

CYT002-NicQb

a Novel Vaccine for Nicotine Addiction

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About Nicotine Addiction

The World Health Organization estimates that there are 1.3 billion smokers today. With 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 lung disease and stroke. Despite widespread knowledge of tobacco's dangerous health effects, smoking continues to pose a serious public health threat since the number of smokers, and especially of teenage smokers, is increasing rapidly.

Nicotine, an alkaloid derived from tobacco leaves, has been shown to be 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 neurons in specific regions of the brain. Stimulation of these neurons 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.

Despite recent advances in behavioral and pharmacological treatments, the vast majority of cigarette smokers who try to quit ultimately fail. Most commonly used medications are nicotine replacement therapy (nicotine containing gum, inhaler, spray, sublingual tablets and patches) and antidepressants. However, clinical trials have shown that long-term abstinence rates (6 to 12 months) using these medications are only 6-10% above the placebo control (2).

Clearly novel approaches are needed for the treatment and prevention of nicotine addiction. Cytos Biotechnology's Immunodrug™ candidate CYT002-NicQb is a therapeutic vaccine aimed at providing an effective and safe treatment option to people willing to quit smoking.



Proposed Mode of Action CYT002-NicQb

Vaccination with the Immunodrug™ candidate CYT002-NicQb induces the production of nicotine-specific antibodies that bind nicotine in the blood. As the nicotine-antibody complex is too big to pass the blood-brain-barrier, nicotine uptake into the brain and the subsequent stimulation of nicotine-sensitive neurons in the brain should be significantly reduced or even prevented. This means that nicotine cannot exert its addiction-driving and satisfaction-inducing properties. The Immunodrug™ candidate CYT002-NicQb aims to prevent relapses after quitting and should help people to break their addiction to nicotine in the long-term.

Preclinical Data CYT002-NicQb

- Vaccination with CYT002-NicQb induced high nicotine-specific IgG antibody titers in mice, which declined over time.
- No antibody cross-reactivity was measured with acetylcholine, an important endogenous neurotransmitter that targets the same receptors in the brain as nicotine does.
- In preclinical safety testing, CYT002-NicQb was safe and well tolerated.
- CYT002-NicQb achieved efficacy in an animal model (mouse). Up to 60% reduction of nicotine uptake into the brain was achieved by vaccination with CYT002-NicQb.

Clinical Development CYT002-NicQb

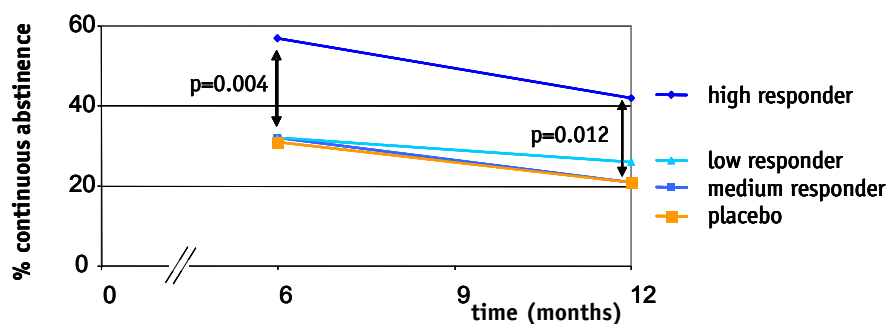
Phase I study

- The randomized and placebo-controlled phase I study, which was initiated on April 23, 2003, evaluated safety, tolerability and immunogenicity of CYT002-NicQb in 40 healthy, non-smoking volunteers.
- Different doses and formulations of CYT002-NicQb were compared in this study.
- CYT002-NicQb was safe, well tolerated, and highly immunogenic. Side effects included mostly local reactions at the injection site such as pain, reddening and swelling. Up to half of the study participants reported flu-like symptoms including “feeling cold”, muscle ache and occasionally increased body temperature, which usually disappeared within 24 hours after injection.
- All the participants who received CYT002-NicQb produced high levels of nicotine-specific antibodies, which corresponds to an immunological response rate of 100%. The participants who received placebo had no measurable nicotine-specific antibodies.
- The nicotine-specific antibody titers were long-lasting but declined over time.

Phase II study

- The phase II study start was announced on January 14, 2004.
- The study was the largest ever performed with a vaccine to treat nicotine addiction and included 341 smokers. It was conducted according to a randomized, double-blind and placebo-controlled design (2/3 of the smokers on active compound and 1/3 of the smokers on placebo).
- The study was conducted in three clinical centers in Switzerland and evaluated safety, tolerability and efficacy of CYT002-NicQb dosed at 100 µg. First results of the study obtained after 6 months have been published in May 2005; the 12-months follow-up results in November 2005.
- Efficacy of the vaccine was assessed by continuous abstinence from smoking during weeks 8 to 24 and weeks 8 to 52 after start of treatment. Continuous abstinence was determined by self-reporting of the study participants and confirmed by independent biochemical validation.
- The vaccine was safe and generally well tolerated. Side effects were reported by up to 70% of the 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 6 and 12, no vaccine-related side effects were reported.
- All smokers who received the vaccine mounted an anti-nicotine antibody response, which corresponds to an immunological response rate of 100%. All smokers who received placebo had no measurable anti-nicotine antibodies in their blood.
- An intent-to-treat analysis of the entire study population at the end of the regular study period of 6 months, as well as the one after the follow-up period 12 months after start of treatment, has not achieved statistical significance. A sub-group analysis based on the induced antibody levels was therefore carried out.
- Into this sub-group analysis all smokers were included from whom complete antibody measurements were available at month 6 and who refrained from using nicotine replacement products (n= 239) (NRT use was considered a major protocol violation). 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 6 and 12 months after 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's analysis.

- The following graph and table provide the values for the continuous abstinence from smoking of the analysis at 6 and 12 months after start of treatment.



Antibody levels		Continuous abstinence from smoking*	
		Month 6	Month 12
CYT002-NicQb	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)

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

- The data show with statistical significance that CYT002-NicQb dosed at 100 µg promoted and sustained continuous abstinence from smoking from week 8 to 52 after start of treatment in participants who achieved high antibody levels upon vaccination ("high responder group") compared to those participants who received a placebo (p=0.012). The therapeutic effect achieved with CYT002-NicQb in the "high responder group" was maintained over 12 months and 42% of the subjects remained continuously abstinent over that long period of time.
- After 6 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).

Clinical dose optimization study

The goal of this clinical dose optimization study was to identify a vaccine dose that would induce antibody levels sufficiently high for efficacy in a majority of vaccinated individuals.

- The first part of this study, which was initiated in October 2005, investigated the safety, tolerability and immunogenicity of CYT002-NicQb dosed at 300 µg in 10 healthy volunteers.
- The 300 µg dose of CYT002-NicQb yielded a 4.2-fold increase in the geometric mean antibody level compared to the one obtained with the 100 µg dose in the phase II study (p=0.0011) (see Figure 1).

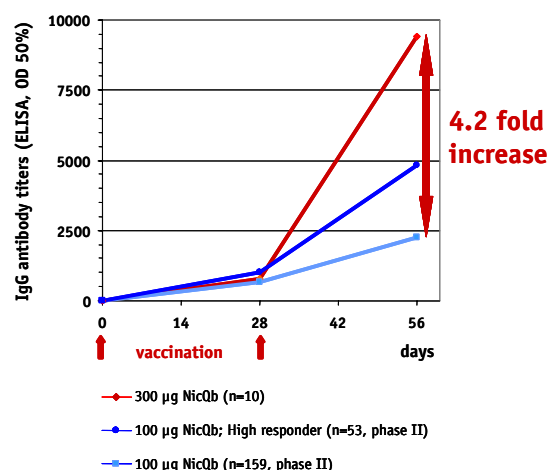


Figure 1: Nicotine-specific IgG antibody responses in humans after two injections with CYT002-NicQb (300 µg each; red curve). The obtained antibody levels (shown are geometric mean antibody levels) are compared to the ones obtained in the previous phase II study with CYT002-NicQb dosed at 100 µg (blue curves).

- A calculation based on the phase II data predicts that a 4.2-fold higher antibody level would have resulted in 87% of the vaccine-treated smokers being in the "high responder group".
- CYT002-NicQb dosed at 300 µg was safe and generally well tolerated with side effects similar to those observed in the phase II study (see above).



Market Potential

Although nearly 75% of smokers in the U.S. report that they want to quit smoking, less than 5% of those who try quitting are able to stay tobacco-free for 3 to 12 months (3). Products in common use include nicotine replacement products and antidepressants, which all have not proved very effective (2). In May 2006, a new chemical compound (varenicline) received market approval for smoking cessation from the U.S. Food and Drug Administration (FDA). Additionally, there are other medications for smoking cessation from several companies currently in clinical development.

There remains, however, a high medical need for new therapies to treat nicotine addiction. It is expected that new and more efficacious approaches will drive the smoking cessation market to nearly US\$ 1.5 billion in 2007 (4). In addition, increasing societal and economical constraints that smokers will face in future (smoke-free public places, expensive health insurances etc.) are foreseen to further drive this market.

CYT002-NicQb at a Glance

Drug candidate	Immunodrug™ CYT002-NicQb.
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.
Proposed mode of action*	Neutralize nicotine by nicotine-specific antibodies and reduce entry of nicotine into the brain.
Development stage	One phase I study with 40 healthy volunteers completed; one phase II study with 341 smokers completed.
Safety	The phase I and phase II data indicate that CYT002-NicQb is safe and generally well tolerated.
Immunogenicity	The phase I and phase II data demonstrate an immunological response rate of 100%.
Efficacy	CYT002-NicQb achieved proof-of-efficacy. The phase II study results demonstrated that CYT002-NicQb is effective in promoting and sustaining 12 months continuous abstinence from smoking in people who achieved high antibody levels ("high responder group").
Patents	The issued U.S. Patent No. 6,932,971 relates to and covers CYT002-NicQb for the treatment of nicotine addiction.
Publications	European Journal of Immunology, 2005, 35:2031 and Current Opinion in Molecular Therapeutics, 2006, 8:11.

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

References

1. World Health Organization; The Tobacco Atlas 2002.
2. The National Institute for Clinical Excellence, UK; A rapid and systematic review of the clinical and cost effectiveness of bupropion SR and nicotine replacement therapy for smoking cessation. February 2002.
3. Surgeon's General Report, USA, 2004.
4. Decision Resources, 2001.

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