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

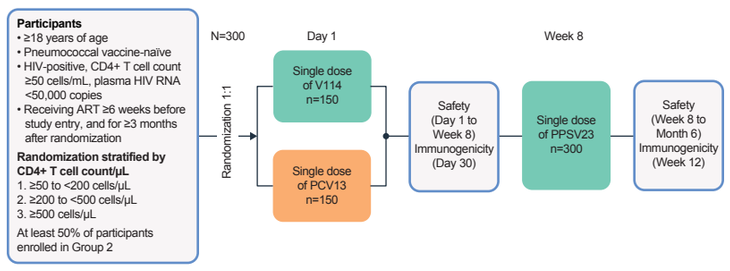
- Individuals infected with human immunodeficiency virus (HIV) are at an increased risk of pneumococcal disease (PD) compared with uninfected individuals[1]
- Despite the success of pneumococcal conjugate vaccines (PCVs) in immunocompromised individuals, PD caused by emergent serotypes not included in licensed vaccines remains a public health concern[2,3]
- The Advisory Committee on Immunization Practices currently recommends sequential vaccination with 13-valent PCV (PCV13), followed by the 23-valent pneumococcal polysaccharide vaccine (PPSV23) at least 8 weeks later for eligible individuals with immunocompromising conditions[4]
- 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, multicenter, randomized, 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 titers (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 randomized 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 randomized	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 categorized 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.

AEs Following Vaccination With V114/PCV13

- Most participants in both vaccination groups experienced at least one AE (**Table 3**)
- The proportions 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 4**)
- 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

Table 3. AEs Following Vaccination With V114/PCV13†

	V114 (n=152)	PCV13 (n=150)
Subjects with ≥1 AE, n (%)	111 (73.0)	94 (62.7)
Injection site	97 (63.8)	82 (54.7)
Systemic	65 (42.8)	54 (36.0)
Subjects with vaccine-related AE, n (%)‡	101 (66.4)	88 (58.7)
Injection site	97 (63.8)	82 (54.7)
Systemic	40 (26.3)	36 (24.0)
Subjects with SAE, n (%)	3 (2.0)	0 (0.0)
Subjects with vaccine-related SAE, n (%)‡	0 (0.0)	0 (0.0)
Subjects with ≥1 solicited AE, n (%)§	103 (67.8)	87 (58.0)
Solicited injection site AEs§	94 (61.8)	80 (53.3)
Injection site pain	87 (57.2)	77 (51.3)
Injection site swelling	18 (11.8)	6 (4.0)
Injection site erythema	7 (4.6)	5 (3.3)
Solicited systemic AEs§	49 (32.2)	39 (26.0)
Fatigue	31 (20.4)	20 (13.3)
Headache	20 (13.2)	14 (9.3)
Myalgia	19 (12.5)	14 (9.3)
Arthralgia	5 (3.3)	6 (4.0)

†Reported AEs include non-serious AEs within 14 days of vaccination and SAEs occurring on Day 1 through Week 8.
‡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; SAE, serious adverse event.

Table 4. AEs Following Vaccination With PPSV23†

	V114 (n=150)	PCV13 (n=148)
Subjects with ≥1 AE, n (%)	91 (60.7)	106 (71.6)
Injection site	83 (55.3)	97 (65.5)
Systemic	49 (32.7)	51 (34.5)
Subjects with vaccine-related AE, n (%)‡	87 (58.0)	99 (66.9)
Injection site	83 (55.3)	97 (65.5)
Systemic	34 (22.7)	36 (24.3)
Subjects with SAE, n (%)	2 (1.3)	6 (4.1)
Subjects with vaccine-related SAE, n (%)‡	0 (0.0)	0 (0.0)
Subjects with ≥1 solicited AE, n (%)§	89 (59.3)	98 (66.2)
Solicited injection site AEs§	83 (55.3)	96 (64.9)
Injection site pain	80 (53.3)	91 (61.5)
Injection site swelling	30 (20.0)	43 (29.1)
Injection site erythema	15 (10.0)	18 (12.2)
Solicited systemic AEs§	39 (26.0)	35 (23.6)
Fatigue	19 (12.7)	16 (10.8)
Myalgia	17 (11.3)	18 (12.2)
Headache	13 (8.7)	13 (8.8)
Arthralgia	4 (2.7)	2 (1.4)

†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.

Immunogenicity at Day 1, Day 30, and Week 12 Post-Vaccination

- V114 and PCV13 were both immunogenic in pneumococcal vaccine-naïve adults infected with HIV, as assessed by OPA GMTs and IgG GMCs at 30 days post-vaccination for all serotypes contained in each vaccine, respectively (**Tables 5** and **6**)
- Following vaccination with PPSV23, serotype-specific OPA and IgG titers 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 (**Tables 5** and **6**)
  - 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
- Immune responses were generally comparable between V114 and PCV13 (data not shown)

Table 5. OPA GMTs at Day 1, Day 30, and Week 12 Post-Vaccination

Timepoint	Day 1†						Day 30‡						Week 12§					
	V114			PCV13			V114			PCV13			V114			PCV13		
Serotype	n‖	GMT	95% CI¶	n‖	GMT	95% CI¶	n‖	GMT	95% CI¶	n‖	GMT	95% CI¶	n‖	GMT	95% CI¶	n‖	GMT	95% CI¶
Common serotypes																		
1	144	7.2	(6.0, 8.6)	143	7.4	(6.2, 8.9)	131	238.8	(173.1, 329.3)	131	200.9	(142.7, 282.7)	122	212.0	(160.5, 280.2)	117	154.0	(111.6, 212.4)
3	145	15.5	(13.3, 18.1)	143	15.1	(13.1, 17.5)	131	116.8	(94.9, 143.7)	130	72.3	(58.6, 89.2)	123	102.8	(83.0, 127.2)	117	96.6	(79.5, 117.4)
4	144	32.7	(27.0, 39.6)	140	41.8	(33.0, 53.0)	130	824.0	(618.8, 1097.2)	131	1465.5	(1154.5, 1860.3)	122	915.4	(722.9, 1159.1)	117	984.7	(772.1, 1255.7)
5	145	18.1	(15.9, 20.5)	143	16.6	(14.8, 18.6)	131	336.7	(242.4, 467.7)	130	276.7	(197.9, 386.7)	123	418.1	(312.1, 560.3)	117	274.5	(199.9, 376.8)
6A	140	277.8	(228.4, 337.8)	136	318.0	(258.5, 391.1)	126	6421.0	(4890.4, 8430.7)	128	5645.1	(4278.9, 7447.4)	118	4065.4	(3052.1, 5415.1)	113	4593.2	(3543.0, 5954.7)
6B	140	144.9	(104.4, 201.0)	141	165.0	(119.3, 228.2)	129	4652.5	(3551.6, 6094.6)	130	3554.0	(2751.0, 4591.4)	122	3661.1	(2735.1, 4900.6)	117	2826.4	(2202.7, 3626.8)
7F	137	351.9	(255.6, 484.5)	139	388.2	(282.4, 533.7)	131	5934.6	(4784.9, 7360.6)	131	6144.3	(4982.8, 7576.6)	122	5983.5	(4788.9, 7476.1)	117	5516.5	(4522.2, 6729.5)
9V	140	516.9	(417.9, 639.4)	142	418.8	(330.0, 531.5)	129	2836.3	(2311.5, 3480.4)	128	2133.9	(1721.8, 2644.5)	120	2454.8	(2008.7, 3000.0)	117	1929.9	(1567.7, 2375.7)
14	142	297.4	(221.5, 399.2)	140	327.8	(243.0, 442.2)	131	3508.7	(2730.6, 4508.5)	130	3000.3	(2350.0, 3830.5)	123	3634.0	(2935.6, 4498.5)	117	2539.3	(1960.6, 3288.9)
18C	143	145.1	(118.0, 178.5)	139	162.9	(131.8, 201.2)	129	3002.2	(2435.5, 3700.8)	129	1560.3	(1213.8, 2005.6)	122	2511.5	(1958.7, 3220.3)	115	1753.8	(1428.6, 2153.1)
19A	142	219.9	(165.5, 292.1)	137	283.2	(212.5, 377.3)	131	4240.7	(3415.4, 5265.3)	131	3715.9	(2949.2, 4681.8)	123	3358.1	(2679.6, 4208.4)	117	3300.3	(2638.7, 4127.7)
19F	141	203.7	(164.2, 252.6)	140	239.4	(188.9, 303.4)	131	2438.6	(1972.7, 3014.6)	131	2042.0	(1618.9, 2575.5)	123	2230.7	(1803.6, 2759.0)	116	1994.1	(1630.7, 2438.4)
23F	137	76.2	(58.7, 99.0)	134	86.3	(65.6, 113.6)	129	1669.9	(1233.1, 2261.4)	127	1787.0	(1309.9, 2437.9)	120	1641.2	(1217.2, 2212.9)	116	1266.5	(944.3, 1698.5)
Two serotypes unique to V114																		
22F	127	59.1	(37.7, 92.7)	132	62.9	(40.0, 98.8)	128	3943.7	(3049.2, 5100.5)	116	109.3	(66.2, 180.3)	121	3399.9	(2697.6, 4285.0)	116	2870.0	(2165.7, 3803.2)
33F	141	1783.2	(1338.3, 2376.0)	141	1623.4	(1241.1, 2123.5)	131	11,342.4	(9184.3, 14,007.6)	129	1807.6	(1357.3, 2407.3)	123	10,576.3	(8383.1, 13,343.4)	117	11,595.0	(8892.6, 15,118.8)

†Day 1 is pre-vaccination with V114/PCV13.
‡Day 30 is 30 days following vaccination with V114/PCV13.
§Week 12 is 30 days following vaccination with PPSV23.
‖Number of subjects contributing to the analysis.
¶The within-group 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.
CI, confidence interval; GMT, geometric mean titer (1/dil); OPA, opsonophagocytic activity; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

Table 6. IgG GMCs at Day 1, Day 30, and Week 12 Post-Vaccination

Timepoint	Day 1†						Day 30‡						Week 12§					
	V114			PCV13			V114			PCV13			V114			PCV13		
Serotype	n‖	GMC	95% CI¶	n‖	GMC	95% CI¶	n‖	GMC	95% CI¶	n‖	GMC	95% CI¶	n‖	GMC	95% CI¶	n‖	GMC	95% CI¶
Common serotypes																		
1	148	0.24	(0.20, 0.30)	149	0.26	(0.21, 0.31)	139	3.16	(2.48, 4.01)	138	4.27	(3.31, 5.50)	130	2.80	(2.25, 3.49)	129	4.04	(3.27, 5.00)
3	148	0.09	(0.08, 0.11)	149	0.13	(0.11, 0.15)	139	0.57	(0.48, 0.68)	136	0.50	(0.41, 0.60)	130	0.51	(0.43, 0.61)	128	0.59	(0.50, 0.70)
4	148	0.14	(0.12, 0.17)	149	0.15	(0.13, 0.18)	138	1.14	(0.90, 1.44)	138	2.00	(1.56, 2.55)	130	1.26	(1.01, 1.57)	129	1.61	(1.31, 1.98)
5	148	0.61	(0.52, 0.70)	149	0.56	(0.49, 0.63)	139	2.38	(1.89, 3.01)	138	2.03	(1.56, 2.64)	130	2.61	(2.08, 3.28)	129	2.13	(1.69, 2.68)
6A	148	0.22	(0.17, 0.27)	149	0.25	(0.20, 0.32)	139	5.13	(3.73, 7.04)	138	4.91	(3.49, 6.91)	130	3.12	(2.27, 4.30)	129	3.71	(2.74, 5.03)
6B	148	0.30	(0.24, 0.38)	149	0.33	(0.27, 0.41)	139	7.17	(5.34, 9.63)	138	5.23	(3.73, 7.35)	130	4.69	(3.52, 6.25)	129	4.35	(3.23, 5.86)
7F	148	0.21	(0.17, 0.25)	149	0.26	(0.21, 0.31)	139	2.61	(2.00, 3.41)	138	3.74	(2.91, 4.81)	130	2.45	(1.91, 3.15)	129	3.17	(2.60, 3.87)
9V	148	0.32	(0.27, 0.38)	149	0.35	(0.28, 0.43)	139	3.35	(2.71, 4.14)	137	3.55	(2.77, 4.56)	130	2.92	(2.39, 3.57)	128	3.24	(2.62, 4.01)
14	148	1.57	(1.19, 2.06)	149	1.55	(1.19, 2.02)	139	15.44	(11.69, 20.39)	138	15.22	(11.56, 20.03)	130	13.68	(10.34, 18.10)	129	14.37	(11.25, 18.36)
18C	148	0.30	(0.24, 0.37)	149	0.33	(0.27, 0.40)	139	5.58	(4.33, 7.18)	138	5.07	(3.97, 6.48)	130	3.96	(3.08, 5.09)	129	3.96	(3.18, 4.95)
19A	148	0.96	(0.80, 1.15)	149	0.99	(0.85, 1.17)	139	9.09	(7.08, 11.67)	138	9.61	(7.36, 12.56)	130	7.23	(5.80, 9.02)	129	8.54	(6.80, 10.72)
19F	148	0.50	(0.40, 0.63)	149	0.55	(0.44, 0.68)	139	6.41	(4.89, 8.39)	138	6.21	(4.73, 8.15)	130	5.19	(4.06, 6.62)	129	5.84	(4.67, 7.30)
23F	148	0.24	(0.19, 0.31)	149	0.29	(0.23, 0.35)	139	3.92	(2.94, 5.22)	138	4.90	(3.54, 6.77)	130	3.21	(2.42, 4.25)	129	3.74	(2.85, 4.91)
Two serotypes unique to V114																		
22F	148	0.21	(0.17, 0.25)	149	0.20	(0.16, 0.24)	139	3.97	(3.06, 5.15)	137	0.20	(0.17, 0.25)	130	3.94	(3.07, 5.05)	129	3.50	(2.75, 4.45)
33F	148	0.65	(0.52, 0.80)	149	0.71	(0.58, 0.86)	139	6.83	(5.14, 9.07)	138	0.77	(0.62, 0.95)	130	6.18	(4.72, 8.09)	129	9.20	(7.19, 11.77)

†Day 1 is pre-vaccination with V114/PCV13.
‡Day 30 is 30 days following vaccination with V114/PCV13.
§Week 12 is 30 days following vaccination with PPSV23.
‖Number of subjects contributing to the analysis.
¶The within-group 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.
CI, confidence interval; GMC, geometric mean concentration (μg/mL); IgG, immunoglobulin G; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

Conclusions

- In pneumococcal vaccine-naïve adults infected with HIV:
  - V114 is generally well tolerated
  - V114 induces immune responses for all 15 pneumococcal serotypes, as assessed by OPA GMTs and IgG GMCs at 30 days post-vaccination with V114
  - 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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