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Safety, reactogenicity and immunogenicity of a novel pneumococcal protein-based vaccine in adults: A phase I/II randomized clinical study☆

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ABSTRACT

Background: New vaccines containing highly conserved *Streptococcus pneumoniae* proteins such as pneumolysin toxoid (dPly) and histidine-triad protein D (PhtD) are being developed to provide broader protection against pneumococcal disease. This study evaluated the safety, reactogenicity and immunogenicity of different pneumococcal protein-containing formulations in adults.

Methods: In a phase I double-blind study (www.clinicaltrials.gov: NCT00707798), healthy adults (18–40 years) were randomized (1:2:2:2:2:2:2) to receive two doses of one of six investigational vaccine formulations 2 months apart, or a single dose of the control 23-valent pneumococcal polysaccharide vaccine (23PPV; *Pneumovax23*™, Sanofi Pasteur MSD) followed by placebo. The investigational formulations contained dPly alone (10 or 30 μg), or both dPly and PhtD (10 or 30 μg each) alone or combined with the polysaccharide conjugates of the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV; *Synflorix*™, GlaxoSmithKline Vaccines). Two groups primed with a formulation containing dPly and PhtD (10 or 30 μg each) continued to the follow-up phase II study (NCT00896064), in which they received a booster dose at 5–9 months after primary vaccination.

Results: Of 156 enrolled and vaccinated adults, 146 completed the primary immunization and 43 adults received a booster dose. During primary and booster vaccination, for any formulation, ≤8.9% of doses were followed by grade 3 solicited local or general adverse events. No fever >39.5 °C (oral temperature) was reported. Unsolicited adverse events considered causally related to vaccination were reported following ≤33.3% of investigational vaccine doses. No serious adverse events were reported for adults receiving investigational vaccine formulations. Formulations containing dPly with or without PhtD were immunogenic for these antigens; polysaccharide conjugate-containing formulations were also immunogenic for those 10 polysaccharides.

Conclusion: Investigational vaccine formulations containing dPly and PhtD were well tolerated and immunogenic when administered to healthy adults as standalone protein vaccine or combined with PHiD-CV conjugates.

Abbreviations: 23PPV, 23-valent pneumococcal polysaccharide vaccine; AE, adverse event; anti-PD, NTHi protein D antibody; ATP, according to protocol; dPly, pneumolysin toxoid; ELISA, enzyme-linked immunosorbent assay; GMC, geometric mean concentration; GMT, geometric mean titer; LU, Luminex units; OPA, opsonophagocytic activity; PCV, pneumococcal conjugate vaccine; PHiD-CV, 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine; PhtD, histidine-triad protein D; Ply, pneumolysin; PS-conjugates, capsular polysaccharide conjugates; SAE, serious adverse event; TVC, total vaccin.

☆ *Previous publications*: The results of this study were presented in part at the 8th International Symposium on Pneumococci & Pneumococcal Diseases, Iguaçu Falls, Brazil, March 11–15, 2012.

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1. Introduction

Streptococcus pneumoniae is frequently involved in common mucosal bacterial infections such as pneumonia, and can lead to invasive disease including sepsis, meningitis and invasive pneumonia [1,2]. Worldwide, this pathogen is responsible for approximately 11% of mortality in children under 5 years old [2].

Pneumococcal conjugate vaccines (PCVs) have decreased the burden of pneumococcal disease in children in many countries and provided indirect effect in decreasing vaccine-type disease in non-vaccinated populations [3–5]. However, shifts in serotype epidemiology have occurred and consequently considerable disease burden remains, largely owing to serotypes not included in the currently used PCVs [4–6].

The use of highly conserved pneumococcal proteins as vaccine antigens has the potential to provide broader protection against pneumococcal disease than PCVs. Two candidate antigens for a protein-based pneumococcal vaccine are pneumolysin (Ply) and histidine-triad protein (PhtD). Ply is a thiol-dependent toxin that is present in nearly all pneumococcal serotypes [7]. Its toxoid derivatives (dPly) induce protection against pneumococcal infection in animal models [8–11]. PhtD is exposed on the surface of intact bacteria [12] and may be involved in lung-specific virulence [13]. Immunization with PhtD elicits functional antibodies [14–16] and provides protection against pneumonia in animal models [11,15]. Antibodies against PhtD prevent pneumococcal adherence to human airway epithelial cells [16]. An investigational vaccine containing 10 or 30 μg PhtD was shown to have an acceptable reactogenicity profile in adults, with no safety concerns, and dose-dependent immunogenicity when comparing the 10 and 30 μg formulations [17].

This phase I study provides a safety and reactogenicity assessment of investigational pneumococcal protein-containing formulations in healthy adults before progressing to the target pediatric population. We evaluated six different formulations containing dPly alone or with PhtD, or a combination of dPly and PhtD with the conjugates of the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV). After the two-dose primary series, two primed cohorts received a booster dose of a 10 or 30 μg dPly/PhtD formulation in the follow-up phase II study.

2. Methodology

2.1. Study design and objectives

A phase I, randomized, controlled study (primary vaccination study; NCT00707798) was conducted between June 2008 and January 2009. Two groups were further evaluated in a follow-up phase II study (booster vaccination study; NCT00896064) between May and August 2009. Both studies were conducted at a single center in Belgium. The primary vaccination study was open in step 1 (for the group receiving 10 μg dPly). For steps 2 and 3 (encompassing all other groups), data were collected in an observer-blinded manner (vaccine recipients and those responsible for evaluation of any study endpoint were unaware which vaccine was administered) (Fig. 1).

The primary objective of both studies was to assess the safety and reactogenicity of the different investigational pneumococcal vaccine formulations. Secondary objectives included evaluation of the dPly and PhtD protein antibody responses. We also evaluated the non-typeable *Haemophilus influenzae* (NTHi) protein D antibody (anti-PD) response and opsonophagocytic activity (OPA) of vaccine serotypes for the formulations containing capsular polysaccharide conjugates (PS-conjugates).

The study protocols were approved by the Ethics Committee of the Ghent University Hospital. The studies were conducted in line with the Declaration of Helsinki and Good Clinical Practice. Informed consent was obtained from each study participant before enrolment.

These studies have been registered at www.clinicaltrials.gov (NCT00707798; NCT00896064). Protocol summaries are available at http://www.gsk-clinicalstudyregister.com (GSK study IDs: 111651; 112993).

2.2. Participants and vaccines

Eligible participants were healthy adults (18–40 years old), without a history of bacterial pneumonia or invasive pneumococcal disease within 3 years before vaccination. Exclusion criteria included vaccination with diphtheria/tetanus toxoids within 1 month preceding the first study vaccine dose, and chronic administration (>14 days) of immunosuppressants or immune-modifying drugs within 6 months before vaccination. Participants were screened by clinical laboratory analysis (supplementary methods); those with hematological or biochemical abnormalities were not enrolled. Participants were not to use any investigational or non-registered product other than the study vaccine from 30 days before the first vaccine dose until study end. Women of childbearing potential were asked to practice adequate contraception from 30 days pre-vaccination until 2 months after completing the vaccination series.

Participants were enrolled sequentially in three steps preceded by a safety review (Fig. 1). They were randomized (1:2:2:2:2:2:2, block size 4 [step 1], 7 [step 2] and 5 [step 3]) using a central internet randomization system (SBIR) to receive a two-dose primary vaccination series with one of six investigational vaccine formulations (GlaxoSmithKline Vaccines) or a single dose of the 23-valent pneumococcal polysaccharide vaccine (23PPV; *Pneumovax23*™, Sanofi Pasteur MSD) followed by placebo (150 mM NaCl) (Fig. 1; supplementary methods). All vaccines and the placebo were administered intramuscularly into the deltoid region of the non-dominant arm.

Two investigational vaccines contained 10 or 30 μg of dPly alone (dPly-10 and dPly-30, respectively). Two other formulations contained both dPly and PhtD, each at a dose of 10 μg (dPly/PhtD-10) or 30 μg (dPly/PhtD-30). The remaining two formulations contained the 10 PHiD-CV PS-conjugates (serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) [18], in combination with 10 or 30 μg of both dPly and PhtD (PHiD-CV/dPly/PhtD-10 and PHiD-CV/dPly/PhtD-30). Production of PhtD and dPly is described in supplementary methods.

The control group received one dose of 23PPV, containing 25 μg of each capsular polysaccharide for pneumococcal serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F, and placebo (150 mM NaCl) as a second dose.

Participants from the dPly/PhtD-10 and dPly/PhtD-30 groups were invited to participate in the booster vaccination study, to receive a booster dose 5–9 months after completion of the two-dose primary series.

2.3. Safety and reactogenicity assessment

Solicited local and general symptoms were recorded during the 7-day post-vaccination period and unsolicited adverse events (AEs) during the 31-day post-vaccination period. Symptom intensity was graded on a scale of 1 (mild) to 3 (severe). Grade 3 symptoms were defined as follows: for redness or swelling, a diameter >50 mm; for fever, oral temperature >39.5 °C; and for all other events, preventing normal activity.

Serious adverse events (SAEs) were recorded throughout the duration of each study, and were defined as any medical occurrence that resulted in death, disability or incapacity, was life-threatening,

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