. It also shows the journal information: Nicotine Tob Res. 2025 Aug 30;ntaf181. doi: 10.1093/ntr/ntaf181. Online ahead of print. On the right side, there are buttons for 'Save', 'Email', 'Send to', and 'Display options'. Below the title, there are buttons for 'Cite', 'Collections', and 'Permalink'. At the bottom, there is a 'PAGE NAVIGATION' section.

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> Nicotine Tob Res. 2025 Aug 30;ntaf181. doi: 10.1093/ntr/ntaf181. Online ahead of print.

Efficacy and Safety of NFL-101 as a Smoking Cessation Therapy: A Randomized Phase II Clinical Trial CESTO2

Claire Lafay-Chebassier¹, Pierre-Olivier Girodet², Fabrice Laine³, Jean-Sébastien Allain⁴, Gisele Pickering⁵, Mathilde Latreille⁶, Anastasia Demina⁷, Hugues Chevassus⁸, Isabelle Ingrand⁹, Eric Tartour¹⁰, Nadine Benhamouda¹⁰, Marie-Laure Fraisse¹¹, Liliya Chamitava¹², Yannick Plétan¹¹, Julie Balland¹³, Yves Donazzolo⁶, Bruno Lafont¹¹

Affiliations + expand

PMID: 40884488 DOI: 10.1093/ntr/ntaf181

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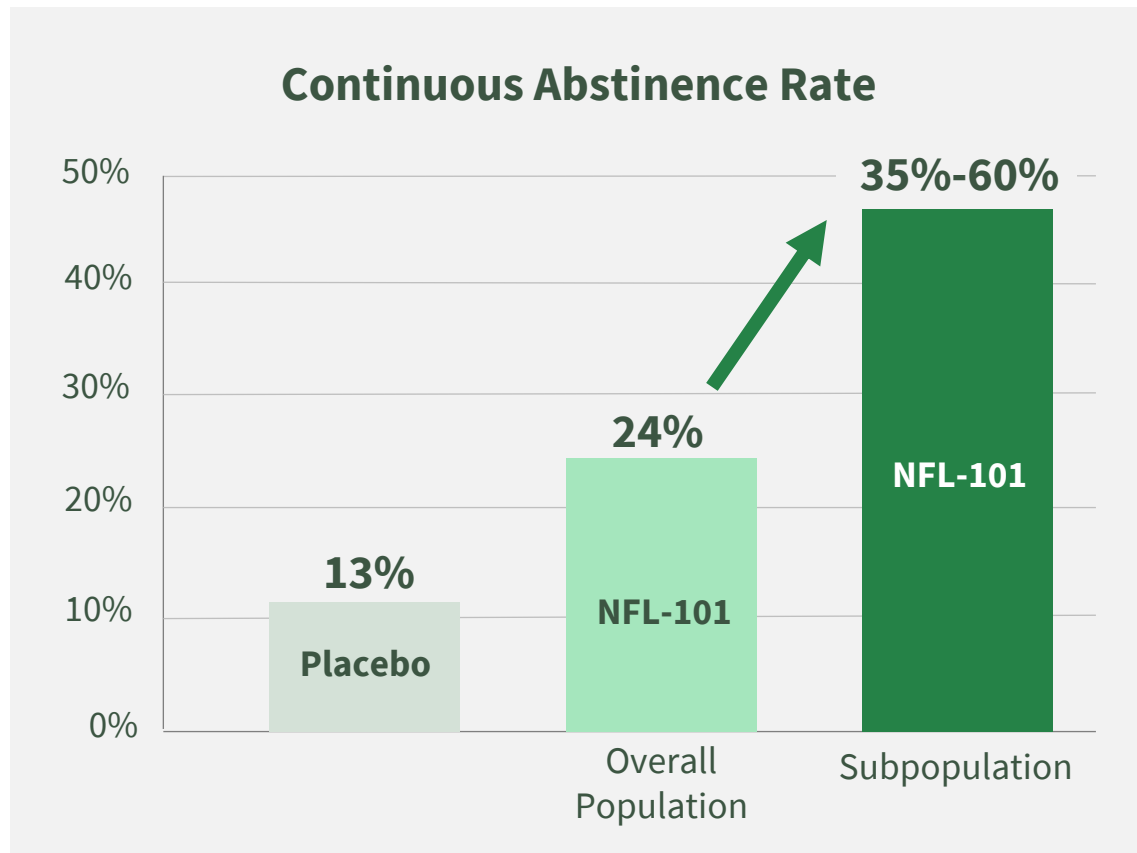
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PAGE NAVIGATION

The scientific article, entitled “[*Efficacy and Safety of NFL-101 as a Smoking Cessation Therapy: A Randomized Phase 2 Clinical Trial CESTO2*](#)”, has been published in *Nicotine & Tobacco Research* — an international peer-reviewed reference journal, the official journal of the Society for Research on Nicotine and Tobacco (SRNT), and published by Oxford University Press

First Targeted Therapy in Smoking Cessation

Exploratory analyses of CESTO2 participants reveal that a subpopulation with certain characteristics has higher rate of continuous abstinence than the overall study population.



- Subpopulation shows an abstinence rate between 35% and 60%
- Efficacy higher than on the general population (24,1%)
- Subpopulation estimated to represent 1/3 of overall population
- Full CESTO2 analysis will refine these estimates
- Biomarker analysis to be developed under GLP



NFL-102

A more comprehensive mechanism of action



CESNIT: Proposed Phase 2b Randomized Clinical Trial

Dose selection

Randomized (placebo 100/50/100/100/100), double-blind, placebo control Phase 2b in 10 clinical centres in France

An independent Data and Safety Monitoring Board (DSMB) will review safety data after the first 50 participants

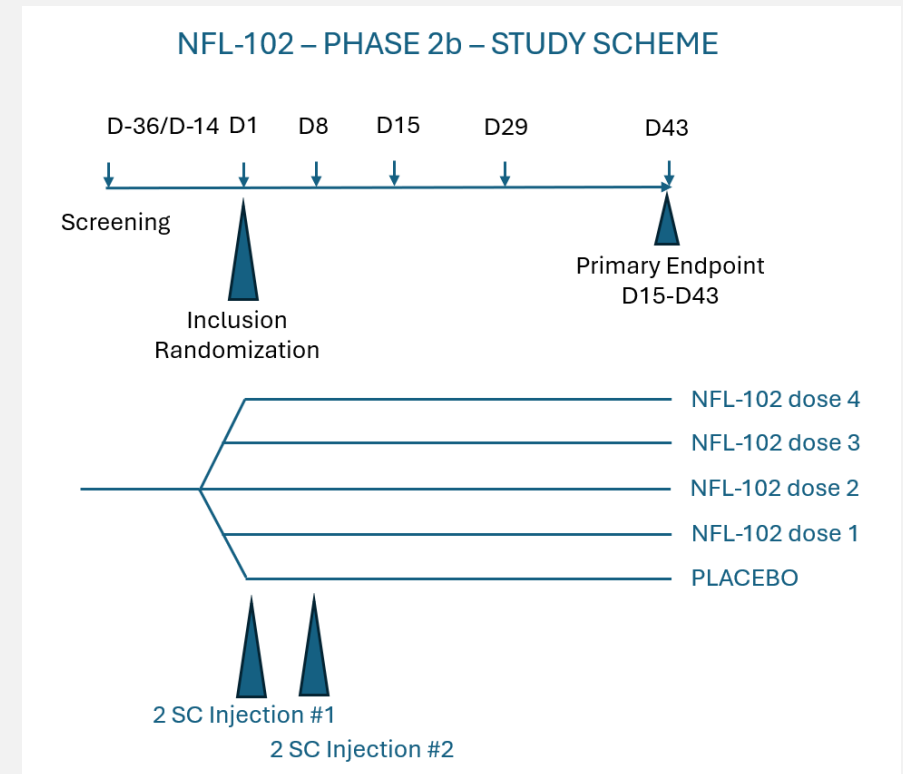
Primary endpoint

Success in achieving continuous abstinence defined as self-reported abstinence without the use of non-study smoking cessation products or e-cigarettes, confirmed by urinary cotinine $<50 \mu\text{g/mL}$, for at least **28 consecutive days** between Day 15 and Days 43-50 (4wCA)

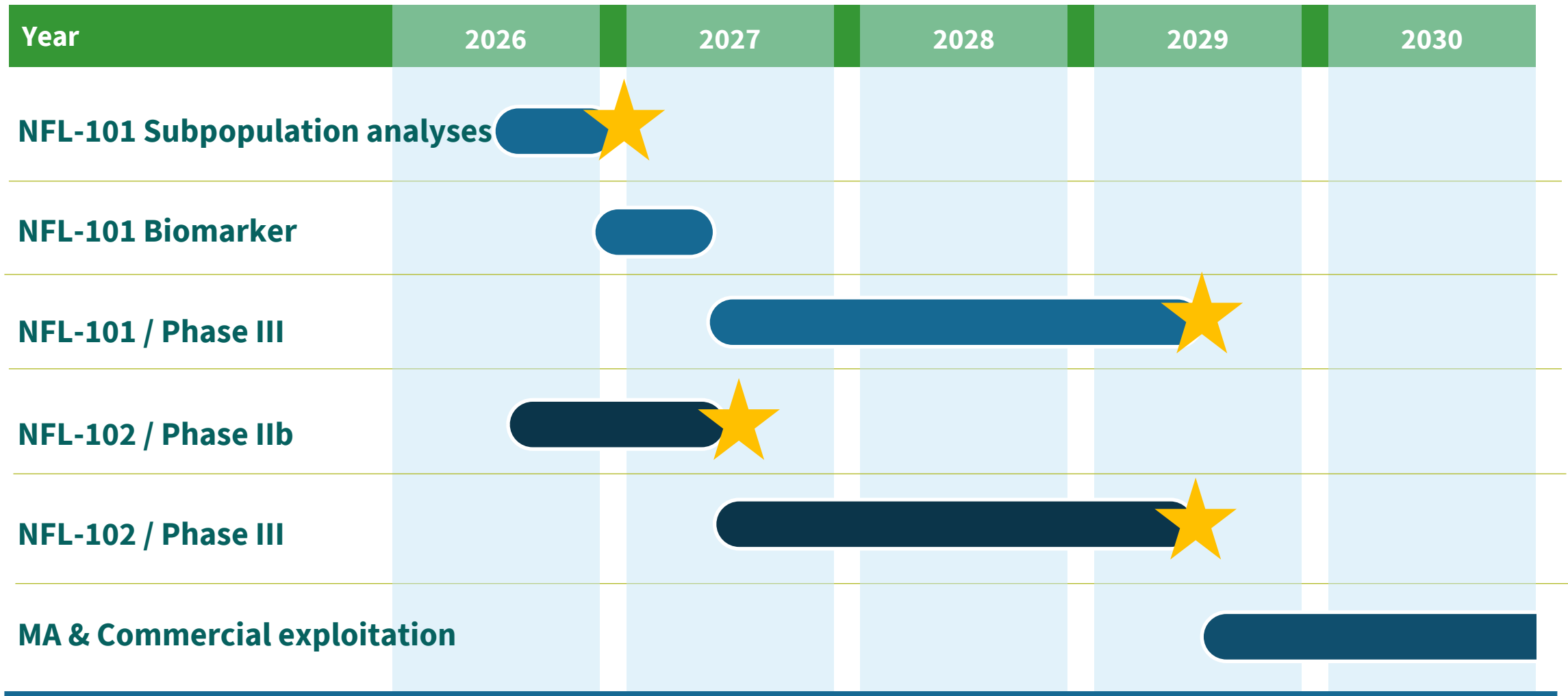
Objectives

- **Confirm superior efficacy of NFL-102**
- Dose selection
- Deliver results within 12-month from start of inclusions
- Prepare Phase 3

450 participants 



Future clinical development planning





Tobacco Leaf Extracts

Commercial strategy



Long and Multifaceted Exclusivity Allowing Protection Until 2051

Patent family 2006

Use of tobacco leaf extracts for the treatment of tobacco addiction

Europe	Russia
USA +3 years PTA	Ukraine
Canada	Israel
Japan	India
South Korea	Mexico

2031/34

Expiration, with pharmaceutical extensions

Patent family 2016

Use of specific constituents of tobacco leaves for the treatment of tobacco dependence

USA
Europe
Israel
Lebanon
PCT procedure 20 countries

2040/41

Expiration, with pharmaceutical extensions

Patent family 2023

Use as a pretreatment alone or in association with other treatments

Request for patent filed in the US in October 2022
PCT in preparation

2047/48

Expiration, with pharmaceutical extensions

Patent family 2026

Patent selection based on Patent family 2016

Request for patent planned to be filed in January 2026
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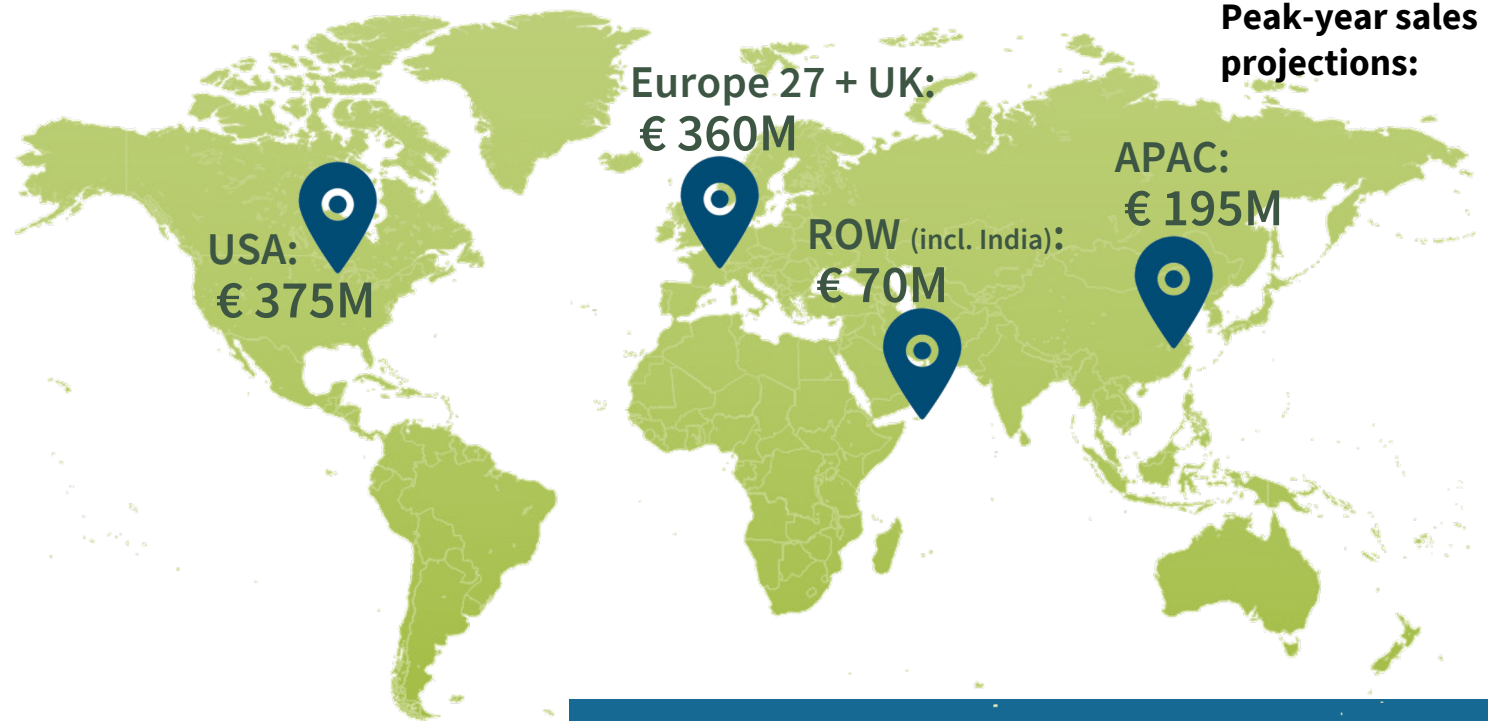
2050/51

Expiration, with pharmaceutical extensions

A Potential Annual Peak Sales of a Minimum of € 1 Billion

NFL-101/2 Full treatment prices

Countries	2024 Price of Marlboro 20-Pack (EUR)	Retail price (EUR)	Days of NO SMOKING to pay for NFL-101
United States	8,3	498	60
Europe Top 10	9,6	210	22
Germany	8,6	240	28
France	12,6	240	19
United Kingdom	18,0	240	13
Italy	6,3	186	30
Spain	5,8	174	30
Poland	6,0	180	30
Romania	5,5	162	30
Netherlands	12,6	240	19
Belgium	10,5	240	23
Greece	5,5	162	30
Asia Top 2	3,5	162	46
Japan	3,8	174	46
South Korea	3,0	138	46
China	3,3	120	36
India	3,9	120	31



- No tolerance and safety issues expected
- Much easier to use than existing products
- Effect probably in synergy with other products
- Possible transition to OTC later in commercial cycle

High compliance can drive superior sales for an equivalent number of smokers treated with NFL-101/2, positioning it as the only solutions universally suitable for smokers, regardless of other cessation therapies they have or have not adopted

Tobacco Leaf Extracts : Five Main Advantages vs the Competition

Promising efficacy: NFL-101 demonstrated excellent efficacy in a Phase II2b clinical trial, in line with the efficacy of Champix (In a comparison between studies)



Craving reduction: NFL-101 reduces craving and compulsivity to smoke, the main relapsing factors



Disruptive MoA: By acting downstream of nicotinic receptors, aiming to correct the neural circuits underlying relapse vulnerability, a revolution in the smoking cessation therapy landscape



Potential game changer: NFL-102 could potentially show much higher efficacy than products currently in the market



Higher compliance: The treatments require only two subcutaneous injections administered one week apart, compared to existing treatments that require multiple administrations over 12 weeks





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