Phase 3 study of safety, tolerability and immunogenicity of V114 pneumococcal vaccine compared with PCV13 in a 2+1 regimen in healthy infants (PNEU-PED-EU-2)

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Background

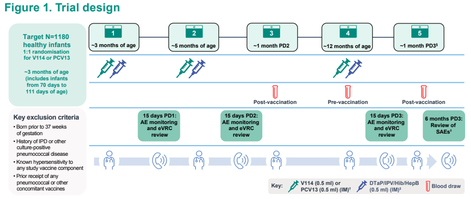
- Despite the availability of pneumococcal conjugate vaccines (PCVs) in children, there has been an increase in the burden of pneumococcal disease caused by non-vaccine serotypes.[1,2]
  - Serotypes 22F and 33F have emerged as important causes of invasive pneumococcal disease (IPD) during the PCV era.[3,4]
- V114 (VAXNEUVANCE™, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA) is a 15-valent PCV containing the 13 serotypes in 13-valent PCV (PCV13; Prevenar 13™; Pfizer Inc.) plus two additional serotypes (22F and 33F), providing broader protection against pneumococcal disease.[5,6]
- This Phase 3 study evaluated the safety and immunogenicity of a 2+1 regimen of V114 compared with PCV13 in healthy infants and concomitant administration of V114 or PCV13 with diphtheria, tetanus and pertussis (DTaP)/inactivated poliovirus (IPV)/*Haemophilus influenzae* type b (Hib)/hepatitis B (HepB) vaccine administered at 3, 5 and 12 months of age.

Methods

Study design

- PNEU-PED-EU-2 was a Phase 3, randomised, multisite, double-blind, parallel group, active-comparator controlled study to evaluate the safety, tolerability and immunogenicity of a three-dose regimen of V114 in healthy infants (V114-026, NCT04016714; EudraCT 2018-003788-70; **Figure 1**).
- Healthy infants were randomised in a 1:1 ratio to receive either V114 or PCV13 administered as a two-dose primary series at ~3 and 5 months of age, followed by a toddler dose at ~12 months of age.
- Solicited injection-site and systemic adverse events (AEs) were collected for 14 days following each vaccination, and serious AEs (SAEs) were collected throughout the duration of the study. Body temperature was measured daily for 7 days following each vaccination.
- Serotype-specific antibodies were measured at 30 days post-dose 2 (PD2; following second primary infant dose), immediately before receipt of dose 3 and 30 days post-dose 3 (PD3; following toddler dose).

Figure 1. Trial design



[1]Vaccines were dispensed and administered in a blinded fashion by unblinded study personnel who were not involved in any subsequent participant assessments.
[2]Participants received MMR and varicella vaccines during Visit 4.
[3]Participants in Norway and Denmark received a second dose of varicella vaccine (locally sourced) during Visit 5 after the final blood draw.
[4]Information about SAEs and deaths were collected throughout the study.
AE, adverse event; DTaP, diphtheria, tetanus and pertussis; eVRC, electronic vaccination report card; HepB, hepatitis B; Hib, *Haemophilus influenzae* type b; IM, intramuscular; IPD, invasive pneumococcal disease; IPV, inactivated poliovirus; MMR, measles, mumps and rubella; PCV13, 13-valent pneumococcal conjugate vaccine; PD1/2/3, post-dose 1/2/3; SAE, serious adverse event; V114, 15-valent pneumococcal conjugate vaccine.

Safety and immunogenicity evaluation

All-participants-as-treated population[1]

Safety evaluation

- Investigators assessed complaints collected directly from participants' legally acceptable representative via an electronic vaccination report card (eVRC) to determine whether they met the protocol-specified definition of solicited and unsolicited AEs. The eVRC was used to record body temperatures (rectal and/or axillary), solicited injection-site and systemic AEs, unsolicited injection-site and systemic AEs, SAEs, concomitant medications and non-study vaccinations during the study.

Per-protocol population[2]

Immunogenicity evaluation

- Serotype-specific immune responses to the 15 serotypes included in V114 were evaluated via:
  - Validated multiplexed opsonophagocytic killing assay (MOPA): to quantify antibodies with opsonophagocytic killing activity.[7]
  - Validated pneumococcal electrochemiluminescence (Pn ECL) immunoassay: to quantify immunoglobulin G (IgG).[8]
- Antigen-specific response rates to DTaP/IPV/Hib/HepB vaccine were also measured.
- The between-treatment difference (V114−PCV13) and its 95% confidence interval (CI) were calculated using the Miettinen and Nurminen method.
- Immune response rates, IgG geometric mean concentrations (GMCs), IgG GMC ratios and their corresponding 95% CIs were calculated using the Miettinen and Nurminen and t-distribution methods.

[1]All randomised participants who received the relevant study vaccination for the timepoint of interest. One participant in each group received both V114 and PCV13 and were excluded from this population.
[2]All randomised participants without protocol deviations that could have substantially affected the results of the immunogenicity analyses.

Primary study objectives

Safety and tolerability: To evaluate the safety and tolerability of V114 with respect to the proportion of participants with AEs.

Immunogenicity:

- To compare the anti-pneumococcal polysaccharide (PnPs) serotype-specific IgG response rates (proportion of participants meeting serotype-specific IgG threshold value of ≥0.35 µg/ml) at 30 days PD3 for participants administered V114 versus participants administered PCV13.
- To compare anti-PnPs serotype-specific IgG GMCs at 30 days PD3 for participants administered V114 versus participants administered PCV13.

Key secondary study objectives

- To compare the antigen-specific response rates to each antigen included in DTaP/IPV/Hib/HepB vaccines at 30 days PD3 for participants administered V114 concomitantly with DTaP/IPV/Hib/HepB versus participants administered PCV13 concomitantly with DTaP/IPV/Hib/HepB.
- To evaluate the anti-PnPs serotype-specific IgG response rates and GMCs at 30 days PD2 by each vaccination group.
- Opsonophagocytic activity (OPA) subset: To evaluate the anti-PnPs serotype-specific OPA geometric mean titres (GMTs) and response rates at 30 days PD3 by each vaccination group.

Results

Participant disposition

- This study was conducted during the coronavirus disease 2019 (COVID-19) pandemic.
- Of 1203 eligible participants, 1191 were randomised.
  - In the V114 (n=595) and PCV13 (n=596) groups, all participants were vaccinated with at least one dose of V114 or PCV13.
  - 23 participants in the V114 group and 16 participants in the PCV13 group discontinued the study owing to reasons including withdrawals by parent/guardian, physician decision, loss to follow-up or death.
- Demographic and baseline characteristics were generally comparable across the two intervention groups (**Table 1**).

Table 1. Participant demographics

	Total (N=1191) %	V114 (n=595) %	PCV13 (n=596) %
Sex			
Male	52.9	54.3	51.5
Female	47.1	45.7	48.5
Age (weeks)			
10	11.0	11.8	10.2
11	17.1	17.1	17.1
12	22.1	21.8	22.3
13	24.4	25.5	23.3
14	17.9	16.6	19.1
15	7.5	7.1	7.9
Mean, weeks (range)	12.4 (10–15)	12.4 (10–15)	12.5 (10–15)
Race			
White	97.2	97.3	97.1
Asian	0.5	0.3	0.7
American Indian/ Alaska Native	0.2	0.2	0.2
Multiple	2.1	2.2	2.0
Ethnicity			
Not Hispanic/Latino	95.2	94.8	95.6
Hispanic/Latino	4.0	4.4	3.7
Not reported	0.5	0.5	0.5
Unknown	0.3	0.3	0.2

Table includes data from all vaccinated participants.
PCV13, 13-valent pneumococcal conjugate vaccine; V114, 15-valent pneumococcal conjugate vaccine.

Safety

Safety results

- The proportions of participants with AEs, including injection-site, systemic and vaccine-related AEs, and SAEs following any dose of V114 or PCV13 were comparable between vaccination groups (**Table 2**).
  - The majority of participants (>99%) in the V114 and PCV13 vaccine groups experienced at least one AE.
  - One participant in the V114 group died due to brain neoplasm that was not related to the vaccine.

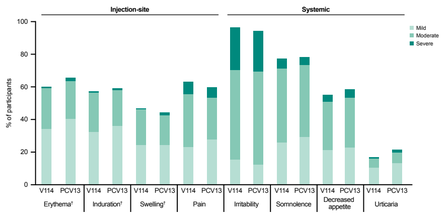
Table 2. Summary of AEs after vaccination with V114 or PCV13

	V114 (n=595) %	PCV13 (n=594) %	Percentage point difference [V114−PCV13] (95% CI)[†]
Any AEs	99.3	99.7	−0.3 (−1.4, 0.6)
Injection-site	88.2	89.4	
Systemic	98.8	98.8	
Any vaccine-related AEs[‡]	99.2	99.2	0.0 (−1.2, 1.2)
Injection-site	88.2	89.4	
Systemic	97.6	97.5	
Any SAEs	5.0	4.7	0.3 (−2.2, 2.8)
Any vaccine-related SAEs[‡]	0.3	0.3	−0.0 (−0.9, 0.9)
Deaths	0.2[§]	0.0	0.2 (−0.5, 0.9)
Solicited injection-site AEs	87.6	88.7	
Erythema	60.0	65.5	−5.5 (−11.0, 0.0)
Induration	57.0	59.1	−2.1 (−7.7, 3.5)
Pain	63.0	59.6	3.4 (−2.1, 8.9)
Swelling	46.4	44.1	2.3 (−3.4, 7.9)
Solicited systemic AEs	97.6	97.1	
Decreased appetite	54.8	58.2	−3.5 (−9.1, 2.2)
Irritability	96.3	94.1	2.2 (−0.2, 4.7)
Somnolence	77.3	77.9	−0.6 (−5.4, 4.1)
Urticaria	16.8	21.4	−4.6 (−9.1, −0.1)

Reported AEs include non-serious AEs that occurred within 14 days of vaccination and SAEs that occurred after dose 1 (~3 months of age) through completion of study participation.
[†]Estimated differences and CIs calculated based on Miettinen and Nurminen method and are provided in accordance with the statistical analysis plan.
[‡]Determined by the investigator to be related to the vaccine.
[§]One participant in the V114 group died due to brain neoplasm that was assessed by the investigator as not related to the study vaccine.
AE, adverse event; CI, confidence interval; PCV13, 13-valent pneumococcal conjugate vaccine; SAE, serious adverse event; V114, 15-valent pneumococcal conjugate vaccine.

- The proportions of participants with solicited injection-site AEs and systemic AEs were generally comparable across both vaccination groups (**Figure 2**).
  - In both vaccination groups, most of the solicited AEs were mild or moderate in intensity and of short duration (≤3 days), with the exception of injection-site induration (≤5 days; data not shown).

Figure 2. Proportion of participants with solicited AEs after vaccination with V114 or PCV13 by maximum intensity (>0% incidence)



AEs were solicited from Day 1 through Day 14 following each vaccination; V114 group (N=595); PCV13 group (N=596).
[a]For injection-site erythema, induration and swelling, mild events were those measuring 0 to ≤1 inch (~2.5 cm), moderate events were >1 to ≤3 inches (~7.5 cm) and severe events were >3 inches.
AE, adverse event; PCV13, 13-valent pneumococcal conjugate vaccine; V114, 15-valent pneumococcal conjugate vaccine.

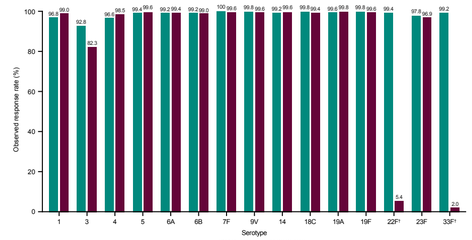
- The most frequently reported AEs following vaccination with V114 were irritability, somnolence and injection-site pain (**Table 2**).
  - Four participants (two in each group) experienced a vaccine-related SAE.
    - Two participants in the V114 group and one participant in the PCV13 group experienced pyrexia.
    - One participant in the PCV13 group experienced febrile convulsion.
- The majority of participants in both groups reported body temperature measurements <39.0 °C and, overall, temperature distribution was comparable between intervention groups following any dose of study intervention (data not shown).

Immunogenicity

Immunogenicity results

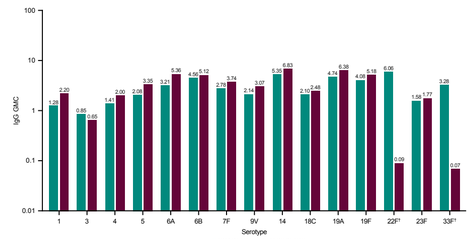
- V114 met non-inferiority criteria for all 13 shared serotypes and superiority criteria for serotypes 22F and 33F, as assessed by immune response rates (proportions of participants meeting the IgG threshold value of ≥0.35 µg/ml) for each serotype (**Figure 3**) and GMCs at 30 days PD3 (**Figure 4**).

Figure 3. Immune response rates at 30 days post-dose 3



Per-protocol population. Response defined as IgG ≥0.35 µg/ml. Per protocol, dose 3 was administered at ~12 months of age. N = number of participants randomised and vaccinated.
[1]Two additional serotypes in V114.
[2]Estimated difference, CI and *P* value are based on the Miettinen and Nurminen method.
[3]For the 13 shared serotypes, a conclusion of non-inferiority of V114 to PCV13 is based on the lower bound of the 2-sided 95% CI for the difference in percentages (V114−PCV13) being >−10 percentage points (1-sided *P* value <0.025). For the two additional serotypes in V114, a conclusion of superiority of V114 to PCV13 is based on the lower bound of the 2-sided 95% CI for the difference in percentages (V114−PCV13) being >10 percentage points (1-sided *P* value <0.025).
CI, confidence interval; IgG, immunoglobulin G; PCV13, 13-valent pneumococcal conjugate vaccine; V114, 15-valent pneumococcal conjugate vaccine.

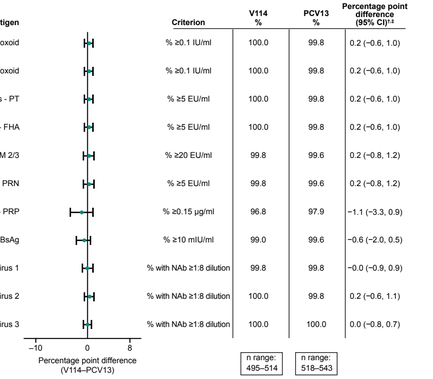
Figure 4. Serotype-specific IgG GMCs at 30 days post-dose 3



Per-protocol population. Per protocol, dose 3 was administered at ~12 months of age. N = number of participants randomised and vaccinated.
[1]Two additional serotypes in V114.
[2]GMC ratio, CI and *P* value are calculated using the t-distribution, with the variance estimate from a serotype-specific linear model utilising the natural log-transformed antibody concentrations as the response and a single term for vaccination group.
[3]For the 13 shared serotypes, a conclusion of non-inferiority of V114 to PCV13 is based on the lower bound of the 2-sided 95% CI for the GMC ratio (V114−PCV13) being >0.5 (1-sided *P* value <0.025). For the two additional serotypes in V114, a conclusion of superiority of V114 to PCV13 is based on the lower bound of the 2-sided 95% CI for the GMC ratio (V114−PCV13) being >2.0 (1-sided *P* value <0.025).
CI, confidence interval; GMC, geometric mean concentration; IgG, immunoglobulin G; PCV13, 13-valent pneumococcal conjugate vaccine; V114, 15-valent pneumococcal conjugate vaccine.

- Immune responses to DTaP/IPV/Hib/HepB vaccine administered concomitantly with V114 met non-inferiority criteria, as assessed by the proportions of participants meeting antigen-specific responses to antigens included in DTaP/IPV/Hib/HepB vaccine at 30 days PD3 (**Figure 5**).
- Serotype-specific IgG response rates and IgG GMCs were comparable for most of the 13 shared serotypes between the intervention groups and were higher for the two additional serotypes (22F and 33F) in the V114 group compared with the PCV13 group at 30 days PD2 (data not shown).
- Serotype-specific OPA response rates and OPA GMTs were generally comparable for the 13 shared serotypes between the intervention groups and were higher for serotype 22F in the V114 group compared with PCV13 group at 30 days PD3. The OPA response rate for serotype 33F was generally comparable between intervention groups at 30 days PD3, while the OPA GMT was higher in the V114 group (data not shown).

Figure 5. Antigen-specific response rates to DTaP/IPV/Hib/HepB vaccines at 30 days post-dose 3



Per-protocol population. Per protocol, dose 3 was administered at ~12 months of age. n = number of participants contributing to the analysis.
[1]Estimated difference and CI are based on the Miettinen and Nurminen method.
[2]A conclusion of non-inferiority of DTaP/IPV/Hib/HepB administered concomitantly with V114 to DTaP/IPV/Hib/HepB administered concomitantly with PCV13 is based on the lower bound of the 2-sided 95% CI for the difference in percentages (V114−PCV13) being greater than the pre-specified non-inferiority margin (1-sided *P* value <0.025).
CI, confidence interval; DTaP, diphtheria, tetanus and pertussis; EU, endotoxin unit; FHA, filamentous haemagglutinin; FIM 2/3, fimbriae types 2 and 3; HBsAg, hepatitis B surface antigen; HepB, hepatitis B; Hib, *Haemophilus influenzae* type b; IPV, inactivated poliovirus; IU, international unit; NAb, neutralising antibodies; PCV13, 13-valent pneumococcal conjugate vaccine; PRN, pertactin; PRP, polyribosylribitol phosphate; PT, pertussis toxin; V114, 15-valent pneumococcal conjugate vaccine.

Conclusions

In healthy infants and toddlers receiving a two-dose infant series followed by a toddler dose of either V114 or PCV13:

- V114 is well tolerated, with a safety profile generally comparable to PCV13.
- V114 is non-inferior to PCV13 for the 13 shared serotypes and superior to PCV13 for the two additional serotypes (22F and 33F) following both the toddler dose and the two-dose primary series, as assessed by serotype-specific IgG response rates and GMCs.
- V114 induces functional antibodies (OPA) capable of bactericidal killing of *Streptococcus pneumoniae* after the toddler dose.
- V114 can be administered concomitantly with licensed paediatric vaccines, including DTaP/IPV/Hib/HepB vaccines.

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