Phase 3 study of safety, tolerability and immunogenicity of V114 compared with PCV13 in 2+1 (full-term) and 3+1 (pre-term) regimens in healthy infants (PNEU-PED-EU-1)

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Background

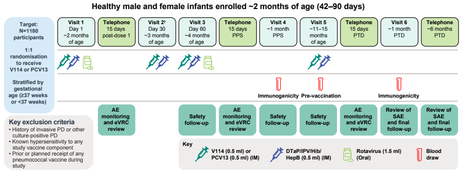
- Despite widespread use of pneumococcal conjugate vaccines (PCVs) in children, pneumococcal disease (PD) caused by non-vaccine serotypes (NVTs) remains a concern.[1,2]
  - The presence of NVTs can alter the distribution of PCV serotypes and increase the incidence of PD, leading to higher morbidity and mortality in children.[1]
  - Consequently, higher valent vaccines (including additional serotypes, such as 22F and 33F) are being developed.[1]
- V114 (VAXNEUVANCE™, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA) is a 15-valent PCV that contains all 13 serotypes in the 13-valent PCV (PCV13; Prevenar 13™; Pfizer Inc.) plus two epidemiologically important serotypes, 22F and 33F, providing broader protection for PD.[3,4]
- This Phase 3 study evaluated the safety and immunogenicity of V114 compared with PCV13 administered as a 2+1 dosing regimen in healthy and pre-term infants, along with concomitant administration with diphtheria, tetanus and pertussis (DTaP)/inactivated poliovirus (IPV)/*Haemophilus influenzae* type B (Hib)/hepatitis B (HepB) and rotavirus vaccines.

Methods

Study design

- PNEU-PED-EU-1 was a Phase 3, multicentre, randomised, double-blind, active comparator-controlled study to evaluate the safety, tolerability and immunogenicity of a three-dose regimen of V114 in healthy infants (V114-025, NCT04031846, EudraCT 2018-003787-31; **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 2 and 4 months of age, followed by a toddler dose at 11–15 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-primary series (PPS), immediately before receipt of toddler dose, and 30 days post-toddler dose (PTD).

Figure 1. Trial design



[1]During Visit 2, V114/PCV13 vaccination was given to pre-term infants only (additional dose), and legally acceptable representatives were contacted by telephone 15 days after visit.
AE, adverse event; DTaP, diphtheria, tetanus and pertussis; eVRC, electronic vaccination report card; HepB, hepatitis B; Hib, *Haemophilus influenzae* type B; IM, intramuscular; IPV, inactivated poliovirus; PCV13, 13-valent pneumococcal conjugate vaccine; PD, pneumococcal disease; PPS, post-primary series; PTD, post-toddler dose; SAE, serious adverse event; V114, 15-valent pneumococcal conjugate vaccine.

Safety and immunogenicity evaluation

All-participants-as-treated population†

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 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‡

Immunogenicity evaluation

- Serotype-specific immune responses to the 15 serotypes included in V114 were evaluated via:
  - Validated pneumococcal electrochemiluminescence (Pn ECL) immunoassay: to quantify immunoglobulin G (IgG).[5]
  - Validated multiplexed opsonophagocytic killing assay (MOPA): to quantify antibodies with opsonophagocytic killing activity.[6]
- 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 unstratified 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. [2]All randomised participants without protocol deviations that could have substantially affected the results of the immunogenicity analyses.

Primary 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), as well as IgG GMCs at 30 days PTD (post-dose 3 for full-term infants; post-dose 4 for pre-term infants) for participants administered V114 versus PCV13.

Key secondary objectives

- To compare the antigen-specific response rates to each antigen included in the DTaP/IPV/Hib/HepB vaccine 30 days PTD for participants administered V114 versus PCV13.
- To compare anti-rotavirus immunoglobulin A (IgA) geometric mean titres (GMTs) at 30 days PPS for participants administered the rotavirus vaccine concomitantly with V114 versus PCV13.
- To evaluate the anti-PnPs serotype-specific opsonophagocytic activity (OPA) GMTs and response rates at 30 days PTD by each vaccination group.

Results

Participant disposition

- This study was conducted during the coronavirus disease 2019 (COVID-19) pandemic.
- Of 1188 eligible participants who were randomised, 1184 were included in the final analysis:
  - In the V114 group (N=591), 588 participants were vaccinated with at least one dose of V114.
  - In the PCV13 group (N=593), 591 participants were vaccinated with at least one dose of PCV13.
  - Reasons for discontinuation included protocol deviation, withdrawal, physician decision and loss to follow-up.
- Across the V114 and PCV13 groups, demographic and baseline characteristics were generally comparable (**Table 1**).
- Approximately 6% of participants were pre-term infants.

Table 1. Participant demographics

	Total (N=1179) %	V114 (n=588) %	PCV13 (n=591) %
Sex			
Female	48.2	48.1	48.2
Male	51.8	51.9	51.8
Age (weeks)			
6	11.6	13.1	10.2
7	13.7	13.6	13.9
8	26.5	27.4	25.7
9	26.5	25.7	27.4
10	10.9	9.0	12.7
11	7.0	7.3	6.6
12	3.7	3.9	3.6
Mean, weeks (range)	8.5 (6.0–12.0)	8.4 (6.0–12.0)	8.5 (6.0–12.0)
Race			
White	96.9	97.1	96.6
American Indian/Alaska Native	0.8	0.7	0.8
Black or African American	0.6	0.7	0.5
Asian	0.8	0.7	0.8
Multiple	1.0	0.9	1.2
Ethnicity			
Not Hispanic/Latino	88.7	88.8	88.7
Hispanic/Latino	11.1	11.2	11.0
Not reported	0.1	0.0	0.2
Unknown	0.1	0.0	0.2
Gestational age (weeks)			
<37	5.8	5.4	6.1
≥37	94.2	94.6	93.9

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

Safety

Safety results

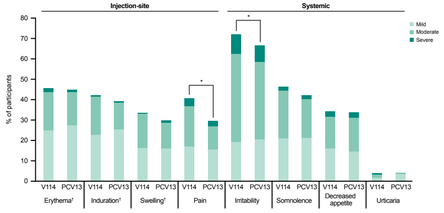
- The proportions of participants with AEs, including injection-site, systemic and vaccine-related AEs, and SAEs were comparable between vaccination groups (**Table 2**).
  - No deaths were reported in either group.
- The proportions of participants with solicited injection-site AEs and systemic AEs were generally comparable across both vaccination groups (**Figure 2**).
  - Higher proportions of participants in the V114 group compared with the PCV13 group were observed with solicited AEs of injection-site pain and irritability.
  - Of the participants in the V114 group with solicited AEs, the majority had events with a maximum intensity of mild or moderate and were of short duration (≤3 days).
- The most frequently reported AEs following vaccination with V114 were irritability, somnolence and injection-site erythema (**Table 2**).
  - No vaccine-related SAEs were reported in participants receiving V114.
- The majority of participants in the V114 group reported body temperature measurements <38.5 °C and, overall, temperature distribution was comparable to PCV13 and consistent with the overall study population (data not shown).
- V114 was well tolerated in pre-term participants, with a safety profile comparable to PCV13 and consistent with the overall study population (including full-term and pre-term infants).

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

	V114 (n=587) %	PCV13 (n=591) %	Percentage point difference [V114–PCV13] (95% CI)†
Any AEs	94.5	93.1	1.5 (−1.3, 4.3)
Injection-site	72.7	67.3	
Systemic	91.3	89.0	
Any vaccine-related AEs‡	91.1	88.8	2.3 (−1.1, 5.8)
Injection-site	72.7	67.3	
Systemic	82.3	78.0	
Any SAEs	9.7	11.8	−2.1 (−5.7, 1.4)
Any vaccine-related SAEs‡	0.0	0.2	−0.2 (−1.0, 0.5)
Deaths	0.0	0.0	0.0 (−0.6, 0.7)
Solicited injection-site AEs	72.7	66.7	
Erythema	45.3	44.7	0.6 (−5.0, 6.3)
Induration	41.9	39.1	2.8 (−2.8, 8.4)
Pain	40.5	29.3	11.3 (5.8, 16.6)
Swelling	33.6	29.4	4.1 (−1.2, 9.4)
Solicited systemic AEs	81.6	77.3	
Decreased appetite	33.9	33.5	0.4 (−5.0, 5.8)
Irritability	71.7	66.3	5.4 (0.1, 10.7)
Somnolence	46.2	41.8	4.4 (−1.3, 10.0)
Urticaria	3.7	3.9	−0.1 (−2.4, 2.1)

Reported AEs include non-serious AEs that occurred within 14 days of vaccination and SAEs that occurred after dose 1 (~2 months of age) through completion of study participation.
†Estimated differences and CIs calculated based on Miettinen & Nurminen method and are provided in accordance with the statistical analysis plan.
‡Determined by the investigator to be related to the vaccine.
AE, adverse event; CI, confidence interval; PCV13, 13-valent pneumococcal conjugate vaccine; SAE, serious adverse event; V114, 15-valent pneumococcal conjugate vaccine.

Figure 2. Proportion of participants with solicited AEs after vaccination with V114 or PCV13 by maximum intensity (≥5% incidence)



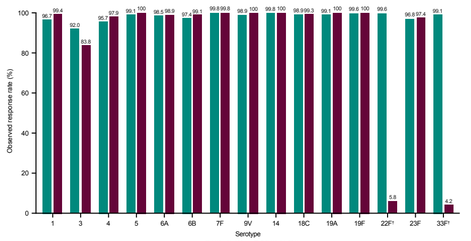
AEs were solicited on the eVRC from Day 1 through Day 14 following each vaccination; V114 group (N=587), PCV13 group (N=591).
*Statistically significant with $P<0.05$.
†For injection-site erythema, induration and swelling, mild events were those measuring 0 to ≤1 inch (~2.5 cm), moderate events were >1 to ≤3 inches (~7.5 cm) and severe events were >3 inches.
AE, adverse event; eVRC, electronic vaccination report card; PCV13, 13-valent pneumococcal conjugate vaccine; V114, 15-valent pneumococcal conjugate vaccine.

Immunogenicity

Immunogenicity results

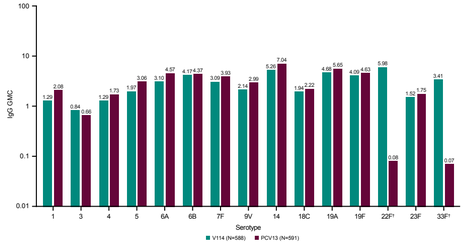
- V114 met non-inferiority criteria for the 13 shared serotypes, as assessed by the proportions of participants meeting the threshold value of ≥0.35 µg/ml (response rate) for each serotype (**Figure 3**) and serotype-specific IgG GMCs at 30 days PTD (**Figure 4**).
- V114 met superiority criteria for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

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



Per-protocol population. Response defined as IgG ≥0.35 µg/ml. Note: Per protocol, the toddler dose was administered at ~11–15 months of age.
N = number of participants randomised and vaccinated.
†Two additional serotypes in V114.
‡Estimated difference, CI and *P* value are based on the Miettinen and Nurminen method.
§For the 13 shared serotypes, a conclusion of non-inferiority of V114 to PCV13 is based on the lower bound of the 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 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.

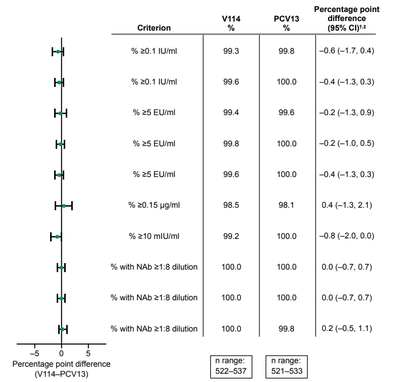
Figure 4. Serotype-specific IgG GMCs at 30 days post-toddler dose



Per-protocol population. Note: Per protocol, the toddler dose was administered at ~11–15 months of age. N = number of participants randomised and vaccinated.
†Two additional serotypes in V114.
‡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.
§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 (µg/ml); IgG, immunoglobulin G; PCV13, 13-valent pneumococcal conjugate vaccine; V114, 15-valent pneumococcal conjugate vaccine.

- Immune responses to DTaP/IPV/Hib/HepB administered concomitantly with V114 met non-inferiority criteria, as assessed by antigen-specific responses rates to each antigen at 30 days PTD (**Figure 5**).
- Immune response to rotavirus vaccine administered concomitantly with V114 met non-inferiority criteria, as assessed by anti-rotavirus IgA GMTs at 30 days PPS (**Table 3**).
- 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 V114 recipients compared with PCV13 recipients at 30 days PTD. The OPA response rate for serotype 33F was higher in V114 recipients at 30 days PPS and was generally comparable between intervention groups at the pre-toddler dose; OPA GMT for serotype 33F was higher in V114 recipients at 30 days PPS and at the pre-toddler dose (data not shown).

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



Per-protocol population. Note: Per protocol, the toddler dose was administered at ~11–15 months of age. n = number of participants contributing to the analysis.
†Estimated difference, CI and *P* value are based on the Miettinen and Nurminen method.
‡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; 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.

Table 3. Anti-rotavirus IgA GMTs at 30 days post-primary series

Antigen	V114 (n=588) IgA GMT	PCV13 (n=591) IgA GMT	GMT ratio† (V114/PCV13) Estimate (95% CI)‡
Rotavirus	45.39	47.07	0.96 (0.80, 1.16)

Per-protocol population. Note: Per protocol, the toddler dose was administered at ~11–15 months of age.
†GMT 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.
‡A conclusion of non-inferiority of rotavirus vaccine administered concomitantly with V114 compared with concomitant administration with PCV13 is based on the lower bound of the 2-sided 95% CI for the GMT ratio (V114/PCV13) being >0.5 (1-sided *P* value <0.025).
CI, confidence interval; GMT, geometric mean titre (U/ml); IgA, immunoglobulin A; PCV13, 13-valent pneumococcal conjugate vaccine; V114, 15-valent pneumococcal conjugate vaccine.

Conclusions

In healthy infants ~2 months of age:

- 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) at 30 days PTD, as assessed by serotype-specific IgG responses (response rates and GMCs).
- V114 induces functional antibodies (OPA) capable of bactericidal killing of *Streptococcus pneumoniae* PPS and PTD.
- V114 can be administered concomitantly with licensed paediatric vaccines (DTaP/IPV/Hib/HepB and rotavirus).

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