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Safety, reactogenicity and immunogenicity of two investigational pneumococcal protein-based vaccines: Results from a randomized phase II study in infants

Roman Prymula,⇑ Leszek Szenborn, Sven-Arne Silfverdal, Jacek Wysocki, Piotr Albrecht, Magali Traskine, Asparuh Gardev, Yue Song, Dorota Borys

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A B S T R A C T

Introduction: Vaccination with formulations containing pneumococcal protein antigens such as pneumolysin toxoid (dPly) and histidine-triad protein D (PhD) may extend serotype-related protection of pneumococcal conjugate vaccines (PCVs) against Streptococcus pneumoniae.

Methods: This phase II, multi-center, observer-blind trial conducted in Europe (NCT01204658) assessed 2 investigational vaccines containing 10 serotype-specific polysaccharide conjugates of PHiD-CV and either 10 or 30 μg of dPly and PhD each. Infants randomized 1:1:1:1 received 4 doses of PHiD-CV/dPly/PhD-10, PHiD-CV/dPly/PhD-30, PHiD-CV, or 13-valent PCV (PCV13), co-administered with DTPa-HBV-IPV/Hib, at ages 2, 3, 4 and 12–15 months. Occurrences of fever >40.0 °C following primary vaccination with PHiD-CV/dPly/PhD vaccines compared to PHiD-CV (non-inferiority objective), dose superiority, safety and immunogenicity were assessed.

Results: 575 children received primary vaccination, and 564 booster vaccination. The non-inferiority objective was met; no fever >40.0 °C causally related to vaccination was reported during primary vaccination. Incidence of adverse events appeared similar between the 3 PHiD-CV groups. Serious adverse events were reported in 13, 9, 21 (1 related to vaccination), and 17 children in the PHiD-CV/dPly/PhD-10, PHiD-CV/dPly/PhD-30, PHiD-CV, and PCV13 groups, respectively. PHiD-CV/dPly/PhD-30 was superior to PHiD-CV/dPly/PhD-10 in terms of post-dose 3 anti-Ply and Anti-PhD antibody levels. Anti-Ply and anti-PhD antibody levels were higher in both PHiD-CV/dPly/PhD groups than in controls and increased from post-primary to post-booster timepoint. Post-primary and booster vaccination, for each PHiD-CV serotype, ≥98.5% of participants in PHiD-CV/dPly/PhD groups had antibody concentrations ≥0.2 μg/mL, except for 6B (≥72.3%) and 23 F (≥82.7%) post-primary vaccination. Similar results were observed in the PHiD-CV group. Immune responses to protein D and DTPa-HBV-IPV/Hib were within similar ranges for the 3 PHiD-CV groups.

Conclusion: Both PHiD-CV/dPly/PhD formulations co-administered with DTPa-HBV-IPV/Hib in infants were well-tolerated and immunogenic for dPly and PhD antigens, while immune responses to serotype-specific, protein D and co-administered antigens did not appear altered in comparison to PHiD-CV group.

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1. Introduction

Streptococcus pneumoniae causes severe infectious diseases such as meningitis, bacteremia and pneumonia, and common illnesses including sinusitis and otitis media [1,2].
Three licensed pneumococcal conjugated vaccines (PCVs) contain polysaccharides of 7, 10, or 13 pneumococcal serotypes out of the more than 90 known [3]. Although these PCVs have significantly decreased the burden of invasive pneumococcal disease [4,5], the incidence of non-vaccine pneumococcal serotypes has increased [6].

The use of conserved pneumococcal protein antigens in next-generation vaccines could potentially provide protection against *S. pneumoniae* regardless of the capsular serotypes [7]. Two investigational vaccine formulations containing pneumolysin toxoid (dPly) and pneumococcal histidine-triad protein D (PhtD) have been shown to be well-tolerated and immunogenic when administered as a single dose to 2–4-year-old children in The Gambia [8], or as a 2+1 schedule to European toddlers [9].

Currently, in infant vaccination programs, several vaccines are co-administered. This increases the risk of post-immunization febrile reactions and febrile seizures [10,11] and in consequence may require use of antipyretics, medical visits, or hospitalization. New antigens or vaccines should not increase reactogenicity when they are combined or co-administered.

This study assessed the safety, reactogenicity and immunogenicity of 2 investigational vaccine formulations, containing either 10 or 30 μg of dPly and PhtD each and the serotype-specific polysaccharide conjugates of the pneumococcal nontypeable *Haemophilus influenzae* protein D-conjugate vaccine (PHiD-CV; Synflorix, GSK, Belgium), when co-administered with DTPa-HBV-IPV/Hib (Infanrix hexa, GSK, Belgium) to healthy infants. The primary objectives of the study were to compare the pneumococcal protein-containing vaccines to PHiD-CV with respect to the occurrence of febrile reactions (rectal temperature >40.0 °C) with causal relationship to primary vaccination, using pre-defined non-inferiority criteria.

### 2. Methods

#### 2.1. Study design and participants

This phase II, randomized, multicenter, observer-blind, controlled study was conducted in the Czech Republic, Germany, Poland and Sweden between 24 September 2010 and 1 October 2012.

Inclusion/exclusion criteria are detailed in Supplementary Material, Text S1. Healthy infants aged 6–14 weeks at the time of first vaccination were randomized (1:1:1:1) to receive PHiD-CV/dPly/PhtD-10, PHiD-CV/dPly/PhtD-30, PHiD-CV, or the 13-valent PCV (PCV13; Prevenar 13TM, Pfizer). Treatment allocation at the investigator site was performed using an internet central randomization system. Sub-randomization to generate serology subsets comprising ±50% of participants from each group for the analyses of opsonophagocytic activity (OPA) and of immune responses to co-administered vaccine components was done at GSK using SAS.

Due to differences in physical appearance of the study vaccines, the study was conducted in an observer-blind manner, meaning that vaccine recipients, persons evaluating study endpoints, and laboratory staff were unaware of the vaccine administered. Authorized medical personnel with no further role in the study prepared and administered the vaccines.

The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. Written informed consent was obtained from the infants’ parents or legally accepted representatives before study enrollment. The study protocol, amendments, and informed consent forms were reviewed and approved by national/regional Independent Ethics Committees. The study is registered at ClinicalTrials.gov (NCT01204658) and available at http://www.gsk-clinicalstudyregister.com (ID: 113994).

#### 2.2. Study vaccines

The 2 investigational formulations contained, in addition to the conjugated polysaccharides of PHiD-CV, dPly and PhtD either at 10 μg of each (PHiD-CV/dPly/PhtD-10) or at 30 μg of each (PHiD-CV/dPly/PhtD-30) [8,12,13]. Control groups received PHiD-CV or PCV13. Vaccines were administered at 6–14 weeks, 3 and 4 months of age (primary doses), and 12–15 months of age (booster dose).

All groups received DTPa-HBV-IPV/Hib concomitantly at each vaccination visit. Vaccines were administered intramuscularly into the right (pneumococcal vaccines) or left thigh (DTPa-HBV-IPV/Hib).

#### 2.3. Outcomes

The first co-primary objective was to compare PHiD-CV/dPly/ PhtD-10 to PHiD-CV with respect to the occurrence of febrile reactions (fever >40.0 °C) causally related to primary vaccination. The second co-primary objective compared PHiD-CV/dPly/PhtD-30 to PHiD-CV in the same manner. Non-inferiority of PHiD-CV/dPly/ PhtD formulations to PHiD-CV was to be demonstrated if an increase in the percentage of infants with rectally measured temperature >40.0 °C causally related to primary vaccination above 5% plus half the incidence in the PHiD-CV group (null hypothesis) was ruled out with a 1-sided p-value < 0.05. The objectives were assessed sequentially.

The first confirmatory secondary objective compared the PHiD- CV/dPly/PhtD formulations; superiority of one formulation over the other was to be demonstrated post-primary vaccination, if the upper limits of the 95% confidence intervals for the geometric mean concentration (GMC) ratio (10 μg/30 μg or 30 μg/10 μg) for anti-Ply and anti-PhtD antibodies were <1. Other secondary objectives assessed immune responses to pneumococcal proteins, pneumococcal serotype-specific polysaccharides, protein D, and DTPa-HBV-IPV/Hib, as well as safety and reactogenicity in all study groups.

#### 2.4. Safety and reactogenicity assessment

Solicited local and general symptoms occurring within 7 days after each vaccination, and unsolicited adverse events (AEs) occurring within 31 days after each vaccination were recorded on diary cards. Large swelling reactions were solicited post-booster, and serious adverse events (SAEs) throughout the entire study (Text S2). AE intensity was graded on a scale from 1 (mild) to 3 (severe). All solicited local reactions were considered causally related to vaccinations. The causality of all the other AEs was assessed by the investigator.

#### 2.5. Immunogenicity assessment

Blood samples were collected pre-vaccination, 1 month post-dose 3, pre-booster (8–11 months post-primary vaccination) and 1 month post-booster (Fig. S1). Sera were stored at −20 °C until analysis. Assays are detailed in Table S1. Statistical analyses are described in Text S2.

### 3. Results

#### 3.1. Demographics

Out of the 576 enrolled infants, 575 were included in the total vaccinated cohort of primary vaccination, and 537 in the immuno-
genicity according-to-protocol cohort; the booster total vaccinated cohort counted 564 toddlers, of which 527 were included in the immunogenicity according-to-protocol cohort (Fig. 1). Demographic characteristics were similar between all groups (Table S2).

3.2. Safety and reactogenicity

No fever >40.0 °C was reported during the primary vaccination for any of the 4 groups, thus non-inferiority criteria were met, as the null hypothesis was ruled out with a 1-sided p-value of 0.003. Post-primary vaccination, the most frequently reported local symptom at the pneumococcal vaccine injection site was redness in all groups (after 33.6%–38.1% of vaccine doses); post-booster vaccination, redness in the PHiD-CV/dPly/PhtD-10 (47.9%) and PHiD-CV (41.0%) groups, and pain in the PHiD-CV/dPly/PhtD-30 (45.7%) and PCV13 (44.3%) groups were most common. Local grade 3 symptom incidence remained under 6% following each dose in all groups. Symptoms at pneumococcal vaccines or DTPa-HBV-IPV/Hib injection sites had similar incidences across all groups (Fig. 2A and B). Irritability was the most frequently reported general symptom for both primary (after 55.0%–56.6% of doses) and booster (59.0%–66.0%) vaccination in all groups (Fig. 2C). No apparent increases in the incidences of solicited local and general symptoms were observed following consecutive doses of either

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Fig. 1. Flow chart for study participants with reasons for elimination from according-to-protocol analyses. *One infant was enrolled, but no study vaccine doses were administered. N, number of children in each group; ATP, according-to-protocol; SAE, serious adverse event; AE, adverse event.
PHiD-CV/dPly/PhtD-10 or PHiD-CV/dPly/PhtD-30 during the primary vaccination period, but there was a trend towards higher incidences following booster vaccination (Fig. 2). Most solicited symptoms were reported within the first 4 days of each vaccination (Fig. S2).

Post-booster dose, no large swelling reactions at the injection site of the investigational vaccines were reported, while 6 cases were reported for other vaccines (4 for DTPa-HBV-IPB/Hib, 1 for PHiD-CV and 1 for PCV13).

During primary vaccination, at least 1 unsolicited symptom was reported after 16.9% of PHiD-CV/dPly/PhtD-10 and 21.4% of PHiD-CV/dPly/PhtD-30 doses, and after 20.1% of PHiD-CV and 20.0% of PCV13 doses (Table S3). The most frequently reported unsolicited symptoms were conjunctivitis, bronchitis, nasopharyngitis and rhinitis. At least 1 unsolicited symptom assessed by the investigator to be causally related to vaccination was reported after 0.2% and 0.5% of doses for PHiD-CV/dPly/PhtD-10 and PHiD-CV/dPly/PhtD-30 groups, 0.9% for PHiD-CV, and 0.2% for the PCV13 group.

Fig. 2. Incidence of solicited local symptoms during the 7-day period following administration of pneumococcal vaccine (A) and DTPa-HBV-IPV/Hib vaccine (B) and incidence of solicited general symptoms (C), post-each dose and overall/dose for the first 3 doses (total vaccinated cohort). Note: Error bars indicate 95% confidence intervals. Grade 3 solicited symptoms were defined as “crying when limb was moved” (pain); surface diameter >30 mm (redness/swelling); “rectal temperature >40 °C or tympanic/oral/axillary temperature >39.5 °C” (fever); “crying that could not be comforted or which prevented normal activities” (irritability/fussiness); “preventing normal activity” (drowsiness); and “not eating at all” (loss of appetite).

Table 1

Superiority of the PHiD-CV/dPly/PhtD-30 vs PHiD-CV/dPly/PhtD-10 formulation (according-to-protocol cohort for immunogenicity, primary vaccination phase).

<table>
<thead>
<tr>
<th>Antibody</th>
<th>PHiD-CV/dPly/PhtD-10</th>
<th>PHiD-CV/dPly/PhtD-30</th>
<th>Adjusted GMC ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Adjusted GMC (ELU/mL)</td>
<td>N</td>
</tr>
<tr>
<td>Anti-Ply</td>
<td>131</td>
<td>9527.68</td>
<td>129</td>
</tr>
<tr>
<td>Anti-PhtD</td>
<td>131</td>
<td>1498.46</td>
<td>129</td>
</tr>
</tbody>
</table>

Note: Bolded values indicate that superiority criteria were met. Adjusted GMC, geometric mean antibody concentration adjusted for baseline concentration; N, number of children with both pre- and post-vaccination results available; ELU, ELISA Units; 95% CI, 95% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for baseline concentration - pooled variance); ELISA, enzyme-linked immunosorbent assay.

* PHiD-CV/dPly/PhtD-10 group over PHiD-CV/dPly/PhtD-30 group.

Post-booster vaccination, at least 1 unsolicited symptom was reported for 27.8% and 18.6% of PHiD-CV/dPly/PhtD-10 and PHiD-CV/dPly/PhtD-30 recipients, for 19.3% of PHiD-CV, and 24.3% of PCV13 recipients. Vaccination-related unsolicited symptoms were reported for none of the PHiD-CV/dPly/PhtD vaccines, for 1.4% of PHiD-CV, and 0.7% of PCV13 vaccines.

SAEs were reported for 56 children during the primary vaccination course (12 in PHiD-CV/dPly/PhtD-10 group, 9 in PHiD-CV/dPly/PhtD-30 group, 21 in PHiD-CV group, and 14 in PCV13 group), and for 4 in the post-booster period (1 in PHiD-CV/dPly/PhtD-10 group and 3 in PCV13 group). No fatal events were reported. One hypotonic-hyporesponsive episode on the day of the first PHiD-CV dose was considered causally related to vaccination; the event resolved without sequelae after 6 days. Four SAEs not causally related to vaccination did not resolve by study end (2 cases of psychomotor retardation in PHiD-CV/dPly/PhtD-10 and PHiD-CV groups each, 1 type I diabetes mellitus in the PHiD-CV/dPly/PhtD-30 group, and 1 thermal burn in the PCV13 group).
### Table 2

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Anti-Ply antibodies 12 EL.U/mL</th>
<th>N</th>
<th>% (95% CI)</th>
<th>Anti-PhtD antibodies 17 EL.U/mL</th>
<th>N</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-pri</td>
<td>132 100 (97.2–1212.46)</td>
<td>100</td>
<td>100 (97.2–1449.60)</td>
<td>131 100 (97.3–1325.73)</td>
<td>100</td>
<td>100 (97.3–1635.43)</td>
</tr>
<tr>
<td>Post-pri</td>
<td>130 100 (97.2–1205.81)</td>
<td>100</td>
<td>100 (97.2–1246.11)</td>
<td>134 100 (97.3–1117.49)</td>
<td>100</td>
<td>100 (97.3–129838.18)</td>
</tr>
<tr>
<td>Pre-bst</td>
<td>128 100 (97.2–1246.11)</td>
<td>100</td>
<td>100 (97.2–129838.18)</td>
<td>129 100 (97.2–13844.44)</td>
<td>100</td>
<td>100 (97.2–29838.18)</td>
</tr>
<tr>
<td>Post-bst</td>
<td>129 100 (97.2–13844.44)</td>
<td>100</td>
<td>100 (97.2–29838.18)</td>
<td>129 100 (97.2–13844.44)</td>
<td>100</td>
<td>100 (97.2–29838.18)</td>
</tr>
</tbody>
</table>

N, number of children with antibody concentrations ≥ 12 EL.U/mL; %, percentage of children with antibody concentration higher or equal to the assay cut-off; GMC, geometric mean concentration; 95% CI, 95% confidence interval; ELISA, enzyme-linked immunosorbent assay; Pre-pri, pre-primary vaccination; Post-pri, 1 month post-primary vaccination; Pre-bst, pre-booster vaccination; Post-bst, 1 month post-booster vaccination.

3.3. Immunogenicity

Superiority of PHiD-CV/dPly/PhtD-30 over PHiD-CV/dPly/PhtD-10 in terms of post-dose 3 antibody concentrations against Ply and against PhtD was demonstrated (Table 1). Higher anti-Ply and anti-PhtD antibody geometric mean concentrations (GMCs) were observed following vaccination with PHiD-CV/dPly/PhtD-30 than with the PHiD-CV/dPly/PhtD-10 formulation.

3.3.1. Pneumococcal proteins

At all timepoints, all children in the PHiD-CV/dPly/PhtD groups were seropositive for Ply and PhtD, whereas in the control groups, not all were seropositive for PhtD during the booster phase (Table 2). In both PHiD-CV/dPly/PhtD groups, anti-Ply antibody GMCs increased from pre- to post-primary vaccination, remained higher than baseline levels up to booster vaccination, and mounted again post-booster dose. In control groups, antibody GMCs declined from baseline to post-primary vaccination and tended to increase again at the subsequent timepoints, although values remained below the baseline. For PhtD, antibody GMCs increased 1 month post-primary vaccination only in PHiD-CV/dPly/PhtD groups. In all groups, pre-booster vaccination, anti-PhtD antibody GMCs tended to be lower than baseline values, and in control groups lower values than post-primary vaccination were observed. Following booster dose, anti-PhtD antibody GMCs increased in both PHiD-CV/dPly/PhtD groups, while they remained below baseline in control groups (Table 2). At any timepoint, higher GMCs for Ply and PhtD antibodies were observed in the PHiD-CV/dPly/PhtD groups than in control groups as a consequence of immune response in the PHiD-CV/dPly/PhtD groups and decreased antibody level in the control groups.

3.3.2. Pneumococcal serotypes and protein D

One month post-primary vaccination, for 8 out of the 10 common serotypes (except 6B and 23F), at least 98.5% of infants in the PHiD-CV/dPly/PhtD groups, and at least 97.7% and 96.2% in the PHiD-CV and PCV13 groups had antibody concentrations ≥ 0.2 μg/mL (Table S4). For serotypes 19A, 6A, and 3, the percentages of infants with antibody concentrations ≥ 0.2 μg/mL were at least 96.2% in the PCV13 group, while in the 3 PHiD-CV groups, the percentages ranged between 46.3–46.9% for serotype 19A, 31.8–33.8% for 6A, and 10.8–13.6% for serotype 3.

In all groups, for each PHiD-CV serotype, antibody GMCs were higher post-primary and post-booster vaccination compared to baseline. Pre-booster, for each PHiD-CV serotype, antibody GMCs had decreased but remained above baseline levels, except for 6B in PHiD-CV groups, for which an increasing trend in antibody GMCs over time was observed (Table 3). For serotypes 19A and 6A, an increase in antibody GMCs across timepoints was evident post-booster vaccination, for all PHiD-CV groups. In the PCV13 group, antibody GMCs increased post-primary and post-booster vaccination for serotypes 19A, 6A and 3 (Table 3).

One month post-primary vaccination, for each of the 10 PHiD-CV serotypes, at least 88.9% and 91.1% of infants in PHiD-CV/dPly/PhtD-10 and PHiD-CV/dPly/PhtD-30 groups had OPA titers >8, except for serotype 1 (66.7% and 57.9%, respectively), while this percentage was ≥87.7% in the PHiD-CV group and ≥88.9% in the PCV13 group, except for serotype 1 (61.5% and 83.9% respectively) (Table S5).

In increases in OPA titers were observed for each PHiD-CV serotype following primary and booster doses in the PHiD-CV/dPly/PhtD groups, as well as in the control groups. For serotype 6A, an increase in OPA titers post-booster dose with respect to primary vaccination was observed in all PHiD-CV groups. There was no apparent increase in OPA titers for serotype 3 in PHiD-CV groups, following subsequent vaccine doses (Table 4).
The percentage of infants with anti-protein-D antibody concentrations ≥ 100 ELISA Units (ELU)/mL increased from 12 to 19% pre-vaccination to at least 93.4% in the PHID-CV groups and 40.9% in the PCV13 group post-primary vaccination. Pre-booster dose, these percentages ranged between 95.4 and 97.7% for groups receiving protein D-containing formulations, and decreased to 28.7% for the PCV13 group (Table S4). anti-PD antibody GMC values in the 3 PHID-CV groups increased following primary and booster vaccination, and were higher than those in the PCV13 group at all post-vaccination timepoints (Table 3).
post-booster antibody GMC, which was lower in the PCV13 group than in the 3 PhID-CV groups (Table S6).

4. Discussion

This is the first study assessing the safety and reactivity of 2 investigational vaccine formulations combining pneumococcal proteins with the 10 conjugated PhID-CV polysaccharides administered according to a 3+1 schedule in infants 6–14 weeks of age at first vaccination.

In the context of pediatric vaccination, the occurrence of fever post-vaccination is a major concern for both parents and physicians [14]. The current study demonstrated that the addition of Ply and PhD to the PhID-CV formulation does not significantly increase incidences of post-vaccination fever >40.0 °C compared to the licensed PhID-CV, when co-administered with DTPa-HBV-IPV/Hib, which is a vaccine commonly included in pediatric immunization programs.

The reactivity profile of both PhID-CV/dPly/PhD formulations appeared to be similar to that of PhID-CV. No apparent increased reactivity was observed after consecutive primary doses of the vaccines, while post-booster dose, incidences of local and general solicited symptoms seemed to be higher than those observed for primary vaccination. Incidences of unsolicited AEs appeared similar within the 3 PhID-CV groups, and in line with previous reports on PhID-CV co-administration with DTPa-HBV-IPV/Hib [15]. No fatal SAEs were reported in this study.

The induction of immune responses against Ply and PhD by both investigational PhID-CV/dPly/PhD vaccines post primary vaccination seemed to be dose-dependent, with a higher response for the 30 μg formulation. This result complements previous studies assessing immune response induced by the 2 formulations against pneumococcal proteins in toddlers [9] and is in agreement with observations made in adults for other vaccines containing different doses of PhD [16,17] or dPly [18]. Pre-vaccination levels of Ply and PhD antibodies appeared similar to those observed in adult studies for other vaccines containing different doses of PhD [9].

Table 4

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>PhID-CV vaccine serotypes</th>
<th>PHID-CV</th>
<th>PHID-CV/dPly/PhD-10</th>
<th>PHID-CV/dPly/PhD-30</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>GMT (95% CI)</td>
<td>N</td>
<td>GMT (95% CI)</td>
<td>N</td>
</tr>
<tr>
<td>Post-pri</td>
<td>63</td>
<td>38.6 (24.6–60.5)</td>
<td>57</td>
<td>27.8 (17.5–44.2)</td>
</tr>
<tr>
<td>Pre-bst</td>
<td>44</td>
<td>12.4 (7.6–20.1)</td>
<td>40</td>
<td>13.2 (8.3–21.1)</td>
</tr>
<tr>
<td>Post-bst</td>
<td>68</td>
<td>373.5 (253–550.8)</td>
<td>56</td>
<td>369.2 (252.8–539.4)</td>
</tr>
<tr>
<td>Pre-pri</td>
<td>41</td>
<td>703.7 (533–928.2)</td>
<td>57</td>
<td>844.4 (660.8–1079.0)</td>
</tr>
<tr>
<td>Post-bst</td>
<td>68</td>
<td>36.2 (19.1–68.4)</td>
<td>36</td>
<td>48.3 (25.0–90.6)</td>
</tr>
<tr>
<td>Pre-pri</td>
<td>60</td>
<td>1370.7 (1014.3–1816.6)</td>
<td>57</td>
<td>1634.8 (1284.8–2080.3)</td>
</tr>
<tr>
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<td>63</td>
<td>47.3 (33.6–66.6)</td>
<td>56</td>
<td>60.6 (44.1–83.3)</td>
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<td>Pre-pri</td>
<td>63</td>
<td>9.3 (6.9–12.5)</td>
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<td>10.5 (6.9–16.1)</td>
</tr>
<tr>
<td>Post-bst</td>
<td>68</td>
<td>1545.1 (1118.1–2348.4)</td>
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<td>166.8 (118.4–2348.4)</td>
</tr>
<tr>
<td>Pre-pri</td>
<td>61</td>
<td>399.6 (249.6–640.6)</td>
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<td>454.7 (259.6–688.7)</td>
</tr>
<tr>
<td>Post-bst</td>
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<td>103.2 (56.5–188.4)</td>
<td>36</td>
<td>174.5 (102.1–298.2)</td>
</tr>
<tr>
<td>Pre-pri</td>
<td>66</td>
<td>802.1 (531.7–1210.0)</td>
<td>58</td>
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<td>68</td>
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<td>Post-bst</td>
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<td>7.8 (5.4–11.2)</td>
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</tbody>
</table>

N, number of children with available results; 95% CI, 95% confidence interval; GMT, geometric mean titer; Post-pri, 1 month post-primary vaccination; Pre-bst, pre-booster vaccination; Post-bst, 1 month post-booster-vaccination.
responses against pneumococcal proteins have been established yet, so the clinical significance of this finding is unknown. Although protective effect of pneumococcal Ply and PhdT proteins against lethal challenge, pneumonia or colonization has been well documented in animals [23–29], no effect of immunization with pneumococcal proteins on nasopharyngeal colonization was observed in the Gambian infants [22]. Another study has been ongoing to determine an effect on clinical disease endpoints such as AOM (ClinicalTrials.gov, NCT01545375).

Immune responses against the 10 PHID-CV serotypes following administration of PHID-CV/dPly/PhdT-10 and PHID-CV/dPly/PhdT-30 were in the same ranges as those induced by the PHID-CV vaccine. Addition of dPly and PhdT in quantities of either 10 or 30 μg each to the PHID-CV polysaccharides did not appear to impact immune responses to vaccine serotypes.

We did not observe any interference in the immune response induced by DTPa-HBV-IPV/Hib when co-administered with PHID-CV/dPly/PhdT vaccines. Immune responses against DTPa-HBV-IPV/Hib components did not seem to differ between the 3 PHID-CV groups and were in line with previous results for co-administration with PHID-CV [30]. This result, together with the safety assessment, suggests that both PHID-CV/dPly/PhdT formulations can be co-administered with DTPa-HBV-IPV/Hib in infants.

The study has several strengths. High compliance rates with the protocol-defined procedures, including vaccination schedules, were observed, which supports the validity of safety and immunogenicity analyses. The study was designed to demonstrate 2 confirmatory objectives. Study limitations include the fact that, for the pneumococcal proteins, immunogenicity assessment was carried out by measuring antibody levels, for which the correlate of protection has not yet been established [31]. Although functional assays for pneumococcal protein antibodies may be better suited to characterize immune response, they were not available at the time of the analysis. No statistical comparisons between the 2 comparator vaccines were carried out, and OPA testing was performed in a limited subset of participants; therefore, comparison of the 2 licensed PCVs and OPA results should be interpreted with caution, bearing also in mind that the clinical relevance of the difference in immunogenicity profiles of these vaccines remains unknown and that evidence has grown on the comparability of their effect on pneumococcal diseases [32]. Lastly, anti-Ply and anti-PhdT antibody concentrations were determined through an assay not calibrated for values expressed in μg/mL, so a comparison with data reported in SI units is not possible.

5. Conclusions

PHID-CV/dPly/PhdT-10 and PHID-CV/dPly/PhdT-30 formulations co-administered with DTPa-HBV-IPV/Hib according to a 3+1 schedule during the first two years of life have shown a similar reactogenicity profile as the licensed PHID-CV in terms of incidence of febrile reactions causally related to primary vaccination. Immune responses to vaccine pneumococcal serotypes and to co-administered DTPa-HBV-IPV/Hib vaccine antigens elicited in PHID-CV/dPly/PhdT groups did not appear altered in comparison to those in the PHID-CV group. Both formulations had a clinically acceptable profile with regard to tolerability and immunogenicity, comparable to PHID-CV.

5.1. Trademark statement

Synflorix and Infanrix hexa are trademarks of the GSK group of companies. Prevenar 13/ Prevenar 13 is a trademark of Pfizer Inc.

Conflict of interest

R. Prymula reports grants from GSK group of companies during the conduct of the study and grants from GSK group of companies, Novartis, Sanofi Pasteur outside the submitted work. L. Szenborn reports grants from GSK group of companies during the conduct of the study and grants for participation in conferences and honoraria as speaker from Sanofi Pasteur, Pfizer, Novartis and GSK group of companies outside the submitted work. S.A. Silfverdal has received board membership payment in 2008–2012 from the GSK Sweden Advisory Board on pneumococcal vaccines. J. Wysocki reports grants from GSK group of companies during the conduct of the study. P. Albrecht reports grants and grants for participation in conferences and honoraria as speaker from Pfizer, MSD and GSK group of companies outside the submitted work. M. Traskine, Y. Song, D. Borsys are employees of GSK group of companies. D. Borsys owns restricted shares of the GSK group of companies. A. Gardev was employed by the GSK group of companies.

Author’s contribution


Funding

GlaxoSmithKline Biologicals SA was the funding source and was involved in all stages of the study conduct and analysis. GlaxoSmithKline Biologicals SA also took responsibility for the development and publishing of the present manuscript.

Previous publications

The results of this study were presented in part as follows:


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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2017.07.008.

References


