Safety and Immunogenicity of V114, a 15-Valent Pneumococcal Conjugate Vaccine (PCV), in Adults Infected With Human Immunodeficiency Virus (HIV): A Phase 3 Trial

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Introduction

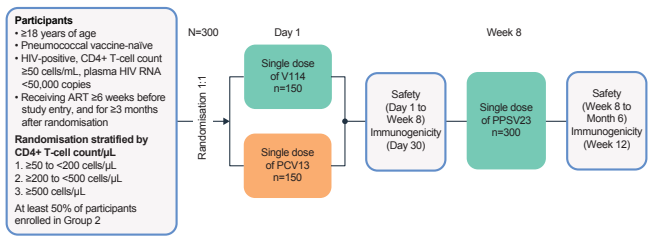
- Individuals infected with human immunodeficiency virus (HIV) are at an increased risk of pneumococcal disease (PD) compared with uninfected individuals[1]
- In many countries, vaccination against PD is recommended for adults infected with HIV, irrespective of an individual's CD4+ T-cell count[1–3]
- Sequential vaccination with 13-valent pneumococcal conjugate vaccine (PCV13) followed by the 23-valent pneumococcal polysaccharide vaccine (PPSV23) may be recommended, with an interval of at least 8 weeks between these two vaccinations[2]
- Despite the success of PCVs in reducing PD caused by *Streptococcus pneumoniae* serotypes covered by currently available pneumococcal vaccines,[3] the prevalence of PD caused by serotypes not covered by these vaccines remains a concern[4,5]
- V114, an investigational 15-valent vaccine containing the 13 serotypes included in PCV13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F), plus two additional serotypes (22F and 33F), was developed to provide broader serotype coverage
- This phase 3 trial evaluated the immunogenicity and safety of V114 followed by PPSV23 8 weeks later in adults infected with HIV

Methods

Study Design

- Phase 3, multicentre, randomised, double-blind, active comparator-controlled study that evaluated the safety, tolerability and immunogenicity of V114 followed by administration of PPSV23 8 weeks later in adults infected with HIV (V114-018, PNEU-WAY, NCT03480802; **Figure 1**)

Figure 1. Study Design Overview



ART, antiretroviral therapy; HIV, human immunodeficiency virus; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; RNA, ribonucleic acid.

Study Objectives

Primary Endpoints

- Safety profile following V114/PCV13 administration:
  - Solicited injection site adverse events (AEs; Day 1 to Day 5)
  - Solicited systemic AEs (Day 1 to Day 14)
  - Vaccine-related serious adverse events (SAEs; Day 1 to Week 8)
- Immunogenicity:
  - Serotype-specific opsonophagocytic activity (OPA) geometric mean titres (GMTs) and immunoglobulin G (IgG) geometric mean concentrations (GMCs) for V114 serotypes (Day 30)

Secondary Endpoints

- Safety profile following PPSV23 administration:
  - Solicited injection site AEs (Day 1 to Day 5 post-PPSV23)
  - Solicited systemic AEs (Day 1 to Day 14 post-PPSV23)
  - Vaccine-related SAEs (Week 8 to Month 6)
- Immunogenicity:
  - Serotype-specific OPA GMTs and IgG GMCs for V114 serotypes (Week 12)

Results

Participant Disposition

- All randomised participants (N=302) received either V114 or PCV13, and 298 participants (98.7%) received PPSV23 (**Table 1**)
- 292 (96.7%) participants completed the study
- The number of study discontinuations and the reasons for study discontinuation were generally comparable across vaccination groups

Table 1. Participant Disposition Across Intervention Groups

Characteristic, n (%)	V114	PCV13
Participants randomised	152	150
Vaccinated with		
PCV (Day 1)	152 (100.0)	150 (100.0)
PPSV23 (Week 8)	150 (98.7)	148 (98.7)
Trial disposition		
Completed	145 (95.4)	147 (98.0)
Discontinued	7 (4.6)	3 (2.0)
Lost to follow-up	5 (3.3)	1 (0.7)
Withdrawal by subject	2 (1.3)	1 (0.7)
Other	0 (0.0)	1 (0.7)

PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

Participant Demographics and Baseline Characteristics

- Demographic and baseline characteristics were generally comparable for participants across vaccination groups (**Table 2**)
- Most participants were male and aged between 18 and 49 years

Table 2. Participant Demographics and Baseline Characteristics

Characteristic	V114 (n=152)	PCV13 (n=150)
Age, median (range), years	40.0 (23–74)	41.5 (21–69)
Gender, n (%)		
Female	32 (21.1)	32 (21.3)
Male	120 (78.9)	118 (78.7)
Race, n (%)		
American Indian or Alaska Native	0 (0.0)	1 (0.7)
Asian	24 (15.8)	30 (20.0)
Black or African American	51 (33.6)	43 (28.7)
Multiple	36 (23.7)	26 (17.3)
Native Hawaiian or other Pacific Islander	0 (0.0)	2 (1.3)
White	41 (27.0)	48 (32.0)
Ethnicity, n (%)		
Hispanic or Latino	49 (32.2)	45 (30.0)
Not Hispanic or Latino	102 (67.1)	104 (69.3)
Not reported	1 (0.7)	1 (0.7)
CD4+ T-cell count, n (%)		
≥50 to <200 cells/µL	2 (1.3)	2 (1.3)
≥200 to <500 cells/µL	76 (50.0)	76 (50.7)
≥500 cells/µL	74 (48.7)	72 (48.0)
Viral load†, n (%)		
Detectable HIV RNA	29 (19.1)	36 (24.0)
Undetectable HIV RNA	123 (80.9)	114 (76.0)

†HIV viral load results of <20 copies/mL and negative are categorised as undetectable because the lower limit of detection of the HIV viral load assay is 20 copies/mL. Detectable viral load is 20–50,000 copies.
HIV, human immunodeficiency virus; PCV13, 13-valent pneumococcal conjugate vaccine; RNA, ribonucleic acid.

AEs Following Vaccination With V114/PCV13

- Most participants in both vaccination groups experienced at least one AE (**Table 3**)

Table 3. AEs Following Vaccination With V114/PCV13† and subsequent PPSV23‡

	Vaccination with V114/PCV13		Vaccination with PPSV23	
	V114 (n=152)	PCV13 (n=150)	V114 (n=150)	PCV13 (n=148)
Subjects with ≥1 AE, n (%)	111 (73.0)	94 (62.7)	91 (60.7)	106 (71.6)
Injection site	97 (63.8)	82 (54.7)	83 (55.3)	97 (65.5)
Systemic	65 (42.8)	54 (36.0)	49 (32.7)	51 (34.5)
Subjects with vaccine-related AE, n (%)§	101 (66.4)	88 (58.7)	87 (58.0)	99 (66.9)
Injection site	97 (63.8)	82 (54.7)	83 (55.3)	97 (65.5)
Systemic	40 (26.3)	36 (24.0)	34 (22.7)	36 (24.3)
Subjects with SAE, n (%)	3 (2.0)	0 (0.0)	2 (1.3)	6 (4.1)
Subjects with vaccine-related SAE, n (%)§	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with ≥1 solicited AE, n (%)‖	103 (67.8)	87 (58.0)	89 (59.3)	98 (66.2)
Solicited injection site AEs‖	94 (61.8)	80 (53.3)	83 (55.3)	96 (64.9)
Injection site pain	87 (57.2)	77 (51.3)	80 (53.3)	91 (61.5)
Injection site swelling	18 (11.8)	6 (4.0)	30 (20.0)	43 (29.1)
Injection site erythema	7 (4.6)	5 (3.3)	15 (10.0)	18 (12.2)
Solicited systemic AEs‖	49 (32.2)	39 (26.0)	39 (26.0)	35 (23.6)
Fatigue	31 (20.4)	20 (13.3)	19 (12.7)	16 (10.8)
Headache	20 (13.2)	14 (9.3)	17 (11.3)	18 (12.2)
Myalgia	19 (12.5)	14 (9.3)	13 (8.7)	13 (8.8)
Arthralgia	5 (3.3)	6 (4.0)	4 (2.7)	2 (1.4)

†Reported AEs include non-serious AEs within 14 days of vaccination and SAEs occurring on Day 1 through Week 8.
‡Reported AEs include non-serious AE within 14 days of vaccination and SAE occurring Week 8 (Day 1 relative to vaccination with PPSV23) through Month 6.
§Determined by the investigator to be related to the vaccine.
‖Injection site erythema, injection site pain and injection site swelling were solicited from Day 1 to Day 5 following vaccination. Arthralgia, fatigue, headache and myalgia were solicited from Day 1 to Day 14 following vaccination.
Medical Dictionary for Regulatory Activities version 22.1 was used in the reporting of this study.
AE, adverse event; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; SAE, serious adverse event.

- The proportion of participants who experienced SAEs was low (≤2%) in both vaccination groups, and none of the SAEs were considered by the investigator to be related to the study vaccine
- No participants died or discontinued the study vaccine because of an AE
- The proportions of participants with injection site AEs, systemic AEs and vaccine-related systemic AEs were generally comparable across vaccination groups

AEs Following Vaccination With PPSV23

- As observed for post-vaccination with V114 and PCV13, most participants in both vaccination groups experienced at least one AE post-vaccination with PPSV23 (**Table 3**)
- The proportion of participants who experienced SAEs was low (<5%) in both intervention groups, and none of the SAEs were considered by the investigator to be related to the study vaccine
- No participants died
- The proportions of participants with injection site AEs, systemic AEs and vaccine-related systemic AEs post-vaccination with PPSV23 were generally comparable across intervention groups

Immunogenicity at Day 30 Post-Vaccination

- V114 and PCV13 were immunogenic in vaccine-naïve adults infected with HIV for all serotypes contained in each vaccine, as shown by OPA GMTs and IgG GMCs at Day 1 (pre-vaccination) and 30 days post-vaccination (**Figure 2**)
- There were trends towards higher serotype-specific OPA GMTs and IgG GMCs at 30 days post-vaccination with PCV13 and V114 in participants with CD4+ T-cell counts of ≥500 cells/µL and undetectable viral load compared with those with counts of ≥200 to <500 cells/µL and detectable viral load (**Figure 3 and Figure 4**)

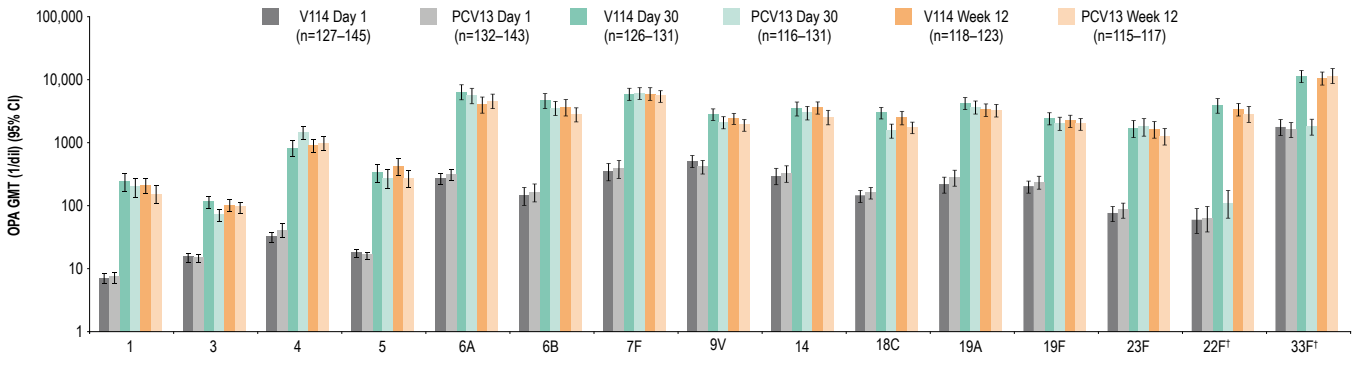
Immunogenicity at Week 12 Post-Vaccination

- Following vaccination with PPSV23, serotype-specific OPA and IgG titres were measured for the 15 serotypes in V114, which included 14 shared serotypes between V114 and PPSV23 and one serotype unique to V114 (6A)
- Serotype-specific OPA GMTs and IgG GMCs at 30 days post-vaccination with PPSV23 (Week 12) were generally comparable with those observed at 30 days post-vaccination with V114 and PCV13 for all serotypes, respectively (**Figure 2**)

Other Immunogenicity Endpoints

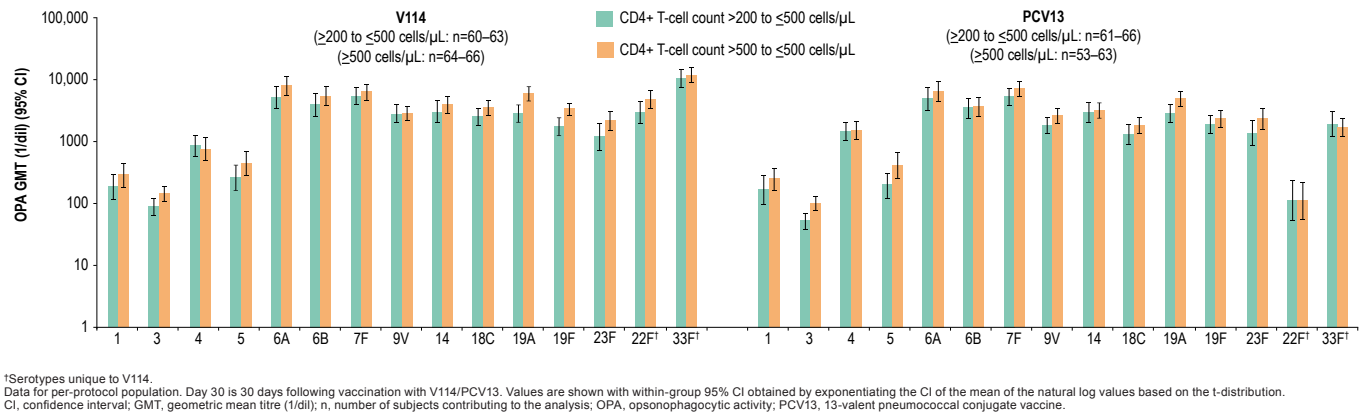
- PPSV23 elicited an immune response for serotypes 22F and 33F at 30 days post-vaccination with PPSV23 in the PCV13 group
- Serotype-specific geometric mean fold-rises from baseline, proportions of participants with a ≥4-fold rise from baseline and reverse cumulative distribution curves were also assessed for OPA and IgG responses at Day 30 and Week 12 and demonstrated generally comparable immune responses between V114 and PCV13 (data not shown)

Figure 2. OPA GMTs at Day 1, Day 30 and Week 12 post-vaccination



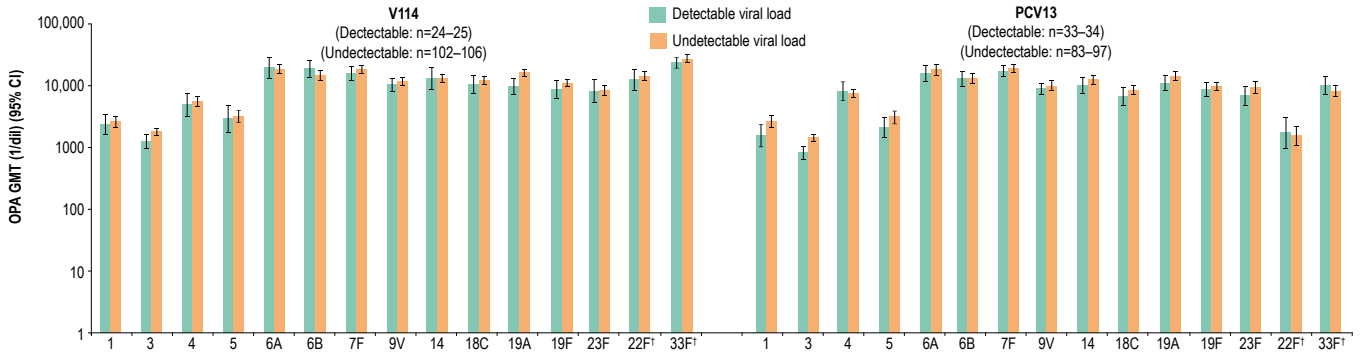
†Serotypes unique to V114.
Data for per-protocol population. Day 1 is pre-vaccination with PCV. Day 30 is 30 days following vaccination with V114/PCV13. Week 12 is 30 days following vaccination with PPSV23. Values are shown with within-group 95% CI obtained by exponentiating the CI of the mean of the natural log values based on the t-distribution. CI, confidence interval; GMT, geometric mean titre (1/dil); n, number of subjects contributing to the analysis; OPA, opsonophagocytic activity; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

Figure 3. OPA GMTs at Day 30 according to CD4+ T-cell count



†Serotypes unique to V114.
Data for per-protocol population. Day 30 is 30 days following vaccination with V114/PCV13. Values are shown with within-group 95% CI obtained by exponentiating the CI of the mean of the natural log values based on the t-distribution. CI, confidence interval; GMT, geometric mean titre (1/dil); n, number of subjects contributing to the analysis; OPA, opsonophagocytic activity; PCV13, 13-valent pneumococcal conjugate vaccine.

Figure 4. OPA GMTs at Day 30 by viral load



†Serotypes unique to V114.
Data for per-protocol population. Day 30 is 30 days following vaccination with V114/PCV13. Values are shown with within-group 95% CI obtained by exponentiating the CI of the mean of the natural log values based on the t-distribution. CI, confidence interval; GMT, geometric mean titre (1/dil); n, number of subjects contributing to the analysis; OPA, opsonophagocytic activity; PCV13, 13-valent pneumococcal conjugate vaccine.

Conclusions

- In pneumococcal vaccine-naïve adults infected with HIV:
  - V114 is generally well tolerated
  - V114 induces immune responses to all 15 pneumococcal serotypes, as assessed by OPA GMTs and IgG GMCs at 30 days post-vaccination
  - There is a trend toward higher serotype-specific OPA GMTs and IgG GMCs at 30 days post-vaccination with V114 in participants with CD4+ T-cell count ≥500 cells/µL and undetectable viral load versus those with CD4+ T-cell count ≥200 to <500 cells/µL and detectable viral load
  - V114 can be followed by PPSV23 at 8 weeks, as the immune response was maintained for shared serotypes and sequential administration was well tolerated

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