

StaphVAX® (*Staphylococcus aureus* Polysaccharide Conjugate Vaccine) is an investigational polysaccharide conjugate vaccine that presents a novel approach to the prevention of *S. aureus* infections. These common community and hospital-acquired infections are among the most drug-resistant and most deadly. Current therapies to treat these infections include a host of antibiotics whose efficacy is decreasing at an alarming rate due to the rapid emergence of antibiotic-resistant pathogens. It is currently estimated that in intensive care units of U.S. hospitals, up to 55 percent of *S. aureus* infections are resistant to methicillin.<sup>1</sup> In 1996, the first *S. aureus* strains with notably reduced sensitivity to vancomycin, the last line of therapy for *S. aureus* infections, were discovered in Japan.<sup>2</sup> To date, these strains have been isolated in the U.S., Europe and Japan, and have contributed to patient deaths in these regions. In 2002, the first two vancomycin-resistant strains of *S. aureus* were reported in the United States.<sup>3</sup>

StaphVAX is designed to provide immunity against the major forms of *S. aureus* infections. Nabi Biopharmaceuticals is developing StaphVAX for patients who are at high risk of *S. aureus* infections and who are able to respond to a vaccine by producing their own antibodies. StaphVAX is intended to stimulate a patient's immune system to produce antibodies to *S. aureus* that provide active, long-term protection from the bacteria. StaphVAX targets *S. aureus* types 5 and 8, which are responsible for approximately 85 percent of *S. aureus* infections.<sup>4</sup>

#### WHO COULD BENEFIT FROM STAPHVAX?

*Staphylococci* are a group of bacteria that normally colonize in the human nose and skin. They rarely cause systemic infections in otherwise healthy individuals and, therefore, are considered opportunistic pathogens. Normally, mucosal and epidermal barriers (skin) protect against *S. aureus* infections. Interruption of these natural barriers as a result of injuries — such as burns, trauma or surgical procedures (particularly those involving indwelling medical devices) — dramatically increases the risk of infection. Diseases that compromise the immune system (e.g., diabetes, end-stage kidney disease) also increase the risk of infection. As such, *S. aureus* infections are most often associated with hospitalization, and are most typically hospital-acquired.<sup>5</sup> Nabi Biopharmaceuticals is developing StaphVAX for the estimated 12 million patients at risk for developing these infections each year in the U.S.<sup>6</sup> Individuals at greatest risk include:

- Surgical patients, particularly those undergoing lengthy cardiac and orthopedic procedures
- Trauma and burn patients
- Individuals undergoing invasive outpatient procedures
- Patients receiving an implanted medical device or prosthetic
- Newborns whose immune systems are not yet developed
- Individuals in long-term care
- Kidney patients on dialysis
- Type 1 diabetics
- Immunocompromised individuals, such as cancer patients, patients with acquired immune deficiency syndrome (AIDS) and patients receiving immunosuppressive treatment<sup>7,8</sup>

#### RESULTS OF STAPHVAX IN PHASE III CLINICAL TRIALS

In October 2005, Nabi Biopharmaceuticals announced positive results from a consistency lots study, which was a double-blinded study testing the safety and immune response of three commercial scale lots of StaphVAX produced by the company's contract manufacturer.

The data gathered from this study demonstrated that StaphVAX can elicit high levels of Anti-staphylococci antibodies, and that it can be consistently and successfully manufactured. The data also demonstrated that the manufacturing process is both well controlled and reproducible.

StaphVAX is in a confirmatory U.S. Phase III clinical trial for the prevention of *S. aureus* bloodstream infections in end-stage renal (kidney) disease (ESRD) patients. Top-line data from this trial is expected in late October or early November 2005. The company is on schedule to file the U.S. Biologics License Application (BLA) in the fourth quarter of 2005.

In October 2004, StaphVAX was granted Fast Track Designation by the Food and Drug Administration (FDA) for this Phase III study.

The initial Phase III double-blinded, placebo-controlled and randomized clinical trial of StaphVAX in 1,804 hemodialysis patients with ESRD was completed in late 2000. Study participants were evaluated at intervals for up to a year to evaluate vaccine safety and *S. aureus* infection rates. Results showed that a single injection of StaphVAX was safe and showed a statistically significant reduction in the incidence of *S. aureus* bacteremia by almost 60 percent through 10 months post-vaccination. The reduction in bacteremia one year after vaccination was 26 percent. The decrease in effect from 10 to 12 months was associated with declining levels of antibodies. No significant side effects attributable to the vaccine were noted. Results of the trial were published in the *New England Journal of Medicine* in February 2002.<sup>4</sup>

These results in ESRD patients are especially relevant because these patients are severely immunocompromised and therefore generally respond poorly to vaccines. Based upon previous clinical studies in normal, healthy volunteers, other less immunocompromised patients who are at risk for *S. aureus* infections are expected to respond more favorably with higher levels of antibody to StaphVAX than ESRD patients.

A repeated dosing study was initiated in September 2005. The study is designed to evaluate the ability of StaphVAX to provide continuous protection in patient populations who are at high chronic risk for *S. aureus* infections. The trial will evaluate StaphVAX in ESRD patients on dialysis who are at high risk of contracting a *S. aureus* infection during their invasive and longer-term treatment.

## WHAT IS STAPHVAX MADE OF?

StaphVAX contains the same sugar molecules, or polysaccharides, found on the outer coating of the most dangerous strains of *S. aureus*, types 5 and 8, which are responsible for approximately 85 percent of *S. aureus* infections. The outer coating serves as a stealth mechanism that allows the bacteria to evade the body's immune system. StaphVAX, however, contains the purified *S. aureus* sugar molecules linked to a large carrier protein. This combination is readily recognizable as foreign to the immune system, triggering the body to synthesize antibodies to the *S. aureus* sugars in response to vaccination.

## HOW DOES STAPHVAX WORK?

Pre-clinical studies indicate that StaphVAX has a unique mechanism of action. Normally, invading bacteria have the ability to trick the immune system into thinking that *S. aureus* is not a pathogen by producing an outer coat or capsule made of polysaccharides (sugar molecules). However, these polysaccharides do not elicit the production of protective levels of antibodies by the immune system, and therefore people remain at risk of repeated infections with *S. aureus*. StaphVAX is made by linking the polysaccharides purified from *S. aureus* to a carrier protein, a nontoxic form of *Pseudomonas aeruginosa* exotoxin, called rEPA. When the polysaccharides are injected into the body in this form, they elicit high levels of antibodies specific to the *S. aureus* polysaccharide. When *S. aureus* invades the blood upon infection, these antibodies attach to the surface of the bacteria and, like a flashing radar beacon, announce the bacteria's invasion to the immune system, which then unleashes the white blood cells that kill the bacteria and clear it from the blood.

## STAPHVAX IMMUNOGENICITY STUDIES IN ORTHOPEDIC AND CARDIOVASCULAR SURGERY PATIENTS

In July 2005, Nabi Biopharmaceuticals announced positive results from its Phase IIb U.S. StaphVAX immunogenicity study in cardiac patients. A second, unblinded phase of the study, which will provide more comprehensive assessment of the duration of vaccine effect, by following patients for up to six months, is still ongoing. Results from this study are expected to be part of the U.S. BLA filing in the fourth quarter of 2005.

In May 2005, the first clinical immunogenicity study was initiated in Europe for patients undergoing orthopedic surgery with implantation of prosthetic devices. The results of this study are expected by the end of 2005. In September 2005, Nabi Biopharmaceuticals announced positive results from its U.S. StaphVAX immunogenicity study in orthopedic surgery patients with implanted devices. Results from this study are expected to be part of the U.S. BLA filing in the fourth quarter of 2005.

## STAPHVAX IN EUROPE

In December 2004, Nabi Biopharmaceuticals submitted a Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) under the Centralized Procedure for approval to market StaphVAX within the European Union (EU). The MAA filing was based on data from the first U.S. Phase III clinical trial in ESRD patients.

In January 2005, the MAA was accepted for review by the EMA and the EMA's Committee for Medicinal Products for Human Use (CHMP) will evaluate the application to determine whether to recommend approval for the marketing of StaphVAX in all 25 member states of the EU. Based on the normal schedule for reviewing submissions, Nabi Biopharmaceuticals anticipates coordinating an inspection at the contract manufacturer's facility and responding to questions about the research, clinical and manufacturing data during 2005. If Nabi Biopharmaceuticals' responses are adequate, the EMA should respond to the submission before the end of 2005.

## STAPHVAX 336

In July 2005, Nabi Biopharmaceuticals initiated a U.S. Phase I study for its vaccine being developed to prevent *S. aureus* type 336 infections in at-risk patients. *S. aureus* type 336 accounts for 15–20 percent of all Gram-positive hospital-acquired infections. Results from the trial are expected in the fourth quarter 2005.

## S. EPIDERMIDIS VACCINE

In May 2005, Nabi Biopharmaceuticals initiated its first human clinical study of this vaccine in at-risk patients. *S. epidermidis* accounts for approximately 20% of all *Staphylococci* infections.

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