

NIC002 (formerly CYT002-NicQb)

a Novel Vaccine for Nicotine Addiction

(in collaboration with Novartis)

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About Nicotine Addiction

Smoking is a global pandemic of enormous proportions. The World Health Organization estimates that there are 1.3 billion smokers worldwide. With nearly 5 million tobacco-related deaths per year, tobacco use is the leading cause of preventable death in the world ¹. Death is mainly caused by lung cancer, coronary heart disease, chronic obstructive pulmonary disease and stroke. Despite widespread knowledge of tobacco's dangerous effects, smoking continues to pose a serious public health threat since the number of smokers, and especially teenage smokers, is increasing steadily.

Nicotine is an alkaloid derived from tobacco leaves and the principal addictive component of tobacco. It is thus the major reason for cigarette smoking and consumption of other tobacco-containing products. Like other drugs of abuse, nicotine exerts its addictive properties in the brain, where it stimulates nerve cells in specific regions.

Stimulation of these nerve cells leads to the release of messenger molecules (neurotransmitters), which give rise to an almost immediate reward and a feeling of pleasure. This is critical to the dependence-producing properties of nicotine. The reinforcing effect of nicotine itself, combined with conditional reinforcement by ritual and sensory cues, maintain nicotine addiction and cause a high relapse rate following attempts to quit.

Despite recent advances in behavioral and pharmacological treatment, the vast majority of cigarette smokers who try to give up smoking ultimately fail. Almost 75% of smokers report that they want to stop smoking but less than 5% of those who make a quitting attempt are successful ².

Commonly used medications include nicotine replacement devices (nicotine gum, inhaler, spray, sublingual tablets and patches) and antidepressants, which approximately double long-term abstinence rates compared to placebo (i.e. dummy drug) ³. Recently, a new chemical compound was approved for smoking cessation that is centrally acting in the brain and is reported in clinical trials to exceed commonly achieved abstinence rates ⁴.

The therapeutic vaccine NIC002 (formerly called CYT002-NicQb) represents a unique and novel approach to help people overcome their addiction to nicotine and stop smoking permanently ⁵.



Clinical Development of NIC002

Phase I study⁶

- Clinical development of NIC002 began in April 2003.
- A randomized and placebo-controlled phase I study evaluated safety, tolerability and immunogenicity of NIC002 in 40 healthy, non-smoking volunteers.
- Different doses and formulations were compared in four study groups with 10 volunteers in each group.
- The study showed that NIC002 was safe, well tolerated, and highly immunogenic.
- All participants who received NIC002 displayed high levels of nicotine-specific antibodies, which corresponds to an immunological response rate of 100%. The participants who received placebo showed no nicotine-specific antibody response.
- The nicotine-specific antibody responses were long-lasting but declined over time.
- Adverse events reported included mostly local reactions at the injection site and flu-like symptoms such as “feeling cold”, muscle ache and occasionally increased body temperature in up to half of the study participants. Those symptoms usually disappeared within 24 hours after injection.

NIC002 Mode of Action

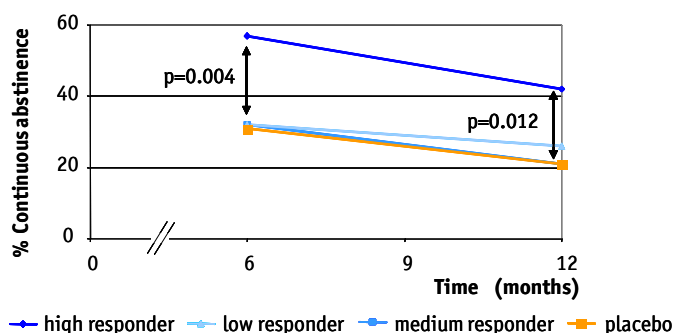
Upon inhalation of cigarette smoke, nicotine passes into the bloodstream and within seconds crosses the blood-brain-barrier to enter the brain, where it exerts its addictive effects. In clinical trials, vaccination with NIC002 has been shown to induce nicotine-specific antibodies that bind to nicotine in the blood. The resulting complex of nicotine attached to an antibody is too big to pass through the blood-brain-barrier, so the uptake of nicotine into the brain and the subsequent stimulation of nicotine-sensitive nerve cells should be minimized. NIC002 aims to interrupt the reward-inducing and addiction-driving cycle of nicotine, and thus to help people give up smoking permanently by preventing relapses.

One of the challenges of designing a vaccine for nicotine addiction is that as a small molecule nicotine is not immunogenic *per se*. NIC002 uses Cytos Biotechnology's Immunodrug™ technology to directionally place several hundred nicotine molecules by chemical crosslinking onto the surface of a repetitively structured carrier particle called a "virus-like particle". In this way, the nicotine molecules are displayed in a highly organized array to the immune system so that a strong antibody response is induced.

Phase II study⁷

- The phase II study included 341 smokers and was randomized, double-blind and placebo-controlled (with 2/3 of the participants on active compound and 1/3 on placebo).
- The multi-centre study evaluated safety, tolerability and efficacy of NIC002.
- Study participants received five injections of the vaccine or placebo at monthly intervals. In addition, all participants received regular counselling at each visit for three months.
- Efficacy of the vaccine was assessed by continuous abstinence from smoking during weeks 8 to 24 and weeks 8 to 52 after the start of treatment. Continuous abstinence was determined by self-reporting of the study participants and confirmed by independent biochemical validation.
- First results of the study six months after the start of treatment were published in May 2005, and 12-month follow-up results in November 2005.
- The study showed that NIC002 was safe and generally well tolerated. Side effects were reported by up to 70% of study participants and commonly included local injection site reactions and flu-like symptoms, which usually resolved within 24 hours after injection. In the follow-up period between months six and 12, no vaccine-related side effects were reported.
- All smokers who received the vaccine displayed an anti-nicotine antibody response, which corresponds to an immunological response rate of 100%. Smokers who received placebo showed no measurable anti-nicotine antibodies.
- An intent-to-treat analysis of the entire study population at the end of the regular study period of six months, and again after the 12-month follow-up period, did not achieve statistical significance. Therefore, a sub-group analysis was performed based on antibody levels and this analysis established a clinical proof-of-concept for this novel vaccine candidate.

- For the sub-group analysis, all smokers were included from whom complete antibody measurements were available at month six and who refrained from using nicotine replacement products # (n = 239). The vaccine-treated smokers were divided into three equal groups of increasing antibody levels ("low", "medium", and "high responder group"), and efficacy analysis was performed on each group at six and 12 months after the start of treatment. Participants who could not be recruited for their follow-up visits up to month 12 were counted as smokers in the 12-month analysis.
- The following graph and table show the continuous abstinence values at six and 12 months after start of treatment.

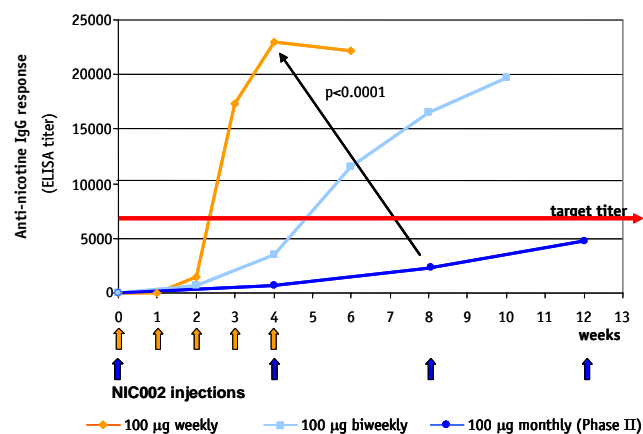


	Antibody levels	Cont. abstinence from smoking*	
		Month 6	Month 12
NIC002	High responder	57% (30/53)	42% (22/53)
	Medium responder	32% (17/53)	21% (11/53)
	Low responder	32% (17/53)	26% (14/53)
Placebo	- - -	31% (25/80)	21% (17/80)

- The data showed with statistical significance that NIC002 promoted and sustained continuous abstinence from smoking in participants who achieved high antibody levels upon vaccination. After 12 months, 42% of those in the high responder group remained continuously abstinent compared to 21% in the placebo group.
- After six months, overall cigarette consumption in the high responder group was less than half of that seen in the placebo group (p=0.004). Moreover, the average cigarette consumption by those people who did not achieve continuous abstinence was also lower in the high responder group than in the placebo group (p=0.16).
- The phase II study results demonstrated that NIC002 dosed at 100 µg helped smokers to overcome their addiction to nicotine when high antibody levels were induced upon vaccination.
- As a next step, dose, regimen and formulation optimization studies were performed with the goals of increasing antibody levels by at least a factor of three; reducing the incidence of fever and flu-like symptoms; and developing a convenient treatment regimen.

Dose, regimen and formulation optimization for NIC002

- A study with healthy volunteers revealed that a higher dose of NIC002 (i.e. 300 µg) induced a mean antibody level four times higher than the 100 µg dose used in the phase II study.
- Another study investigated a new treatment regimen. It tested five weekly and five bi-weekly injections of NIC002 and compared the induced antibody levels to the monthly dose regimen used in the phase II study. As shown in the graph below, the mean antibody levels obtained by the weekly regimen (orange line) were 10 times higher than those obtained by the monthly regimen in the phase II study (dark blue line).



- Also a new formulation of NIC002 was tested in order to optimize the tolerability of the vaccine. With this new formulation, the incidence of fever was reduced from nearly 40% as reported in the phase II study to almost zero. Also the incidence of flu-like symptoms was reduced from up to 70% as reported in the phase II study to about 10%.
- This successful optimization work will be very valuable for late-stage development of NIC002.

use of nicotine replacement products is believed to have a different effect on the two treatment groups (NIC002 and placebo) and was therefore defined as a protocol violation.

* in parenthesis: number of continuously abstinent subjects / total number of subjects in group.



Collaboration between Cytos Biotechnology and Novartis

In April 2007, Cytos Biotechnology entered into an exclusive global commercial license agreement with Novartis to develop, manufacture and commercialize NIC002. Under the terms of the agreement, Novartis is granted world-wide exclusive rights for NIC002 and is responsible for late-stage clinical development, manufacturing, and commercialization of the vaccine. In return, Cytos Biotechnology is eligible to receive up to CHF 600 million in upfront and potential development, regulatory approval and sales milestone payments based on the successful development and commercialization of NIC002. In addition, Cytos Biotechnology will receive royalty payments on net sales of products. Licensing this phase II product candidate to Novartis, a top-tier healthcare company with strong in-house vaccines' expertise, maximizes the opportunity to build NIC002 as a first-in-class product to treat nicotine addiction.

NIC002 at a Glance

Drug candidate	NIC002, a therapeutic vaccine based on Cytos Biotechnology's Immunodrug™ technology.
Drug components	Nicotine chemically coupled to the virus-like particle Qb.
Indication	Treatment of nicotine addiction. The vaccine aims to prevent relapses after quitting attempts.
Mode of action §	Neutralize nicotine by nicotine-specific antibodies and reduce entry of nicotine into the brain.
Development stage	Phase I study with 40 healthy volunteers completed; phase II study with 341 smokers completed.
Safety	The phase I and phase II data indicate that NIC002 is safe and generally well tolerated.
Immunogenicity	The phase I and phase II data demonstrate an immunological response rate of 100%.
Efficacy	NIC002 achieved clinical proof-of-concept. The phase II study results demonstrate that NIC002 promotes and sustains abstinence from smoking in smokers who achieved high antibody levels.

§ note that the described mode of action has been analyzed in animals

References

1. World Health Organization; Facts about smoking and health, Fact Sheet May 30, 2006.
2. Centers for Disease Control and Prevention USA; Surgeon's General Report 2004.
3. New England Journal of Medicine; Treatment of tobacco use and dependence; 2002, 346:506.
4. Journal of the American Medical Association; Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial; 2006, 296:56.
5. Current Opinion in Molecular Therapeutics; Therapeutic vaccines for nicotine dependence; 2006, 8:11.
6. European Journal of Immunology; A therapeutic vaccine for nicotine dependence: preclinical efficacy, and phase I safety and immunogenicity; 2005, 35:2031.
7. Proceedings of the American Society for Clinical Oncology; A therapeutic vaccine for nicotine dependence: results of a phase I and randomized phase II study; 2005, 24:Abstract 1008.

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