

Vaccines and Related Biological Products Advisory Committee - November 7, 2017

Clinical Development of Pfizer's Investigational
Staphylococcus aureus Vaccine for Prevention
of Postoperative Infection in Elective
Orthopedic Surgeries



Overview

- Investigational vaccine:
- Staphylococcus aureus 4-antigen vaccine (SA4Ag).

- Status of clinical development:
- Clinical trial in progress: randomized, double-blind, placebo-controlled clinical endpoint study (study B3451002) to evaluate prevention of invasive S. aureus disease in adults ≥ 18 through 85 years of age scheduled to undergo elective instrumented spinal fusion surgery.

- Proposed Indication for Use:
- “prevention of invasive disease caused by Staphylococcus aureus in adults 18 years of age and older who are undergoing elective orthopedic surgery.”

- Topic for discussion: factors to consider when assessing the degree to which safety and efficacy data in a spinal fusion surgery population can be generalized to all elective orthopedic surgery populations.

Pathophysiology of *S. aureus*

- Nasopharyngeal colonization in ~30% of humans
- Multiple virulence factors and immune evasion strategies.
- Phenotype and protein expression profiles vary depending on host factors and site of infection.
- Protective immune mechanisms incompletely understood, particularly the adaptive immune response(s)

Clinical manifestations of *S. aureus*

- Very broad range of clinical manifestations
 - Food-borne illness, skin/soft tissue infection, pneumonia, bacteremia/systemic infections
- Multiple populations at risk
 - End stage renal disease patients, athletes, long term care facility populations, **patients undergoing elective surgery**
- SA4Ag targets patients at risk for postoperative *S. aureus* infection
 - *S. aureus* Surgical Site Infection (SSI): serious and recurring problem despite current preventive interventions

Risk factors for postoperative infection

- **Patient-related:** nasal carriage, comorbidities, age, health status
- **Procedure-related:** duration of surgery, implantation of prosthetic material (and the nature of the material itself), anatomical structures and tissues, perioperative care and preventive interventions
- **Key issues:**
 - Extent of heterogeneity of risk factors across different elective orthopedic surgeries; and
 - Anticipated impact of specific risk factors on the efficacy of a preventive immune response

Previous *S. aureus* vaccine clinical trial outcomes

- Bivalent *S. aureus* Glycoconjugate Vaccine (Nabi)
 - Two trials in end-stage renal disease patients failed to demonstrate efficacy
- *S. aureus* 0657nl iron surface determinant B (Merck)
 - Clinical trial in patients undergoing cardiothoracic surgery failed to demonstrate efficacy
 - Safety signal for more severe infection among subjects who had postoperative *S. aureus* infection

Understanding factors relevant to the question of generalizability

- Pathophysiology
- Clinical manifestations
- Risk factors for postoperative invasive *S. aureus* infection

Charge to the committee: assist in understanding if/how these factors inform the central question of whether data from one elective surgery population are generalizable to other elective surgery populations.



Vaccine development for specific populations

- The term “vaccine” is typically used in the context of a public health intervention intended to decrease risk of disease across large populations of generally healthy individuals.*
- More vaccines are now being developed to target specific populations and/or to address specific issues, such as antibiotic resistance.
- These programs raise particular challenges, e.g.:
 - evolution of pathogen virulence in health care settings
 - limited available subjects affecting study feasibility
 - generalizability of benefit-risk
- These issues require careful consideration, anchored in science-based reasoning.

*Laughlin, Scheif, and Heilman. “Addressing viral resistance through vaccines.” [Future Virol.](#) 2015;10(8):1011-1022.



Today's Agenda

Scientific Considerations: Pathogenesis of *Staphylococcus aureus* Infection

- Michael Otto, PhD, MS Chief, Pathogen Molecular Genetics Section, NIAID/NIH

Clinical Considerations: Postoperative *Staphylococcal* Infection, Disease Manifestations, and Therapeutic Options

- Richard Proctor, MD Professor Emeritus of Medical Microbiology and Immunology, University of Wisconsin School of Medicine and Public Health

FDA Presentation

- Tina Mongeau, M.D. Medical Officer FDA/CBER/Office of Vaccines Research and Review (OVRR)

Pfizer Presentation



Discussion Topics for the Committee

1. Assuming that the ongoing study of SA4Ag achieves its pre-specified primary efficacy objective in a population undergoing elective, posterior-approach, instrumented, multilevel spinal fusion surgery, please discuss the reasons why efficacy should or should not be generalized to other elective orthopedic surgical populations.
2. Assuming that the ongoing study of SA4Ag demonstrates safety in a population undergoing elective, posterior-approach, instrumented, multilevel spinal fusion surgery, please discuss the reasons why safety should or should not be generalized to other elective orthopedic surgical populations.