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Considerations for Pfizer's Investigational Staphylococcus aureus Vaccine Intended for Pre-Surgical Prophylaxis in Elective Orthopedic Surgical Populations

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Outline

1. Overview of *Staphylococcus aureus* surgical site infections
2. Clinical development of *S. aureus* vaccines to date
3. Overview of Pfizer's investigational *S. aureus* vaccine (SA4Ag) and proposed clinical development plan
4. Discuss considerations for the clinical development plan proposed by Pfizer for SA4Ag

OVERVIEW OF *STAPHYLOCOCCUS AUREUS* SURGICAL SITE INFECTIONS

Staphylococcus aureus Surgical Site Infections (SSIs)

- SSIs accounted for 36.4% of healthcare-associated infections occurring between 2011 and 2014 in the U.S.*
  - *S. aureus* was the most frequently isolated pathogen from SSIs (20.7%).*
  - 43-45% of SSI-causing *S. aureus* isolates were methicillin-resistant (MRSA).*
- *S. aureus* can form a biofilm, which predisposes it to cause infections associated with surgical implants. These infections are generally difficult to manage.

* Weiner LM et al. Infect Control Hosp Epidemiol. 2016;37:1288-1301

Categorization of SSIs

- Superficial incisional SSIs
  - manifest within 30 days after the operative procedure and involve only the skin and subcutaneous tissue of the incision.
- Deep incisional SSIs
  - manifest within 30 to 90 days after the operative procedure and involve deep soft tissue of the incision (e.g., fascial and muscle layers).
- Organ/Space SSIs
  - manifest within 30 to 90 days after the operative procedure and involve any part of the body deeper than the fascial/muscle layer that is opened or manipulated during the procedure.

CDC SSI Procedure-associated Module.
https://www.cdc.gov/nhsn/pdfs/pscmanual/ 9pscssicurrent. pdf

Current Approaches to Prevention of SSIs

Infection control

- Hand hygiene
- Contact precautions
- Environmental infection control

Perioperative prevention

- Patient showers/bathes with soap or antiseptic agent on at least the night prior to the procedure
- Pre-op skin preparation with alcohol-based agent
- Maintain glycemic control and normothermia during procedure
- Increased fraction of inspired oxygen
- Antimicrobial prophylaxis*
- Screening and decolonization**

Currently, there is no licensed *S. aureus* vaccine available.

* Bratzler DW et al. Am J Health-Syst Pharm. 2013;70:195-283.
** Ban KA et al. Surg Infect. 2017;18:379-382.

Treatment of SSIs

- Treatment recommendations:*
  - incision and drainage, antibiotics, surgical debridement
  - Implant-associated SSIs may require ≥ 1 debridement procedures and prolonged antibiotics to eradicate or control the SSI. The implant is typically removed or exchanged.
- Few antibiotics are available to treat MRSA infections. Vancomycin has been mainstay of parenteral therapy.
- Vancomycin-resistant and vancomycin-intermediate *S. aureus* isolates have been identified.

* Stevens DL et al. CID. 2014;59:e10-e52.

CLINICAL DEVELOPMENT OF *S. AUREUS* VACCINES TO DATE

Bivalent *S. aureus* Glycoconjugate Vaccine (StaphVAX*), Nabi Biopharmaceuticals

- Contained 100 µg each of capsular polysaccharide types 5 and 8 individually conjugated to a recombinant non-toxic variant of *Pseudomonas aeruginosa* exoprotein A**
- Study 1356: a randomized, double-blind, placebo-controlled Phase 3 trial evaluating a single dose of "StaphVAX" in 1804 adults with end-stage renal disease (ESRD) on hemodialysis did not meet the pre-specified primary study objective (significant reduction in bacteremia in the year following vaccination)
  - Primary analysis: 26% (95% CI -24, 57) reduction in bacteremia at 1 year**

* StaphVAX was the proprietary name proposed by Nabi Biopharmaceuticals.

** Shinefield H et al. NEJM. 2002;346:491-496.

"StaphVAX"

- Study 1371: A second, randomized, placebo-controlled, double-blind Phase 3 study evaluated 2 doses of "StaphVAX" administered at weeks 0 and 35 in 3,359 ESRD patients receiving hemodialysis
  - This study did not demonstrate vaccine efficacy in reducing the incidence of *S. aureus* bacteremia for up to 8 months following the first dose of the vaccine (primary study objective).
  - Safety analyses revealed no significant differences in rates of serious adverse events or deaths between vaccine and placebo groups.

Fattom A et al. Hum Vaccin Immunother. 2015;11:632-641.

"StaphVAX"

- Possible factors contributing to vaccine failure discussed in scientific literature* include:
  - Further investigation suggested possible suboptimal quality (manufacturing) of the vaccine lot for CP8 (lower affinity antibodies to CP8 in study 1371 compared to study 1356)
  - General immune suppression associated with uremia and/or dialysis in patients with ESRD
  - Anticapsular antibodies alone may not be sufficient to protect against invasive S. aureus infections.

* Fattom A et al. Human Vaccines & Immunotherapeutics. 2015;11:632-641.

V710 (IsdB), Merck

- V710 contains *S. aureus* 0657nI iron-regulated surface determinant B (IsdB).
- In a randomized, double-blind, placebo-controlled Phase 3 trial, the safety and efficacy of a single dose of V710 (60 µg) was evaluated in adults ≥ 18 years of age scheduled for cardiothoracic surgery involving full median sternotomy.
  - Primary objective: to demonstrate that a single dose of V710, when administered 14 to 60 days prior to full median sternotomy, results in a reduction in the proportion of adults with postoperative *S. aureus* bacteremia and/or deep sternal wound infections through post-op day 90 by at least 20% relative to placebo

Fowler VG Jr. JAMA. 2013;309:1368-1378.

V710 Phase 3 Study Results

- Study permanently closed after 2nd interim analysis due to identified safety concern and low probability of success
  - 7,983 subjects vaccinated
    - 22 cases in V710 group
    - 27 cases in placebo group
  - Vaccine efficacy: 18.5% (95% CI -48.6%, 55.8%)

Fowler VG Jr. JAMA. 2013;309:1368-1378.

V710 Phase 3 Study Results

- Among subjects experiencing any postoperative *S. aureus* infection:
  - V710 subjects had a higher mortality rate compared to placebo subjects
  - V710 subjects had a higher rate of death with multiorgan failure compared to placebo subjects

Fowler VG Jr. JAMA. 2013;309:1368-1378.

V710

- Causal relationship between V710 and higher rates of mortality has not been established
- Possible factors contributing to vaccine failure discussed in scientific literature* include:
  - Modest and transient functional antibody response in V710 group*
  - Anti-IsdB antibodies alone may not be sufficient for protection*
  - Undetectable pre-existing IL-2 and IL-17a levels**
    - Post-hoc analysis suggests that undetectable baseline (pre-vaccination and pre-operative) IL-2 levels and undetectable pre-operative IL-17a levels were each associated with mortality in V710 recipients experiencing any post-op *S. aureus* infection.**

* Fowler VG Jr. JAMA. 2013;309:1368-1378.

** McNeely TB et al. Human Vaccines & Immunotherapeutics. 2014;10:3513-3516.

PFIZER'S SA4AG VACCINE

SA4Ag, Pfizer

- 4 surface-expressed *S. aureus* antigens
  - Capsular polysaccharide serotypes 5 and 8 each conjugated to CRM_{197}
  - Recombinant *S. aureus* clumping factor A
  - Recombinant *S. aureus* manganese transporter C protein
- Proposed Dosage and Administration:
  - Single dose, administered intramuscularly (IM) between 10 and 60 days prior to elective orthopedic surgery
- Proposed indication:
  - Active immunization for the prevention of postoperative invasive disease caused by *S. aureus* in adults ≥ 18 years of age undergoing elective orthopedic surgery

SA4Ag Clinical Endpoint Study

- Ongoing study B3451002: randomized (1:1), double-blind, event-driven, global study evaluating the safety and efficacy of a single, IM dose of SA4Ag versus placebo in adults ≥ 18 through 85 years of age when administered 10 to 60 days prior to undergoing an elective, open, posterior spinal fusion procedure with multilevel instrumentation

- Definitions:
  - Spinal fusion: surgical arthrodesis (fusion of vertebrae) which may involve the cervical, thoracic, lumbar or sacral vertebrae or the pelvis
  - Instrumentation: implantation of prosthetic material (e.g., rods, screws, plates, hooks, wires, and bone cages composed of titanium or cobalt-chromium alloys, plastics, or stainless steel)
  - Multilevel: instrumentation involving ≥ 3 vertebrae. A single fusion involving 2 vertebrae is permitted if instrumentation spans ≥ 3 vertebrae

Study B3451002: Select Eligibility Criteria

- Subjects with comorbidities are eligible to participate
- Select exclusion criteria:
  - ESRD or nephrotic syndrome, immunocompromising conditions or other illnesses requiring treatment with known immunosuppressant therapies
  - Any known or suspected malignancy to the spine
  - History of major surgery (open procedure that enters a body cavity, organ or joint space) within prior 3 months
  - History of spinal surgery performed within prior 6 months
  - History of any previous spinal surgery resulting in postoperative blood stream or surgical site infection
  - Antibiotic therapy for microbiologically confirmed invasive *S. aureus* disease within prior 12 months

Study B3451002

- Primary objective: to assess the efficacy of SA4Ag in the prevention of postoperative *S. aureus* bloodstream infections and/or deep incisional or organ/space SSIs* occurring within 90 days of the index surgery and confirmed by the event adjudication committee
    - Success criterion: assuming true vaccine efficacy ≥ 70%, lower bound ≥ 20% on the 95% confidence interval
- Prospective criteria for multiple organ failure events
- Safety and efficacy (secondary efficacy endpoints) evaluated through 180 days post-surgery

*SSIs may involve the primary posterior incision or a secondary incision associated with the spinal fusion procedure or with the harvesting of autologous bone graft material.

Pfizer's Proposal

Pfizer proposes to use safety and efficacy data from Study B3451002 (in elective, open, posterior approach, multilevel, instrumented spinal fusion surgery) as the *primary data* supporting the proposed indication in adults undergoing any elective orthopedic surgery.

Pfizer's Proposal

Pfizer proposes that vaccine safety and efficacy demonstrated in study B3451002 can be ***generalized*** to other elective orthopedic surgical populations, because

1) study B3451002 constitutes a "***stringent***" assessment of vaccine efficacy; on average, the study population undergoes a longer and more complex procedure compared to other elective orthopedic populations, resulting in a higher incidence of postoperative invasive *S. aureus* disease (1.4% vs 0.2-0.5%); and

2) the study population is ***representative*** of other elective orthopedic surgical populations with regards to risk factors associated with postoperative SSIs and the immunopathogenicity of postoperative *S. aureus* SSIs.

SSI Risk Factors

- Patient-related risk factors:
  - *S. aureus* nasal carriage, comorbidities, age, health status, immune competence
- Procedure-related risk factors:
  - Perioperative care, duration of surgery, implantation of prosthetic material, implant material, length of incision, wound characteristics, surgical site, anatomical structures and tissues, allogeneic blood transfusion

Immunopathogenicity

- Immunopathogenicity of postoperative *S. aureus* infections:
  - Source of inoculation, early pathophysiology of *S. aureus* SSIs, *S. aureus* isolates associated with infections, presence of cellular and humoral immune components at surgical sites

Assuming Study B3451002 Meets its Primary Objective, Can Vaccine Safety and Efficacy be Generalized to Adults Undergoing *Any* Elective Orthopedic Surgery?

- Considerations include:
  - the extent to which dissimilarities across different elective orthopedic surgical populations/procedures are relevant:
    - patient-related risk factors for SSIs
    - procedure-related risk factors for SSIs
    - immunopathogenicity of postoperative SSIs
  - whether the B3451002 study population and index surgical procedures are representative of other elective orthopedic surgical populations and procedures
  - whether study B3451002 represents a stringent evaluation of vaccine efficacy


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Extra Slides

V710 Phase 3 Study Results

- Among subjects experiencing any postoperative *S. aureus* infection:
  - V710 subjects had a higher mortality rate compared to placebo subjects
    - V710: 23.0 deaths/100 person-years (95% CI 12.9, 37.9)]
    - Placebo: 4.2 deaths/100 person-years (95% CI 1.2, 10.8)]
    - Rate difference: 18.8 deaths/100 person-years (95% CI 8.0, 34.1)
  - V710 subjects had a higher rate of death with multiorgan failure compared to placebo subjects
    - V710: 7.6 deaths/100 person-years (95% CI 2.5, 17.7)]
    - Placebo: 0 deaths/100 person-years (95% CI 0.0, 3.9)]
    - Rate difference: 7.6 deaths/100 person-years (95% 3.2, 17.8)

Fowler VG Jr. JAMA. 2013;309:1368-1378.

V710 Phase 3 Study Results

- Among subjects experiencing postoperative *S. aureus* bacteremia and/or deep sternal wound infections (primary endpoint):
  - V710 subjects had a higher mortality rate [7 deaths; 35.7 deaths per 100 person-years (95% CI 14.4, 73.6)] relative to placebo [2 deaths; 7.8 deaths per 100 person-years (95% CI 0.9, 28.1)]
    Difference: 28.0% (95% CI 2.0, 66.7)
  - V710 subjects had a higher rate of death with multiorgan failure [3 deaths; 14.9 deaths per 100 person-years (95% CI 3.1, 43.4)] relative to placebo [0 deaths; 0 deaths per 100 person-years (95% CI 0.0, 14.2)
    Difference: 14.9 (0.0, 43.7)

V710

- Causal relationship explaining higher rates of mortality among *S. aureus* infected V710 subjects has not been established
- Possible factors contributing to vaccine failure discussed in scientific literature* include:
  - Modest and transient functional antibody response in V710 group*
    - ≥ 4-fold rise in opsonophagocytic antibody titer achieved by 29% (95% CI 24, 35) at 14-60 days and 17% (95% CI 10, 26) at 90 days*
    - Opsonophagocytic antibodies induced by V710, if not accompanied by bacterial killing) could theoretically permit intracellular survival of *S. aureus*.*
  - Anti-IsdB antibodies alone may not be sufficient for protection*
    - The role of cell-mediated immunity has become an area of interest

* Fowler VG Jr. JAMA. 2013;309:1368-1378.

V710

- Possible factors contributing to vaccine failure discussed in scientific literature include:
  - MRSA infections were more common among *S. aureus* infected V710 recipients compared to placebo recipients [34% (95% CI 23, 46) vs. 19% (95% CI 11, 28)] and resulted in a higher mortality rate in V710 recipients compared to MSSA infections [33% (95% CI 16, 55) vs 14% (95% CI 6, 27)].* None of the 17 placebo recipients with MRSA infections died.
  - Undetectable pre-existing IL-2 and IL-17a levels**
    - Post-hoc analysis suggests that undetectable baseline (pre-vaccination and pre-operative) IL-2 levels and undetectable pre-operative IL-17a levels were each associated with mortality in V710 recipients experiencing any post-op *S. aureus* infection.**

* Fowler VG Jr. JAMA. 2013;309:1368-1378.

** McNeely TB et al. Human Vaccines & Immunotherapeutics. 2014;10:3513-3516.