Anti-smoking vaccines: expect a long, hard fight between NABI and Cytos

LONDON, UK----06 May 2008----ExpertREACT. Recently US-based biopharmaceutical company NABI announced that the European patent (EPO) office upheld a patent that covers its NicVAX anti-smoking vaccine. Challenges were made by a rival company Cytos which is also developing a vaccine with the same mechanism of action. Because Cytos is already partnered with pharmaceutical giant Novartis and the commercial rewards are high, NABI will need a strong partner to maintain its position.

Tobacco smoking is a major cause of a variety of health disorders mainly of the cardiovascular and pulmonary systems. For example, diseases such as chronic bronchitis, emphysema/COPD, stroke and lung cancer all have a strong connection with chronic tobacco use. The US Department of Health and Human Services (US DHHS) states that tobacco smoking is the single leading cause of death in the United States killing an estimated 430,000 Americans each year. On a global level, tobacco smoking kills one person every six seconds and causes one in ten deaths among adults. This equates to more than 5 million people per year. The World Health Organisation (WHO) predicts that unless urgent action is taken by 2030 the annual death toll due to tobacco smoking will reach more than eight million people (1).

Tobacco contains the highly addictive alkaloid drug, nicotine which is responsible for smoking's psychoactive and addictive effects. 10-15 min after smoking a cigarette, peak levels of nicotine (25-50 ng/ml) are reached in the blood. Nicotine crosses the blood/brain barrier where evidence suggests it binds to cholinergic receptors which then serve to activate dopaminergic reward pathways promoting a sense of pleasure. Withdrawal of nicotine during smoking cessation or "quitting" causes unpleasant symptoms including irritability, craving, cognitive and attentional deficits, sleep disturbances, and increased appetite. These symptoms make smoking cessation difficult to maintain. For example, a study by the US DHHS estimates that only about 6 percent of people who try to quit are successful for more than a month (2).

Many therapies have been developed to address nicotine addiction and mainly comprise of three drug classes. The major type is nicotine replacement therapy (NRT) with products normally available OTC or "over the counter". NRT aims to replace the amount of nicotine the smoker usually gains from smoking and involves transdermal patches, sprays or gums. Key brands include Nicorette, Nicoderm (GSK) and Nicotinell (Novartis). Despite its widespread availability, NRT has several drawbacks in that its nicotine penetration has a much slower onset and so does not provide the same reward gained from smoking. NRT treatments are inconvenient and can cause nausea, sleep disturbance and increased nervousness.

Other smoking cessation drugs include GSK's antidepressant Zyban (bupropion), the oral noradrenaline & dopamine inhibitor and the recently launched Chantix (varenicline), the partial nicotinic receptor agonist marketed by Pfizer. These drugs seek to alleviate some of the symptoms associated with nicotine withdrawal e.g. craving either by blocking nicotine at its receptor or replacing it. For example, clinical data shows that Zyban (300 mg/day) has been shown to double rates of cessation (four week abstinence) compared to placebo with an increased cessation rate when used in conjunction with NRT (3). In six clinical studies Chantix has also been shown to increase abstinence rates over placebo at weeks 9-12 and weeks 9-52 (4).

Despite their positive effect on smoking cessation, Zyban and Chantix can be associated with central-acting side effects such as nausea, sleep disturbance and changes in behavior. For example, in January 2008, as a precautionary measure Pfizer in concert with the FDA instigated a label change to Chantix stating that current users (now estimated 5 million) should be observed for "serious neuropsychiatric symptoms, including changes in behavior, agitation, depressed mood, suicidal ideation and suicidal behavior."

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Many physicians believe that current smoking cessation treatments fall short on long-term efficacy. Because treatments are largely ineffective (~20% quit rates) patients, who often have multiple attempts, fail and then withdraw completely. It is also estimated that of patients willing to quit (20-40% total smokers), two-thirds do not seek treatment because of their low expectations of a successful outcome.

In order to address the weaknesses of current approaches, new therapies with different mechanisms of action are being pursued. One main area of research is anti-smoking vaccines which are designed to elicit the production of anti-nicotine antibodies. Mechanistically, these antibodies bind nicotine in serum, lower its unbound concentration and reduce nicotine distribution to the brain so blocking the addictive cycle (5). Other perceived advantages could be lower CNS side effects, the avoidance of daily administration and longer-term abstinence.

The two most advanced anti-nicotine vaccines within clinical development are NABI's NicVax (Phase II) and Cytos (Nic002) (Phase II) which is partnered with Novartis Pharma. Both vaccines are different in that they use distinct methods to conjugate the low molecular weight nicotine hapten to an immunogenic carrier. The NABI vaccine is based on the recombinant *Pseudomonas aeruginosa* exo-protein A (rEPA) previously used in the company's StaphVAX program. The Cytos "immunodrug" program is based on Virus-like particle technology (VLP).

Clinical data with both vaccines is encouraging; hence the heightened antagonism between each company. For example, 40% of smokers (n=159) vaccinated with Nic002 showed continuous abstinence from smoking between weeks 8-24 after study start. In high antibody responders the result was more pronounced at ~57% (6). In a Phase IIb study NicVAX met the primary endpoint of eight weeks continuous abstinence from smoking between weeks 19-26. The benefit was again most apparent in high-antibody responders. Importantly, further data analyses of both vaccine studies show marked continuous long-term abstinence over placebo at 12 months. As further studies progress it is highly likely the vaccines will be superior to current small molecule approaches.

Novartis Pharma's willingness to pay an upfront payment of $30M with total milestone payments of $500M based on Nic002 Phase II data signals a vote of confidence in the vaccine's mechanism of action and commercial potential. It is no surprise that the Swiss giant is eager to protect its investment in Cytos against a potential "me-too" product from NABI. Although in financial terms NABI has recovered some ground by selling its Biologics division to BioTEST AG, the company needs a strong committed partner to protect, further develop and market NicVAX. Both companies will face high sales and marketing costs in commercializing each vaccine which may only be useful in a subset of smokers. However, with 1.3 billion potential customers, many of which reside in emerging economies, it is clear that the opportunity is worth fighting for.

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