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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 [a,*], Leszek Szenborn [b], Sven-Arne Silfverdal [c], Jacek Wysocki [d,e], Piotr Albrecht [f], Magali Traskine [g], Asparuh Gardev [g,1], Yue Song [g], Dorota Borys [g]

[a] Department of Social Medicine, Faculty of Medicine in Hradec Králové, Charles University in Prague, Šimkova 870, 500 38 Hradec Králové, Czech Republic
[b] Department and Clinic of Pediatric Infectious Diseases, Wroclaw Medical University, 2-2A, Chalubinskiego, 50-368 Wroclaw, Poland
[c] Clinical Sciences, Pediatrics, Umeå University, SE-90185 Umeå, Sweden
[d] Poznań University of Medical Sciences, ul. H.Święcickiego 6, 60-781 Poznań, Poland
[e] Regional Medical Center for Mother and Child, ul. Smoluchowskiego 11, 60-179 Poznań, Poland
[f] Medical University of Warsaw, Department of Paediatric Gastroenterology and Nutrition, ul. Żwirki i Wigury 63A, 02-091 Warsaw, Poland
[g] GSK, Av. Fleming 20, 1300 Wavre, Belgium

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ABSTRACT

Introduction: Vaccination with formulations containing pneumococcal protein antigens such as pneumolysin toxoid (dPly) and histidine-triad protein D (PhtD) 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 PhtD each. Infants randomized 1:1:1:1 received 4 doses of PHiD-CV/dPly/PhtD-10, PHiD-CV/dPly/PhtD-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/PhtD 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/PhtD-10, PHiD-CV/dPly/PhtD-30, PHiD-CV, and PCV13 groups, respectively. PHiD-CV/dPly/PhtD-30 was superior to PHiD-CV/dPly/PhtD-10 in terms of post-dose 3 anti-Ply and Anti-PhtD antibody levels. Anti-Ply and anti-PhtD antibody levels were higher in both PHiD-CV/dPly/PhtD 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/PhtD 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/PhtD formulations co-administered with DTPa-HBV-IPV/Hib in infants were well-tolerated and immunogenic for dPly and PhtD antigens, while immune responses to serotype-specific, protein D and co-administered antigens did not appear altered in comparison to PHiD-CV group.

1. Introduction

Streptococcus pneumoniae causes severe infectious diseases such as meningitis, bacteremia and pneumonia, and common illnesses including sinusitis and otitis media [1,2].

* Corresponding author.
E-mail addresses: prymula@fnhk.cz (R. Prymula), leszek.szenborn@umed.wroc.pl (L. Szenborn), sven.arne.silfverdal@umu.se (S.-A. Silfverdal), jwysocki@ump.edu.pl (J. Wysocki), dr.piotr.albrecht@gmail.com (P. Albrecht), magali.x.traskine@gsk.com (M. Traskine), agardev@gmail.com (A. Gardev), yue.x.song@gsk.com (Y. Song), dorota.d.borys@gsk.com (D. Borys).
[1] Current address: AstraZeneca, CRR-CEE, Bulgaria.

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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 non-typeable *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* 13™, 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-

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