

Tobacco use is the single leading preventable cause of death in the United States and is responsible for more than 440,000 deaths each year.¹ According to the U.S. Centers for Disease Control and Prevention (CDC), approximately 45.8 million adults² and 3.1 million high school students³ in the U.S. smoke, triggering an estimated \$75.5 billion in excess medical costs and another \$81.9 billion in mortality-related productivity losses each year.⁴ The World Health Organization (WHO) estimates that there are 1.3 billion smokers worldwide and nearly 5 million tobacco-related deaths each year.⁵ Despite widespread knowledge of tobacco's dangerous health effects, smoking continues to pose a serious public health threat, as many smokers are unable to quit, due in large part to tobacco's addictive properties. According to the CDC, an estimated 70 percent of smokers want to quit, but less than five percent of those who try to quit abstain from smoking for 3 to 12 months.⁶

NicVAX[™] (Nicotine Conjugate Vaccine) is a novel and proprietary investigational vaccine being developed by Nabi Biopharmaceuticals to prevent and treat nicotine addiction and aid in smoking cessation.

WHY IS TOBACCO SO ADDICTIVE?

Nicotine is responsible for the psychoactive and addictive effects of smoking. Smoking a cigarette immediately releases nicotine into the blood, where it passes through the blood/brain barrier and enters the brain. Once in the brain, nicotine stimulates the release of neurotransmitters (such as dopamine) that generate positive sensations, such as pleasure, relaxation and appetite suppression. It is this release of neurotransmitters, especially dopamine that is responsible for tobacco users' addiction to nicotine.⁷

QUICK FACTS ON TOBACCO USE AND ADDICTION

- According to the CDC, the 440,000 deaths in the U.S. attributable to cigarette smoking are equivalent to one-fifth of all U.S. deaths. More deaths are caused each year by tobacco use than by alcohol use, illegal drug use, suicides, motor vehicle accidents, murders and HIV combined.⁸
- Among nonsmokers in the U.S., approximately 3,000 lung cancer deaths and 35,000 coronary heart disease deaths occur each year as a result of exposure to secondhand smoke.⁹
- According to the 2004 Surgeon General's Report, nearly three quarters of smokers express a desire to quit and each year approximately 15 million smokers quit for at least a day, but fewer than 5 percent are able to stay tobacco-free for 3 to 12 months!¹
- Smoking harms nearly every organ of the body, causing many diseases and reducing the health of smokers in general!¹
- Quitting smoking has immediate as well as long-term benefits, reducing risk for diseases caused by smoking and improving health in general!¹
- WHO estimates that half of the smokers in the world today, approximately 650 million people, will die from tobacco-related disease.⁵

WHAT IS NicVAX? HOW DOES IT WORK?

NicVAX[®] (Nicotine Conjugate Vaccine) is a nicotine derivative bound chemically to a specially selected carrier protein using Nabi Biopharmaceuticals' patented vaccine technology.

NicVAX is designed to cause the immune system to produce antibodies that bind to nicotine and prevent it from entering the brain. It is believed that these nicotine antibodies will act like a "sponge" soaking up nicotine as it circulates in the bloodstream and preventing it from reaching the brain. The positive stimulus in the brain that is normally caused by nicotine would then no longer be present. Preclinical studies showed that vaccination with NicVAX can prevent nicotine from reaching the brain and block the effects of nicotine, including effects that can lead to addiction or can reinforce and maintain addiction.

WHO COULD BENEFIT FROM NicVAX?

NicVAX is being developed to help the millions of patients in the U.S. and potentially billions worldwide who are addicted to smoking tobacco products, or are at risk of becoming addicted.

CLINICAL DEVELOPMENT

The Phase IIb study is a double-blinded, placebo-controlled and dose-ranging study comprised of 301 patients and is designed to establish proof of concept and the optimal dose for the Phase III program. This study was designed in collaboration with the U.S. Food and Drug Administration and other global regulatory agencies and incorporates the most current clinical trial standards and prevailing protocol design for smoking cessation studies.

The trial's primary endpoint is the rate of carbon monoxide (CO)-confirmed, continuous abstinence from smoking during weeks 19-26 after first vaccination. Full evaluation of abstinence at the six month primary endpoint will include reported cigarette consumption, chemical markers of



nicotine in the bloodstream, and behavioral assessment. Secondary endpoints include the abstinence rate at 12 months, total cigarette consumption, antibody levels, safety and nicotine dependency. The efficacy rates in this study incorporate the benefits of other elements of standard of care in smoking cessation programs, including counseling and behavior modification.

On May 2, 2007, we announced that a statistically significant number of patients with a high anti-nicotine antibody response met the primary endpoint of eight weeks of continuous abstinence between weeks 19-26 in its ongoing Phase IIb proof of concept study for NicVAX® (Nicotine Conjugate Vaccine), the company's innovative and proprietary investigational vaccine being developed to treat nicotine addiction and prevent smoking relapse.

Data from the drug-treated population was divided into those who quit and those who continued to smoke and then analyzed for antibody levels throughout the trial. In an analysis of completers, patients who showed continuous abstinence between weeks 19-26 had significantly higher antibody levels than those who did not quit ($p=0.03$ and $p=0.02$ at the beginning and end of the eight-week assessment period, respectively). In an analysis of the intent to treat population, patients who quit smoking had a median total antibody level that was significantly greater than patients who continued smoking ($p=0.002$).

To further examine the relationship between antibody and quit rate, the top 30% of antibody responders (61 of the total 201 patients receiving drug) were examined in detail. A statistically significant number of these patients, (24.6%; $p=0.04$) showed continuous abstinence between weeks 19-26 compared to only 13.0% for the 100 patients receiving placebo. The quit rate of those patients who did not have a high antibody response was not statistically significant from placebo. The trial enrolled a total of 301 heavy smokers who smoked an average of 24 cigarettes per day prior to enrollment. In no case did any of these patients smoke less than 15 cigarettes per day prior to enrollment.

Current drugs for smoking cessation were approved using a four-week continuous quit rate at the end of the treatment period. NicVAX high antibody responder patients showed a high rate of continuous abstinence (31.1%; $p=0.006$) when assessed for an analogous four-week period between 23-26 weeks after their first vaccination.

This double-blind, placebo-controlled and dose-ranging study tested two antigen doses, 200 mcg and 400 mcg per injection, and two

different regimens of administration. The efficacy data trends were both vaccine dose-proportional and antibody level-dependent. In the responder group, antibody levels increased with time and number of doses. Individual patients were tracked on a continual basis and were seen to be more likely to abstain from smoking as their antibody levels rose after vaccination; thus definitively providing proof of concept.

NicVAX was well-tolerated throughout the six months of dosing to date, and showed a favorable adverse events profile with no difference between placebo and each dose group. The most common local reactogenicity events were minor ache and tenderness. Systemic reactogenicity events – such as general discomfort, headache and muscle ache – were mild to moderate in severity, resolved quickly and did not increase with number of injections. Fever and nausea were seen in less than 10% of all patients.

The Phase IIb trial is continuing after all patients received a booster at six months. The study will assess a series of secondary endpoints at 12 months, including abstinence rate, total cigarette consumption, antibody concentration, safety and the degree of nicotine dependency.

In March 2006, NicVAX received Fast Track Designation from the U.S. Food and Drug Administration (FDA).

In September 2005, the company was awarded a \$4.1 million grant by the U.S. National Institute on Drug Abuse (NIDA) for partial funding of the NicVAX program. The grant will enable the company to advance the NicVAX program into a Phase III clinical trial.

In September 2004, Nabi Biopharmaceuticals reported positive results from its U.S. Phase II clinical trial. In January 2006, a European Phase II dose-ranging clinical trial was completed and showed NicVAX was well tolerated. The vaccine for this study was manufactured at commercial scale in an optimized formulation at the company's Boca, Florida, vaccine manufacturing facility.

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5 World Health Organization. Tobacco Free Initiative: Why is tobacco a public health priority?. Available from <http://www.who.int/tobacco/about/en/> Accessed on July 12, 2004.

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7 U.S. Department of Health and Human Services. National Institute on Drug Abuse Research Report Series – Nicotine Addiction. National Institutes of Health, printed July 1998, reprinted August 2001. Last updated November 25, 2002. Available from <http://www.nida.nih.gov/pdf/nicotinerr.pdf> Accessed on July 12, 2004.

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