INVEST SECURITIES

BIOTECHNOLOGIES

NFL BIOSCIENCES

BUY

TARGET PRICE : 4,9€ +36%

INITIATION REPORT

AN INNOVATIVE APPROACH TO TREAT ADDICTION

Following the success of the IPO, we initiate with a BUY recommendation and a fully-diluted TP of €4.9/share with an upside of +36%. We appreciate the positioning of NFL BIOSCIENCES in treating addiction—to tobacco, cannabis and alcohol— with three botanical drugs in its pipeline. The preliminary results for its flagship product, NFL-101, confirmed safety and efficacy. The treatment will now start Phase II/III clinical trials with results expected in Q3 2023. As things stand, we expect the product to launch on the market in 2026 and a peak sales of €900m. The €5m capital increase should offer a financial visibility until Q3 23 according to our estimates.

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NFL-101 is set to revolutionise treatment for tobacco addiction

NFL Biosciences specialises in treating addiction—to tobacco, cannabis and alcohol—and has three botanical drugs in its pipeline. Its flagship product NFL-101 is in clinical trials and is progressing to Phase II/III for addiction to smoking. The market for this glaringly unmet medical need is growing at a rate of 5.6% a year and will be worth more than $8 billion in 2028. The company has embarked on an ambitious clinical program in a bid to shift the needle and find a next-generation cure for smoking. The upcoming Phase II/III trial due to be launched in Australia in the third quarter of this year is the next step to prove the efficacy of the botanical product's innovative mechanism of action, developed after promising results from a retrospective study. The results for the two endpoints approved by the FDA in the United States and the EMA in Europe are expected in Q3 2023. At the same time, the company will run an exploratory study in association with NRTs and expects to have results also in Q3 2023. Both these studies should provide support to launch more comprehensive confirmation trials in both Europe and the US in Q4 2023. The product could be on the market in mid-2026.

Launch of NFL-101 in 2026, peak sales estimated at €900m

Compared with the treatments currently available on the market (Pfizer's Champix® notably), the potential benefits of NFL-101 are significant, but still to be confirmed in later-stage clinical trials. We are targeting four regions at this stage, Europe, US/Australia, the APAC countries and India, and a very specific category of smokers, namely people who are highly dependent on tobacco and want a drug to help them quit. Our assumptions put NFL Biosciences in a position to sign licence agreements as soon as 2024 in India and in 2026 in Europe/US/APAC for a total of €125 million. We expect the product to launch on the market in Europe/US/Australia/India in mid-2026 and in the main APAC countries in 2028. We see sales of NFL-101 peaking at €900 million in 2034 for over 15 million doses per year.

BUY recommendation, TP of €4.9/share, financial visibility until Q3 23

We initiate with a BUY recommendation and a TP of €4.9/share. Our valuation is the sum of NFL-101's rNPV to 2036 in four regions: Europe, US/Australia, the main APAC countries and India. Following the capital increase of €5m, we estimate the financial visibility until Q3 23, which coincides with the potential release date of CESTO-2 results.

in € / share	2021e	2022e	2023e
Adjusted EPS	-0,18	-0,53	-1,04
chg.	*n.s.*	*n.s.*	*n.s.*
estimates chg.	*+0,0%*	*+0,0%*	*+0,0%*

au 31/12	2021e	2022e	2023e
PE	n.s.	n.s.	n.s.
EV/Sales	n.s.	n.s.	n.s.
EV/Adjusted EBITD	n.s.	n.s.	n.s.
EV/Adjusted EBITA	n.s.	n.s.	n.s.
FCF yield*	n.s.	n.s.	n.s.
Div. yield (%)	n.s.	n.s.	n.s.

* After tax op. FCF before WCR

key points	
Closing share price 03/09/2021	3,6
Number of Shares (m)	5,2
Market cap. (€m)	19
Free float (€m)	3
ISIN	FR0014003XT0
Ticker	ALNFL-FR
DJ Sector	Health Technology

	1m	3m	Ytd
Absolute perf.	+5,6%	n.d.	n.d.
Relative perf.	+3,9%	n.d.	n.d.

Source : Factset, Invest Securities estimates

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FINANCIALS

Share information	2020	2021e	2022e	2023e	2024e	2025e	2026e	2027e
Published EPS (€)	-0,07	-0,19	-0,56	-1,10	-1,31	-1,94	9,17	8,41
Adjusted EPS (€)	**-0,06**	**-0,18**	**-0,53**	**-1,04**	**-1,24**	**-1,84**	**8,70**	**7,97**
Diff. I.S. vs Consensus	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Dividend	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Valuation ratios	2020	2021e	2022e	2023e	2024e	2025e	2026e	2027e
P/E	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
EV/Sales	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
EV/Adjusted EBITDA	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
EV/Adjusted EBITA	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Op. FCF bef. WCR yield	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Op. FCF yield	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Div. yield (%)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

NB : valuation based on annual average price for past exercise

Entreprise Value (€k)	2020	2021e	2022e	2023e	2024e	2025e	2026e	2027e
Share price in €	*n.s.*	*3,6*	*3,6*	*3,6*	*3,6*	*3,6*	*3,6*	*3,6*
Market cap.	n.s.	18 792	18 792	18 792	18 792	18 792	18 792	18 792
Net Debt	27	-4 963	-2 817	1 460	6 570	14 158	-21 673	-53 256
Minorities	0	0	0	0	0	0	0	0
Provisions/ near-debt	0	0	0	0	0	0	0	0
+/- Adjustments	0	0	0	0	0	0	0	0
Entreprise Value (EV)	**n.s.**	**13 829**	**15 976**	**20 252**	**25 362**	**32 950**	**-2 880**	**-34 464**

Income statement (€k)	2020	2021e	2022e	2023e	2024e	2025e	2026e	2027e
Sales	0	0	0	0	3 305	0	49 350	48 796
chg.	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Adjusted EBITDA	-276	-767	-2 300	-4 582	-4 825	-8 130	47 959	44 212
adjusted EBITA	**-276**	**-767**	**-2 300**	**-4 582**	**-4 825**	**-8 130**	**47 959**	**44 212**
chg.	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***
EBIT	-313	-805	-2 336	-4 606	-4 841	-8 140	47 933	43 994
Financial result	0	0	0	0	0	0	0	0
Corp. tax	52	51	153	305	-284	542	-11 990	-11 053
Minorities+affiliates	0	0	0	0	0	0	0	0
Net attributable profit	-262	-754	-2 183	-4 300	-5 125	-7 598	35 943	32 941
Adjusted net att. profit	**-262**	**-754**	**-2 183**	**-4 300**	**-5 125**	**-7 598**	**35 943**	**32 941**
chg.	***-2%***	***+188%***	***+190%***	***+97%***	***+19%***	***+48%***	***-573%***	***-8%***

Cash flow statement (€k)	2020	2021e	2022e	2023e	2024e	2025e	2026e	2027e
EBITDA	-276	-767	-2 300	-4 582	-4 825	-8 130	47 959	44 212
Theoretical Tax / EBITA	0	0	0	0	0	0	-11 990	-11 053
Capex	-32	-32	0	0	0	0	-20	-214
Operating FCF bef. WCR	**-308**	**-799**	**-2 300**	**-4 582**	**-4 825**	**-8 130**	**35 949**	**32 945**
Change in WCR	0	0	0	0	0	0	-119	-1 362
Operating FCF	**-308**	**-799**	**-2 300**	**-4 582**	**-4 825**	**-8 130**	**35 830**	**31 583**
Acquisitions/disposals	0	0	0	0	0	0	0	0
Capital increase/decrease	0	5 738	0	0	0	0	0	0
Dividends paid	0	0	0	0	0	0	0	0
Other adjustments	52	51	153	305	-284	542	0	0
Published Cash-Flow	**-256**	**4 990**	**-2 147**	**-4 277**	**-5 110**	**-7 588**	**35 830**	**31 583**

Balance Sheet (€k)	2020	2021e	2022e	2023e	2024e	2025e	2026e	2027e
Assets	109	103	67	44	28	18	12	8
Intangible assets/GW	109	103	67	44	28	18	12	8
WCR	68	68	68	68	68	68	187	1 549
Group equity capital	150	5 134	2 951	-1 349	-6 474	-14 072	21 871	54 812
Minority shareholders	0	0	0	0	0	0	0	0
Provisions	0	0	0	0	0	0	0	0
Net financial debt	**27**	**-4 963**	**-2 817**	**1 460**	**6 570**	**14 158**	**-21 673**	**-53 256**

Financial ratios	2020	2021e	2022e	2023e	2024e	2025e	2026e	2027e
EBITDA margin	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	97%	91%
EBITA margin	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	97%	91%
Adjusted Net Profit/Sales	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	73%	68%
ROCE	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	24106%	2840%
ROE adjusted	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	164%	60%
Gearing	17,9%	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
ND/EBITDA (in x)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	-0,5x	-1,2x

Source : company, Invest Securities Estimates

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INVESTMENT CASE

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SWOT ANALYSIS

STRENGTHS

- Large market with significant unmet medical need
- Innovative plant-based approach to quitting
- Convincing initial clinical trial results

WEAKNESSES

- Clinical development at an early stage
- Mechanism of action requiring clarification
- Administration not suitable for OTC

OPPORTUNITIES

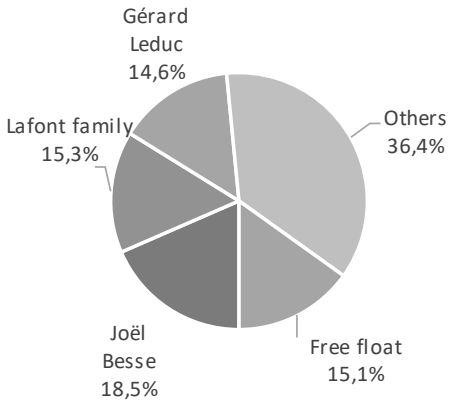
- Licence agreements
- New administration methods
- Expanding the pipeline to other addictions

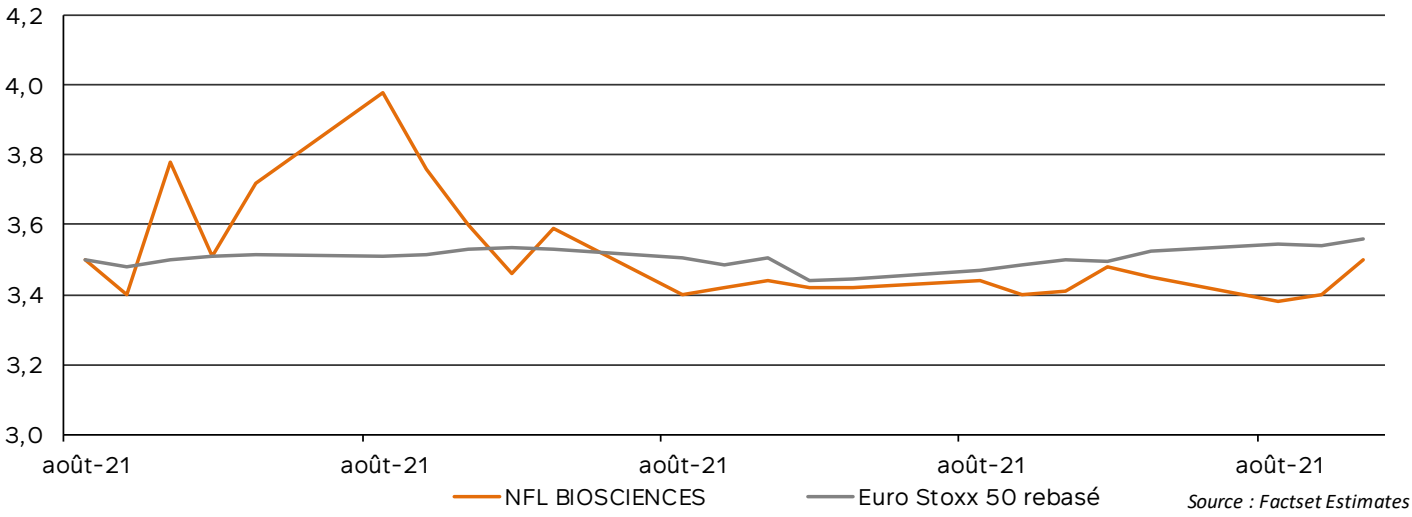
THREATS

- Clinical failure
- Regulatory and patent risk
- Risk of new entrants

ADDITIONAL INFORMATION

Fully-diluted shareholders





Source : Factset Estimates

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CONTENTS

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1-SMOKING CESSATION, A MARKET WITH CONSEQUENTIAL MEDICAL NEEDS

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1- Smoking cessation, a market with consequential medical needs

1.1 Introduction

❖ Tobacco addiction is a health and financial scourge

There are more than 1.1 billion cigarette smokers in the world and more than 8 million smoking-related deaths every year. Addiction to smoking kills more people that HIV/AIDS, malaria and tuberculosis combined. Smoking kills more than half of long-term smokers and is the leading cause of death from avoidable illness worldwide (over 80% of lung cancer deaths in men and 50% in women are linked to smoking).

According to the World Health Organization, the burden of disease and death from smoking is disproportionately high in the developing world, accounting for some 70% of deaths from smoking. This is a very valuable target market, since more than 80% of young people aged 10 to 24 live in developing countries.

Besides the negative impact of smoking on health, the full economic cost of smoking (health spending and loss of productivity) is estimated at around $2,000 billon per year, or 2.6% of global GDP. Close to 40% of this cost is borne by developing countries, illustrating the high burden on these countries. For example, the estimated cost in the US is greater than $300 billion every year.

All forms of smoking are damaging and there is no threshold below which exposure poses no danger. Cigarette smoking is the most common form of tobacco use, but there are other products, such as the water pipe, smokeless tobacco, cigars, cigarillos, rolling tobacco, pipe tobacco, bidis and kreteks.

❖ Most recent innovations on the market

- **Heated tobacco products (HTP)**

Like all tobacco products, heated tobacco products are intrinsically toxic and contain carcinogenic substances. They must be treated like all other tobacco products in anti-smoking policies. They generate aerosols containing nicotine and other toxic chemicals when the tobacco is heated, or when the device containing the tobacco (vaporizer) is activated.
For years, manufacturers have been touting heated tobacco products as “less harmful” or as helpful in quitting smoking. But these products expose users to toxic emissions, many of which are carcinogenic, with not enough evidence to back claims that these are less harmful than conventional cigarettes.

- **E-cigarettes**

Electronic nicotine distribution systems (ENDS) and electronic non-nicotine distribution systems (ENNDS), together known as e-cigarettes, are devices that heat a liquid with or without nicotine to produce an aerosol that the user inhales. The main constituents of the solution by volume are propylene glycol, with or without glycerol, and flavourings. E-cigarettes don’t contain tobacco but are harmful to health and entail risks. But, it is still too soon to determine the long-term impact of using or being exposed to these products.
E-cigarettes are particularly dangerous when used by children and adolescents. Nicotine is highly addictive and young people's brains continue to develop until they are about 25 years old.

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1- Smoking cessation, a market with consequential medical needs

1.2 Tobacco dependence: risks and solutions

❖ Exposure to tobacco smoke: a risk factor

The nicotine in tobacco is highly addictive and smoking is a major risk factor for cardiovascular and respiratory conditions, for more than 20 types of sub-types of cancer and many other debilitating conditions.

With smoking, the danger comes from the gases that are released on combustion. According to the experts, tobacco contains more than 4,000 chemicals, including carbon monoxide, tar, arsenic, formaldehyde and benzene. Approximately 50 of these are known cancer-causing agents in humans.

Exposure to secondary cigarette smoke has been identified as damaging to health and is responsible for 1.2 million deaths every year. Experimental and clinical epidemiological studies have shown that even a small amount of smoke is linked to disproportionate cardiovascular (CV) risk. These findings explain why cardiovascular risk for passive smokers is 25 to 30% higher. Almost half of children breathe air polluted by tobacco smoke. 65,000 children a year die from illnesses related to secondary smoke. Asthma and repeat ear infections affect the children of smokers more than those born to non-smokers because of the damage to their mucous membranes. Smoking during pregnancy can cause the baby to have lifelong health problems.

❖ Main diseases linked to smoking

On average, non-smokers can expect to live 10 years longer than smokers. Smoking is the No. 1 cause of chronic respiratory problems and is implicated in 10 to 30% of deaths from cardiovascular disease.

Smoking is one of the main risk factors for many diseases, such as:

- hypertension,
- cardiovascular disease and stroke: smokers have a 70% higher risk of dying from heart disease (32% of all deaths) than non-smokers. Arteriosclerosis can also affect the arteries in the legs causing intermittent claudication, which may require surgery or even amputation,
- chronic bronchitis and emphysema, leading to respiratory failure or heart failure,
- cancer: lung cancer (87% of deaths), cancer of the mouth, esophageal cancer, bladder cancer, etc.
- erectile dysfunction: the risk for smokers is twice that for non-smokers
- peptic ulcer: nicotine increases acid secretion in the stomach, a condition that can aggravate the symptoms of gastro-esophageal reflux,
- during and after pregnancy: miscarriage, complications during pregnancy, underweight newborn, sudden infant death syndrome

Smoking can have a range of other consequences over time, such as coughing, shortness of breath, headaches and digestive issues. What's more, smokers' skin ages faster.

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1- Smoking cessation, a market with consequential medical needs

❖ **Main symptoms**

When a person stops smoking they usually experience a range of symptoms linked to physical and psychological withdrawal. Most symptoms reduce dramatically in the first few days after stopping, and then fade gradually but more slowly during the second and third week of not smoking. In other words, the first few days are the hardest.

When smokers quit nicotine, they experience withdrawal symptoms. These symptoms are most severe after a few days of withdrawal but can last for several weeks or even months. That said, nicotine is eliminated from the body quickly: 4 days after stopping smoking, no nicotine is detected in the blood.

The main symptoms of withdrawal that usually lead to relapse are:

- tension and irritability
- craving to smoke
- dry mouth and throat
- anxiety
- shakes
- insomnia
- headaches
- increased appetite
- craving for sugar and sweet things
- diarrhoea, constipation and stomach cramps

❖ **Smoking cessation: a pressing need rather than a solution**

In general, the benefits of quitting are felt very quickly—no matter how much a person smoked. In as little as 24 hours after the last cigarette, the risk of myocardial infarction reduces, the lungs begin to eliminate mucus and smoke residue, and CO_2 is removed from the blood. In the weeks after stopping, cardiovascular risk (coronary spasm and thrombosis) falls, and within two weeks platelet dysfunction is normalised. After 5 years of not smoking, the risk is almost equivalent to that of a person who has never smoked. However, lung damage may be irreversible after several years of smoking, although breathlessness and coughing does reduce. The younger the person, the greater the benefits of quitting. The risk of lung cancer is the same as for non-smokers 10 to 15 years after stopping.

1.3 How available treatments work

❖ **Mechanisms underlying addiction**

Stopping smoking is defined as tobacco cessation. Relapses are common because it's hard to quit and cigarettes contain a lot of ingredients that reinforce the addiction.

There are three mechanisms underlying the addiction to smoking: pharmacological (addiction to the products in the smoke, nicotine essentially), psychological (the need to light a cigarette regularly), and emotional and behavioural (the reflex of lighting up), such as the pleasure of the gesture and association with pleasant experiences (cues such as the first coffee, meals with friends, etc.).

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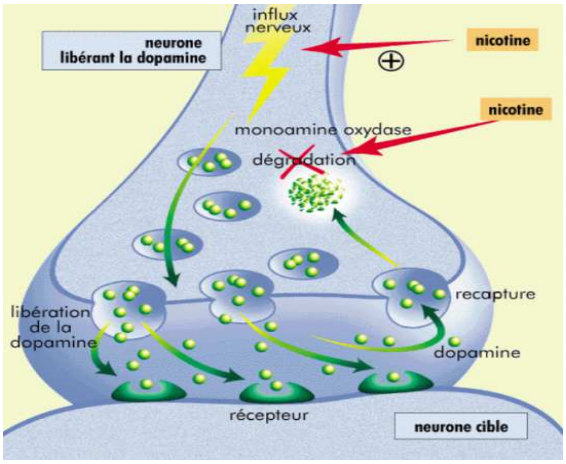
1- Smoking cessation, a market with consequential medical needs

Addiction to nicotine takes place in the brain. Nicotine activates receptors that release dopamine (neurotransmitter), a chemical messenger that plays a key role in the neurological perception of pleasure. Dopamine reduces anxiety, lifts mood, improves memory and reduces appetite. For someone who wants to quit smoking, losing these benefits is a very big step to take.

Contract area between the neurotransmitter that produces dopamine



Dopamine is released into the narrow space between the two neurons (synaptic cleft). It acts by binding to receptors carried by the target neuron. Dopamine is then taken up by the transmitting neuron and destroyed by an enzyme, monoamine oxidase. **Nicotine** stimulates the neurotransmitter (the nerve impulse) and prevents the dopamine from being destroyed after reuptake by inhibiting the monoamine oxidase.

Every time dopamine is released, the dopamine receptors go on alert. They become gradually desensitized and satisfaction is reduced. The usual dopamine levels are no longer enough and “craving” sets in. The smoker is tempted to smoke more to get the additional stimulation needed to produce the same effect.

Several components of tobacco have an addictive effect through their action on the human brain. Nicotine is the best known, which acts on the brain by stimulating nicotine acetylcholine receptors (nAChRs) and by increasing the release of several neurotransmitters, such as dopamine. These elevated levels of dopamine activate the reward pathways in the brain and induce a feeing of pleasure, calm, reduced appetite— and tobacco addiction. Other constituents of tobacco include anabasine, anatabin, nornicotine, β-Carboline and one of its derivatives (harman). These significantly reduce the action of monoamine oxidases (MAO) in smokers. MAO is an enzyme that catalyses dopamine and increases its sensory effects. Tobacco also disrupts the link between the noradrenergic and serotonin systems in the central nervous system (CNS). Taken together, they lead to behavioural changes and increase the reactivity of the dopamine neurons responsible for tobacco addiction.

We now know that addiction to smoking is also due to other mechanisms involving other areas and pathways in the central nervous system. For example, smokers’ behaviour varies according to genetic and environmental factors.

❖ **How available treatments work**

Plants cause the addiction in the first place, but they are also the two main therapies for treating the problem: nicotine replacement therapies (NRT) and varenicline, marketed by Pfizer under the names Champix® or Chantix® since 2006.

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1- Smoking cessation, a market with consequential medical needs

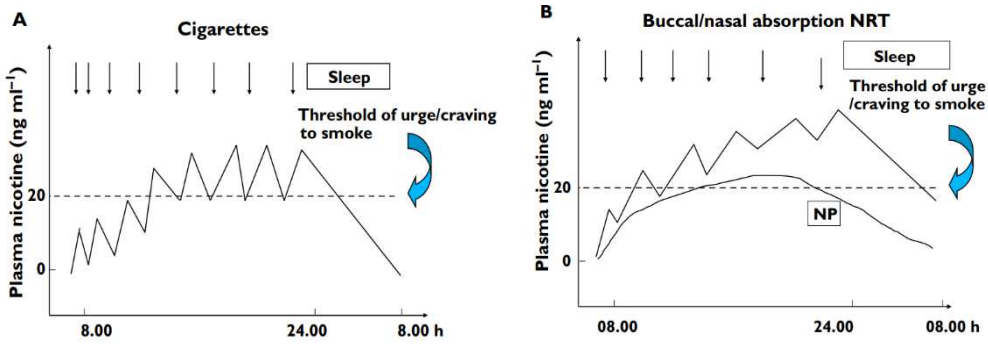
There are a number of different strategies to treat addiction to tobacco: *behavioural* therapies to increase motivation and provide support to stop smoking, and *therapeutic* to reduce nicotine reinforcement and withdrawal symptoms.

- **Nicotine replacement therapies (NRT):**

Nicotine is a botanical alkaloid found in tobacco paper. The first treatments developed to help people quit smoking, NRTs, targeted nicotine. Nicotine replacement therapies are now available without medical prescription, in the form of patches, nicotine gum, tablets or sprays. The aim is to replace the nicotine in tobacco by taking daily doses, which are tapered to gradually reduce nicotine dependence. These are still the most popular treatments used by people who want to stop smoking, but their long-term effectiveness is limited.

When inhaled in cigarette smoke, nicotine is close to 100% bioavailable due to the large surface area of absorption in the lungs and the direct delivery of nicotine to the brain via the pulmonary arteries and the cardio-carotid circulation. The bioavailability of nicotine from NRT is much lower than from cigarette smoke. Transdermal patches provides continuous nicotine delivery over 16 or 24 hours (Figure 1), depending on the brand. In contrast, oral formulations (absorbed by mouth) have a short duration of action. Users can adjust the dose over time according to their needs. So, oral NRTs give smokers a coping strategy when they feel the urge to smoke.

The graphs below give a schematic view of plasma nicotine concentrations in the blood of a smoker over a 24-hour period (A) and in a non-smoker using a nicotine patch (NP) and orally/nasally absorbed nicotine replacement products (B). Combining NP and oral/nasal fast-acting nicotine replacement products increases the area under the plasma nicotine concentration curve and in peak nicotine concentrations. This gives a longer time above the plasma nicotine concentration threshold of urge/craving to smoke and better mimicking of self-titrated nicotine peaks.



Source: Journal of COPD, Foulds et al.

- **Cytisine:**

Cytisine is a plant alkaloid derived from the seeds of the *Laburnum anagyroides*. Cytisine is structurally similar to nicotine and has both an agonist and antagonist mechanism of action with nicotine receptors in the brain. It is used as a treatment to stop smoking and has been sold by Sopharma in Central and Eastern Europe for over 40 years under the brand name Tabex.

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1- Smoking cessation, a market with consequential medical needs

- **Varenicline:**

Pfizer developed varenicline (Champix®®) by copying the properties of cytisine but with a symmetrical structure (cytisine is asymmetrical). Varenicline's significant side-effects dented its commercial potential, although it turned in peak annual sales in 2019 of more than $1 billion. Pfizer's main US patent for the product went into the public domain in November 2020. The patent for Europe will expire in 2021 and for Japan in 2022.

- **Bupropion:**

Bupropion was the first non-nicotine pharmacologic treatment approved to help people quit smoking. It was first approved as an atypical antidepressant in the US and other countries, before being used for smoking cessation. Bupropion is derived from beta phenylethylamine, which explains its stimulant properties. It preferentially blocks the reuptake of norepinephrine and dopamine in the central nervous system and is also a nicotine receptor antagonist, which means it blocks the reinforcing effects of nicotine to some extent.

1.4 Typology of smokers

In our research, we attempted to determine the levels of addiction of smokers in the population. Measures of tobacco addiction are mainly used in clinical settings, and information on the general population is scarce.

The most recent study of this type on a general population was conducted in 2002-2003 in Italy. Two surveys were conducted using a Fagerström test for nicotine dependence (FTND) on a sample of 6,773 individuals aged 15 and over, representative of the Italian adult population.

The Fagerström test is used to screen and assess the intensity of physical addiction to nicotine. It has six questions on smoking habits. It can be used to tailor strategies to help stop smoking.

Here are the six questions in the test:

1. "How long after you wake up do you smoke?": within 5 minutes (3), 6-30 minutes (2), 31-60 minutes (1), after 60 minutes (0)
2. "Do you find it difficult to refrain from smoking in places where it is prohibited?": yes (1), no (0)
3. "What is the cigarette you would not like to see disappear?": the first one in the morning (1), all the others (0)
4. "How many cigarettes do you smoke per day?" 10 or fewer (0), 11-20 (1), 21-30 (2), 31 or more (3)
5. "Do you smoke more often during the first few hours after waking than during the rest of the day?" yes (1), no (0)
6. "Do you smoke if you are so sick that you stay in bed most of the time?": yes (1), no (0)

The higher the total Fagerström score, the more intense the person's dependence on nicotine:

0-2	très faible	**3-4**	faible	**5**	intermédiaire	**6-7**	élevée	**8-10**	très élevée

The study concluded that 1,837 smokers (27.1% of the sample of 6,773 surveyed) had different Fagerström test scores.

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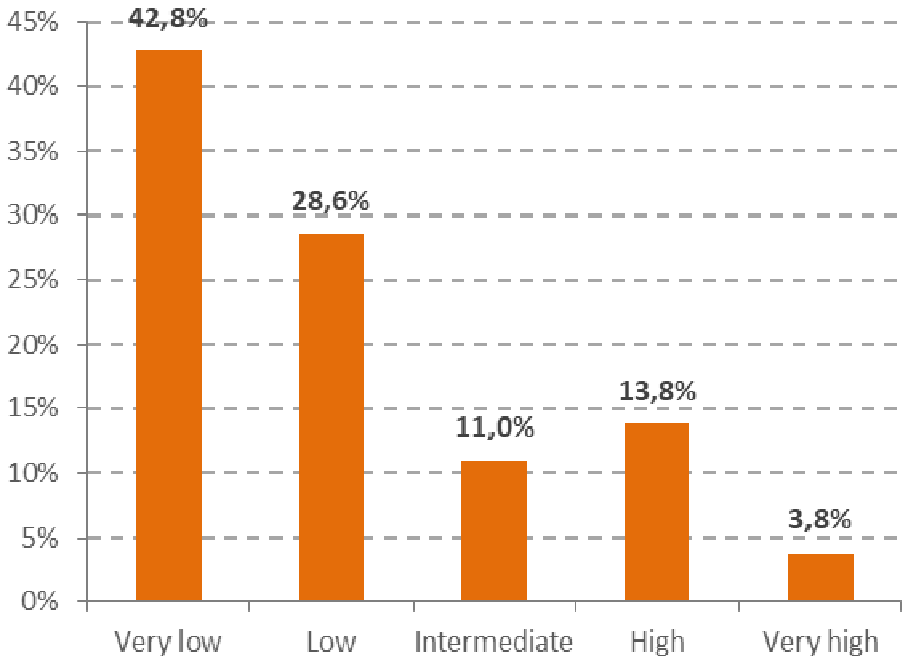
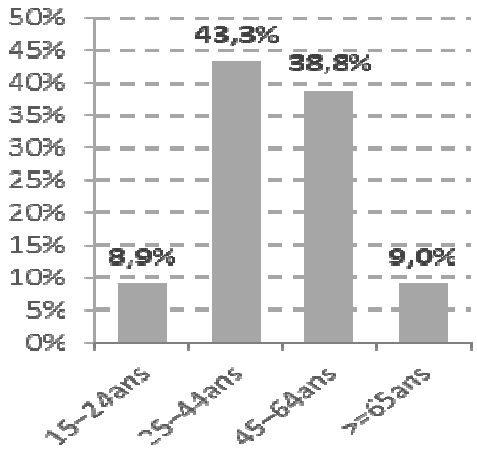
The findings are shown in the graph below:

Dependency score for the Italian population



17.6% of the smokers scored high on the Fagerström scale (> 6) and the most intense dependency is found in the 25-64 age group.

Breakdown of smokers by age in Italy



With respect to the characteristics of smokers in the Western world, the study showed that among smoking is most prevalent amongst 25 to 44 year-olds. In terms of dependence, in the U.S., 67% of smokers are aged 25-44 and 45-64, compared with 75.5% in Italy. Finally, it is well established that the majority of smokers are men. For example, in this study, 57.0% of smokers were men and 43.0% women.

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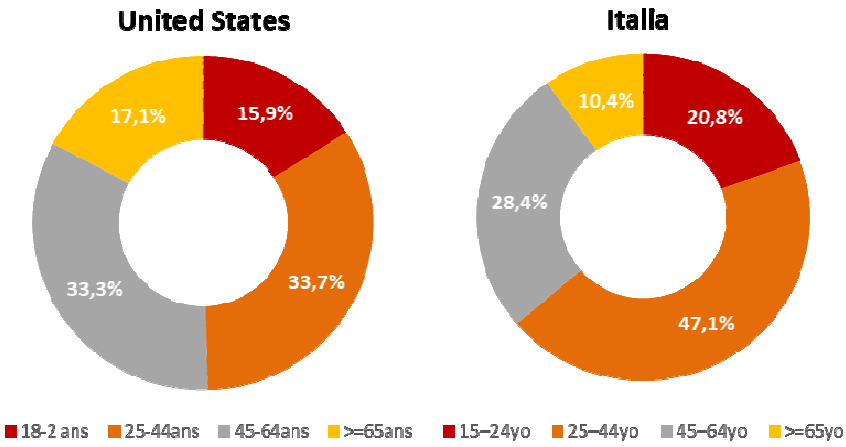
Percent of adult smokers by age bracket in 2018, US vs. Italy (2003 study data)

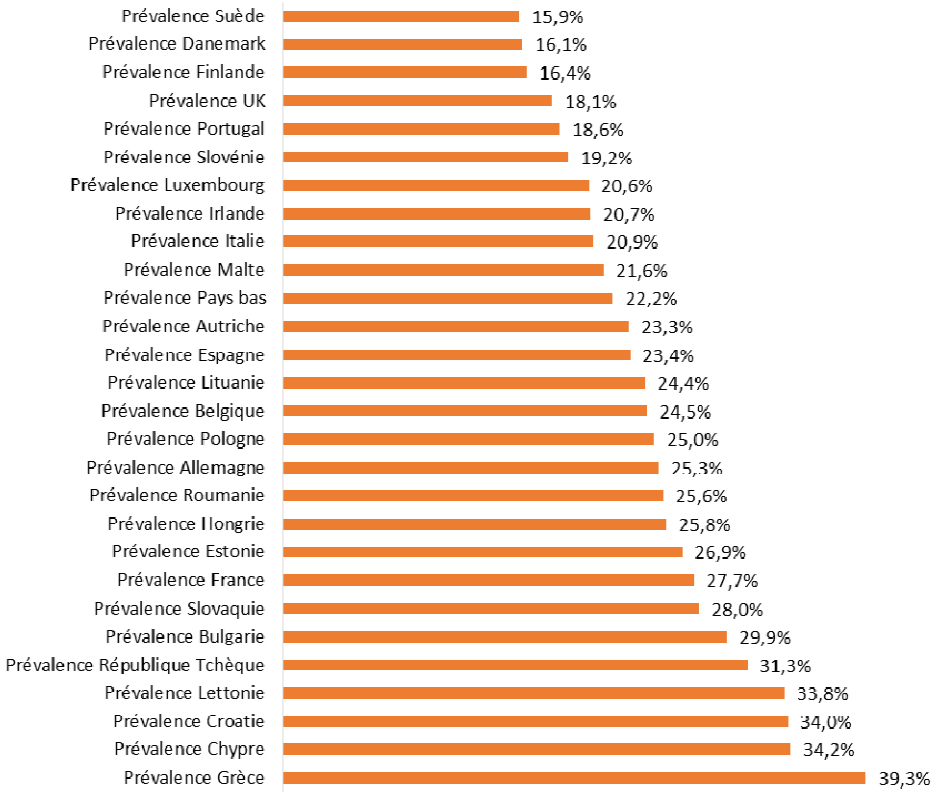


Source : mordorontelligence.com

1.5 The smoking cessation market

❖ Prevalence of smoking

According to the WHO, 18.7% of adults (aged over 15) were addicted to tobacco in 2020. Its target is to cut this rate to 15.5% by 2025, the projected decline is lower than this, to 17.3%. The data in the WHO report on trends in tobacco use show that "smokers" account for the vast majority of tobacco users. The average prevalence in EU member states (27 + UK) is around 24.7% of the population in 2020, equating to approximately 120 million individuals.



Source: WHO, Global report on trends in prevalence of Tobacco smoking 2000-2025

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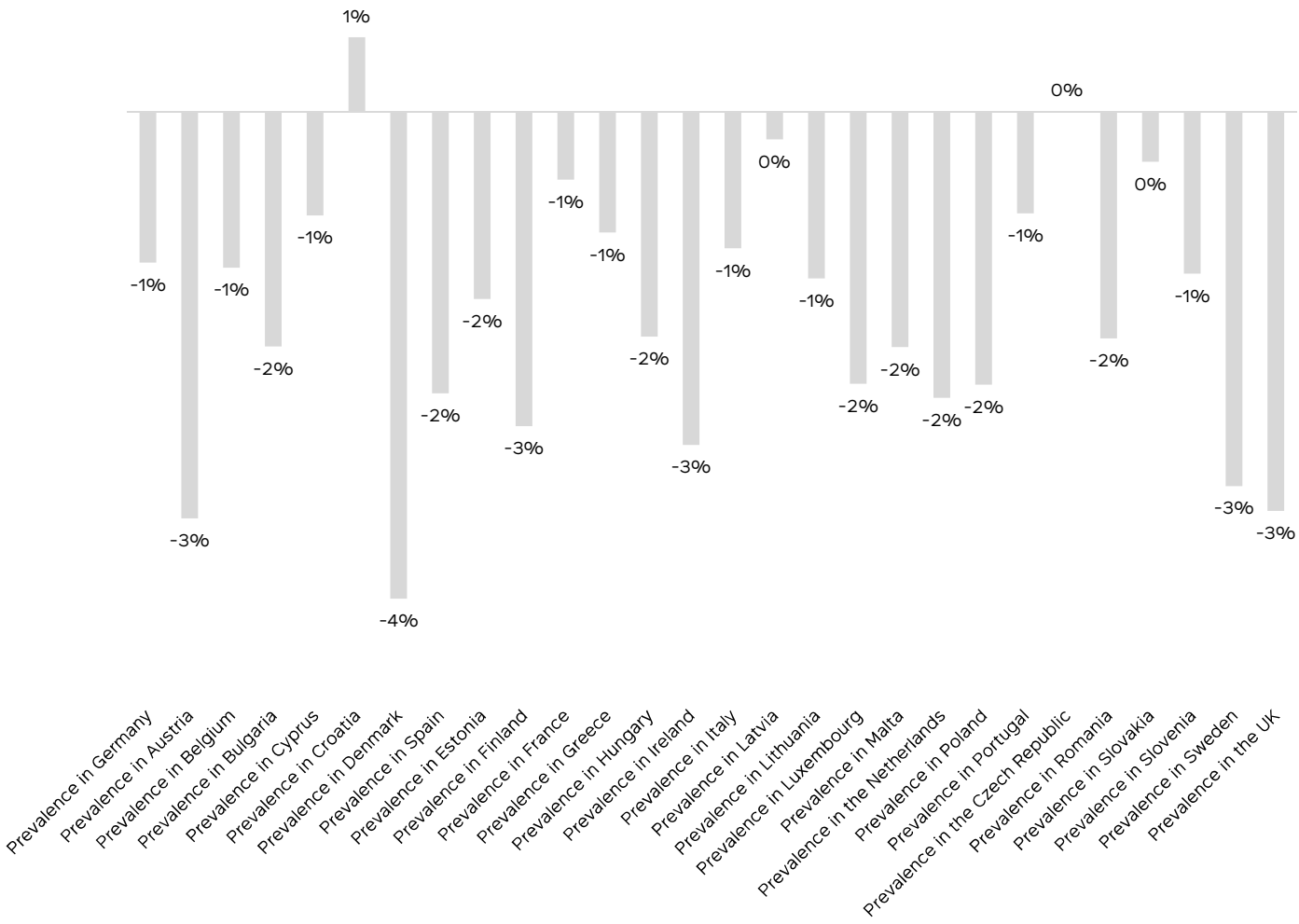
Greece has the highest prevalence in Europe at 39.3% (close to 4.2 million people). However, if we concentrate on the countries with the highest number of smokers, Germany is top of the list (21 million), followed by France (18.6 million) and Italy (12.6 million).

Thanks to campaigns to raise awareness of the dangers of cigarettes and anti-smoking policies (higher prices and taxes on packs of cigarettes, advertising ban) the number of smokers has fallen and is expected to decline in Europe in the period covered by the estimates (2020-2025e). The biggest decline in this period will be in the Nordic countries and Austria.

2020 prevalence and annualised change (2025 projection) of addiction in Europe



Source: WHO, Global report on trends in prevalence of Tobacco smoking 2000-2025

The United States is the biggest market for smoking cessation treatments because of higher prices. The WHO estimated the prevalence in 2020 at 23.0%. Tracking the trend in Europe, the rate is expected to decline -1.6% in the estimate period (2020-2025e).

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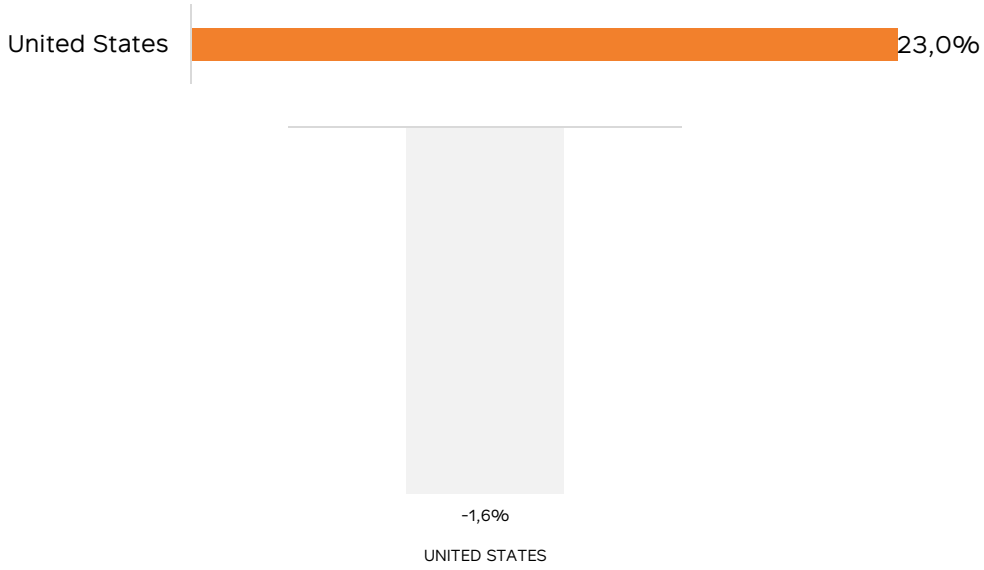
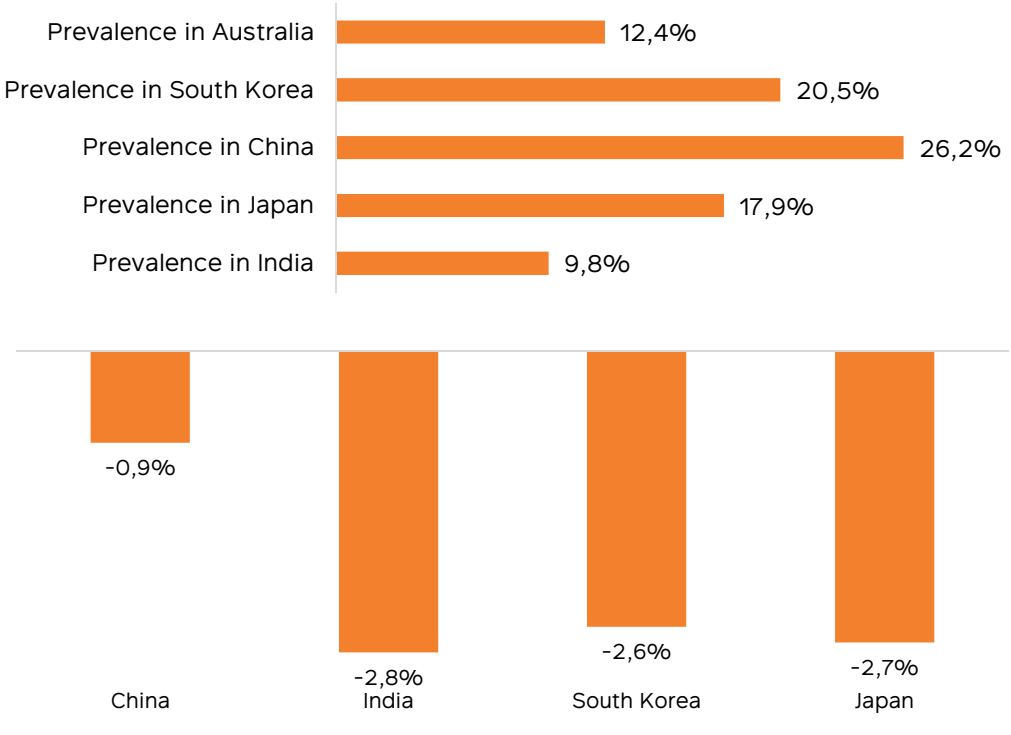
2020 prevalence and annualised change (2025 projection) of addiction in the US



Asia and South-East Asia in particular have high rates of tobacco use. Prevalence in China is 26.2%, or some 370 million smokers, placing China at the top of the table with the biggest number of smokers in the world. At 9.8%, India has 130 million smokers. Prevalence in South Korea and Japan is 20.5% and 17.9%, respectively, giving 10.6 and 22.6 million smokers. Prevalence of tobacco use in Australia is 12.4% (3.2 million smokers).

2020 prevalence and annualised change (2025 projection) of addiction in the APAC region



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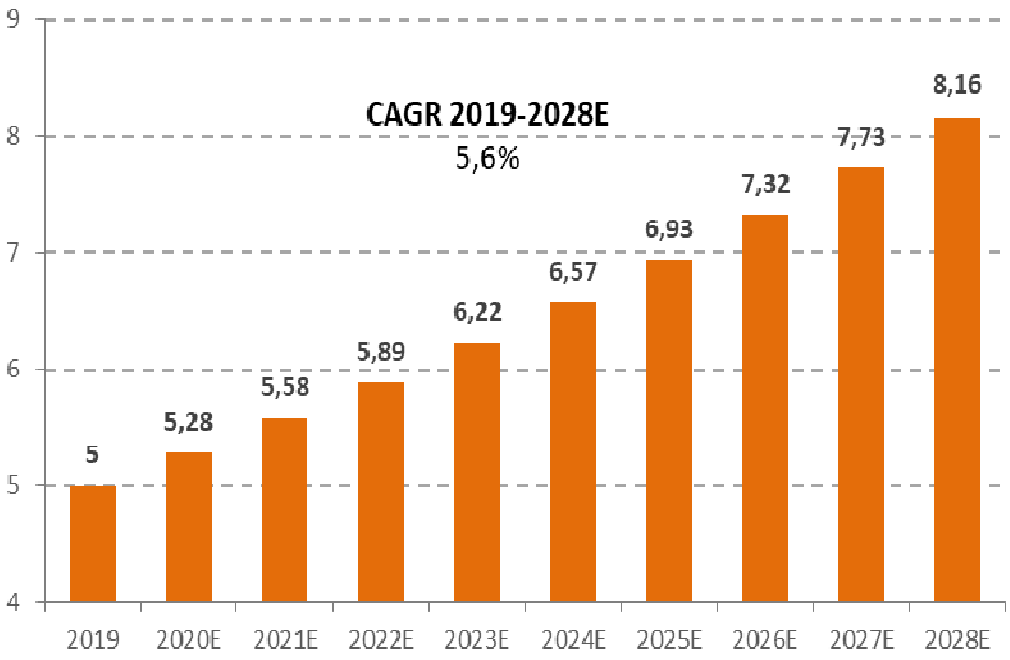
❖ **Considerable smoking cessation market**

The global market for smoking cessation is worth approximately $5.3 billion. But help to quit smoking is not available to everyone. For now, developed countries are the core of this market, since cost is an obstacle for the developing world.

There are treatments with modest efficacy rates to help stop smoking, particularly behavioural therapies and drugs approved by the FDA. 89 different products and services are on the market, as well as 12 alternatives to tobacco that are not specifically indicated for quitting. FDA-approved drug therapies include various forms of nicotine replacement therapy (NRT) in the form of transdermal patches, gum, nasal sprays, oral inhalers and lozenges, or drugs such as bupropion (tablet) and varenicline (tablet), as of 2006.

The market for NRTs and other drugs to help quit smoking in the period 2019 to 2028e (in $ bn).



Source: Report Global Smoking Cessation and Nicotine De-Addiction Products Market Coherent Market Insights

As things stand, NRTs make up the bulk of the market ($2.8 billion by 2020) and are sold as generics by a large number of different players. They offer a much wider range of delivery options, allowing them to cater for those with contraindications to certain dosages. What's more, NRTs are far more affordable than other drug treatments and are sold over the counter in many countries. Drugs may require a doctor's prescription.

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❖ **Main catalysts in the smoking cessation market**

Growth in the market and uptake of smoking cessation therapies depend on a number of factors:

- **Public awareness of the damaging effects of tobacco.**
- **Higher prices and taxes.**

According to the CDC (US Centers for Disease Control and Prevention), increasing the price of tobacco products is the best way of cutting consumption. Taxes on tobacco are seen as the most cost-effective way to reduce smoking, especially amongst young people and low-income groups. A tax increase that puts an additional 10% on the price of tobacco brings down tobacco consumption by around 4% in high-income countries and about 5% in low- and middle-income countries.

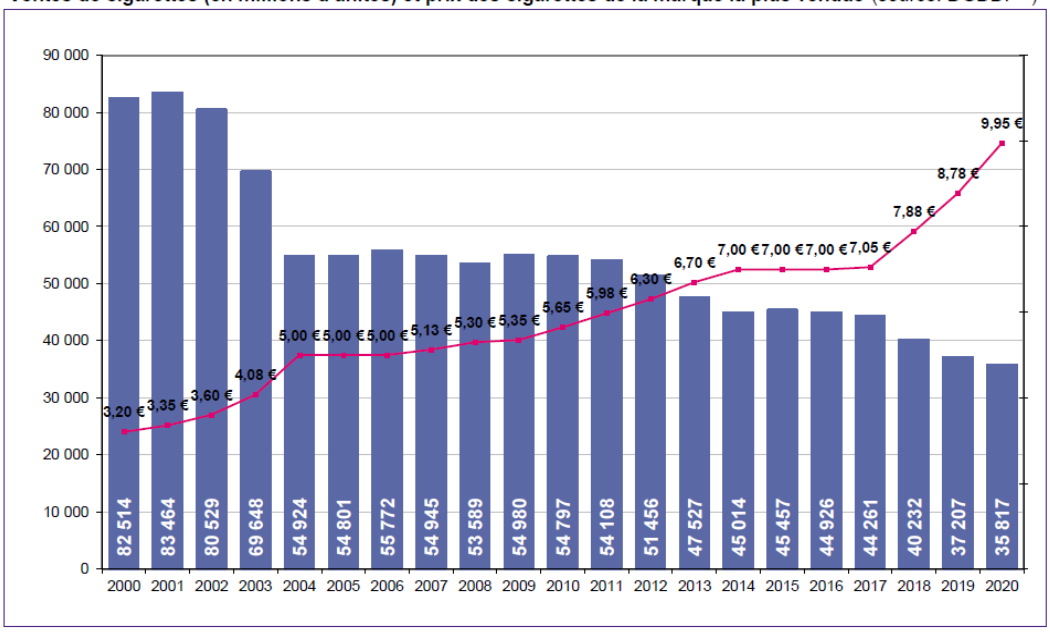
Research on smoking suggests that:

✓ youths and young adults are two to three times more likely to respond to price increases than adults;
✓ low-income groups are more likely to increase their attempts to quit or cut down if prices are increased, although the desire to quit and successfully quitting are not necessarily the same across racial/ethnic groups.

The decline in tobacco consumption, particularly cigarette consumption, in developed countries does not affect the increase in sales of smoking cessation treatments— which aim to lower consumption.

The French Monitoring Centre for Drugs and Drug Addiction (OFDT) publishes very detailed reports on cigarette consumption and the use of smoking cessation products.

Ventes de cigarettes (en millions d'unités) et prix des cigarettes de la marque la plus vendue (source: DGDDI [1])



Source: DGDDI

We note a negative correlation between price hikes on cigarettes and smoking.

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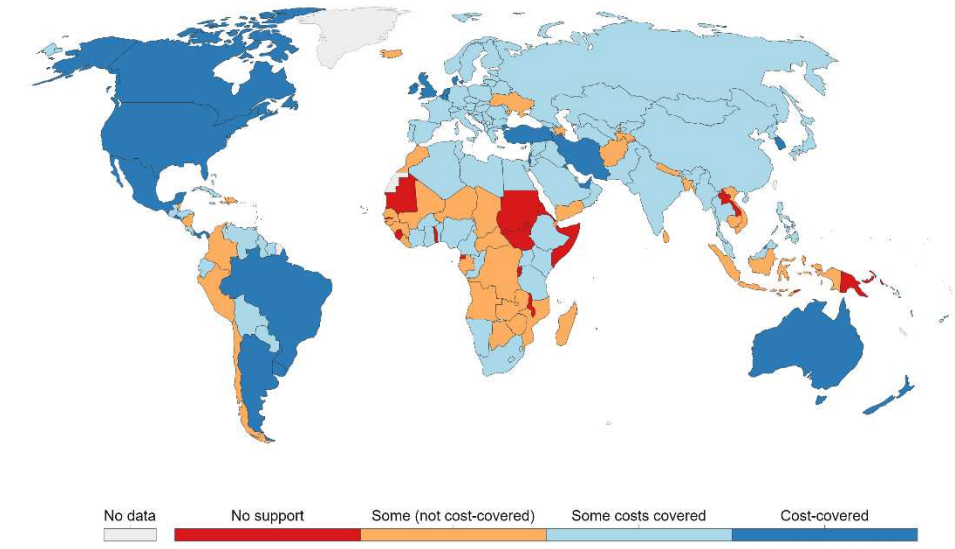
- **Reimbursement policies**

France recently changed the rules on reimbursement. In 2018, nicotine replacement therapies (gums, lozenges, patches) became eligible for reimbursement under the general scheme. Previously reimbursed at a flat rate of €150 per year per insured person, 65% of the price is now reimbursed. The aim is to make these therapies more affordable for people on modest incomes.

In the US, many of the treatments are eligible for reimbursement, depending on whether the patient is covered by Medicare or Medicaid. Behavioural (consultations, etc.) and emotional aids, drugs approved by the FDA and, for some, funding of two attempts to stop smoking per year are eligible for reimbursement. All in all, health authorities are in favour of reimbursing all products proven to be effective. The impact in terms of health costs as a whole have been demonstrated.

Geographical breakdown of countries that reimbursed treatment for tobacco addiction in 2014



Source: World Health Organization Global Health Observatory (GHO) CC BY

Treatment prices vary by region. Prices in high-income countries are higher and most therapies are partially reimbursed by health insurance. Reimbursement are not always as generous in lower-income countries. Treatment duration is usually 12 weeks and includes either one NRT, a combination of NRTs or drugs to treat addiction. The price differential between the US and the rest of the world is striking.

The table below summarises the main treatments on the market by geographical region:

Regions / countries	NRT	Champix®
Europe	€183	€238
United States	€344	€1,117
China	€98	€218
India	€111	€111

Source: NFL BIOSCIENCES

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The majority of treatments are generics and cost relatively little, compared with patented therapies. But let's not forget the financial burden for smokers of smoking one packet of cigarettes a day: in France, it adds up to €3,832 a year. So, we can reasonably assume that the price of the treatments is not an obstacle to quitting— especially in countries where smoking is expensive or where price rises are set to continue.

- **Competitive environment and new products in development**

The smoking cessation market is dominated by big names in the pharmaceutical industry such as Pfizer, GlaxoSmithKline, Takeda, J&J and Teva. One feature of this market is that there has been no new treatment since varenicline was introduced in 2006. Medical need is still unmet, since current therapies not only are associated with many adverse effects, but their efficacy is also limited over time. Finally, compliance is relatively poor, providing scope for innovation in this area.

Product	Company	Date of 1st marketing	Sales 2020	Sales 2026	CAGR 2020-2026E
Habitrol	GSK	31/12/1989	213.8	231.4	1.3%
NicoDerm CQ	GSK	31/12/1991	190.1	103.0	-9.7%
Chantix	Pfizer	01/08/2006	805.0	81.5	31.7%
AXS-05	Axsome Therapeutics	31/12/2021		80.1	
Tabex	Achieve Life Sciences	31/12/2023		84.5	
Nicotine Polacrilex	Cipla	30/06/2012	18.1	23.2	4.2%
NicoDerm CQ	Perrigo	31/12/1992	35.0	18.8	9.8%
Nicorette	GSK	10/09/2001	16.2	15.7	-0.5%
Zyban	GlaxoSmithKline	14/05/1997	14.0	14.2	0.3%
Nicotine Polacrilex	Teva	30/08/1999	14.0	10.3	-5.1%
Nicotine Polacrilex	Perrigo	20/07/2011	4.9	5.4	1.4%
Nicotine Polacrilex	Perrigo	30/09/2004	2.3	2.6	1.6%
Varenicline Tartrate	Viatris	30/06/2021		2.2	
Varenicline Tartrate	Teva	30/06/2021		2.2	
NicoDerm CQ	Taisho Pharmaceutical	01/07/2008	1.6	1.6	-0.5%
Bupropion Hydrochloride	Teva	30/05/2004	10.8	1.2	-30.3%
Zyban	Bausch Health	30/06/2004	0.3	0.2	-1.0%

Source: Evaluate Pharma

New products will probably arrive on the market with new promising approaches and could have greater therapeutic benefits than current treatments.

Tobacco addiction pipeline

Status	Product	Company	Molecule	Mechanism of action (MoA)
Submitted	VLN	22nd Century Group	NICOTINE	Nicotinic acetylcholine receptor (nAChR) agonist
Phase III	Tabex	Achieve Life Sciences	Cytisine	Nicotinic acetylcholine receptor (nAChR) partial agonist
	Nicotine ODF	NAL Pharma	NICOTINE	Nicotinic acetylcholine receptor (nAChR) agonist
	Nicotine & Alcohol Addiction	Centre for Addiction and Mental Health	-	14-3-3 protein inhibitor
	BRAND B	22nd Century Group	NICOTINE	Nicotinic acetylcholine receptor (nAChR) agonist
Phase II	AXS-05	Axsome Therapeutics	dextromethorphan hydrobromide	Dopamine reuptake inhibitor; (NMDA) receptor antagonist; Norepinephrine reuptake inhibitor
	Saxenda	Novo Nordisk	liraglutide [rDNA origin]	Glucagon-like peptide 1 (GLP-1) receptor agonist
	PPAR Gamma	Omeros	pioglitazone hydrochloride	PPAR-gamma agonist
	INV102	Invion	nadolol	Beta adrenoceptor antagonist
	AD04	ADial Pharmaceuticals	ondansetron hydrochloride	5-HT3 (serotonin) receptor antagonist
	AD04	University of Virginia	ondansetron hydrochloride	5-HT3 (serotonin) receptor antagonist
	X-22	22nd Century Group	NICOTINE	Nicotinic acetylcholine receptor (nAChR) agonist

Source: Evaluate Pharma

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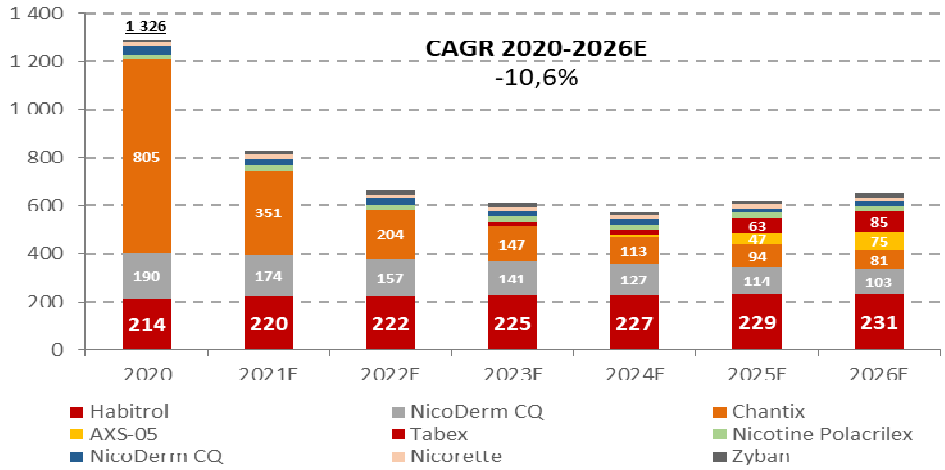
1- Smoking cessation, a market with consequential medical needs

Excluding generic NRTs, Achieve Life Sciences, Axsome Therapeutics and Novo Nordisk are also developing products to help people quit smoking. If effective, we expect considerable growth in market size. As you can see in the graph below, Champix® sales will have a big impact on the value of the market. This graph illustrates the crying need for new therapies to energise the market.

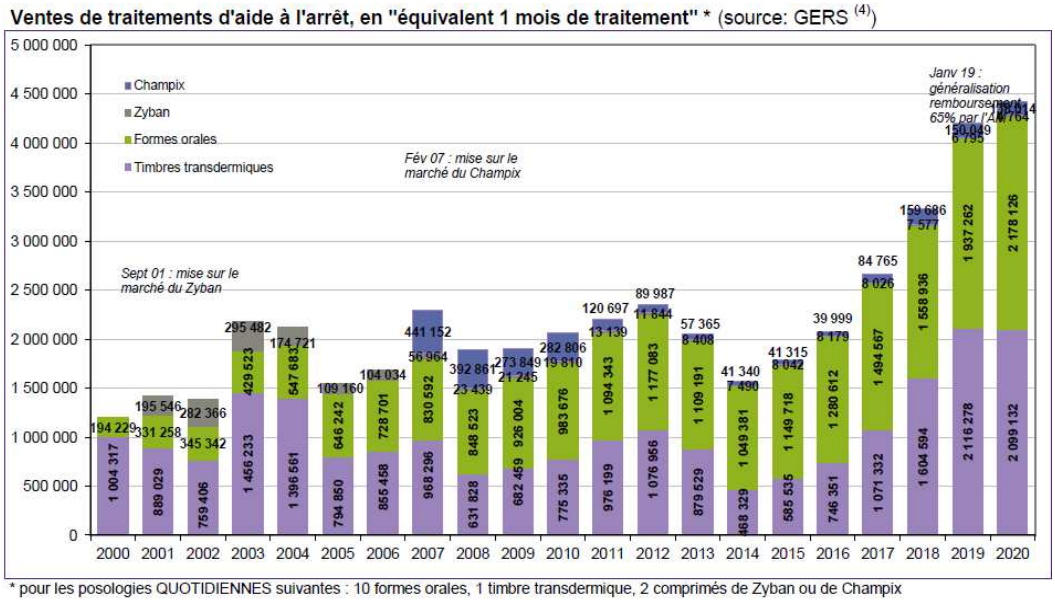
Estimated global sales of the nine main products to help quit smoking (2020-2026E)



Source: Evaluate Pharma

This graph shows sales of treatments for stopping smoking in France from 2000 to 2020. Note the market penetration of Champix® very soon after launching in 2006, reflecting the intensity of the unmet medical need. Sales subsequently declined as side effects and poor patient adherence to treatment were identified, before ticking up again. This pattern highlights the degree of pent-up demand for smoking cessation treatments as new products come to market.

Ventes de traitements d'aide à l'arrêt, en "équivalent 1 mois de traitement" * (source: GERS [4])



* pour les posologies QUOTIDIENNES suivantes : 10 formes orales, 1 timbre transdermique, 2 comprimés de Zyban ou de Champix

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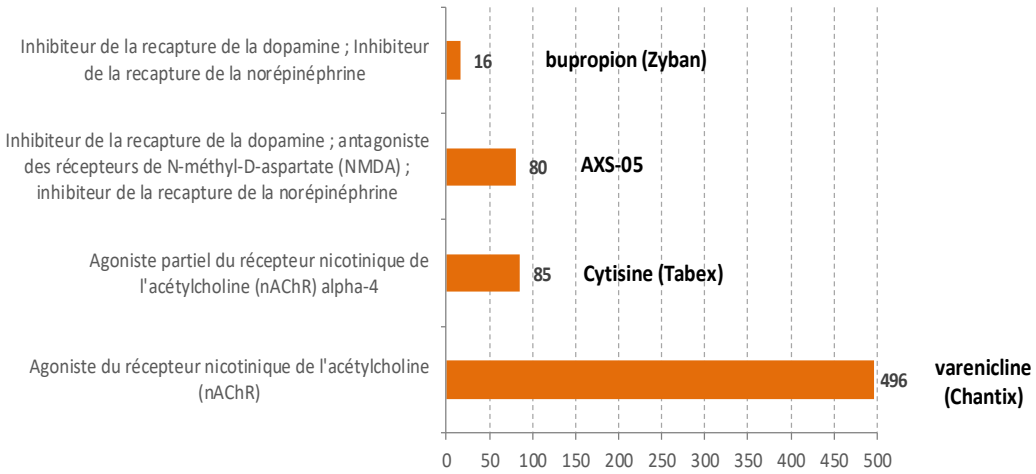
1- Smoking cessation, a market with consequential medical needs

There is no real differentiation between approved treatments on the market as regards their mechanisms of action. They nearly all work the same, a fact that underscores the need to develop new mechanisms of action.

Global market by mechanism of action in 2026e



Source: Evaluate Pharma

Varenicline *(Champix®)* is a prescription drug. It is the first alpha4beta2 (α4-β2) nicotinic receptor partial agonist to be approved. Varenicline copies the properties of cytisine but with a symmetrical structure (cytisine is asymmetrical), which avoids obtaining a racemic mixture of both enantiomers during synthesis.

Cytisine *(Tabex)* is a fairly ineffective partial agonist of nicotinic acetylcholine receptors, which are thought to play a key role in nicotine's effect on the reward pathways. Cytisine is structurally similar to nicotine and has both an agonist and antagonist mechanism of action with nicotine receptors in the brain. In the United States, Achieve Life Sciences (ACHV) is in phase III trials for FDA approval.

Bupropion *(Zyban)* is a noradrenalin and dopamine reuptake inhibitor (IRCN) that helps reduce craving and ease the symptoms of nicotine withdrawal by inhibiting dopamine reuptake, which is involved in the nicotine reward pathways.

AXS-05 is a novel, oral, NMDA receptor antagonist, also known as a glutamate receptor modulator, a potentially new mechanism of action for smoking cessation. The medication consists of dextromethorphan and bupropion and uses the Axsome metabolic inhibition technology to increase bioavailability of the dextromethorphan. The two components of AXS-05 are acetylcholine nicotinic receptor antagonists, a useful mechanism for treating nicotine dependence.

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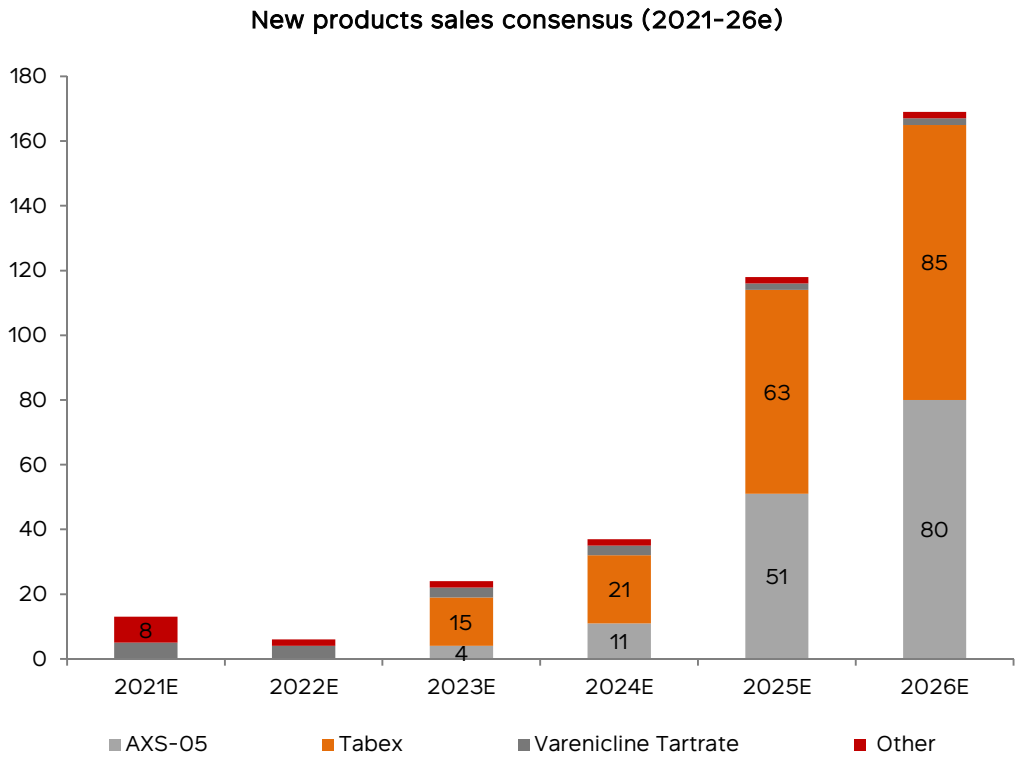

Source: Evaluate Pharma

Over the forecast period 2020-2026e, sales of new therapies (AXS-05 and TABEX) are expected to grow at a robust annual rate of close to 67.0%, far outstripping growth in the market for NRTs and other drugs (5.6% CAGR in the period 2019 to 2028[E]). Combined sales of AXS-05 and Tabex after its approval in the US are expected to top $160 million in 2026e.

These new mechanisms of action will add therapeutic diversity and respond to more specific needs. They also provide an option when other treatments are contraindicated. This substitution effect will be another factor helping to grow the potential market.

Although the demand for smoking cessation solutions is highest in industrialised countries (notably North America, the European Union, Australia and Japan) due to firmly-established anti-smoking policies, this trend is expected to continue to grow across the world in coming years.

1.6 Comparative read-out of clinical trial results

❖ **Clinical trial methodology**

We have extracted some clinical guidelines for the development of drugs to help quit smoking from a 2008 EMEA (European Medicines Agency) document. This information provides insight into how the clinical results presented later in this presentation are analysed.

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- **Subject selection and characteristics**

Smokers who expressed the intention of quitting are eligible. Trials must include both men and women. In principle, the cohort must be as broad as possible. Subjects can be classified by intensity of nicotine dependence or prior use of other pharmacological treatments. Dependency and other patient-specific characteristics can be measured by the Fagerström test for nicotine dependency (FTND).

- **Definition of primary endpoints**

To date, the primary endpoint in smoking cessation studies has been the rate of abstinence from smoking. It must be a **continuous abstinence rate** with no slip-ups or relapses throughout the entire monitoring period.
Long-term follow-up data must be collected since the rate of early relapse is not a predictor of long-term abstinence from smoking, which is seen as more relevant. **The primary endpoint approved by the EMA is continuous abstinence for six months. The primary endpoint approved by the FDA is continuous abstinence for four weeks. Currently approved products are administered over a treatment period of 12 weeks. In practice, to maximise their chances of success in the US, pharma companies record four weeks' continuous abstinence during weeks 9 to 12 (at the end of the treatment).**

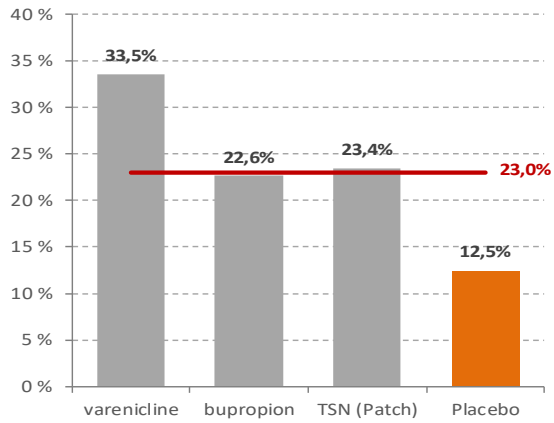
- **Efficacy results of approved treatments**

Despite the treatment options, many people continue to find it difficult to quit, and especially to remain abstinent over time. Craving and withdrawal symptoms are strong and persistent, and the risk of gaining weight as a consequence of quitting smoking holds no attraction. What's more, there are limited treatment options for some specific patient groups due to the contraindications of established treatments. As a result, despite the established efficacy of current treatment options, the development of alternative pharmacological therapies is encouraged. The most successful study of smoking cessation (EAGLES, Pfizer) was published in 2016. The study was conducted to identify potential "clinically significant" adverse events in 8,144 patients receiving varenicline, bupropion, NRTs or placebo. A multi-centre trial conducted in 140 centres in 16 countries, it remains the most reliable trial in terms of assessing success rates. It confirms the low efficacy of NRTs and prescription drugs over a period of 12 and 24 weeks.

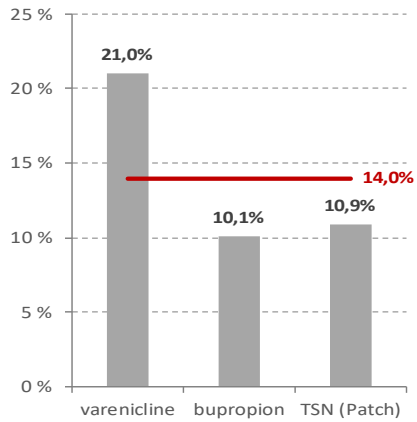
EAGLES efficacy results at week 12 (three months):

Primary endpoint: continuous abstinence rate at four weeks (exhaled carbon monoxide <10 ppm)

Taux d'abstinence vs. Placebo



Taux d'abstinence ajusté du Placebo



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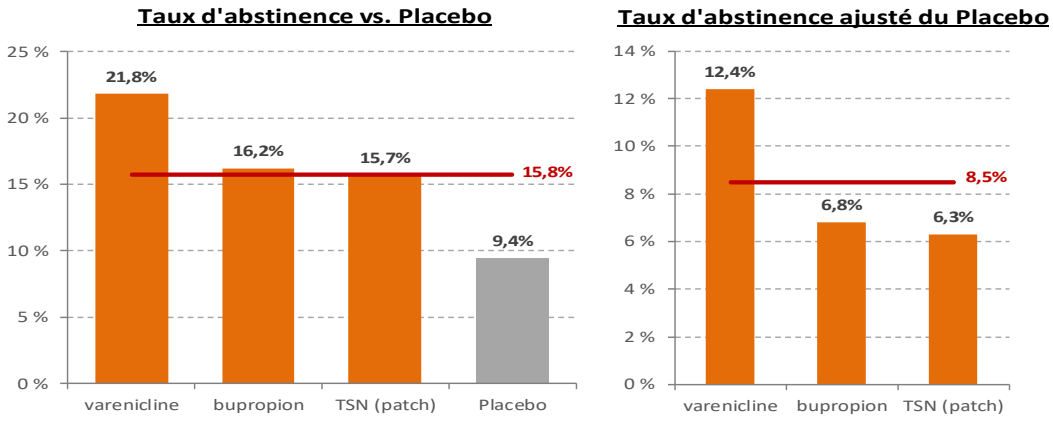
Following the 12th week of treatment, varenicline was found to be the most effective and was 10% superior to bupropion and NRT vs. placebo. Results for bupropion and NRTs were similar, with slightly higher efficacy for NRTs, an outcome that is all the more evident when the data is adjusted for placebo. Efficacy for varenicline was 21.0% compared to 10.1% and 10.9% for bupropion and NRTs, respectively. Statistical significance was also achieved (p<0.001).

EAGLES efficacy results at week 24 (6 months):

Primary endpoint: continuous abstinence rate at 4 weeks (exhaled carbon monoxide <10 ppm)

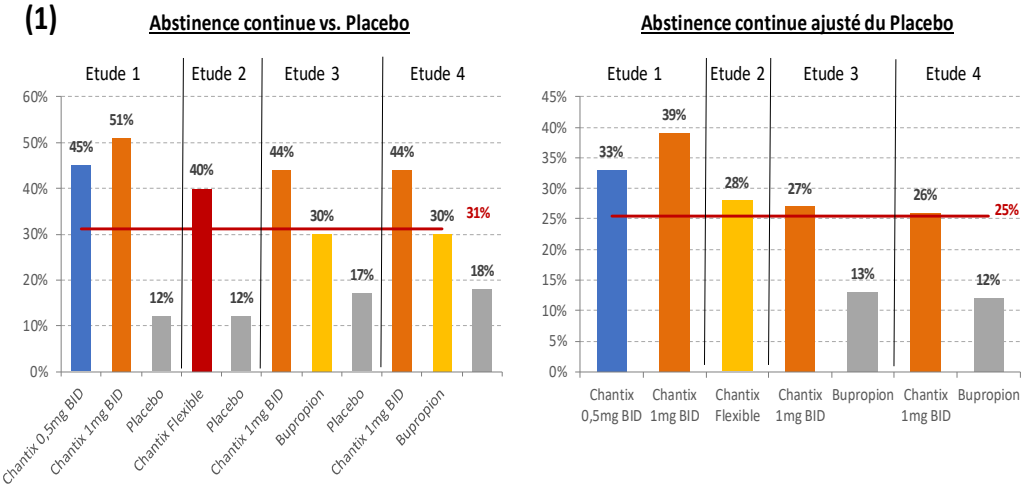


At the end of week 24 of treatment, the overall abstinence rate was 9.4% on average, versus 26.5% after week 12. The number of abstinent smokers fell between these two periods. This treatment failure may be related to side effects, a sudden relapse or poor adherence to treatment. Yet, varenicline was still twice as effective as bupropion and NRT (placebo adjusted). Statistical significance was also achieved.

Other different studies were also conducted by Pfizer and formed the core of the clinical evidence in the approval process for varenicline in the US in 2006. These studies were designed to assess the efficacy of varenicline (Champix®) at various doses versus placebo and versus bupropion.

Summary of efficacy results for Champix® in four comparative studies at week 12 (1)and week 52 (2)

Primary endpoint: continuous abstinence rate (exhaled carbon monoxide <10 ppm)



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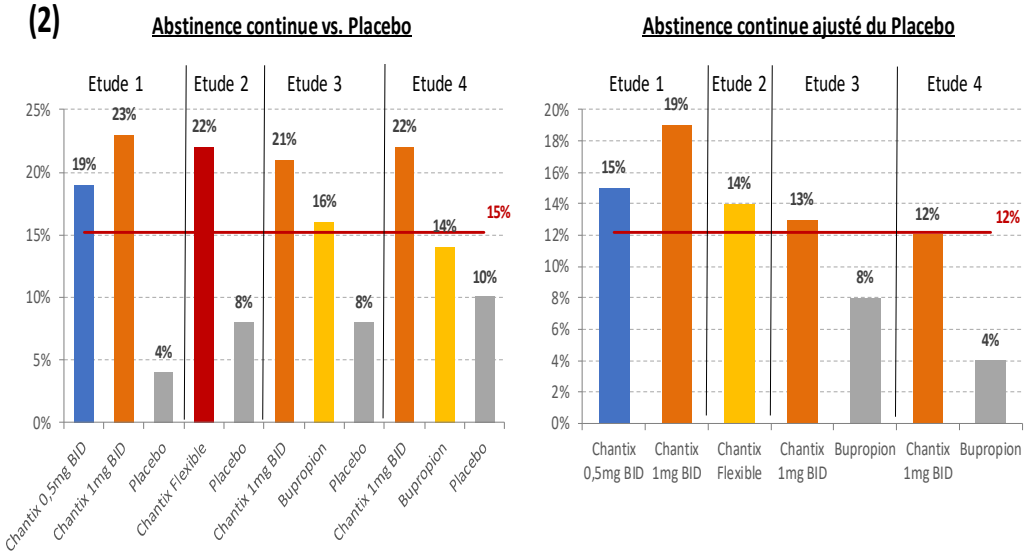
1- Smoking cessation, a market with consequential medical needs

The comparative study results, especially regarding dosage of Champix®, demonstrate that 1mg BID (twice a day) produces the best efficacy results at 12 weeks at almost 39% (adjusted for placebo) in study 1. Average efficacy was close to 25% (adjusted for placebo) in studies 3 and 4.

(2)



After the 52nd week of treatment the average treatment efficacy was halved compared to week 12. However, Champix® 1mg was still the highest at 19% in study 1, vs. 13% and 12% in study 3 and 4. Remember, efficacy at 24 weeks was 12.4% for the same dose, 1mg (BID) in the EAGLES study.

Efficacy results for Champix® (1 mg) in week 24 to 52

The graph below shows the results of a Champix® study over a duration of up to 52 weeks with 1,510 patients, showing how treatment efficacy evolves over time.

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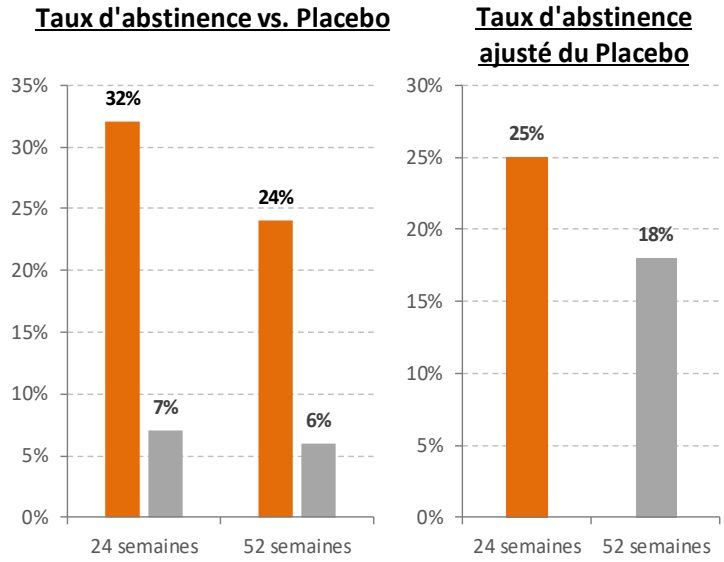

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This latest Champix® study confirms the previous findings at weeks 24 and 52. Versus placebo, efficacy varies around 25% at 24 weeks and around 18% at 52 weeks. Although these results are better compared with other treatments, they are not very effective in the long term. Market need is now centred on new mechanisms of action delivering long-term efficacy with few side effects.

- **Current treatments hampered by many side effects**

It's important to remember that treatments on the market require adherence for at least 12 weeks, with daily doses or patches and, for varenicline, significant side effects. In practice, most patients discontinue treatment early, which significantly reduces actual efficacy.

This falling efficacy is explained by **poor adherence (compliance) of users** due to **potential side effects** and **limited perceived efficacy**.

- ✓ **Nicotine replacement treatments (NRT)**: not very effective in practice. Users who try to quit without specific follow-up have success rates similar to those who quit with no help whatsoever. The efficacy of NRTs depends in large part on sticking with the treatment over 12 weeks. But most users abandon the therapy early. According to a study by Cochrane, only 36.8% of smokers using NRT used the treatment properly. NRTs will ease withdrawal symptoms (nervousness, irritability, anxiety, etc.) in the initial period after quitting, but their effect on the craving to smoke is very limited.

- ✓ There are two **drugs to help people stop smoking,** which are available on prescription in most countries. Varenicline (Champix®®, Pfizer) has been on the market since 2006, and bupropion (Zyban®, GlaxoSmithKline) since 1997. Each of them has an effect on the Central Nervous System (SNC). They cause significant adverse effects, including nausea, sleep disturbance, allergic reactions, cardiovascular problems, etc. Like the NRT, their effectiveness reported shall depend on the strict adherence to 12 weeks of treatment, with two tablets to be taken each day. In practice, given the cost of treatment and the significant adverse effects, a full course is rarely taken. A survey taken on more than 1,000 participants under actual conditions showed a low adhesion rate of 33% to the varenicline. The varenicline shall reduce both the symptoms related to tobacco craving at the start of withdrawal and shall also reduce the desire to smoke.

- ✓ Amongst the principle adverse effects observed in the clinical studies, we have observed the following: infections of the upper respiratory region, nightmares, nausea, insomnia, headaches, tiredness, nasopharyngitis, gastroenteritis, anxiety, vomiting, constipation, diarrhoea, arterial hypertension.

The most relevant adverse effects are those caused by Champix® in terms of behaviour as testified by the results of the EAGLES survey (see graph below). It should be emphasized that in 2008 the analysts' expectations in 2012 (source: Evaluate Pharma) were more than 2.3 billion $ before any adverse effects occurred. The awareness of these recurring and sometimes serious adverse effects resulted in a significant decline in expectations. In 2012, the Champix ® sales finally amounted to 670 m$. This significant discrepancy reflects the significant market need for a drug with an impeccable security profile.

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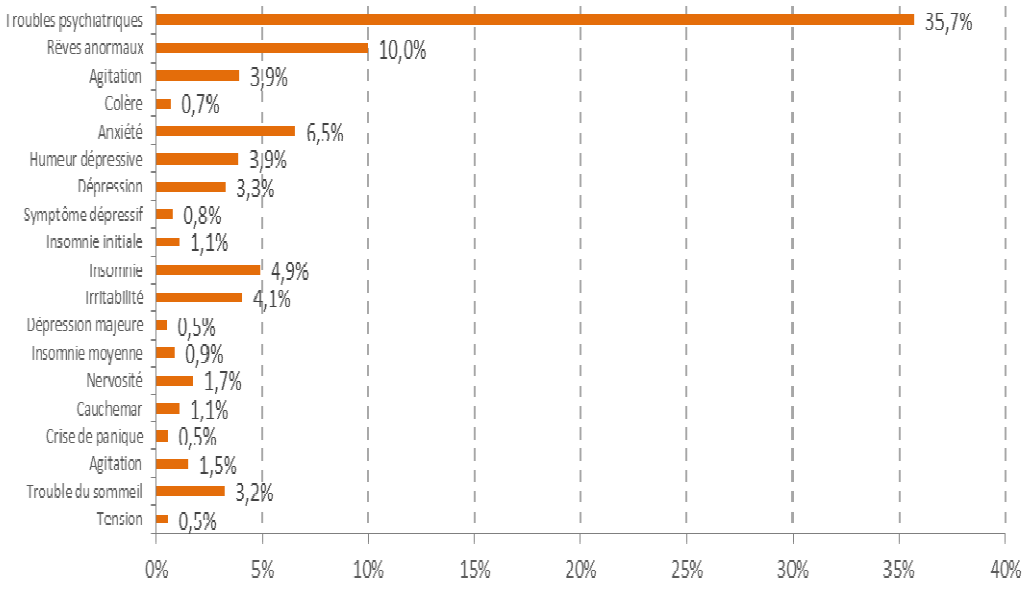

Source: FDA

- **Observance evaluated for the current treatments**

A survey was carried out in the United States on attitudes with regard to nicotine withdrawal with smokers: Satisfaction for smokers with regard to the processing available by Achieve Life Sciences.

Method

Achieve Life Science carried out an online survey of 15 minutes with adult participants (aged 19 to 64) who were current daily smokers or smokers who had stopped smoking during the past year (but not during the last month). 1,122 smokers responded to the survey between 27th of August and 3rd September 2019. The population included "current smokers" (n=986) and "recent smokers" (n=136).

Results

The full course of treatment (12 weeks) was not followed by most of those participants taking the Px pills (Px=prescribed), i.e., the varenicline and bupropion. Amongst the 325 previous users of ℞ pills who responded, 53% terminated ≤ 1 month of treatment. The adverse effects (61%) and the lack of effectiveness (27%) were the most frequent reasons for the cessation of treatment. Previous analyses of reclamation data stipulate that 76% of patients under varenicline do not terminate a 3 month treatment.
All the data subjects must have taken a pill under prescription (℞) approved by the FDA (varenicline or bupropion) and/or a substitution treatment for nicotine (NRT), or through the intermediary of a medical prescription (℞), or on over-the-counter sale (OTC), at least once during a previous attempt to stop smoking. The details of medication used are presented in *table* 1. Overall, more than one half of the participants had tried taking a pill ℞.

Drug administration method.

Status	Pill (Px)	NRT (Px)	NRT OTC	Total
Current smokers	467	281	238	986
Recent abandons	64	37	35	136
Total	531 47.3%	318 28.3%	273 24.3%	1122

Px (medical prescription)

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Amongst the 591 participants who had not taken the ℞ pill, the fear of the adverse effects (49%), the cost (46%), the risk of suicidal thoughts (44%) and the lack of effectiveness (42%) were quoted as reasons for not initiating ℞ therapies.
The most effective treatments were considered as effective or leading to satisfaction with regard to the treatment for less than one third of the participants:

Effectiveness and satisfaction with regard to the treatment.

	Effectiveness	Satisfaction
Champix® (varenicline)	29%	30%
Zyban (bupropion)	22%	24%
e-cigarettes	30%	33%
Behavioural advice	28%	30%
NRT (Px)	22%	23%
NRT OTC	17%	18%

Conclusions

The general satisfaction and effectiveness resulting from the treatments available were minimal, the NRT sold over the counter were the lowest on both criteria. The majority of the participants taking ℞ pills do not finish the full three month course. The concerns concerning the adverse effects were presented the most frequently for the abandon or absence of the initiation of a treatment taking the ℞ pill with the varenicline/bupropion. More tolerable and effective treatment options are necessary to help smokers to manage to stop smoking.

- **Results for the effectiveness of subsequent treatments**

  - ✓ **AXS-05: Axsome Therapeutics**

AXS-05 is a new experimental antagonist for NMDA receptors, administered orally and with a multimodal activity, under clinical development for the treatment of major depression issues (TDM), agitation related to Alzheimer's (MA) and stopping smoking. The medication includes dextromethorphane (DM) and bupropion and uses the Axsome inhibition metabolic technology. The company has scheduled to meet the FDA in T3 21 to discuss the continuation of the clinical development of the AXS-05 as help for treatment in stopping smoking. Accordingly, the company is reflecting on the agency's comments.

In the context of this short phase II survey on 58 patients, the principal evaluation criteria was the reduction of the number of cigarettes smoked per day versus buprobion. The latter was reached in comparison with the bupropion (average reduction of cigarettes per day of 8.49 with the AXS-05 and 6.79 with the bupropion, p=0.0016). On the other hand, the statistical significance was not reached (p>0,05) on the secondary evaluation criteria which was the continuous abstention rate at 3 weeks. The latter is currently the principal evaluation criteria in a regulatory approval process.

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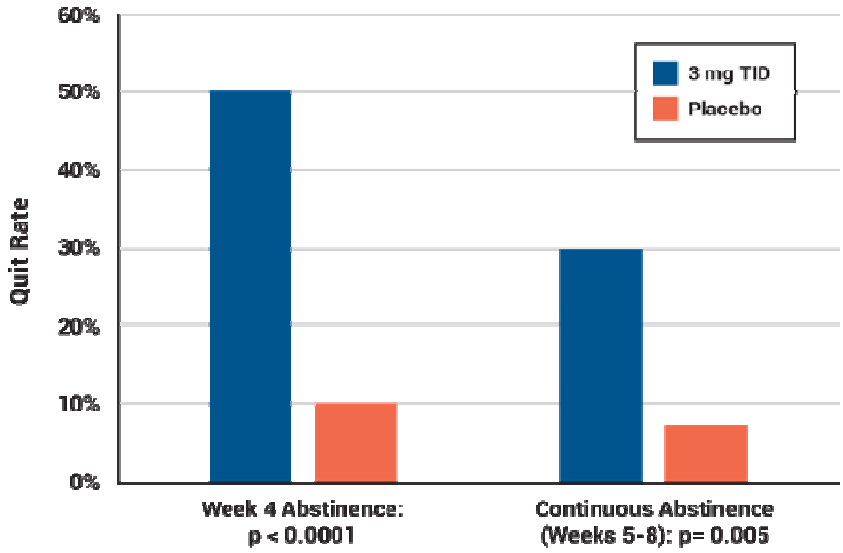
✓ **Cytisinicline (cytisine): Achieve Life Sciences**

Due to its partial agonist/antagonistic activity, the cytisine is intended to contribute to a reduction in nicotine craving, the withdrawal symptoms, and the recompense and satisfaction related to smoking. The company launched a phase III clinical trial in T4, with 20 out of 750 patients, with the close of recruitment scheduled for mid 2021. The clinical Phase III study currently in progress intends to compare the effectiveness of the cytisine with that of a placebo.

The group carried out a phase IIb survey over a period of 8 weeks on a population of 254 smokers with convincing results on the effectiveness and security issues (a 98% observance rate).

Continuous abstention rate between the weeks 5 and 8 (criteria not validated by the FDA)



Source: Achieve Lifesciences

✓ **Liraglutide: Novo Nordisk**

Novo Nordisk initiated a clinical trial for Phase II on November 29, 2018 on 80 volunteers. An innovative approach based on animal studies showing that the receptor agonists of glucagon-like peptide-1 (GLP-1) mitigate the recompense induced by alcohol, cocaine, amphetamines and nicotine. In mice, the treatment by an agonist of GLP-1 of one dose without any other behavioural effect, mitigates the locomotive stimulation induced by nicotine, the release of dopamine and reduces the expression of place preference. The glucagon-like-peptide-1 agonists receptive (GLP-1) are amongst the reference treatments for diabetes, and are constantly gaining market shares. One of the properties of GLP-1 is related to weight loss. This element may provide a therapeutic solution for smokers intending to stop smoking but who do not stop through fear of weight gain. Nonetheless, at this stage, we do not have any clinical result for the effectiveness of liraglutide on continuous abstinence.

Newsflow pipeline

Calendrier	Société	Type de Catalyst	Catalyst	Médicament	Etape de développement	Programme	Méchanisme d'action
S1 2021	Achieve Life Sciences	Avancées cliniques	Finalisation du recrutement	Cytisine	Phase III	ORCA-2	Partial agonist of α4-β2
T3 2021	Axsome Therapeutics	Avancées réglementaires	Lancement de Phase IIb/III	AXS-05	Phase II	-	NMDA receptor agonist
T4 2021	Achieve Life Sciences	Données cliniques	Résultats cliniques de Phase III	Cytisine	Phase III	ORCA-2	Partial agonist of α4-β2
T3 2022	Novo Nordisk	Données cliniques	Résultats cliniques de Phase II	Liraglutide	Phase II	-	GLP-1 receptor agonist

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2– NFL-101: A BOTANICAL DRUG TO HELP QUIT SMOKING

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2- NFL-101: A botanical drug to help quit smoking

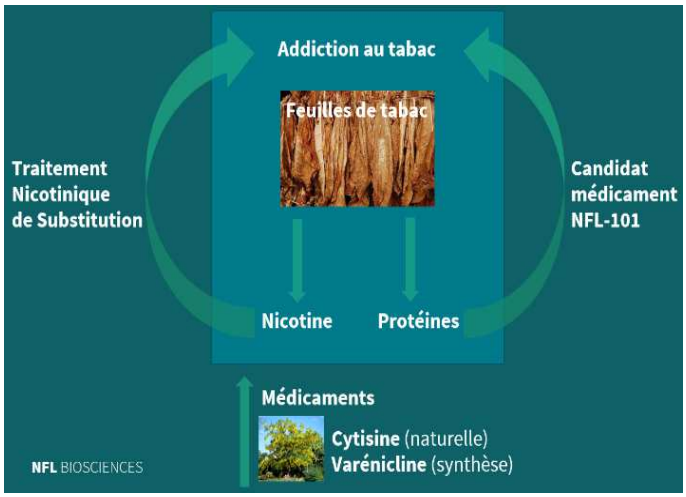
Through an ambitious clinical program on its principal drug candidate, NFL-101, the company intended to change the paradigm for stopping smoking treatment which requires a significant medical support with currently commercialized drugs with mitigated results, in particular in terms of security. The upcoming Phase II/III trial due to be launched in Australia in the third quarter of this year is the next step to prove the efficacy of the botanical product's innovative mechanism of action, developed after promising results from a retrospective study. The results for the two endpoints approved by the FDA in the United States and the EMA in Europe are expected in Q3 2023. At the same time, the company will run an exploratory study in association with NRTs and expects to have results also in Q3 2023. Both these studies should provide support to launch more comprehensive confirmation trials in both Europe and the US in Q4 2023. The product could be on the market in mid-2026. The group also intended to extend its pipeline with two new botanical drug candidates for cannabis addiction (NFL-201) and alcohol addiction (NFL-301, a partnership under due diligence). Even although they concern very important sanitary issues, we shall not include these active principles in our valorization model due to the initial stages of clinical development.

2.1 When an allergy to tobacco meets NFL-101

❖ Product history

The plants are the origin of tobacco addiction like the principal treatments for this addiction. Nicotine is a botanical alkaloid found in tobacco paper. The first treatments developed to help people quit smoking, NRTs, targeted nicotine. The medication available on the market is either botanical (such as cytisine) or synthetic (the varenicline). During the past years, numerous adverse effects have been observed on the use of varenicline. With regard to cystisine, the clinical trials showed a better continuity of treatment and better security with fewer adverse effects. These better results may be related to the drug's botanical origins.

The tobacco addiction and its treatments are of botanical origin.



Source: NFL BIOSCIENCES

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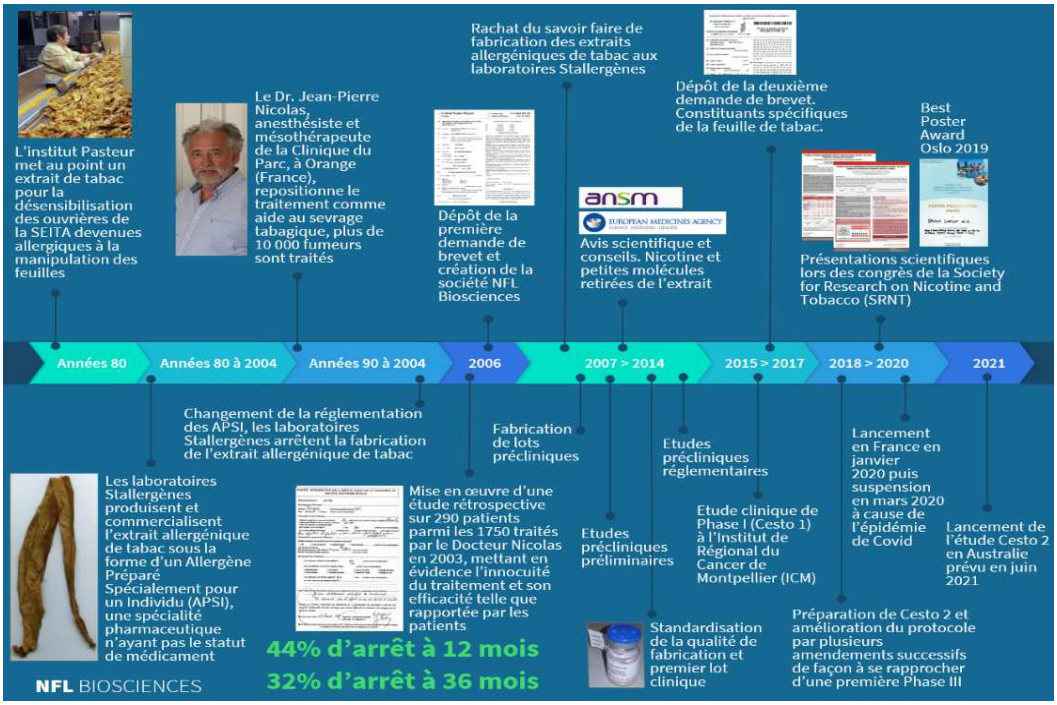
NFL BIOSCIENCES is part of the continuity of these developments for the treatments and botanical drugs by using the proteinaceous part of the tobacco paper rather than nicotine or a comparable alkaloid. Furthermore, and as the case for the cystine, it was through acknowledging a genuine effectiveness that the pharmaceutical development of NFL-101 was initiated.

NFL-101 is a proteinaceous extract of tobacco paper without nicotine, originating from an allergenic extract developed by the Pasteur Institute in the 1980s to treat the allergy to tobacco paper for the SEITA employees in daily contact with this paper by successive subcutaneous injections. The Dr Jean-Pierre Nicolas (co-founder of NFL BIOSCIENCES), anaesthetist at the Clinic Parc à Orange and mesotherapist, then had the idea of administering the allergen extract of tobacco papers to smokers to help them in their attempt to stop smoking. The Dr. Nicolas administered the product with off-label use for 10 years, until his production was stopped by the pharmaceutical laboratory Stallergenes (now known as Stallergenes-Greer).



Source: NFL BIOSCIENCES

He uses it to help smokers to stop smoking. The doses used in the context of stopping smoking are much stronger than those injected for the treatment of the allergy. They are not delivered over a long period, but in the form of a single sub-cutaneous injection. The smokers undertake to stop smoking on a certain date corresponding to the date of first administration. The patients who have difficulty in stopping smoking may request a second injection which is possible 7 to 10 days after the first injection upon the patient's request and without additional costs. This new administration enables the patients to have another attempt at stopping smoking.

Following the introduction of new regulations in 2004, Stallergenes suspended its production. As there exists few or no longer any personnel in direct and continuous contact with the tobacco paper in the French plants, the anti-allergenic use shall no longer be justified: accordingly, no potential market existed for the Stallergenes product.

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The company's activity was fully launched in 2010 with the acquisition of know-how from Stallergenes in terms of manufacturing the tobacco extracts for its exclusive use for stopping smoking. NFL then entered into negotiations with Stallergenes for the sub-contracting of the manufacturing of the first pre-clinical trial lots.

NFL BIOSCIENCES then set an objective to transform this pharmaceutical speciality of eliminating the allergy from those allergic to tobacco paper into a drug to help smokers stop smoking, **NFL-101**. This transformation resulted in the company improving and standardizing the production quality, accomplishing regulatory pre-clinical trials and establishing safety and effectiveness in the clinical trials.

❖ Founding retrospective results

The tolerance and effectiveness of the anti-allergy product Pasteur/Stallergenes were studied in 2006 retrospectively on the smokers treated by the Dr. Nicolas in 2003. These results established the effectiveness and a high level of tolerance to the extract used to stop smoking. Out of the 1,750 patients who have received one or two injections during that year, 445 were selected and 290 were successfully contacted by telephone. The patients then completed, signed and returned a questionnaire. The continuous abstention rates are provided below:

A retrospective study on the patients treated in 2003.

Duration of continuous abstention since the administration of treatment	Telephone (n=290)	Address (n=171)
1 month	70%	74%
3 months	57%	63%
6 months	54%	60%
1 year	44%	53%
> 3 years	32%	44%

Source: NFL BIOSCIENCES

Out of all of the 1,750 patients, 44% of them declared a continuous abstention of at least one year after the administration of the extract and 32% an abstention of at least three years, i.e., a success rate much higher than the solutions currently commercialized. Concerning the tolerance, nine adverse effects have been reported (n=171), but they may be related to stopping smoking. They include tiredness and somnolence (3/171), nervosity (3/171), feelings of depression (3/171). No adverse or serious effect has been reported.

NFL BIOSCIENCES then presented the hypothesis that the administration of NFL-101 triggered immunity and then a neurological response, resulting in sensorial and attitude changes: the latter were at the origin of a reduction or withdrawal of the desire to smoke within the days following the treatment. This data was obtained retrospectively and shall not be admissible from a scientific or regulatory standpoint.

Nonetheless, the effectiveness reported in terms of volume and scale by Dr. Nicolas' patients resulted in NFL BIOSCIENCES' founders creating their company in September 2006.

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2.2. A clinical activity to be confirmed for the microglial cells

Currently, only a partial understanding exists of the mechanisms in which nicotine and other tobacco components cause the addiction to tobacco consumption. As mentioned by the President of the National Congress of the French Tobacco Company in 2018: "the current challenges in the tobacco sector are still numerous: the understanding of the tobacco addiction mechanisms is still disparate". It cannot be stated with certainty that they are, amongst the substances in tobacco, those with addictive properties. The mechanisms of tobacco addiction are still extremely complicated as they imply different branches of the Central Nervous System (CNS) and are influenced by genetic, environmental factors or various molecules. The significance of neuronal immunity is now known for the development and withdrawal of the addiction.

New results obtained through the tomography by issuance of position (TEP) also establish the importance of the translocation protein (TSPO) in the consumption and addiction to tobacco. The studies have established a significant reduction in the activation of the TSPO in smokers' brains compared to non-smokers' brains. Yet, the TSPO is a microglia biomarker. Even although it is not directly related to the synaptic functioning, the microglia cells are important physiological elements for the functioning of the central nervous system (CNS). They play a role that is just as important as the neurones as they contribute to the processing of information by the brain and the body. Accordingly, it may be assumed that the reduction of microglia activity enhances the addiction to tobacco.

NFL-101 generates pro-inflammatory cytokines and specific G immunoglobulins (IgG): the correlation observed between the immunity process and the addiction to tobacco suggests that NFL-101 may stimulate the microglia activity and influence the desire and addiction on tobacco. These new discoveries with regard to the functioning of tobacco addiction certify the relevance of the "full plant" process resulting rom the NFL-101 development.

In this regard, NFL BIOSCIENCES are currently seeking the action mechanism(s) for the NFL-101 in partnership with the Saclay CEA. The latter would require surveys to be carried out to test whether the NFL-101 caused a **neuro-immune reaction**. It is assumed that this reaction is at the origin of the reduction of the desire to smoke and the non-desire for tobacco related to the administration of NFL-101. The purpose of the study was to prove the effect of the injections on the glial brain cells. The examination of mechanisms must be made with the assistance of techniques such as Magnetic Resonance Imaging (IRM) or the Tomography by the Issuance of Positrons (TEP).

2.3 Intellectual protection at least until 2036

As from 2006 the company adopted a strategy for the management and protection of knowledge, resulting in the filing of two patents guaranteeing the exclusivity of its product. The company filed two patent applications (1/aqueous extract of tobacco paper, its use in the treatment of the addiction and 2/tobacco paper extract and its use for the treatment of tobacco addiction).

The first was issued in numerous countries, the second was issued in France and Israel and in the process of a regional and national PCT extension. **The technology on which the NFL-101 is based is protected until 2036, currently in France and Israel and could soon be protected in numerous other countries.**

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In Europe, in the event of the approval of NFL-101 in 2026, the second patent may be granted a complementary 5-year protection offering protection until 2041. Similarly, in the United States where an extension of protection is possible if the NFL-101 is commercialized in 2026 for 4 supplementary years, i.e., until 2040. This **second** covers the use of specific components for the treatment of stopping smoking. These specific components are difficult to replicate insofar as it concerns a standardized combination of proteins of tobacco paper and not simply a molecule like the Pfizer varenicline. France (2019), Israel (2021) and more recently the United States (2021) have already received the patent authorization. It is currently under examination in the following countries: Europe, China, Japan, Canada, South Korea, Australia, Brazil, India, Indonesia, Mexico, the Philippines, Eurasia, Saudi Arabia, the United Arab Emirates and Nigeria. **New patents may be filed, in particular concerning the administration method for NFL-101.**

2.4 A promising clinical development in smoking cessation

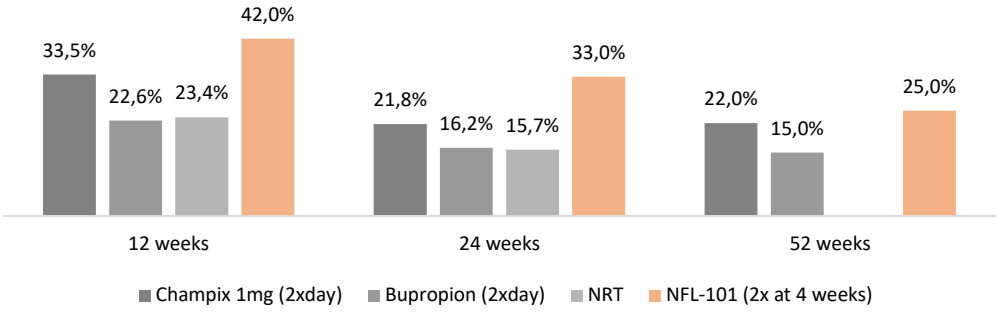
❖ **Convincing effectiveness and security in phase 1 (CESTO 1)**

A first clinical phase 1 study, called CESTO 1, evaluating the safety and effectiveness of the NFL-101 as a therapy for stopping smoking was carried out between June 2015 and April 2017. As the principal objective was to evaluate the safety of the drug being tested, the patients were injected at 4 weeks' interval without any fixed target date (similar to a vaccine protocol), whereas in the retrospective study, the patients were treated by the Dr. Nicolas with one or two doses at 7 to 10 days interval and simultaneously with an attempt at stopping smoking, which is fundamental in treating the addiction. This phase I nature shall not enable an optimal effectiveness. 24 heavy smokers were recruited with a Fagerström score of 6.25, including a first cohort of 12 patients not attempting to stop smoking and a second cohort of 12 volunteers trying to stop smoking (recruited through a press release). The results were presented at the Research Company's congress on Nicotine and Tobacco (SRNT) in February 2019.

This test confirmed the safety of NFL-101 for humans, already established in the retrospective survey.

Despite un unfavourable nature in terms of effectiveness, CESTO 1 indicated probative signs of effectiveness for stopping smoking. For the first cohort, only 3 patients tried to stop smoking, which is inappropriate in terms of effectiveness. For the second recruitment cohort of 12 patients, the continuous abstention rate at 3 months (i.e. 12 weeks) worked out at 42%, 33% over 6 months (24 weeks, EMA criteria) and 25% at 12 months (i.e. 52 weeks), which is a positive comparison with the treatments currently commercialized. As the nature of competitor studies and the objectives sought are different, the comparison should remain relative.

Probative effectiveness on the second cohort (continuous abstention of 4 weeks)



Source: Champix® prescribing information for the results at 52 weeks, results of the EAGLES study for non-psychotic smokers for the results at 12 and 24 weeks.

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Furthermore, an immediate reduction of the desire to smoke was observed, even the need to smoke after the administration, with, in certain cases a "non-desire for cigarettes", with a peak on days 3 and 4. The fact that the effect is immediate is a fundamental element in the treatment of the addiction as the 3rd and 4th days are particularly difficult and that is when relapses occur.

Simultaneously, a strong reduction of cigarette consumption was observed on 11 of the 12 patients (91%) of the volunteer cohort. This reduction was -50% at 3 months after treatment, i.e., -10 cigarettes per day on average. Out of the 24 patients evaluated, 8 of whom had significantly reduced their cigarette consumption, declared to have missed the "opportunity to stop", which validates the potential interest of additional injections 3 months following treatment.

- **A rigorous phase II/III nature and well established in Australia**

On the basis of these probative phase I results, the group launched a phase II/III, called CESTO 2, on 318 patients smoking at least 11 cigarettes per day with a Fagerström score greater than 3 (minimal to very high addiction). This study should be extended over a total duration of 2 years. The study which was initiated in France on a provisional sample of 99 patients then 204 patients after an amendment to the protocol by the ANSM in May 2020 was stopped on two occasions (March and October 2020) due to the public health crisis. Accordingly, the group decided to launch its survey in Australia in up to six centres, with two centres located in Tasmania, a region totally exempt from the virus, after having received the approval from the Australian authorities on May 18, 2021. It must be established that Australia has a high quality clinical research even although it concerns a country with a relatively low tendency to smoke (the price of the packet is twice as much as in France). Moreover, the targeted tax credit rate at 43.5% in Australia is attractive.

For this study, the 318 patients are divided into three groups: a placebo group, who receives injections with the placebo dose; a first test group which receives the level 1 dose of NFL-101, i.e., 100µg of tobacco paper proteins for each injection, and a second test group which receives the level 2 dose of NFL-101, i.e. 200µg of each injection. The three divisions are balanced: each includes 106 patients. Unlike the CESTO 1 study, each participant shall receive a first sub-cutaneous injection on a given target date (D1) and a second injection one week later (D8).

In order to introduce the possibility of a gradual treatment of tobacco addiction, like Dr. Nicolas during his administration with off-label use, in addition to an immediate cessation, the protocol also provides that if the patient starts smoking again, then he may benefit from a third injection at the end of the third month. This injection may be administered at the end of the sixth month in the event of abstention until the third month, but a relapse between the third and sixth month. Finally, a fourth injection is possible in the sixth month if the patient smokes in the three months following his third injection. **The third and fourth optional injections of the Phase II/III study provide supplementary opportunities to successfully attempt to stop smoking** for patients who would not have managed to stop smoking with the first two injections and who would have reduced their cigarette consumption. **Accordingly, these patients benefit from another opportunity having first reduced their level of addiction.**

The measure of continuous abstention shall be assessed regularly with biomarkers, commonly used for monitoring patients trying to stop smoking, such as the nicotine level in the urine or an exhaled carbon monoxide test level.

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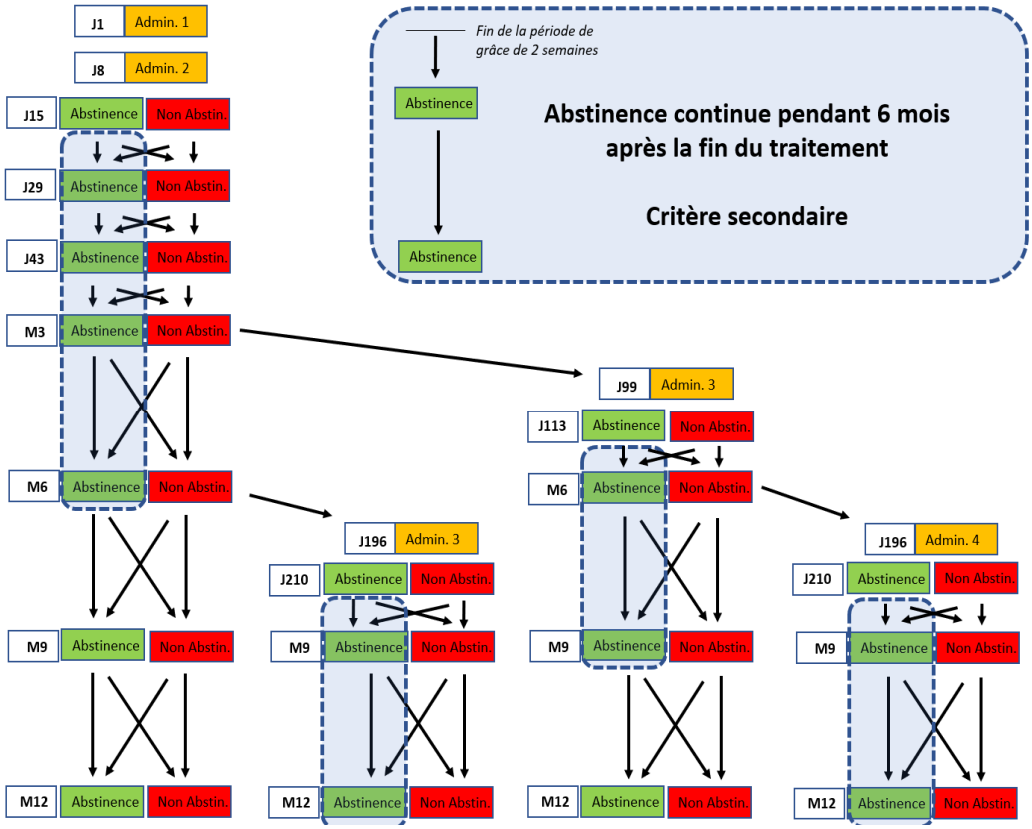
The evaluation criteria are numerous, which shall enable an effective NFL-101 to be specifically established and to effectively adapt the protocol of subsequent pivotal studies. Accordingly, the company shall evaluate as a principle criteria, the continuous 4 week abstention as from the second dose (D15 to D43, or weeks 2 to 6). Furthermore, as a secondary criteria, the study provides for an evaluation of continuous abstention at 6 months as from the target date, with two weeks of "clemency" meaning that the abstention must be integral between the start of the third week (D15) and the sixth month after the start of the treatment. This second criteria meets the EMA requirements to evidence the effectiveness of a stopping smoking drug. In conclusion, if a patient meets the secondary criteria, he shall also meet the primary criteria and vice-versa. With 318 patients, the group seeks to emphasize a significant difference of at least 19% vs placebo on its principal criteria.

Simultaneously, other secondary criteria, measuring the continuous abstention vs placebo for at least 3 months are evaluated as follows: the continuous abstention for 3 months, between D15 and D85, a continuous abstention for 12 months, between D15 and D365.

In order to measure the effectiveness by associating the immediate and progressive cessations, the group also integrated 4 secondary criteria: the continuous abstention for 3 months after the end of the treatment (including the 14-day "clemency" period), the continuous abstention for 6 months after the end of treatment (including the 14-day "clemency" period), the continuous abstention for 3 months between the third and sixth months at the end of the treatment and the continuous abstention for three months in the twelfth month, from D274 (M9) to D365 (M12).

CESTO 2 clinical protocol schema.



Source: NFL BIOSCIENCES

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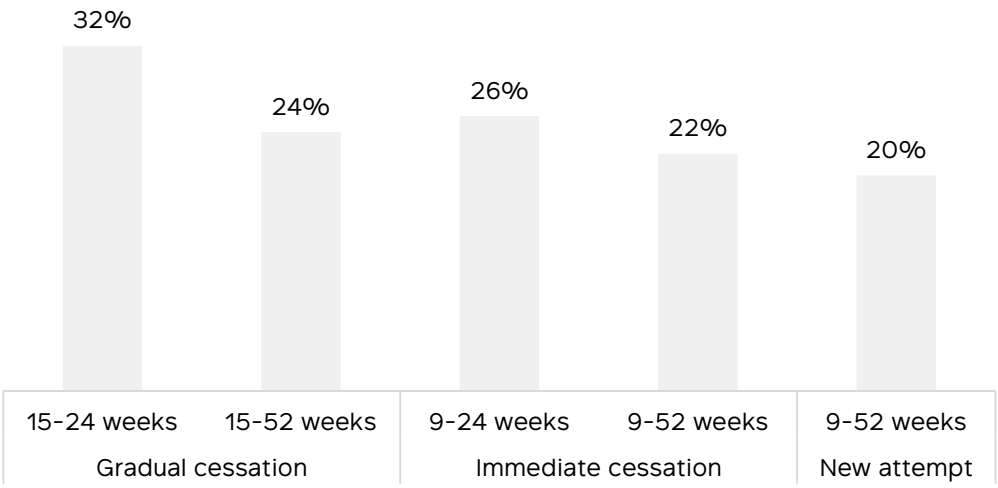
In conclusion, this phase II/III clinical nature appears to us to be ambitious and should provide an exhaustive perspective of the NFL-101's effectiveness in its different doses for both an immediate and gradual withdrawal or a combination of both.

It must be emphasized that Champix® in a study of a duration of 52 weeks on 1,510 smokers, incapable of stopping smoking after 4 weeks but trying to reduce their cigarette consumption, showed a continuous abstention rate of 32% between weeks 15 and 24 (until the 6th month) and 24% between weeks 15 to 52 (see graph below). These gradual withdrawal results are marginally greater than those obtained for the immediate withdrawal. Furthermore, another survey evaluated Champix® on 249 patients who had relapsed or who had not managed to stop smoking but who had tried another attempt. It was established that another attempt with Champix® is not greater in the long term compared to an immediate withdrawal (20% vs an average of 22% in three other surveys).

Continuous abstention with Champix® according to different medical methods.



Source: Champix prescribing information, the EAGLES survey results for the results at 9 to 24 weeks.

The CESTO 2 results shall provide a clear response on the NFL-101's effectiveness on the two regulation criteria for EMA and FDA. The numerous secondary criteria should also be used as a sound basis for the launch of a phase III study in the US and Europe. For the record, the clinical data obtained in Australia is valid in Europe. The exhaustive CESTO 2 nature also makes references to the reduction of the risk of failure of the clinical study.

The first CESTO 2 patient should be recruited in T3 21 with the recruitment of 318 patients, to be finished in T2 22. The CESTO 2 results are expected 12 months after follow-up, i.e., in T3 23, including 3 months of result analysis. We have included the cost of the CESTO-2 study of around 3 million euros.

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❖ Combination studies to enhance market penetration

Simultaneously with CESTO 2, the group intends to evaluate its test drug, NFL-101, in combination with the nicotine replacement therapies (NRT). Studies have shown the rational of the association of different methods to fight against tobacco addiction. A study on 1,504 adults in the United States, smoking more than 10 cigarettes per day and non-psychotics, evaluated 5 therapies alone and in combination, compared to a placebo branch. In detail, the study included 6 branches equally distributed and with globally similar base characteristics: Placebo (n=189), bupropion (n=264), lozenge (n=260), nicotine patch (n=262), bupropion + lozenge (n=262) and patch + lozenge (n=267). The continuous abstention was measured with the 7-day point-prevalence method (prevalent abstentions over 7 days), 8 weeks after the attempt to stop smoking and 6 months after this attempt, i.e., abstention over the last 7 days, after 8 weeks and after 6 months (24 weeks). At 6 months, the results showed a significant improvement of effectiveness for the combination patch + lozenge compared to their effectiveness in monotherapy. This may be explained by a more optimal dosage by associating two nicotine substitutes.

	End of Treatment, 8 wk Postquit			6 mo Postquit		
Treatment	Wald	*P* Value	OR (95% CI)	Wald	*P* Value	OR (95% CI)
Relative to placebo						
Bupropion	4.75	.03	1.55 (1.05-2.31)	5.01	.03	1.63 (1.06-2.51)
Lozenge	4.93	.03	1.57 (1.05-2.33)	6.68	.01	1.76 (1.15-2.70)
Patch	9.64	.002[a]	1.87 (1.26-2.77)	7.70	.006	1.83 (1.20-2.81)
Bupropion + lozenge	18.10	<.001[a]	2.35 (1.59-3.49)	6.42	.01	1.74 (1.13-2.67)
Patch + lozenge	24.02	<.001[a]	2.67 (1.80-3.96)	15.65	<.001[a]	2.34 (1.54-3.57)
Relative to monotherapies						
Bupropion + lozenge	5.95	.02	1.42 (1.07-1.88)	0.00	>.99	1.00 (0.74-1.35)
Patch + lozenge	11.19	.001[a]	1.61 (1.22-2.13)	4.12	.04	1.35 (1.01-1.79)
Monotherapies relative to each other[b]						
Patch vs lozenge	0.97	.32	0.84 (0.59-1.19)	0.05	.83	0.96 (0.67-1.38)
Bupropion vs lozenge	0.003	.96	1.01 (0.71-1.43)	0.38	.54	.89 (0.62-1.28)
Patch vs bupropion	1.09	.30	0.83 (0.59-1.18)	0.38	.54	.89 (0.62-1.28)
Patch + lozenge vs bupropion + lozenge	0.53	.47	0.88 (0.63-1.24)	2.68	.10	0.74 (0.52-1.06)

Source: *Arch Gen Psychiatry, 2009*

The combination Bupropion + lozenge exceeded its expectations at 8 weeks but this is not the case at 6 months. Accordingly, these results are mitigated for the combination drug + NRT, but this could be explained by the fact that bupropion is not a botanical based drug or botanical and is used in tobacco addiction only as an anti-depressant, whereas NFL-101, originally botanical (like nicotine or nicotine supplements) would have an effect on the microglial activity to influence the desire and tobacco dependency. Furthermore, the Champix® + NRT combination is not recommended due to the problems of tolerance with Champix®. In France, Champix® is prescribed if the NRT does not work, whereas in the United States, no distinction is made between the different treatments. **The botanical origin of NFL-101 and its unequivocal safety profile, are strong arguments to justify a combination with the NRT. The combination study shall enable a potential synergy to be evaluated with NFL-101, enabling the reduction of the desire to smoke by deterring smokers and the NRT shall mitigate the withdrawal symptoms.**

The study for establishing the concept evaluating the combination of NFL-101 with the NRT should be launched simultaneously with the CESTO 2 study in the United States or in the United Kingdom. The latter shall be randomized as a double blind test and may relate to around one hundred patients. The patients shall be equally divided in the placebo branches and the NFL-101+ NRT branch. The different effectiveness criteria retained shall be as follows: (i) the continuous abstention over 4 weeks (FDA criteria), (ii) the continuous abstention at 6 months (EMA criteria), (iii) the prevalent abstentions over 7 days, (iv) the reduction of cigarette consumption and (v) other criteria used in tobacco studies (MNSW, FTCQ-12...). The choice of principal criteria shall depend on the number of patients included.

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The protocol could involve administering NFL-101 for the first time one week after the intended stopping date then a second time on the intended stopping date. The NRT were administered in accordance with the recommendations for their market launch authorizations, i.e., at the time of the intended stopping date and for 12 weeks. The NRT could be composed of slow-release forms of nicotine (transdermal stamps) and fast forms (gum to chew).

The study should last for 2 years (6 months for the recruitment, 6 months for the follow-up, 3 months' analysis and 9 months for the manufacturing of a new clinical and regulatory lot) for an issuance of the results in T3 23. Positive results would enhance NFL-101's position on the stopping smoking market, by granting it a complementary status and not simply that of a competitor. A prescription in association would improve the effectiveness without generating secondary effects. We shall include a cost for this exploratory combination study of 1.6 million euros.

❖ **Towards two confirmatory phase III studies in Europe and in the U.S.?**

After the CESTO-2 study and the study in combination with the NRT, two scenarios shall be presented to validate the product in Europe and in the US by EMA and FDA.

The ideal scenario would be for the results to be sufficiently positive on both principal criteria to justify only one confirmative study being carried out simultaneously in the US and Europe. This choice was made by the competitor Achieve Lifescience which only carried out one confirmative study on 750 patients in 15 American centres with, as principle criteria, the continuous 4-week abstention. This is a risky challenge, given the fact that the phase II study by Achieve Lifescience shall not include abstinence as the principal criteria but only the reduction of cigarette consumption. Accordingly, NFL Biosciences shall only be required to carry out one study in Europe and the US in order to meet the requests of both agencies. Such a confirmative study, which in a nature equivalent to that of Achieve Lifescience should include at least 750 patients given the scale of the population targeted by NFL-101, could be prepared prior to the CESTO 2 results and launched simultaneously in several countries (Europe, USA, Australia, UK, Canada, subject to the local regulatory authorizations). We consider that such a study would cost around 15 million euros with 1/3 of the patients recruited in American centres. The clinical stopping smoking studies are relatively minimal in terms of cost (the cost per patient included in a clinical study and followed for one year is around 10 thousand dollars in Europe or Australia, prior to tax credit, 20 thousand dollars in the United States, with possible NIH/NIDA funding).

A more judicious scenario that could be considered at this stage, given the minimal visibility on the effectiveness of NFL-101, would be to carry out two confirmative studies vs placebo in order to reduce the probability of obtaining a success during a study carried out at random. We shall adjust our scenario on the clinical development according to the results of the CESTO-2 scenario. The realization of two confirmative clinical studies on 750 patients should each cost around 22.5 million euros in total according to our estimates. **We consider that these two confirmative studies carried out simultaneously could begin at the end of 2023 to terminate at the end of 2025 with the signature of license agreements at the beginning of 2026 for a potential commercialization of NFL-101 in Europe and the US mid-2026.**

2.5 Cannabis and alcohol: 2 other possibilities at an earlier development stage

The group also intends to explore two other forms of dependency: addiction to cannabis and alcohol. In light of tobacco addiction, such dependencies are destructive. The group intends to develop a new botanical test drug. NFL-201 for cannabis addiction whereas the group intends to sign a research partnership for alcohol addiction with the idea of developing a botanical treatment offer for those dependent on alcohol and tobacco.

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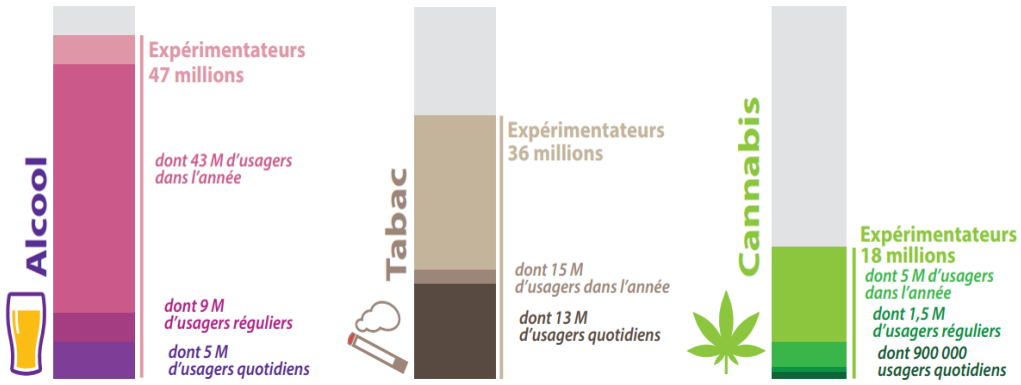
In our opinion, the choice of developing a specific product for cannabis addiction may be explained by the fact that the issue is similar to that of tobacco addiction and that no other competitor products exist on the market. It is envisaged that NFL-201 shall possess a similar action to NFL-101 on the body. It will likely reduce the desire to consume cannabis and tobacco, and even repel smokers from smoking. NFL BIOSCIENCES intends to carry out a pre-clinical non-BMP study (Best Manufacturing Practices) to emphasize its effectiveness on an animal model for cannabis dependency. Then, preliminary toxicity studies and BMP studies shall be carried out and an effectiveness study shall be undertaken. It must be emphasized that the 2016 patent, in particular, very recently approved in the USA, includes the addition of cannabis proteins in the tobacco paper extract.

Concerning alcohol dependency, the idea of signing a research partnership appears to us to be more consistent, insofar as 4 molecules are now approved to ensure continuous abstinence (acamprosate, naltrexone, disulfirame and baclofene) and 2 to reduce consumption. NFL BIOSCIENCES identified a botanical drug, already tested on humans, to be licensed. A due diligence is in progress with a potential partner in the United States. In the event of an agreement, NFL BIOSCIENCES shall integrate the development of this test drug to its pipeline and shall provide its botanical and regulatory know-how acquired with the NFL-101 development since 2009.

Even although they concern very important sanitary issues, we shall not include these active principles in our valorization model due to the initial stages of clinical development. In 2016, there were more than 190 million cannabis consumers globally. The liberalization in progress in numerous developed countries should increase this figure. One in ten cannabis consumers will become dependent and when the consumption started before the age of 18, it concerns one consumer in 6. Similarly, the harmful use of alcohol results in a morbidity charge and a significant economic and social challenge for companies. In 2012, nearly 3.3 million deaths, i.e., 5.9% of all the deaths globally, were attributable to alcohol consumption. Overall, 5.1% of the global charge of disease and traumas, as measured by the years of life to be adjusted due to incapacity (DALY) is attributed to alcohol. In the United States, the federal agency of Centers for Disease Control and Prevention (CDC) emphasizes the social and economic consequences of excessive alcohol consumption. This kills more than 95,000 people each year in the United States. It is heavy responsibility for the American economy with a cost estimated at 249 billion dollars in 2010.

Alcohol, tobacco and cannabis: three addictions that are wide-spread and destructive.



Source: OFDT June 2019, Drugs, Key figures 8th edition

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3- NFL-101: MARKETING MID 2026, PEAK SALES OF €900 MILLION

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3- NFL-101: Marketing mid-2026, peak sales of €900 million

Compared with the treatments currently available on the market (Pfizer's Champix® notably), the potential benefits of NFL-101 are significant, but still to be confirmed in later-stage clinical trials. At this stage, we have targeted 4 geographic zones in Europe (27 + UK), the United States + Australia, the APAC zone (Japan, South Korea, China) and India. In the event of a success of CESTO-2 and confirmative studies (one or two simultaneously) in Europe and the US which could be successive, we anticipate an approval and commercialization in Europe and the US for the NFL-101 mid-2026 with license agreements signed at the start of 2026 on the basis of phase III clinical results which could be published at the end of 2025. In Australia, we consider that society could capitalize on the clinical results obtained in Europe and the US and the CESTO-2 study carried out in Australia to obtain an approval mid-2026 with the signature of a license agreement at the beginning of 2026. Our estimate for a peak of sales in Europe, the US and Australia is 663 million euros. In India, we anticipate a commercial launch in 2026 with a license agreement in 2024, with a partner to take charge of the confirmative country-specific clinical phase. Peak sales of €70 million in India for 2.7 million doses. In the principal countries identified in the APAC zone (China, Japan and South Korea), we anticipate a license in 2026 with one or several partners who shall assume the realization of a country-specific clinical study for a commercial launch in 2028. In these countries, we anticipate a peak of global sales for 235 million euros. In total, we anticipate a sales peak for NFL-101 at 900 million euros in 2034.

3.1 Competitive advantages to be confirmed

As previously explained, NFL-101 could present numerous benefits compared to the drugs currently commercialized, in particular Champix®. More advanced clinical studies shall be carried out to confirm these benefits.

We have observed several elements:

- Unrivalled observation: the current solutions to assist in stopping smoking (NRT, varenicline) all imply the respect of treatment for 12 weeks (or even 24 weeks to meet the expected effectiveness. NFL-101 shall be administered in only 2 sub-cutaneous injections, made at one week's interval (indication for an immediate cessation), with the possibility of receiving 2 supplementary optional injections (indication for a gradual cessation). Such a treatment shall be administered by an authorized health professional and difficult not to be respected by the patients. It should prevent the problems of the observation/follow-up of the treatments. The adhesion rate for the second injection was evaluated at a minimum of 75%, resulting in an observation for the full 2 week treatment of 88%. As mentioned in the first part, the adhesion rate for the treatments currently commercialized is very minimal (between 30/35%) due to the adverse effects, a heavy dosage and a negative perception by the patient in terms of effectiveness. The group intends to assure its sales by selling all the treatment, i.e., the two doses at the same time.

- Confirmed safety: The clinical trial CESTO 1 confirmed the NFL-101's safety for humans, already established by the ten years' practice by Dr. Nicolas, with off-label use. The NFL-101's safety constitutes a significant benefit compared to Champix® or Zyban®.

- Potential effectiveness greater than the care standards: At this stage, the clinical trials are favourable for NFL-101. The retrospective analysis of use for stopping smoking with allergen extracts of tobacco paper having preceded the NFL-101 testifies an unprecedented level of efficacy compared with the solutions available (44% of continuous abstention at 12 months, 32% at 36 months, such as declared by 290 of Dr. Nicolas' former patients from 2003, selected at random).

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Furthermore, CESTO 1 indicated for the second recruitment wave of 12 patients a continuous abstention rate at 6 months of 33% and at 12 months of 25%, with NFL-101 exceeding the therapies currently available. Nonetheless, these results remain to be confirmed on a larger sample with an optimised study compared to placebo. With better safety and efficacy, the 88% compliance of the group appears cautious.

- Unique desired effect: According to the CESTO-1 study, NFL-101 would have an almost immediate effect just after the injection which would reduce a potential relapse and, accordingly, the long-term efficacy of the treatment.

The CESTO-2 study and the confirmative studies which could follow would enable confirmation of these benefits and justify high market share for NFL-101.

3.2 What is NFL-101's estimated positioning for stopping smoking?

- **A treatment for cigarette addiction for heavy smokers, ready to take prescription medication.** Although the NFL-101 targets both cigarettes and all combustion tobacco, and tobacco heated or perhaps even chewed, which is common practice in Asia, at this stage and given the nature of clinical studies specifically targeting cigarette smokers, we have limited the target market to cigarette smokers. Given the preliminary stages of development and administration method (sub-cutaneous injection), rather than targeting the entire population suffering from tobacco addiction and nicotine in all its forms, we have targeted heavy smokers (Fagerström > 6), intending to stop smoking with the assistance of a prescribed drug. It must be emphasized that in the EAGLES study, for the follow-up of patients treated to stop smoking (NRT, Zyban, Champix®, the Fagerström average was 5.8® for patients with a high level of dependency with an average of 21 cigarettes smoked per day. The French National Authority for Health (HAS) recommends the use of Champix® for patients with a very high dependency level (>7). We consider that these smokers will be the first candidates for a treatment with NFL-101.

- **An immediate cessation strategy.** In terms of positioning for the cessation, NFL-101 may be prescribed in different scenarios. The first, which we have included in our estimates, is that of cessation, for intended immediate cessation, which is the principal criterion of the CESTO-2 study. The treatment shall be administered a first time at the time of the date of intended cessation to assist the smoker in succeeding in stopping smoking then a second treatment one week later. Simultaneously, NFL-101 may also be administered at other times for other reasons: for gradual cessation, reduction, after a relapse or preventing a relapse. Given the lack of visibility on the clinical effectiveness of NFL-101 on these different cessation strategies, we limit our estimates to the prescription of NFL-101 to immediate cessation (2 doses). The results of the CESTO-2 study on the secondary evaluation criteria enable us to better appreciate the potential of NFL-101 in other tobacco cessation strategies. **Accordingly, we have included a treatment of 2 doses per year.**

- **A potential front line treatment.** In terms of treatment, contrary to Champix® which is occasionally prescribed as a secondary treatment if the NRT is unsuccessful (for example in France), the study in association with the NTS, could enable NFL-101 to gain high market share. We will adjust the potential market share according to the results of this study. The drug shall be positioned in addition to NRT (>85% of the estimated market value) on a larger scale target population. Accordingly, there will be no cannabilization of NRT sales by the NFL-101 sales, but on the contrary a general increase in market size. **At this stage, we aim for an approval as a second solution, in the event of failure of NRT, but our estimates of market share could be upgraded if the study in combination with NRT were to be found positive.**

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- **A drug administered by a general practitioner or a doctor specialized in addiction.** We consider that NFL-101 will be a drug prescribed by the general practitioners or specialist doctors for the addiction, as it concerns a drug administered as a sub-cutaneous injection. The group intends to develop an alternative administration method to the sub-cutaneous injections, the micro-needle patch. The program shall include finding a partner with the necessary technology, undertaking feasibility tests with NFL-101 prior to proceeding with the manufacturing of clinical batches of micro-needle patches. Bioequivalence test shall be simultaneously undertaken. If a bioequivalence between the sub-cutaneous injection and the micro-needle patch were to be established, the group could envisage marketing NFL-101 in pharmacies, which would necessarily increase potential market share.

- **Treatment at low cost.** The group wants to position NFL-101 as an affordable solution, for rich as well as developing countries, given its low manufacturing cost (± €5/dose according to current estimates, or even lower at €1 per dose in India). Compared with current therapies, the price anticipated by the company is far lower.

Regions / countries	NFL-101 (treatment of 2 injections)
Europe	€150
United States	€300
Japan, Korea, Australia	€150
China	€50
India	€50

Source: NFL BIOSCIENCES

- **4 targeted geographical areas. Our estimates are limited to 4 geographical areas: Europe (27 + UK), the US, Australia and the main APAC countries (China, India, South Korea, Japan). The addition of new geographical areas (Africa, Middle East or Latin America) will depend on the different clinical or commercial success encountered which could facilitate the signing of partnerships with local pharmaceutical companies.**

3.3 Peak sales of €900 million and 15 million doses (8.3 million patients treated a year)

Our sales estimates are based on several assumptions taken from epidemiological data from the second edition of the WHO 2018 report on tobacco addiction and from scientific literature. As previously explained, the prevalence of tobacco addiction tends to decrease with prevention policies and therapeutic solutions to help with cessation (see the WHO prevalence projections in the first section). We will apply the annualised growth levels of prevalence between 2025/2020 up to 2036.

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3- NFL-101: Marketing mid-2026, peak sales of €900 million

❖ **Europe/US/Australia: peak sales of €663 million for 6.4 million doses**

As there are no specific epidemiological studies for Europe, the US and Australia, we assume that the data from the 2004 Italian study (*Tobacco dependence in the general population in Italy, S. Gallus, R. Pacifici, P. Colombo, C. La Vecchia, S. Garattini, G. Apolone & P. Zuccaro*) on the proportion of heavy smokers (17.8% of smokers with a Fagerström score >6) applies to all countries.

In parallel, we will apply the Italian data on the proportion of smokers wanting to stop smoking to all European countries (39%). In the United States, prevention policies are more aggressive, encouraging a larger part of the smoking population to attempt to quit (68% according to CDC data from 2015). The US data is applied to Australia.

Despite a desire to stop smoking, few smokers come forward for prescription medication. Even though NFL-101 is a treatment of botanical origin, the injectable form of NFL-101 could also stop some heavy smokers from coming forward and to continue favouring nicotine replacement therapies. So, according to data from the Italian study, only 7.8% of Italian smokers rely on medication to attempt to quit. This low proportion is explained by the limited efficacy of the currently available treatments. According to the CDC, in the United States, 29% of smokers attempt to quit with a smoking cessation drug. This difference is explained by the high penetration of Champix® in the US compared with Europe (the US represents 80% of the revenue of Champix® in Q1 21). However, with the arrival of a botanical solution such as NFL-101, we believe that the proportion of patients in Europe attempting to stop smoking with a medical support will go towards American levels. The US data is applied to Australia.

As indicated by the company, we will include a compliance rate of 88% with 100% of patients taking the first dose and 75% of patients who would be given the second dose. In terms of market penetration, we anticipate peak market share at 50%. This level will be reached relatively quickly for a drug (about 6 years) given the significant medical need in the tobacco addiction market. It should be noted that this level is not extremely demanding as we have targeted a specific population of smokers, that of highly dependent smokers, wanting to quit with a drug administered by a doctor, which is ultimately only 4% of smokers in Europe and the US.

We will include a price of €300 for the US and €150 for Europe and Australia. This price is reasonable compared with Champix® (€238 in Europe and €1,117 in the US for 12 weeks of treatment). The discounts in relation to the European and US price comes to -37% and -73% respectively. We believe that these discount levels include the impact on the price of the likely arrival of generics of Champix® in the next two years. As a reminder, the patent for Champix® expired in 2020 in the US, expires in 2021 in Europe and in 2022 in Japan. Because of shortages due to product recalls, the FDA has approved in August a generic developed by Par Pharmaceutical. It should also be emphasized that according to the clinical results of NFL-101 and its positioning in the smoking cessation market, the group could insist on higher prices. In addition, the selling prices of €300 in the US and €150 in Europe are lower than a full treatment with NRT (€344 and €183 respectively for 12 weeks of treatment including 84 patches and 300 nicotine gums).

The ambitious clinical program should allow the company to strengthen its reimbursement dossier. In France, Champix® is reimbursed at up to 65%, however, with very mixed results on the safety component explaining a low adherence to the treatment. Champix® was delisted in 2011. Similarly, in France, NRTs are 65% covered. Reimbursement of NFL-101 in the case of a successful clinical pathway seems entirely feasible and justifies significant market penetration. **We anticipate a commercial launch in mid-2026.**

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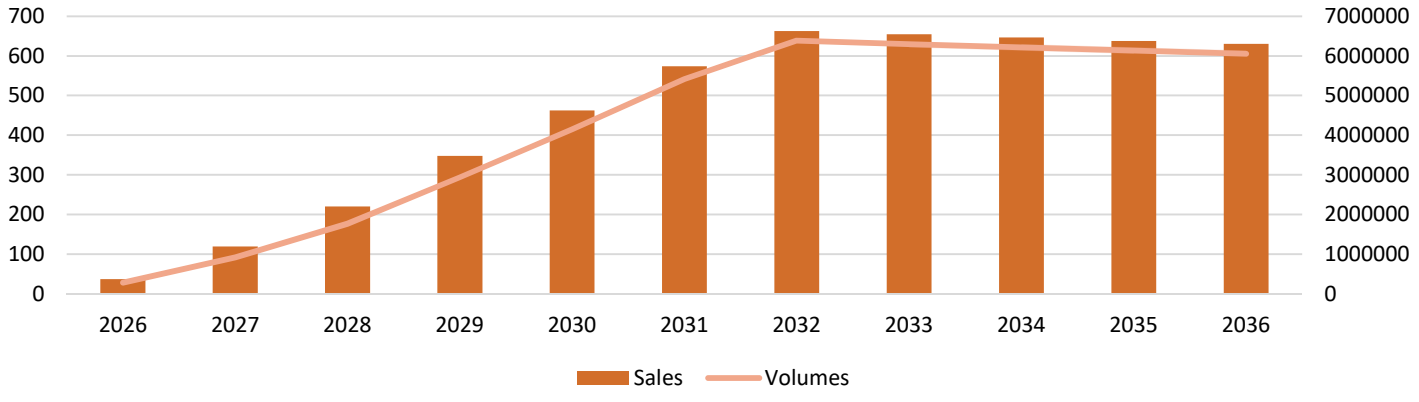
3- NFL-101: Marketing mid-2026, peak sales of €900 million

Peak sales of €663 million

EUROPE (27 + UK)	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036
Prevalence of smoking tobacco (million)	**112.4**	**110.8**	**109.2**	**107.7**	**106.2**	**104.7**	**103.3**	**101.8**	**100.5**	**99.1**	**97.8**
% High to very high dependence (Fagerström>6)	17.6%	17.6%	17.6%	17.6%	17.6%	17.6%	17.6%	17.6%	17.6%	17.6%	17.6%
% Attempting to quit	39.0%	44.9%	51.6%	59.3%	68.2%	68.2%	68.2%	68.2%	68.2%	68.2%	68.2%
% With medical support	7.8%	9.4%	12.6%	17.1%	23.0%	31.1%	35.2%	35.2%	35.2%	35.2%	35.2%
% Compliance with treatment	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%
Target population (million)	**0.5**	**0.7**	**1.1**	**1.7**	**2.6**	**3.4**	**3.8**	**3.8**	**3.7**	**3.7**	**3.6**
% NFL-101 penetration	5.0%	15.0%	25.0%	35.0%	40.0%	45.0%	50.0%	50.0%	50.0%	50.0%	50.0%
NFL-101 price (2x)	€150	€150	€150	€150	€150	€150	€150	€150	€150	€150	€150
Volumes of NFL-101 doses (immediate cessation)	52,946	216,074	551,179	1,181,153	2,066,458	3 094 946	3,839,950	3,787,491	3,736,115	3,685,797	3,636,510
Revenue from NFL-101 treatment (€ million)	**€4**	**€16**	**€41**	**€89**	**€155**	**€232**	**€288**	**€284**	**€280**	**€276**	**€273**

USA	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036
Population (million)	340	342	344	345	347	348	350	351	353	355	356
Prevalence of smoking tobacco (%)	20.9%	20.5%	20.2%	19.9%	19.5%	19.2%	18.9%	18.6%	18.3%	18.0%	17.7%
Prevalence of smoking tobacco (million)	**71**	**70**	**69**	**69**	**68**	**67**	**66**	**65**	**65**	**64**	**63**
% High to very high dependence (Fagerström>6)	17.6%	17.6%	17.6%	17.6%	17.6%	17.6%	17.6%	17.6%	17.6%	17.6%	17.6%
% Attempting to quit	68.0%	68.0%	68.0%	68.0%	68.0%	68.0%	68.0%	68.0%	68.0%	68.0%	68.0%
% With medical support	29.0%	30.5%	32.0%	33.6%	35.2%	35.2%	35.2%	35.2%	35.2%	35.2%	35.2%
% Compliance with treatment	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%
Target population (million)	**2.2**	**2.3**	**2.3**	**2.4**	**2.5**	**2.5**	**2.5**	**2.4**	**2.4**	**2.4**	**2.3**
% NFL-101 penetration	5.0%	15.0%	25.0%	35.0%	40.0%	45.0%	50.0%	50.0%	50.0%	50.0%	50.0%
NFL-101 price (2x)	€300	€300	€300	€300	€300	€300	€300	€300	€300	€300	€300
Volumes of NFL-101 doses (immediate cessation)	216 908	675 241	1 167 799	1 696 512	2 011 916	2 236 835	2 456 195	2 427 362	2 398 866	2 370 705	2 342 875
Revenue from NFL-101 treatment (€ million)	**€33**	**€101**	**€175**	**€254**	**€302**	**€336**	**€368**	**€364**	**€360**	**€356**	**€351**

AUSTRALIA	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036
Population of Australia	27	27	28	28	28	28	29	29	29	29	30
Prevalence of smoking tobacco (%)	10.0%	9.7%	9.4%	9.0%	8.7%	8.4%	8.1%	7.8%	7.6%	7.3%	7.1%
Prevalence of smoking tobacco (million)	3	3	3	3	2	2	2	2	2	2	2
% High to very high dependence (Fagerström>6)	17.6%	17.6%	17.6%	17.6%	17.6%	17.6%	17.6%	17.6%	17.6%	17.6%	17.6%
% Attempting to quit	68.0%	68.0%	68.0%	68.0%	68.0%	68.0%	68.0%	68.0%	68.0%	68.0%	68.0%
% With medical support	29.0%	30.5%	32.0%	33.6%	35.2%	35.2%	35.2%	35.2%	35.2%	35.2%	35.2%
% Compliance with treatment	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%
Target population (million)	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**
% NFL-101 penetration	5.0%	15.0%	25.0%	35.0%	40.0%	45.0%	50.0%	50.0%	50.0%	50.0%	50.0%
NFL-101 price (2x)	€150	€150	€150	€150	€150	€150	€150	€150	€150	€150	€150
Volumes of NFL-101 doses (immediate cessation)	8,338	25,584	43,613	62,452	73,003	80,003	86,592	84,351	82,168	80,042	77,970
Revenue from NFL-101 treatment (€ million)	**€1**	**€2**	**€3**	**€5**	**€5**	**€6**	**€6**	**€6**	**€6**	**€6**	**€6**



Source: Invest Securities Estimates

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3- NFL-101: Marketing mid-2026, peak sales of €900 million

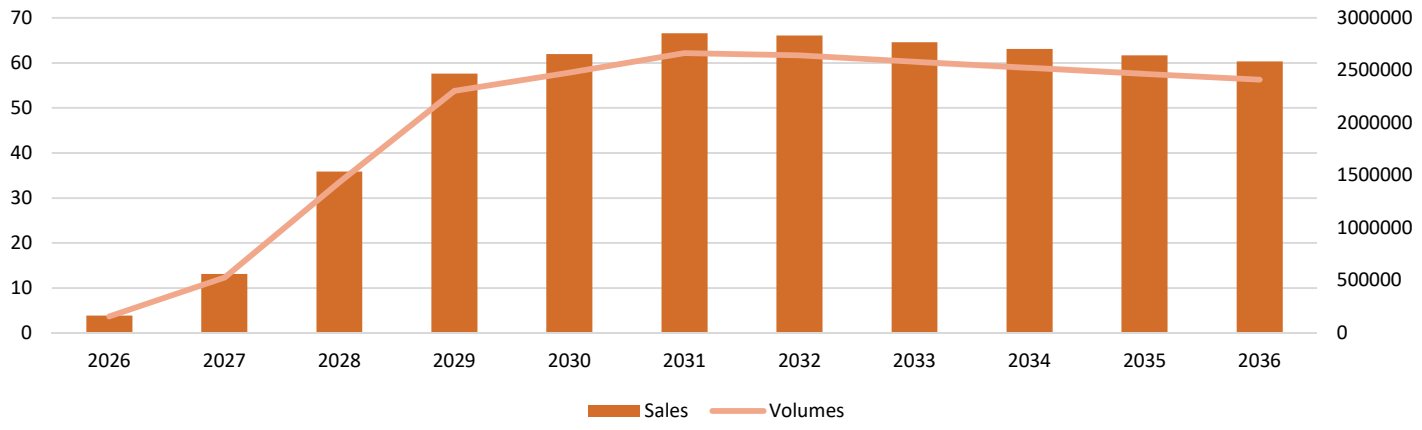
❖ India: peak sales of €70 million for 2.7 million doses

In India, parallel with Europe or the targeted APAC countries, it seems difficult to justify. Accordingly, our estimates of the tobacco smoking population wanting to quit with a drug are taken from data in the Global Adult Tobacco Survey India report (GATS India) dated 2009/2010 and a study on 1569 tobacco users (Factors determining intention to quit tobacco: exploring patient responses visiting public health facilities in India, Rajmohan Panda, Sudhir Venkatesan, Divya Persai, Mayur Trivedi, and Manu Raj Mathur). These studies highlight that in India, tobacco smokers trying to quit (38%) use very little medication (4% vs 29% in the US and 8% in Italy). This is likely to be explained by a low level of economic development. We believe that marketing NFL-101 through a partner who is firmly established in the country will increase the proportion of smokers using a drug to levels closer to those in Italy at present (7.8%).

Ultimately, we are therefore targeting a small proportion of tobacco smokers (2.6%), which is about 2.7 million smokers per year. We will include a market penetration of NFL-101 similar to Europe and the US. In parallel, we expect a price of €50 in line with the company estimates, i.e. -83% below the US price and -67% below the European price. It should be noted that in India, the price of a full treatment with Champix® amounts to €111, equivalent to that of NRTs. We anticipate a commercial launch in mid-2026.

Peak sales of €70 million in India for 2.7 million doses

INDIA	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036
Population (million)	1,408	1,416	1,424	1,432	1,439	1,447	1,455	1,463	1,471	1,479	1,488
Prevalence of smoking tobacco (%)	8.3%	8.0%	7.8%	7.6%	7.4%	7.2%	7.0%	6.8%	6.6%	6.4%	6.2%
Prevalence of smoking tobacco (million)	**116**	**114**	**111**	**109**	**106**	**104**	**101**	**99**	**97**	**95**	**92**
% Attempting to quit	38.0%	38.0%	38.0%	38.0%	38.0%	38.0%	38.0%	38.0%	38.0%	38.0%	38.0%
% With medical support	4.0%	4.6%	5.5%	6.3%	7.0%	7.7%	7.8%	7.8%	7.8%	7.8%	7.8%
% Compliance with treatment	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%
Target population (million)	**1.6**	**1.7**	**2.1**	**2.3**	**2.5**	**2.7**	**2.6**	**2.6**	**2.5**	**2.5**	**2.4**
% NFL-101 penetration	5.0%	15.0%	35.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%
NFL-101 price (2x)	€50	€50	€50	€50	€50	€50	€50	€50	€50	€50	€50
Volumes of NFL-101 doses (immediate cessation)	155,617	524,682	1,435,738	2,305,131	2,478,044	2,663,927	2,643,719	2,583,663	2,524,972	2,467,614	2,411,559
Revenue from NFL-101 treatment (€ million)	**€4**	**€13**	**€36**	**€58**	**€62**	**€67**	**€66**	**€65**	**€63**	**€62**	**€60**



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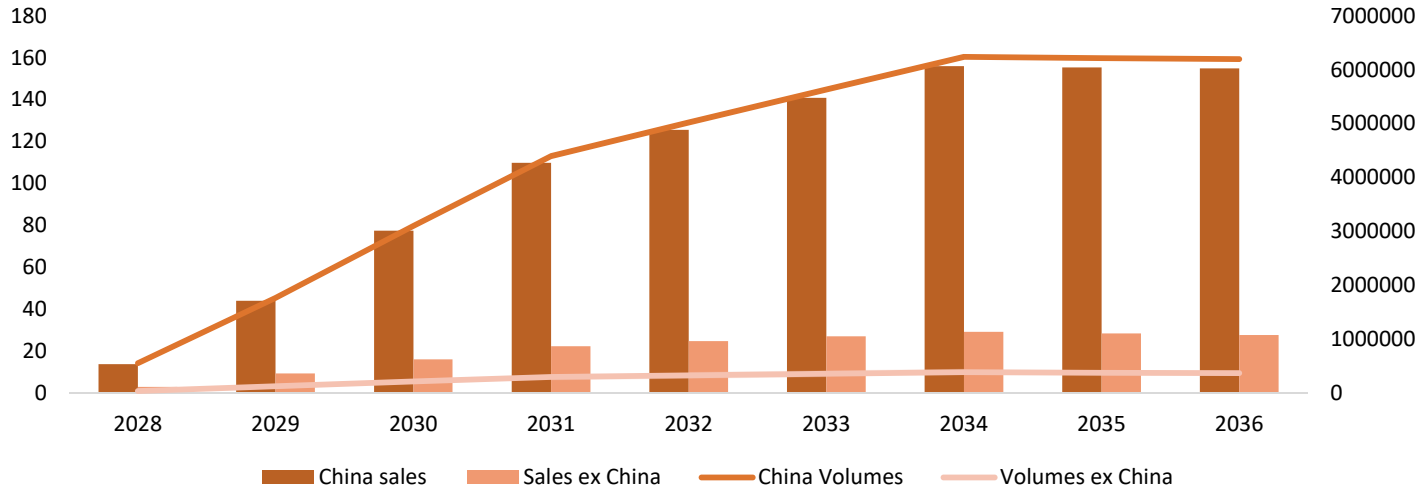
3- NFL-101: Marketing mid-2026, peak sales of €900 million

❖ APAC: peak sales of €185 million for 6.7 million doses

In the targeted APAC countries (Japan, China, South Korea), in the absence of comprehensive epidemiological data, we will include the prevalence of heavy smokers from the Italian study. In parallel, in the filters of attempting to quit with medical support, we will include the average between the US and India, which seems to correctly represent the situation of these Asian countries. We will include a treatment price (2 doses) of €50 in China and €150 in Japan and South Korea. It should be noted that in China, the price of a full treatment with Champix® amounts to €218 and the price of a NRT treatment comes to €98.

We anticipate a commercial launch of NFL-101 in these markets in 2028

APAC (China, Japan, South Korea)	2028	2029	2030	2031	2032	2033	2034	2035	2036
Population of China (million)	1,473	1,481	1,488	1,496	1,504	1,512	1,520	1,528	1,536
Prevalence of smoking tobacco (%)	24.5%	24.3%	24.0%	23.8%	23.6%	23.4%	23.2%	23.0%	22.8%
Prevalence of smoking tobacco (million)	360	359	358	357	356	354	353	352	351
Population of Japan	125	124	124	124	124	123	123	123	123
Prevalence of smoking tobacco (%)	14.4%	14.0%	13.6%	13.2%	12.9%	12.5%	12.2%	11.8%	11.5%
Prevalence of smoking tobacco (million)	18	17	17	16	16	15	15	15	14
Population of South Korea	51	51	50	50	50	50	50	50	50
Prevalence of smoking tobacco (%)	16.6%	16.2%	15.8%	15.4%	15.0%	14.6%	14.2%	13.9%	13.5%
Prevalence of smoking tobacco (million)	8	8	8	8	8	7	7	7	7
Total prevalence of smoking (million)	**387**	**385**	**383**	**381**	**379**	**377**	**375**	**374**	**372**
% High to very high dependence (Fagerström>6)	17.6%	17.6%	17.6%	17.6%	17.6%	17.6%	17.6%	17.6%	17.6%
% Attempting to quit	53.0%	53.0%	53.0%	53.0%	53.0%	53.0%	53.0%	53.0%	53.0%
% With medical support	18.7%	20.0%	21.1%	21.5%	21.5%	21.5%	21.5%	21.5%	21.5%
% Compliance with treatment	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%	88.0%
Target population of China (million)	**5.5**	**5.9**	**6.2**	**6.3**	**6.3**	**6.3**	**6.2**	**6.2**	**6.2**
APAC target population ex China (million)	**0.4**	**0.4**	**0.4**	**0.4**	**0.4**	**0.4**	**0.4**	**0.4**	**0.4**
% NFL-101 penetration	5.0%	15.0%	25.0%	35.0%	40.0%	45.0%	50.0%	50.0%	50.0%
NFL-101 price (Japan, South Korea) (2x)	€150	€150	€150	€150	€150	€150	€150	€150	€150
China NFL-101 price (2x)	€50	€50	€50	€50	€50	€50	€50	€50	€50
Volumes of NFL-101 doses China	554,389	1,764,993	3,101,897	4,399,949	5,025,868	5,635,517	6,241,104	6,220,590	6,200,144
Volumes of NFL-101 doses APAC ex China	40,519	125,723	215,340	297,695	331,407	362,169	390,900	379,719	368,858
China revenue from NFL-101 treatment (€ million)	**€14**	**€44**	**€78**	**€110**	**€126**	**€141**	**€156**	**€156**	**€155**
APAC ex China revenue from NFL-101 treatment (€ million)	**€3**	**€9**	**€16**	**€22**	**€25**	**€27**	**€29**	**€28**	**€28**
APAC revenue from NFL-101 treatment (€ million)	**€17**	**€54**	**€94**	**€132**	**€151**	**€168**	**€185**	**€184**	**€183**



Source: Invest Securities Estimates

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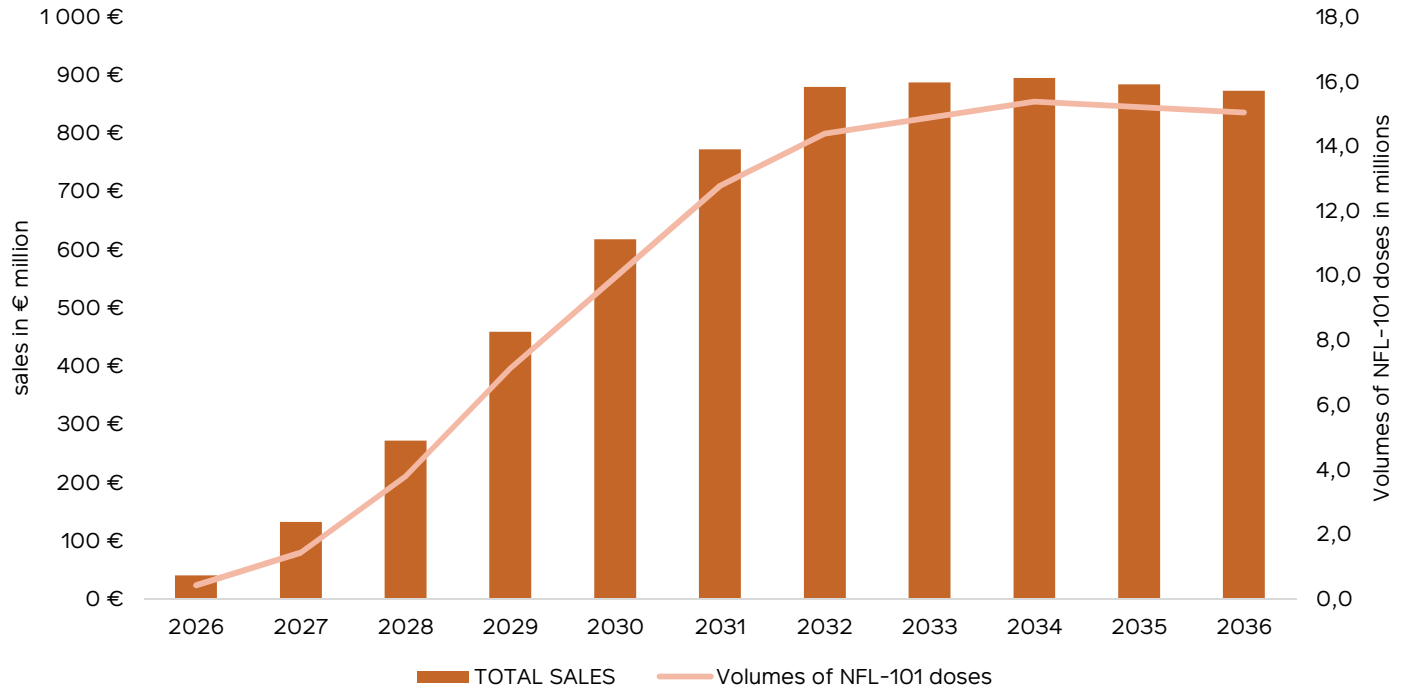
3- NFL-101: Marketing mid-2026, peak sales of €900 million

All in all, at this stage and according to our assumptions, we expect overall peak sales of NFL-101 of €900 million for 15.4 million doses.



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4- DILUTED VALUATION OF €4.9/SHARE, BUY RECOMMENDATION

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4- Diluted valuation of €4.9/share, BUY recommendation

Our fully-diluted TP of €4.9 is based on a sum of NFL-101's rNPV to 2036, expiration date of the main patents, in 4 geographical areas: Europe, US/Australia, the main APAC countries (China, Japan, South Korea) and India. We include in our TP the 5m€ capital increase (1.3 new shares) and the exercise of the dilutive instruments that are in the money (BSA, BSPCE : 2.1m new shares). After the capital increase and the exercise of the dilutive instruments (€0.7m), in order to finance its pipeline, we estimate that the company will need an additional funding of €14m by the end of 2025 and €1.2m before the end of 2023, which coincides with the potential launch date of the confirmatory trials in Europe and in the US.

4.1 rNPV of €26m (€3.5/share) in Europe, the United States and Australia

- **Marketing in Europe, the US and Australia via one/several licence agreements early 2026.** The group wants to conduct clinical development up to its completion in Europe and the US, a reasoned strategy that we will align with taking into account the relatively low cost of studies in tobacco addiction. Late 2025/early 2026, once the confirmatory phases are completed, we anticipate the signing of licence agreements in Europe and the US. According to our estimates, these licence agreements will be signed for a total amount of €100 million (€42 million in Europe, €55 million in the US), i.e. about 15% of the peak sales carried out in each region.

- In detail, we expect the upfront payments in 2026 of a total amount of €32 million (€14 million in Europe, €18 million in the US/Australia), milestone payments of €65 million (€28 million in Europe and €37 million in the US/Australia) depending on certain sales thresholds being reached and royalties of 15% on partner sales.

- The company would like to control the production of NFL-101 for Western countries (Australia, Europe, US). Therefore, the US, European and Australian partners will handle marketing costs, whereas the group will take care of NFL-101 production (COGS and CAPEX). The group will therefore have two sources of revenue in Europe, the US and Australia. The first coming from the payment of royalties (15% on sales made by the partner) and milestone payments, and the second will consist of the sale of NFL-101 doses to the partner (transfer pricing) with a deep discount on the market price (20% of the integrated market price).

- **Relatively limited costs and investments.** It is estimated that a hectare of tobacco would produce tens of millions of doses, consequently with a limited raw material risk. The production cost of one NFL-101 dose is about €5/dose according to current estimates. According to our estimates for volumes of doses sold in Europe, the US and Australia, at the peak the group should sell 6.4 million doses of NFL-101 suggesting that a hectare of tobacco would be sufficient to supply these Western countries. We will include OPEX of €5/dose, CAPEX corresponding to 2% of the transfer revenue and a WCR of 15% of the transfer revenue. We expect total R&D expenses of €-24 million in Europe, the US and Australia to finance the CESTO-2 study, the study in combination with NRTs, confirmatory studies which could follow and regulatory costs. In addition, we will include a tax rate of 25%.

- **POS of 14%.** We will include a probability of success (POS) of 14% for NFL-101, of which 30% for CESTO-2, 57% for confirmatory studies, and 83% for an approval by the regulatory authorities once the pivotal phases have been completed. This POS corresponds to the historical POS of drugs developed for central nervous system (CNS) indications between 2006 and 2015 according to Biomedtracker. In addition to the difficult indication (tobacco addiction), which has had several failures, this low probability is also explained by an early development stage. Depending on the clinical success encountered, we will raise the POS.

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4- Diluted valuation of €4.9/share, BUY recommendation

POS	
CESTO 2	30%
Pivotal	57%
Approval	83%
POS	14%

- **A WACC of 15% and an infinite decrease of -31%.** We will update our FCF with a WACC of 15% up to 2036, expiration date of the main patents. It should be noted that the group could extend the duration of its patents from 4-5 years if an approval was obtained in 2026. However, at this stage, due to the lack of long-term visibility, we are making estimates up to 2036 (16 years of estimates). This discount rate is within the standard of biotechnology companies at an early development stage. In our terminal value after 2036, we apply a decrease to infinite of -31.8% on transfer revenues only. This decrease is equivalent to the annual decline of Champix® after expiry of the patent.

- **An overall valuation of €26 million (€3.5/share).** Our valuation for Europe, the US and Australia comes to €26 million in total including €8m for Europe (€1.1/share) and €18m (€2.4/share) for the US and Australia.

EUROPE VALUATION

Clinical development	P2/3	P2/3	P2/3 & P3	P3	P3	Filing											
	Combi	Combi	Combi														
€ million	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	Infinite
EU - Total sales	**0**	**0**	**0**	**0**	**0**	**4**	**16**	**41**	**89**	**155**	**232**	**288**	**284**	**280**	**276**	**273**	
Upfront + Milestones						14	7		7		7		7				
Royalties (15%)	0	0	0	0	0	1	2	6	13	23	35	43	43	42	41	41	
Revenue from transfers (20% of the sale price)	0	0	0	0	0	1	3	8	18	31	46	58	57	56	55	55	55
EUROPE revenue	**0**	**0**	**0**	**0**	**0**	**15**	**13**	**14**	**38**	**54**	**88**	**101**	**106**	**98**	**97**	**95**	**55**
(-) COGS	0	0	0	0	0	0	-1	-3	-6	-10	-15	-19	-19	-19	-18	-18	-18
(-) R&D	-1	-2	-4	-2	-2	0	0	0	0	0	0	0	0	0	0	0	0
(-) SG&A	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
EBIT	**-1**	**-2**	**-4**	**-2**	**-2**	**15**	**12**	**12**	**32**	**44**	**73**	**82**	**87**	**79**	**78**	**77**	**36**
(-) D&A	0	0	0	0	0	0	0	0	0	-1	-1	-1	-1	-1	-1	-1	-1
(-) Tax	0	0	0	0	0	-4	-3	-3	-8	-11	-18	-20	-22	-20	-20	-19	-9
(-) WCR var.	0	0	0	0	0	0	0	-1	-1	-2	-2	-2	0	0	0	0	0
(-) Capex	0	0	0	0	0	0	0	0	0	-1	-1	-1	-1	-1	-1	-1	-1
FCF	**-1**	**-2**	**-3**	**-2**	**-2**	**11**	**8**	**8**	**22**	**29**	**50**	**57**	**63**	**57**	**56**	**55**	**25**
POS	100%	100%	30%	30%	17%	14%	14%	14%	14%	14%	14%	14%	14%	14%	14%	14%	14%
risk adjusted FCF	-1	-2	-1	-1	0	2	1	1	3	4	7	8	9	8	8	8	3
Discounted FCF	**7.4**																
Discounted terminal value	0.5																
rNPV	**8**																

US VALUATION + Australia

Development			P3 (T4)	P3	P3	Filing											
€ million	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	Infinite
US - Total sales	**0**	**0**	**0**	**0**	**0**	**33**	**101**	**175**	**254**	**302**	**336**	**368**	**364**	**360**	**356**	**351**	
Upfront + Milestones						18	9		9		9		9				
Royalties (15%)	0	0	0	0	0	5	15	26	38	45	50	55	55	54	53	53	
Revenue from transfers (20% of the sale price)	0	0	0	0	0	0	7	21	36	52	61	68	75	74	73	72	72
US revenue	**0**	**0**	**0**	**0**	**0**	**23**	**31**	**47**	**83**	**97**	**121**	**124**	**139**	**128**	**127**	**125**	**72**
(-) COGS	0	0	0	0	0	-1	-4	-6	-9	-10	-12	-13	-13	-12	-12	-12	-12
(-) R&D	0	0	-1	-6	-6	0.0	0	0	0	0	0	0	0	0	0	0	0
(-) SG&A	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
EBIT	**0**	**0**	**-1**	**-6**	**-6**	**22**	**28**	**41**	**74**	**87**	**109**	**111**	**126**	**116**	**114**	**113**	**60**
(-) D&A	0	0	0	0	0	0	0	0	-1	-1	-1	-1	-1	-1	-1	-1	-1
(-) Tax	0	0	0	0	0	-6	-7	-10	-19	-22	-27	-28	-32	-29	-29	-28	-15
(-) WCR var.	0	0	0	0	0	0	-1	-2	-2	-2	-1	-1	-1	0	0	0	0
(-) Capex	0	0	0	0	0	0	0	0	-1	-1	-1	-1	-1	-1	-1	-1	-1
FCF	**0**	**0**	**-1**	**-6**	**-6**	**17**	**19**	**28**	**52**	**61**	**78**	**79**	**91**	**84**	**83**	**82**	**42**
POS	100%	100%	30%	30%	17%	14%	14%	14%	14%	14%	14%	14%	14%	14%	14%	14%	14%
risk adjusted FCF	0	0	0	-2	-1	2	3	4	7	9	11	11	13	12	12	12	6
Discounted FCF	**17**																
Discounted terminal value	1																
rNPV	**18**																

Source: Invest Securities Estimates

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4- Diluted valuation of €4.9/share, BUY recommendation

4.2 rNPV of €5m (€0.6/share) in Japan, South Korea, China and India

- **Licence expected in 2024 in India and 2026 in China, Japan and South Korea.** We believe that, in India, where negotiations are ongoing, the group will sign a licence agreement based on the results of the CESTO-2 study in 2024, whereas in the other targeted APAC countries (China, Japan, South Korea), licence agreements could be signed in 2026 after results of the confirmatory phases in Europe and the US. In these countries, we estimate that an additional, less comprehensive specific clinical study will be needed to obtain approval. Accordingly, we expect a commercial launch in India in 2026 and in the rest of APAC in 2028. This estimates will be adjusted depending on events. In India, we anticipate a licence agreement for a total amount of €7 million (10% of the peak sales) and royalties of 10%. In Japan, South Korea and China, we anticipate licence agreements for a total amount of €20 million (10% of the peak sales) and royalties of 10%. The lower level of royalty rates compared with the Western countries is explained by the need to conduct a new country-specific clinical study.

- **No costs and investments.** The group does not intend to produce doses of NFL-101 for these countries. Development costs allocated to the country-specific clinical study will be chargeable to the partner. We will include a tax rate of 25%.

- **POS of 14%.** Like our rNPV valuation in Europe, the US and Australia, we will include a POS of 14%.

- **A discount rate (WACC) of 15%.** We will not include the terminal value with royalties, which will stop once the patent has expired.

- **An overall valuation of €5m in APAC (€0.6) including €2m (€0.2) in India.**

INDIA VALUATION

Development				Licence	P3	P3/ Filing										
€ million	**2021**	**2022**	**2023**	**2024**	**2025**	**2026**	**2027**	**2028**	**2029**	**2030**	**2031**	**2032**	**2033**	**2034**	**2035**	**2036**
INDIA - Total sales	0	0	0	0	0	4	13	36	58	62	67	66	65	63	62	60
Upfront + Milestones				3		1	1		1		1					
Royalties (10%)	0	0	0	0	0	0	1	4	6	6	7	7	6	6	6	6
INDIA revenue	**0**	**0**	**0**	**3**	**0**	**1**	**2**	**4**	**7**	**6**	**8**	**7**	**6**	**6**	**6**	**6**
(-) COGS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(-) R&D	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(-) SG&A	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
EBIT	**0**	**0**	**0**	**3**	**0**	**1**	**2**	**4**	**7**	**6**	**8**	**7**	**6**	**6**	**6**	**6**
(-) D&A	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(-) Tax	0.0	0.0	0.0	-0.8	0.0	-0.3	-0.6	-0.9	-1.7	-1.5	-1.9	-1.7	-1.6	-1.6	-1.5	-1.5
(-) WCR var.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(-) Capex	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
FCF	**0**	**0**	**0**	**2**	**0**	**1**	**2**	**3**	**5**	**5**	**6**	**5**	**5**	**5**	**5**	**5**
POS	100%	100%	30%	30%	17%	14%	14%	14%	14%	14%	14%	14%	14%	14%	14%	14%
risk adjusted FCF	0	0	0	1	0	0	0	0	1	1	1	1	1	1	1	1
Discounted FCF	**2**															
Discounted terminal value	0															
rNPV	**2**															

APAC VALUATION

Development						Licence	P3	P3/ Filing								
€ million	**2021**	**2022**	**2023**	**2024**	**2025**	**2026**	**2027**	**2028**	**2029**	**2030**	**2031**	**2032**	**2033**	**2034**	**2035**	**2036**
Partner revenue	0	0	0	0	0	0	0	17	54	94	132	151	168	185	184	183
Upfront + Milestones						9	3		3		3		3			
Royalties (10%)	0	0	0	0	0	0	0	2	5	9	13	15	17	19	18	18
APAC revenue	**0**	**0**	**0**	**0**	**0**	**9**	**3**	**2**	**8**	**9**	**16**	**15**	**20**	**19**	**18**	**18**
(-) COGS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(-) R&D	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(-) SG&A	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
EBIT	**0**	**0**	**0**	**0**	**0**	**9**	**3**	**2**	**8**	**9**	**16**	**15**	**20**	**19**	**18**	**18**
(-) D&A	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(-) Tax	0.0	0.0	0.0	0.0	0.0	-2.3	-0.7	-0.4	-2.0	-2.3	-4.0	-3.8	-4.9	-4.6	-4.6	-4.6
(-) WCR var.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(-) Capex	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
FCF	**0**	**0**	**0**	**0**	**0**	**7**	**2**	**1**	**6**	**7**	**12**	**11**	**15**	**14**	**14**	**14**
POS	100%	100%	30%	30%	17%	14%	14%	14%	14%	14%	14%	14%	14%	14%	14%	14%
risk adjusted FCF	0	0	0	0	0	1	0	0	1	1	2	2	2	2	2	2
Discounted FCF	**3**															
Discounted terminal value	0															
rNPV	**3**															

Source: Invest Securities Estimates

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4- Diluted valuation of €4.9/share, BUY recommendation

4.3 Post-money valuation of €36m (€4.9/share), BUY recommendation

Our NFL BIOSCIENCES valuation follows from a sum of the parts (SOP) valuation. Each asset is valued according to the rNPV method with a WACC of 15% and a totally diluted number of shares of 7.4m. At this stage, our valuation only includes the US, Europe (27+UK), India, China, Australia, Japan or South Korea. Likewise, we are not including products in the earlier development phases (NFL-201) and the product for treating alcohol addiction (NFL-301). Moreover, we include the 5m€ capital increase following the success of the IPO as well as the dilutive instruments (BSA/BSPCE). Our totally diluted post-money valuation is €36m, which corresponds to a TP of €4.9/share. We initiate NFL BIOSCIENCES with a BUY recommendation and an upside of +36% compared to the last trading price.

In order to illustrate the significant potential of NFL BIOSCIENCES in the case of clinical success, our *best-case* valuation as of today, including a POS of 100% on NFL-101 would come to €235 million, or €32.7/share. In addition, if the CESTO-2 study is a complete success (POS raised to 50%), the valuation in 2023 would amount to €156 million, or €21.9/share (upside of +540% vs the last trading price).

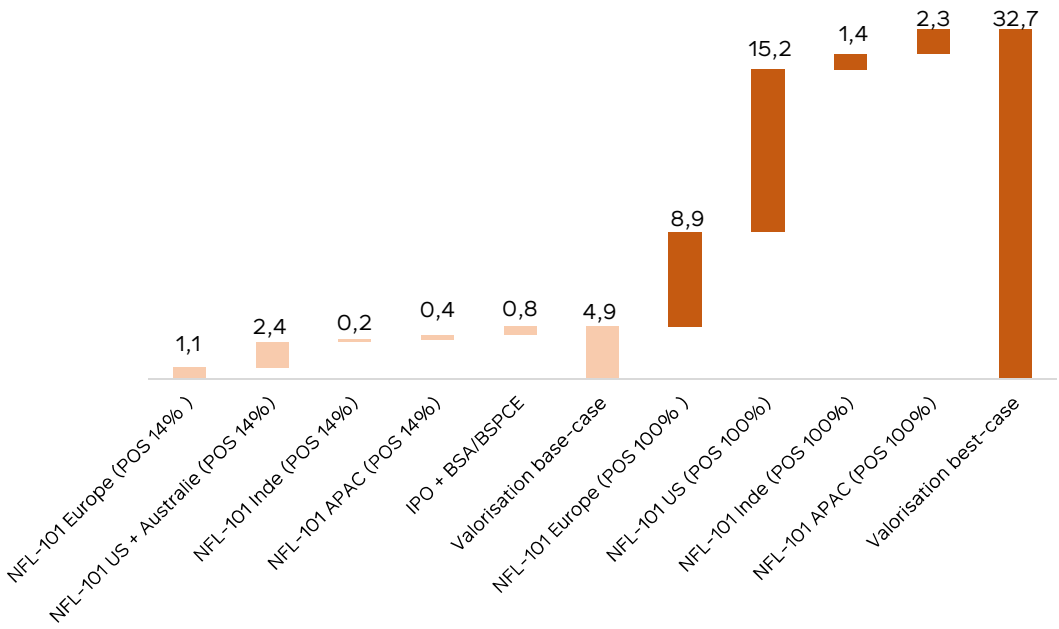

Table of Time sensitivity/overall POS

TP €/share		Year				
		2021e	2022e	2023e	2024e	2025e
POS	5%	2,3 €	2,4 €	2,8 €	3,1 €	3,5 €
	14%	4,9€	5,8 €	6,7 €	7,6 €	8,7 €
	50%	16,6 €	19,0 €	21,9 €	25,3 €	29,3 €
	80%	26,1 €	29,9 €	34,5 €	40,1 €	46,6 €
	100%	32,6 €	37,2 €	43,1 €	50,0 €	58,0 €

Source: Invest Securities Estimates

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4- Diluted valuation of €4.9/share, BUY recommendation

Table of WACC sensitivity/infinite growth

		WACC				
		14,0%	14,5%	15,0%	15,5%	16,0%
Infinite growth	-47,0%	5,3 €	5,0 €	4,8 €	4,6 €	4,4 €
	-31,0%	5,4 €	5,1 €	**4,9 €**	4,7 €	4,4 €
	-15,0%	5,6 €	5,3 €	5,0 €	4,8 €	4,6 €

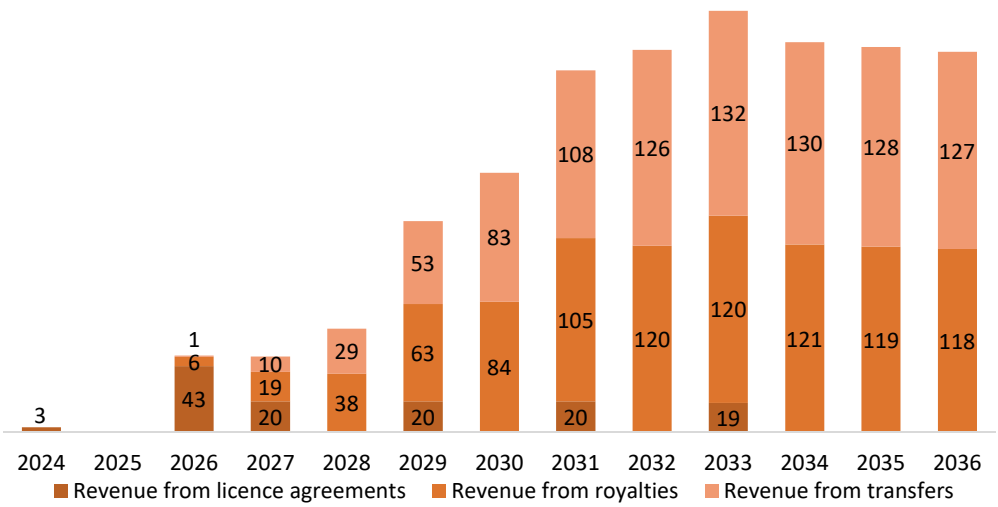
4.4 €14m estimated financial needs by end of 2025 following the success of the IPO

According to our estimates, the group should reach the profitability threshold on net income in 2026. Our assumptions include the operational expenses of different rNPV (SG&A, R&D, COGS) as well as the revenues from licence agreements in the US, direct sales and sales via distributors in Europe.

In total, we estimate that the NFL-101 licence agreements in Europe, US/Australia, India, China, South Korea and Japan, could generate revenues of €125 million (€45 million upfront and €80 million of milestones). Compared with the amounts from signed licence agreements in the tobacco addiction market (see below), our estimates remain relatively conservative.

Phase	Deal Date	Company	Product	Deal Partner	Upfront ($ million)	Deal Value ($ million)
Phase III	16/11/2009	GSK	NicVAX	Nabi Biopharma	40	540
Phase II	05/09/2011	Roche	Sembragiline	Evotec	10	830
Phase II	25/04/2007	Novartis	NIC002	Cytos Biotechnology	30	526
Phase II	18/12/2002	Addex	ADX10061	CeNeS Pharmaceuticals	4.5	5
Pre-clinical	03/01/2018	Indivior	ADX71441	Addex	5	335
Pre-clinical	30/06/2015	AZN	EORA101	Eolas Therapeutics		145
				Average	**18**	**397**

Source: Evaluate Pharma



Source: Invest Securities Estimates

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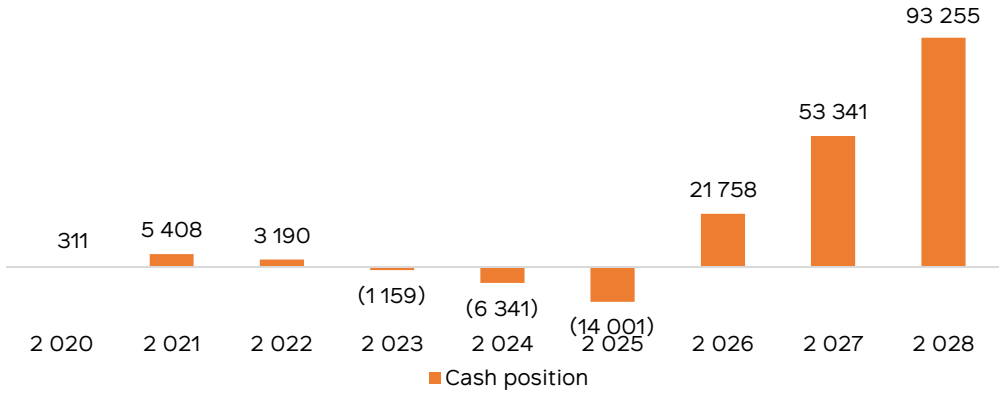
4- Diluted valuation of €4.9/share, BUY recommendation

Estimated P&L

Profit and loss statement (€ thousand)	2019	2020	2021e	2022e	2023e	2024e	2025e	2026e
Revenue	0	0	0	0	0	3 305	0	49 350
var.	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Adjusted EBITDA	-304	-276	-767	-2 300	-4 582	-4 825	-8 130	47 959
Adjusted EBITA	**-304**	**-276**	**-767**	**-2 300**	**-4 582**	**-4 825**	**-8 130**	**47 959**
var.	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***
EBIT	-347	-313	-805	-2 336	-4 606	-4 841	-8 140	47 933
Financial result	0	0	0	0	0	0	0	0
IS	80	52	51	153	305	-284	542	-11 990
SME+Minorities	0	0	0	0	0	0	0	0
Reported net attributable income	-268	-262	-754	-2 183	-4 300	-5 125	-7 598	35 943
Adjusted net attributable income	**-268**	**-262**	**-754**	**-2 183**	**-4 300**	**-5 125**	**-7 598**	**35 943**
var.		***-2%***	***+188%***	***+190%***	***+97%***	***+19%***	***+48%***	***-573%***

Source: Invest Securities Estimates

Following the inclusion of the capital increase (€5m) as well as the exercise of the dilutive instruments that are in the money (€0.7m), we estimate that the company will need an additional funding of €14m by the end of 2025. The funds raised will enable NFL Biosciences to accelerate its development by: (i) carrying out the Phase II/III trial for its drug candidate NFL-101, for tobacco addiction; (ii) recruiting talent to further strengthen its organization; (iii) launching the NFL-201 and NFL-301 programs, for the treatment of cannabis addiction and the reduction of alcohol consumption respectively.



Source: Invest Securities Estimates

4.5 Dilutive instruments

	Number of warrants	Number of shares per warrant	Dilutive impact	Exercise price	Total raised
BSA 2018	100 000	10	-16%	0,50 €	500 000
BSA 2019	12 500	10	-2%	0,30 €	37 500
BSPCE 2018	50 000	10	-9%	0,10 €	50 000
BSPCE 2019	50 000	10	-9%	0,30 €	150 000
				Total raised (in €)	737 500
				Total dilution	-36%

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Appendices: Team

Ignacio Faus

CEO
Board Member

PhD in Biochemistry from Indiana University (Bloomington), a MBA in Entrepreneurship and Finance from Kellogg School of Management (Northwestern University), IESE Business School Executive Education Program. Ignacio Faus has 27 years of experience in large and mid-size pharmaceutical companies, private and public biotechnology companies: Bristol Myers Squibb-INSERM-CNRS, Grupo Uriach, Ferrer, co-founder and CEO of Palau Pharma (sold in 2013), CEO of Mologen AG (MGN). Ignacio Faus is also on the Board for several private biotechnology companies as well as private equity funds in Europe.

Bruno Lafont

Founder, Deputy Managing Director (COO)
Board Member

In charge of the structuring and development of NFL BIOSCIENCES since 2009. Bruno previously spent 12 years in the management team of PCM, an international French industrial group.
Engineer in Biochemistry of National Institute of Applied Sciences (INSA) in Toulouse, EMLYON, Executive MBA EPFL/HEC Lausanne

Joël Besse

President of the Board of Directors

Aerospace Engineer of ISAE Sup'aero and Master's degree from University of Toulouse.
For 30 years venture capitalist (SED Ventures, Atlas Venture), Business Angel (Momentum Biotech, Angels Santé), director (Actelion, Novexel, Novuspharma...), founder and consultant of biotech companies, medtech (CeQur), foodtech and international venture capital funds, particularly in the field of Impact Investing. President of NFL BIOSCIENCES SAS between July 2018 and May 2021

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Appendices: Team

Francis Ahner

Board Member
Intellectual Property Expert

Francis Ahner is a former President of the International Federation of Industrial Property
Attorneys (IFIPA). Chemical Engineering from ENSC, graduate of the Centre for International Intellectual Property Studies (CIIPS) and former professor at CIIPS.
Industrial property consultant, specializing in chemistry, pharmacy and cosmetology, former partner of Regimbeau in Paris, which he joined in 1972. He is also a European agent with the European Patent Office (EPO), responsible for opposition and appeals for private companies and public bodies in France, the United States and Japan.

Michel Huc, Pharm. D.

Board Member
Manufacturing and Regulatory Affairs Expert

PhD in pharmacy, 30 years of experience in the pharmaceutical industry.
Previously managing director and chief pharmacist of several pharmaceutical companies.
16 years with Pierre Fabre Laboratories with expertise in the development, manufacturing, quality control and regulatory affairs of botanical drugs where he was the pharmacist responsible for Pierre Fabre's plant-based drugs.

Dr Yannick Plétan

Scientific consultant -Clinical Development Expert

Graduate in pneumology, immunology, clinical pharmacology and pharmacokinetics - postdoctoral fellow at INSERM and visiting professor at the University of California Davis.
After hospital practice for several years, he joined the pharmaceutical industry where he held management positions for 20 years in R&D and medical affairs: Sanofi, Pierre Fabre Research Institute, Pfizer and Roche-Genentech.
Decisive role in the creation and global development of the nicotine patch, and in the final phase of development and the launch of Chantix®
Harvard Business School + HEC

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Appendices: Team

Dr François Brackman

Scientific consultant -Clinical Development Expert

Graduate of medicine, clinical pharmacology and human pharmacokinetics.
Over 35 years in the pharmaceutical industry, as Vice President (Global Development and Medical Affairs). VP of Medical and Regulatory Affairs, Head of Development Platform.
Board Member, strategic boards for R&D and portfolio management committees. (Servier, Sandoz/Novartis, Fournier, Pierre Fabre).
Involved in regulatory interactions with national/international authorities (FDA, Health Canada, EMA, ANSM, MHRA, Koseisho) for international development programs and marketing authorisations.

Dr. Violaine Desort-Henin

Scientific consultant - Expert in management Head of clinical projects

Violaine Desort-Henin holds a Doctorate in Veterinary Medicine from the University of Lyon, in addition to university degrees in management of toxicology studies, interpretation of clinical trials, training as investigator of clinical trials, product safety and pharmacovigilance, and practical training at the Croix Rousse hospital, Cochin hospital, APHP and Clinique du Parc in Lyon.
For over 10 years, Violaine has worked in preclinical and clinical development of medicines for human use. In particular, she has been responsible for managing clinical trials within the Thea laboratories and start-ups Eyevensys, iDD Biotech and Adocia.

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Appendices: Scientific Board

Prof. Scott Leischow

Board Member - Expert in Strategy and Business Development
Dr Leischow is a **former president of the Society for Research on Nicotine and Tobacco (SRNT)** and founder and Editor-in-Chief of the journal Tobacco Regulatory Science.
He joined Arizona State University in June 2017, and is a Professor and Director of Clinical and Translational Science. Prior to that, he was at the Arizona Mayo Clinic from 2012 to 2017, where he led the Research on Health Equity and Community Health (REACH) Program and co-led cancer prevention and control. He was formerly an Associate Director at the University of Arizona Cancer Control Centre and was also Head of the Tobacco Control Research Division at the National Cancer Institute and Senior Advisor for Tobacco Policy in the Office of the Secretary of the U.S. Department of Health and Human Services.
His research focuses on pharmacologic and behavioural treatments for tobacco dependence, tobacco regulation and population health.

Dr. Mitch Nides

Dr Nides is the President of Los Angeles Clinical Trials, specializing in clinical research and development of products and medications to help smokers stop using combustible tobacco. Dr Nides has been the lead investigator of over 60 smoking cessation trials testing nicotine and non-nicotine products including patches, gums, lozenges, Inhalers, Zyban and Varenicline.
From 1987 to 1999 Dr Nides was a smoking cessation researcher in the Pulmonary and Critical Care Dept. of the UCLA School of Medicine. Over the years, Dr Nides has trained thousands of physicians, pharmacists, nurses, and other health care professionals on ways to help their smokers quit.

Prof. Carole Clair

Dr Clair is the **President Elect of the Society for Research on Nicotine and Tobacco Europe (SRNT-E)**.
Graduate physician from the University of Lausanne (2002), FMH specialist in general internal medicine (2007), PhD thesis (MD) on the link between smoking and diabetes (2008).
After clinical training, she completed a post-doctorate (2009-2011) at the Tobacco Research and Treatment Centre of the Massachusetts General Hospital (Boston), training in clinical epidemiology (Harvard School of Public Health - Boston). Master of Science (2012).
In Switzerland, she obtained a FNS Ambizione Grant (2015) to continue her research (smoking cessation in people with diabetes). She obtained a Privat Docent and MER-clinique title (2016), appointed as assistant professor at PMU (management of the R&D centre).

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Appendices: Scientific Board

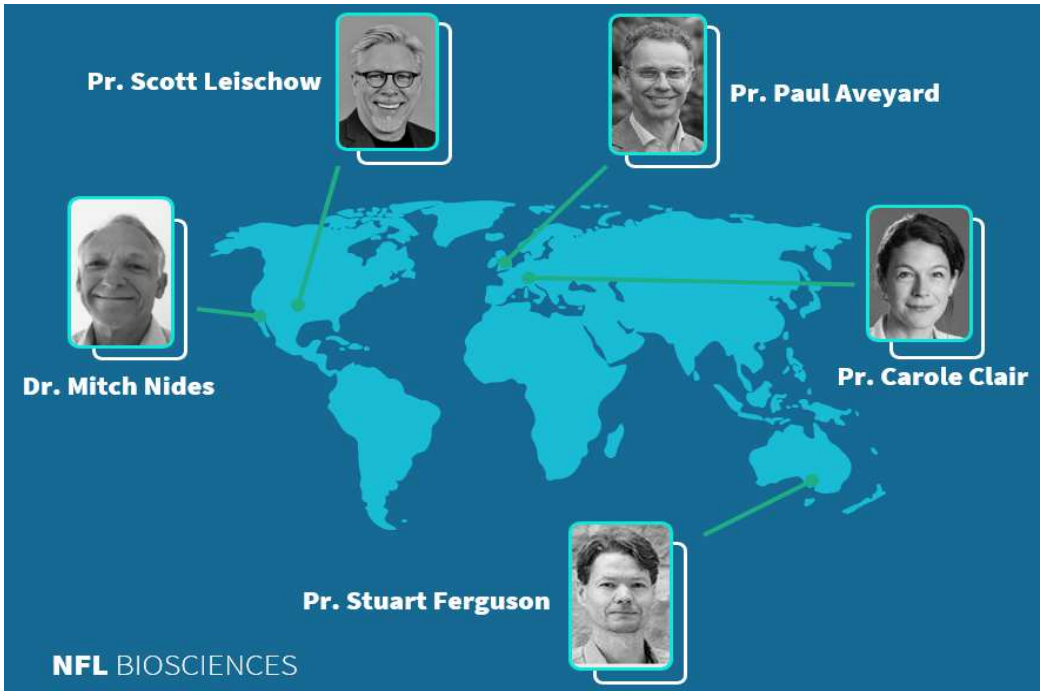
Prof. Stuart Ferguson

Associate Professor Ferguson is a health psychologist at the School of Medicine in the College of Health and Medicine at the University of Tasmania in Australia. He is primarily interested in health-related behaviour change (e.g. quitting smoking, weight management etc).
His primary research interest is exploring the process and drivers of drug relapse, particular among cigarette smokers. He is also interested in treatment efficacy and factors that impact on the likelihood of treatment use, and treatment compliance, as part of quit attempts. To explore these topics Associate Professor Ferguson uses a broad range of research methodologies, from laboratory-based techniques through to sophisticated, near real-time field monitoring.

Prof. Paul Aveyard

Independent Clinical Reviewer

Professor of behavioural medicine (Oxford), member of Wolfson College and Collaboration for Leadership in Applied Health Research and Care (Oxford).
His work focuses on helping people change their behaviour (to prevent or treat serious disease), resting in particular on stopping or reducing tobacco consumption.
He was president of the UK Society of Behavioural Medicine, trustee of the Association for the Study of Obesity and member of the Society for Research on Nicotine and Tobacco.
Editor for the journals: Addiction and Cochrane Tobacco Addiction Group.
Member of NICE and advised the Department of Health on smoking and obesity.



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TARGET PRICE AND RECOMMENDATION

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- BUY: Upside potential of more than 10% (the minimum upside required may be revised upward depending on the company’s risk profile)
- NEUTRAL: Between -10% downside and +10% upside potential (the maximum required may be revised upward depending on the company’s risk profile)
- SELL: Downside potential of more than 10%
- TENDER or DO NOT TENDER: Recommendations used when a public offer has been made for the issuer (takeover bid, public exchange offer, squeeze-out, etc.)
- SUBSCRIBE or DO NOT SUBSCRIBE: Recommendations used when a company is raising capital
- UNDER REVIEW: Temporary recommendation used when an exceptional event that has a substantial impact on the company’s results or our target price makes it impossible to assign a BUY, NEUTRAL or SELL rating to a stock

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12-MONTH HISTORY OF OPINION

Le tableau ci-dessous reflète l'historique des changements de recommandation et d'objectif de cours réalisés par le bureau d'analyse financière d'Invest Securities au cours des 12 derniers mois.

Société couverte	Analyste principal	Date de publication	Opinion	Objectif de Cours	Potentiel vs OC

DETECTION OF CONFLICTS OF INTEREST

	NFL Biosciences
Invest Securities a été chef de file ou co-chef de file dans une offre publique concernant les instruments financiers de cet émetteur durant les douze derniers mois.	Oui
Invest Securities a signé un contrat de liquidité avec l'émetteur.	Oui
Invest Securities et l'émetteur ont signé une convention de prestation de service d'analyse.	Oui
Invest Securities et l'émetteur ont signé une convention de Listing sponsor.	Non
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Le présent document a été communiqué à l'émetteur préalablement à sa publication. Cette relecture n'a pas conduit l'analyste à modifier son objectif de cours et sa recommandation boursière.	Non
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