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# Safety and immunogenicity of pneumococcal protein vaccine candidates: Monovalent choline-binding protein A (PcpA) vaccine and bivalent PcpA–pneumococcal histidine triad protein D vaccine

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ABSTRACT

*Background:* Pneumococcal vaccines based on protein antigens may provide expanded protection against *Streptococcus pneumoniae.*
*Objective:* To evaluate safety and immunogenicity in adults of pneumococcal vaccine candidates comprising *S. pneumoniae* pneumococcal histidine triad protein D (PhtD) and pneumococcal choline-binding protein A (PcpA) in monovalent and bivalent formulations.
*Methods:* This was a phase I, randomized, observer-blinded, placebo-controlled, step-wise dose-escalation study. Following a pilot safety study in which participants received one intramuscular injection of either aluminum hydroxide (AH)–adjuvanted PcpA (25 μg) or PhtD–PcpA (10 μg each), participants in the main study received AH–adjuvanted PcpA (25 μg), AH–adjuvanted PhtD–PcpA (10, 25, or 50 μg each), unadjuvanted PhtD–PcpA (25 μg each), or placebo as 2 injections 30 days apart. Assignment of successive dose cohorts was made after blinded safety reviews after each dose level. Safety endpoints included rates of solicited injection site and systemic reactions, unsolicited adverse events (AEs), serious AEs (SAEs), and safety laboratory tests. Immunogenicity endpoints included levels of anti-PhtD and anti-PcpA antibodies (ELISA).
*Results:* Six adults 18–50 years of age were included in the pilot study and 125 in the main study. No obvious increases in solicited reactions or unsolicited AEs were reported with escalating doses (adjuvanted vaccine) after either injection, or with repeated administration. Adjuvanted vaccine candidates were associated with a higher incidence of solicited reactions (particularly injection site reactions) than unadjuvanted vaccine candidates. However, no SAE or discontinuation due to an AE occurred. Geometric mean concentrations of anti-PhtD IgG and anti-PcpA IgG increased significantly after injection 2 compared with injection 1 at each dose level. No enhancement of immune responses was shown with adjuvanted vaccine candidates compared with the unadjuvanted vaccine candidate. In the dose-escalating comparison, a plateau effect at the 25 μg dose was observed as measured by geometric mean concentrations and by fold increases.
*Conclusions:* Promising safety profiles and immunogenicity of these monovalent and bivalent protein vaccine candidates were demonstrated in an adult population (ClinicalTrials.gov registry no. NCT01444339).

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*Abbreviations:* AE, adverse event; AR, adverse reaction; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; EU, ELISA unit; GMC, geometric mean concentration; IgG, immunoglobulin G; IM, intramuscular; PcpA, pneumococcal choline-binding protein A; PhtD, pneumococcal histidine triad protein D; SAE, serious adverse event.

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## 1. Introduction

Clinical syndromes caused by *Streptococcus pneumoniae*, including pneumococcal pneumonia, acute otitis media, and invasive pneumococcal disease, including meningitis, are important causes of global morbidity and mortality and most frequently affect young children (6 months to 2 years of age) and older adults (age ≥65 years) [1]. Pneumococcal disease is more common and prolonged among children and has been noted to be significantly more common and occur earlier among children in developing countries [2]. According to the World Health Organization, 1.6 million people, including up to 1 million children under the age of 5 years, die of invasive pneumococcal disease annually [3], with the highest mortality rate in the developing countries in Asia and Africa [4]. In 2008, 93% of newborn children were not immunized against *S. pneumoniae* [5]. In recent years, the use of pneumococcal conjugate vaccines has increased, with 55 countries including them in their normal immunization schedule in 2010 [6].

To date, pneumococcal vaccines have been made up of polysaccharides or glycoconjugates. Pneumococcal infection rates have been significantly decreased by glycoconjugate vaccines, including the 7-valent Prevnar® (Pfizer, Madison, NJ; serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) [7] and the 13-valent Prevnar 13® (Pfizer; serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) [8], which are conjugated to the diphtheria $CRM_{197}$ protein, and the 10-valent polysaccharide conjugate vaccine Synflorix® (GlaxoSmithKline, London, UK) serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F), of which 8 serotypes are conjugated to *Haemophilus influenzae* protein D [9]. It has been hypothesized that the large-scale use of conjugate vaccines may result in a continual shift in prevailing serotypes, leading to increased non-vaccine-type disease in older children and adults and diminished effectiveness of the glycoconjugate vaccines over time [10]. In contrast, a protein pneumococcal vaccine has the potential to offer expanded protection against a broad spectrum of pneumococcal serotypes in a single formulation. It may also be more accessible for resource-poor populations where the need is greatest and access is lowest to the complex and expensive glycoconjugate-based vaccines required for vaccination of infants and toddlers [11,12].

The pneumococcal histidine triad protein D (PhtD), a virulence factor [13], is expressed on the bacterial surface and is a target for a humoral immune response in infected individuals [14–16]. Immunization with recombinant PhtD has been shown to provide protection from systemic disease in mice [17] and primates [18]. A single-antigen PhtD vaccine was found to be safe and immunogenic in humans (Seiberling et al., unpublished results). In addition, functionality of the generated antibodies was demonstrated in a passive protection sepsis model providing proof-of-concept for immunization with this protein (Sanofi Pasteur, unpublished results).

Pneumococcal choline-binding protein A (PcpA) is a bacterial surface antigen, and plays a major role in pneumococcal adherence, especially to pulmonary epithelial cells [19,20]. Immunization with PcpA has been shown to be protective in active immunization murine models of both sepsis and pneumonia [19].

We report the results from a phase I, single center, randomized, observer-blinded, placebo-controlled, step-wise dose-escalation study with the primary objective to evaluate a bivalent vaccine candidate that combines PhtD with PcpA. This study evaluated safety and immunogenicity of 2 injections of a single-antigen formulation of PcpA (25 μg) and the bivalent PhtD–PcpA protein vaccine candidate at 3 escalating doses (10, 25, and 50 μg each of PhtD plus PcpA) in healthy adults. Additionally, adjuvanted and unadjuvanted formulations of the bivalent 25 μg PhtD–PcpA vaccine candidate were evaluated.

## 2. Participants and methods

### 2.1. Vaccine candidates

Full-length PhtD without its signal sequence and PcpA lacking the choline-binding domain were cloned from strain 14453 (serotype 6B) of *S. pneumoniae*, expressed in *Escherichia coli* as soluble proteins, and purified by column chromatography. Purified PhtD and PcpA proteins were formulated with aluminum hydroxide adjuvant (Alhydrogel®, Brenntag Biosector, Frederikssund, Denmark) pre-treated with phosphate buffer [21]. Each dose was formulated in a single-use vial and contained 0.28 mg elemental aluminum. Placebo was composed of tris-buffered saline.

### 2.2. Participants

At study entry, participants were 18–50 years of age and in good health as determined by the investigator. Exclusion criteria included being immunodeficient or immunosuppressed; systemic hypersensitivity to any vaccine component or a history of life-threatening reaction to a vaccine containing the same substances; receipt of any vaccination within 4 weeks preceding the first study vaccination or planned vaccination within 4 weeks following any study vaccination; known thrombocytopenia or bleeding disorder contraindicating intramuscular (IM) vaccination; previous vaccination against pneumococcal disease or history of pneumococcal infection within 5 years; or living in a household with children under 5 years of age. Study subjects were not screened for naopharyngeal carriage. Vaccination was postponed in participants with febrile illness (≥38.0 °C) or moderate or severe acute illness/infection on the day of vaccination and follow-up visits were postponed for participants who had received treatment with an antibiotic within 72 h before collecting any blood for immunogenicity testing.

### 2.3. Study design

This was a phase I, single-center, randomized, placebo-controlled, repeated administration, dose-escalating, observer-blinded study to assess the safety and immunogenicity of a single-antigen protein (PcpA) vaccine candidate at one dose level and a bivalent protein vaccine candidate (PhtD–PcpA) at three dose levels (all adjuvanted, with an additional unadjuvanted formulation at the middle dose level). The study was carried out between February and September, 2010. The study protocol was approved by the independent review board at the study site and Study participants provided written informed consent prior to initiation of any study-specific procedures. The study was carried out in accordance with the World Medical Association Declaration of Helsinki. This study was registered under ClinicalTrials.gov no. NCT01444339.

Dose escalation, based on successful step-wise blinded safety reviews by a Sanofi Pasteur safety review committee of the 7-day clinical and biological safety data, occurred at completion of each enrollment cohort (Fig. 1). Before the main study, in a pilot safety assessment, participants in cohort 0 were randomized to receive one injection IM of either adjuvanted PcpA (25 μg) candidate or the adjuvanted bivalent vaccine candidate (PhtD–PcpA) (10 μg of each antigen) into the deltoid region of the arm opposite to the arm used for blood sampling via a 1-ml syringe fitted with a 25-guage, 5/8-in. needle. Clinical and biological safety data up to 7 days post-vaccination were assessed, with a 30-day follow-up after vaccination. Enrollment of participants in the main study proceeded, as no safety issues had been identified in cohort 0. In cohorts 1–8, two vaccinations were administered IM approximately 30 days

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