IMMUNOGENICITY OF THE BOOSTER DOSE OF 2 INVESTIGATIONAL PROTEIN-BASED PNEUMOCOCCAL VACCINE FORMULATIONS IN TODDLERS: A PHASE II RANDOMIZED TRIAL

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INTRODUCTION

- Pneumococcal conjugate vaccines (PVCs) have reduced the incidence of invasive pneumococcal disease worldwide.[1]
- Serotype replacement[2] and the limited number of capsular polysaccharides (PS) that can be included in a PCV may challenge the global control of pneumococcal diseases.
- To extend protection beyond the PS included in PCVs, GSK Vaccines is investigating protein-based vaccine formulations containing the highly conserved pneumococcal proteins pneumolysin (Ply) and pneumococcal histidine-triad protein D (PhtD).
- Two formulations of an investigational pneumococcal vaccine containing Ply toxoid (dPly) and PhtD each at either 10 µg (PHiD-CV/dPly/PhtD-10) or 30 µg (PHiD-CV/dPly/PhtD-30) combined with PS of the pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV, GSK Vaccines [not licensed in the USA]) (**Figure 1**) were immunogenic in adults and toddlers in Europe,[3,4] and in infants and children in the Gambia.[5,6]
- A phase II trial (ClinicalTrials.gov: NCT01204658) conducted in European infants showed that PHiD-CV/dPly/PhtD-10 and PHiD-CV/dPly/PhtD-30 were well tolerated (primary objective) and induced robust immune responses (secondary objectives) after primary vaccination.[7,8]
- We present immunogenicity results following administration of a booster dose of these 2 vaccine formulations in the same study (secondary objectives). Safety outcomes are presented in abstract IDWeek-58483.

METHODS

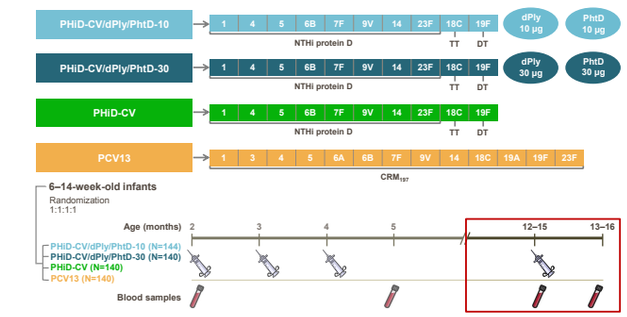
Study design and participants

- Phase II, multi-center, observer-blind, controlled trial conducted in the Czech Republic, Germany, Poland and Sweden.
- Infants (previously not vaccinated against *Streptococcus pneumoniae*) were randomized 1:1:1:1 to receive either PHiD-CV/dPly/PhtD-10, PHiD-CV/dPly/PhtD-30, PHiD-CV or 13-valent PCV (PCV13, Pfizer) at 2, 3, 4 months of age followed by a booster dose given at 12–15 months of age co-administered with diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-*H. influenzae* type b vaccine (DTPa-HBV-IPV/Hib, GSK Vaccines [not licensed in the USA]) (**Figure 1**).
- The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki.

Immunogenicity assessment

- Blood sampling time points are indicated in **Figure 1**.
- Immune responses against pneumococcal Ply and PhtD proteins, and protein D were quantified by enzyme-linked immunosorbent assay (ELISA).
- Immune responses against pneumococcal serotype-specific PS were measured by ELISA with serotype 22F PS adsorption (22F-ELISA).
- Opsonophagocytic activity (OPA) for antibodies against pneumococcal serotypes was measured by a killing-assay using a HL60 cell line.
- Immune responses to co-administered antigens were also evaluated (not shown).
- Analyses were performed in the according-to-protocol (ATP) cohort for immunogenicity.

Figure 1. Vaccine antigens and study design (ClinicalTrials.gov: NCT01204658)



NTHi, non-typeable *Haemophilus influenzae*; **TT**, tetanus toxoid; **DT**, diphtheria toxoid; **dPly**, pneumolysin toxoid; **PhtD**, pneumococcal histidine-triad protein D; **CRM_{197}**, non-toxic cross-reacting mutant of diphtheria toxin; **N**, number of toddlers included in the total vaccinated cohort at booster vaccination; Red rectangle indicates immunogenicity time points for which results are presented here.

RESULTS

Demographic characteristics

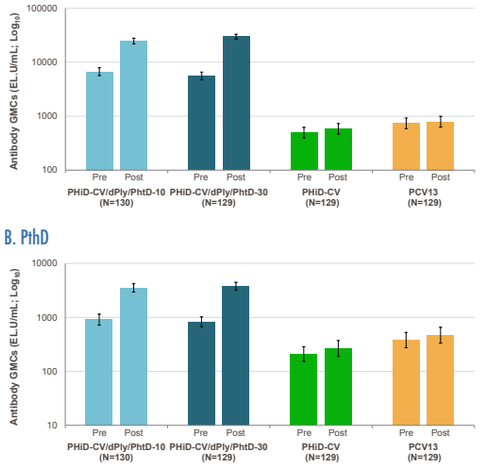
- Of 576 infants enrolled in the primary vaccination, 527 out of 564 toddlers who received booster vaccination were included in the ATP cohort for immunogenicity.
- In the ATP cohort for immunogenicity at booster vaccination, the mean (± standard deviation) age varied between 12.3±0.5 and 12.4±0.6 months, the percentage of girls ranged between 46.6% and 47.7% of toddlers, and ≥98.5% in each group were of white - Caucasian / European heritage; demographic characteristics were similar across groups.

Immunogenicity results

Immune responses to Ply and PhtD proteins

- All vaccinees had pre- and post-booster anti-Ply and anti-PhtD antibody concentrations ≥ assay technical cut-offs (12 and 17 EL.U/mL, respectively), except for PhtD in PHiD-CV and PCV13 vaccinees: ≥96.1% of toddlers.
- Increases in geometric mean antibody concentrations (GMCs) from pre- to post-booster time point were observed in PHiD-CV/dPly/PhtD-10 and PHiD-CV/dPly/PhtD-30 vaccinees only (**Figure 2**).

Figure 2. Ply (A) and PhtD (B) geometric mean antibody concentrations (ATP cohort for immunogenicity)

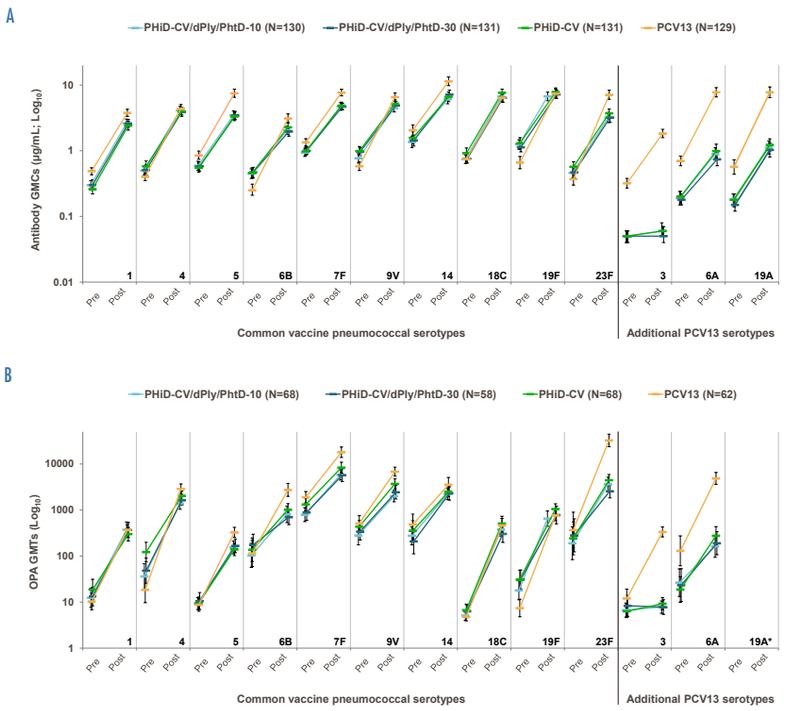


dPly, pneumolysin toxoid; **PhtD**, pneumococcal histidine-triad protein D; **ATP**, according-to-protocol; **GMC**, geometric mean concentration; **EL.U**; enzyme-linked immunosorbent assay units; **N**, maximum number of toddlers with available results; error bars represent the 95% confidence intervals.

Immune responses to serotype-specific pneumococcal PS conjugates

- Before booster vaccination, for each of the common vaccine pneumococcal serotypes, ≥82.5% of toddlers who received protein-based formulations or PHiD-CV had antibody concentrations ≥0.2 µg/mL, except for serotypes 1 (56.9%–69.0%) and 6B (78.6% in the PHiD-CV group). One month post-booster, ≥96.9% of toddlers had antibody concentrations ≥0.2 µg/mL in these groups. For PCV13 vaccinees these percentages were ≥80.5% (except for serotypes 6B [64.3%] and 23F [71.9%]) before and ≥99.2% post-booster.
- For each common vaccine pneumococcal serotype, an increase of antibody GMCs was observed following booster vaccination. Antibody GMCs were in similar ranges in PHiD-CV/dPly/PhtD-10, PHiD-CV/dPly/PhtD-30 and PHiD-CV groups (**Figure 3A**).
- Before booster vaccination, for each of the common serotypes, ≥41.7% of toddlers had OPA titers ≥8, except for serotypes 18C (11.1%–31.4%) and 1 (36.4% in the PHiD-CV/dPly/PhtD-10 group). One month after the booster dose, ≥94.1% of toddlers had OPA titers ≥8 in protein-based formulations or PHiD-CV vaccinees. For PCV13 vaccinees these percentages were ≥42.9% (except for serotypes 1 [34.9%], 18C [14.3%] and 19F [24.4%]) before and 100% post-booster.
- Post-booster geometric mean OPA titers seemed to be similar in PHiD-CV/dPly/PhtD-10, PHiD-CV/dPly/PhtD-30 and PHiD-CV recipients (except for 9V: lower in the PHiD-CV/dPly/PhtD-10 than in the PHiD-CV vaccinees) (**Figure 3B**).

Figure 3. Serotype-specific pneumococcal geometric mean antibody concentrations (A) and OPA titers (B) (ATP cohort for immunogenicity)

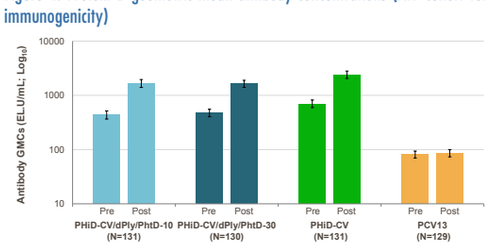


*Results not available. **ATP**, according-to-protocol; **GMC**, geometric mean concentration; **OPA**, opsonophagocytic activity; **GMT**, geometric mean titer; **Pre**, before the booster dose; **Post**, 1 month after the booster dose; **N**, maximum number of toddlers with available results at each time point; error bars represent the 95% confidence intervals.

Immune responses to protein D

- Before and after booster vaccination, ≥95.4% and ≥98.5% of toddlers, respectively, had anti-protein D antibody concentrations ≥100 EL.U/mL in the PHiD-CV/dPly/PhtD-10, PHiD-CV/dPly/PhtD-30 and PHiD-CV groups.
- Protein D antibody GMCs increased following booster dose in the PHiD-CV/dPly/PhtD-10, PHiD-CV/dPly/PhtD-30 and PHiD-CV groups. Antibody GMCs tended to be lower in the protein-based formulation groups than in the PHiD-CV group (**Figure 4**).

Figure 4. Protein D geometric mean antibody concentrations (ATP cohort for immunogenicity)



ATP, according-to-protocol; **GMC**, geometric mean concentration; **EL.U**; enzyme-linked immunosorbent assay units; **N**, maximum number of toddlers with available results; error bars represent the 95% confidence intervals.

Immune responses to co-administered antigens

- Immune responses to antigens included in the DTPa-HBV-IPV/Hib vaccine were within similar ranges among groups receiving protein-based vaccines or PHiD-CV.

CONCLUSIONS

- Both PHiD-CV/dPly/PhtD-10 and PHiD-CV/dPly/PhtD-30 investigational formulations induced booster responses to Ply and PhtD.
- No interference of the pneumococcal protein antigens with the immune responses to pneumococcal serotype-specific conjugates of PHiD-CV was observed when combining dPly and PhtD with the PHiD-CV PS conjugates.

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DISCLOSURES

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