Safety, tolerability and immunogenicity of V114 compared with PCV13 in preterm infants: A pooled subgroup analysis of four Phase 3 studies

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Background

- Risk of invasive pneumococcal disease is three-fold higher in preterm versus full-term infants, mainly due to underlying comorbidities and immunological immaturity.[1,2]
- V114 (VAXNEUVANCE™; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA) is a 15-valent pneumococcal conjugate vaccine (PCV) containing the 13 serotypes in 13-valent PCV (PCV13; Prevenar 13™; Pfizer Inc.) plus two additional serotypes, 22F and 33F.[3,4]
- Pooled subgroup analysis in preterm infants (<37 weeks gestational age) was performed across four Phase 3 paediatric studies evaluating the safety and immunogenicity of four-dose (3+1) regimens of V114 or PCV13.

Methods

- Individual data from preterm infants enrolled in four Phase 3 randomised clinical trials were evaluated for:
  - **Safety and tolerability** of four-dose regimens of V114 and active comparator, PCV13.
    - Solicited and systemic adverse events (AEs) 14 days following each vaccination.
    - Serious AEs (SAEs) throughout the duration of the study.
    - Daily body temperature for 7 days following each vaccination.
  - **Immunogenicity** of four-dose regimens of V114 and active comparator, PCV13.
    - Serotype-specific immunoglobulin G (IgG) geometric mean concentrations (GMCs) and opsonophagocytic activity (OPA) at 30 days post-dose 3 (PD3), immediately before the toddler dose and 30 days post-dose 4 (PD4).
- A validated pneumococcal electrochemiluminescence (Pn ECL) immunoassay was used to quantify IgG.[5]
- A validated multiplexed opsonophagocytic killing assay (MOPA) was used to quantify antibodies with opsonophagocytic killing activity in studies that assessed OPA in a subset of study participants.[6]

Results

- A total of 354 participants were randomised in four previous Phase 3 studies and included in this analysis.
- Participant disposition and demographics are shown in **Table 1** and **Table 2**, respectively.

Table 1. Participant disposition

	V114 (N=174) n (%)	PCV13 (N=180) n (%)
Vaccinated with PCV		
Dose 1 of PCV	174 (100.0)	180 (100.0)
Dose 2 of PCV	172 (98.9)	174 (96.7)
Dose 3 of PCV	168 (96.6)	172 (95.6)
Dose 4 of PCV	164 (94.3)	162 (90.0)
Trial disposition		
Completed	160 (92.0)	161 (89.4)
Discontinued	14 (8.0)	19 (10.6)
Loss to follow-up	8 (4.6)	4 (2.2)
Physician decision	3 (1.7)	3 (1.7)
Withdrawal by parent/guardian	3 (1.7)	12 (6.7)

Table 2. Participant demographics

	V114 (N=174) n (%)	PCV13 (N=180) n (%)
Sex		
Male	113 (64.9)	113 (62.8)
Female	61 (35.1)	67 (37.2)
Gestational age (weeks)		
<29	2 (1.1)	0 (0.0)
≥29 to <32	3 (1.7)	2 (1.1)
≥32 to <37	169 (97.1)	178 (98.9)
Race		
White	120 (69.0)	125 (69.4)
Black or African American	9 (5.2)	11 (6.1)
American Indian/Alaska Native	2 (1.1)	3 (1.7)
Multiple	20 (11.5)	17 (9.4)
Ethnicity		
Not Hispanic/Latino	144 (82.8)	157 (87.2)
Hispanic/Latino	29 (16.7)	23 (12.8)
Not reported	1 (0.6)	0 (0.0)

Safety results

- Proportions of participants with AEs following any dose of V114 or PCV13 were comparable between vaccination groups (**Table 3**).

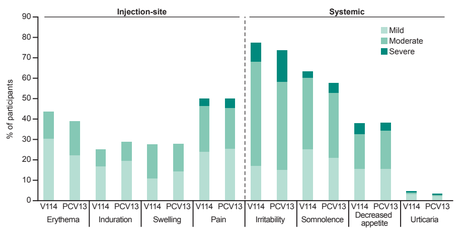
Table 3. Summary of AEs after vaccination with V114 or PCV13

	V114 (N=174) n (%)	PCV13 (N=180) n (%)	Percentage point difference [V114–PCV13] (95% CI)†
Any AEs	167 (96.0)	171 (95.0)	1.0 (−3.7, 5.7)
Injection-site	129 (74.1)	125 (69.4)	
Systemic	164 (94.3)	167 (92.8)	
Any vaccine-related AEs	160 (92.0)	161 (89.4)	2.5 (−3.7, 8.8)
Injection-site	129 (74.1)	124 (68.9)	
Systemic	141 (81.0)	144 (80.0)	
Any SAEs	26 (14.9)	26 (14.4)	0.5 (−7.0, 8.0)
Any vaccine-related SAEs	0 (0.0)	0 (0.0)	0.0 (−2.1, 2.2)
Deaths	0 (0.0)	0 (0.0)	0.0 (−2.1, 2.2)

Reported AEs include non-serious AEs that occurred within 14 days of vaccination and SAEs that occurred after dose 1 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.
CI, confidence interval.

- The proportions of participants with solicited injection-site and systemic AEs were generally comparable between both vaccination groups (**Figure 1**).
  - Most of the solicited AEs were mild or moderate in intensity and of short duration (≤3 days; data not shown).
- Temperature distribution was comparable between vaccination groups following any dose (data not shown).
  - Majority reported temperature <39.0 °C (V114: 87%, PCV13: 85%).

Figure 1. Proportion of participants with solicited AEs after vaccination with V114 or PCV13 by maximum intensity



For injection-site erythema, induration and swelling, mild events were those measuring 0 to ≤1 inch, moderate events were >1 to ≤3 inches and severe events were >3 inches. Every participant is counted a single time for each applicable specific injection-site AE and is classified according to the highest non-missing size rating.

Immunogenicity results

- At 30 days PD3 and PD4:
  - Comparable IgG response rates and IgG GMCs for the 13 shared serotypes were observed between the groups.
  - Higher IgG response rates and IgG GMCs for 22F and 33F were observed in the V114 group compared with the PCV13 group (**Figures 2** and **3**).

Figure 2. Proportion of participants achieving IgG threshold of 0.35 µg/ml at 30 days PD3 and PD4

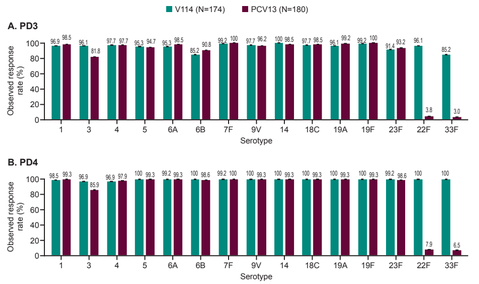
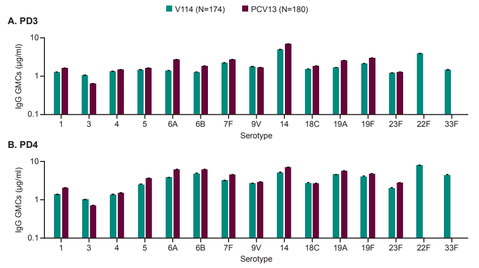
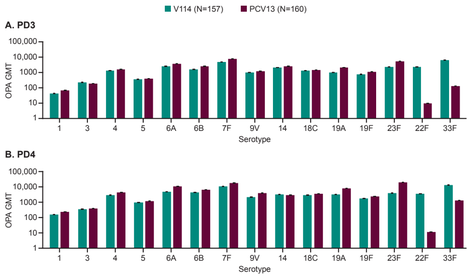


Figure 3. Serotype-specific IgG GMCs at 30 days PD3 and PD4



- At 30 days PD3 and PD4:
  - Comparable OPA geometric mean titres (GMTs) for the 13 shared serotypes were observed between the groups.
  - Higher OPA GMTs for 22F and 33F were observed in the V114 group compared with the PCV13 group (**Figure 4**).

Figure 4. Serotype-specific OPA GMTs at 30 days PD3 and PD4



OPA GMTs were assessed in three out of four studies in a subset of study participants.

Conclusions

- Use of V114 in preterm infants is supported by:
  - Comparable safety profile to PCV13.
  - Comparable IgG and OPA responses to PCV13 for the shared serotypes and higher for the two additional serotypes.

References

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Disclosures

JK is an employee of MSD, London, United Kingdom.
All other authors are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and may own stock and/or stock options in Merck & Co., Inc., Rahway, NJ, USA.

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