A phase 1, randomized, double-blind study to evaluate the safety, tolerability, and immunogenicity of a 21-valent pneumococcal conjugate vaccine (PCV) (V116) in adults

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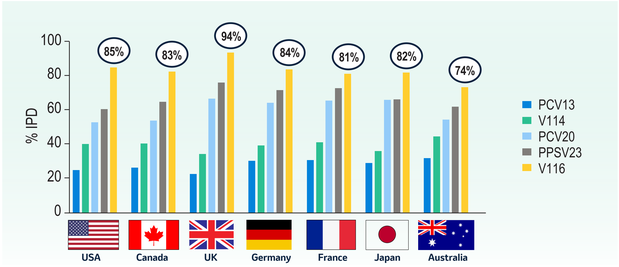
Background

- *Streptococcus pneumoniae* is a major cause of disease, resulting in considerable morbidity and mortality worldwide
- The introduction of pneumococcal conjugate vaccines (PCV) has significantly decreased disease in children and changed the epidemiology in adults
- The major serotypes that cause pneumococcal disease currently vary between adults and children, and the burden of invasive pneumococcal disease (IPD) is currently higher in adults[1-3]
- A vaccine which includes serotypes that are not in the infant PCVs, and which directly targets serotypes associated with higher burden of disease in adults, has potential for greater impact on residual pneumococcal disease in adults[4]
- V116 is an investigational vaccine including 21 serotypes of pneumococcal polysaccharides conjugated to CRM197 without an adjuvant
- Serotypes in V116 were selected, in part, based on an analysis of available epidemiology in older adults following introduction of PCVs into pediatric and adult national immunization plans
- Recent surveillance data (2017-2019) estimate that these serotypes account for ~74%-94%[5-11] of IPD cases in older adults from several countries worldwide where PCV is included in child immunization programs

Serotypes in V116 are responsible for ~74%-94% of IPD in adults ≥65 years

Figure 1. IPD coverage in adults ≥65* by country and vaccine



*Germany data is from age >60, all other countries age ≥65. Surveillance data is from 2019 from USA,[5] 2018 Canada,[6] and Australia,[7] 2017/2018 UK,[8] Germany,[9] and 2017 France,[10] and Japan.[11] PCV13, 13-valent PCV; V114, 14-valent PCV; PCV20, 20-valent PCV; PPSV23, 23-valent unconjugated polysaccharide vaccine.

V116 is an investigational 21-valent PCV with 8 novel serotypes

Figure 2. Serotype composition of licensed pneumococcal vaccines and V116

	Serotype composition																														
PCV7	4	6B	9V	14	18C	19F	23F																								
PCV13	4	6B	9V	14	18C	19F	23F	1	3	5	6A	7F	19A																		
V114	4	6B	9V	14	18C	19F	23F	1	3	5	6A	7F	19A	22F	33F																
PPSV23	4	6B	9V	14	18C	19F	23F	1	3	5		7F	19A	22F	33F	2	8	9N	10A	11A	12F	15B	17F	20							
PCV20	4	6B	9V	14	18C	19F	23F	1	3	5	6A	7F	19A	22F	33F		8		10A	11A	12F	15B									
V116								3			6A	7F	19A	22F	33F		8	9N	10A	11A	12F		17F	20	15A	15C[a]	16F	23A	23B	24F	31	35B

PCV13	V114	PCV20	PPSV23	V116
4 shared serotypes: (3, 6A, 7F, 19A)	6 shared serotypes: (PCV13 + 22F, 33F)	10 shared serotypes: (V114 + 8, 10A, 11A, 12F)	12 shared serotypes: (PCV20 [-6A] + 9N, 17F, 20)	8 unique serotypes compared to currently licensed pneumococcal vaccines

[a]15C is denoted here to represent the serotype protection proposed with deOAc15B, as the molecular structures for deOAc15B and 15C are similar.

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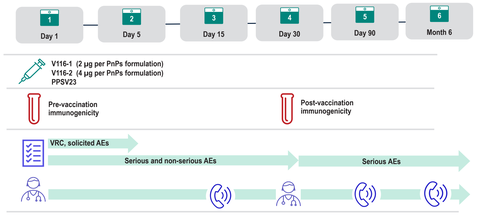
Methods

Study design

Phase 1, randomized, double-blind study registered at clinicaltrials.gov as NCT0416890

Figure 3. Overview of trial design



Key study objectives

Primary objective

To evaluate the safety and tolerability of two V116 formulations

- Primary endpoints:
  - Solicited injection site events (erythema, swelling, pain), days 1-5
  - Solicited systemic events (arthralgia, fatigue, headache, and myalgia), days 1-5
  - Serious vaccine-related adverse events collected through day 180

Secondary objectives

- To describe the serotype-specific opsonophagocytic killing activity (OPA) geometric mean titers (GMT) and IgG geometric mean concentrations (GMC) 30 days post-vaccination
- To describe the serotype-specific geometric mean fold rise (GMFR) from pre-vaccination to 30 days post-vaccination for both OPA and IgG responses

Safety evaluation methods

- Safety was evaluated using the "all participants as treated population" (all randomized participants who received the relevant study vaccination)
- Clinical review of complaints received via vaccination report card (VRC)
- The severity of AEs was categorized as mild (grade 1), moderate (grade 2), severe (grade 3), or potentially life-threatening (grade 4)
- For the solicited injection-site events of erythema and swelling which are assessed by measurement, mild events were those >0 to ≤5 cm, moderate events were >5 to ≤10 cm, and severe events were >10 cm
- All injection-site events were considered to be vaccine-related. For systemic AEs, relatedness to study vaccine was assessed by the investigator
- Blood was collected at baseline (day 1) and at 30 days post-vaccination (day 30) for hematology and chemistry (ie, hepatic, renal, cardiac) clinical laboratory assessments

Immunogenicity evaluation methods

- Immunogenicity was performed in the "per protocol population" (all randomized participants without protocol deviations that could have substantially affected the results of the immunogenicity analyses)
- Serotype-specific immune responses were evaluated using:
  - Microcolony multiplexed opsonophagocytic killing assay (MOPA): to quantify antibodies with opsonophagocytic killing activity[12]
  - Pneumococcal electrochemiluminescence (Pn ECL) immunoassay: to quantify immunoglobulin G (IgG)[13]

Results

Table 1. Baseline characteristics

	V116-1		V116-2		PPSV23	
	n	%	n	%	n	%
Participants in population	30		30		30	
Gender						
Female	16	53.3	19	63.3	24	80.0
Age						
Mean (range)	37.8 (22-49)		34.7 (18-48)		35.2 (22-49)	
Standard deviation	7.4		8.9		8.2	
Race						
White	23	76.7	23	76.7	24	80.0
Black or African American	6	20.0	4	13.3	4	13.3
Asian	1	3.3	1	3.3	2	6.7
Multiple	0	0.0	2	6.7	0	0.0
Ethnicity						
Hispanic or Latino	14	46.7	13	43.3	13	43.3

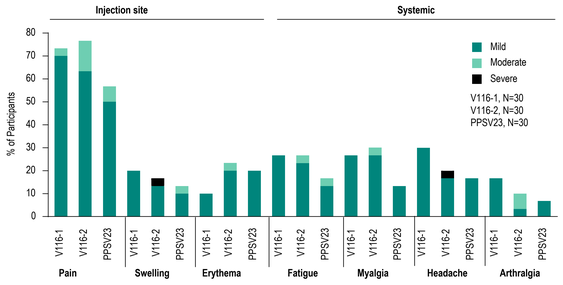
Table 2. Participant disposition

All randomized participants	V116-1 N=30 n (%)	V116-2 N=30 n (%)	PPSV23 N=30 n (%)
Vaccinated	30 (100)	30 (100)	30 (100)
Trial disposition			
Completed	29 (96.7)	29 (96.7)	30 (100)
Discontinued	1 (3.3)	1 (3.3)	0 (0)
Lost to follow-up	0 (0)	1 (3.3)	0 (0)
Withdrawal by participant	1 (3.3)	0 (0)	0 (0)

Safety results

- Solicited adverse events (AE) are shown in Figure 4. Reported injection-site pain and systemic AEs were numerically higher in V116-1 and V116-2 as compared to PPSV23
  - The majority of solicited AEs were mild (Figure 4) and of short duration (≤3 days, data not shown)
- There were no deaths or serious adverse events (SAE) or discontinuations due to AEs in the study
- The maximum reported body temperature was <100.4°F for all participants days 1-5 post-vaccination (data not shown)
- There were no clinically significant laboratory findings following vaccination (data not shown)

Figure 4. Solicited adverse events, days 1-5 post-vaccination



Immunogenicity results

- V116-1 and V116-2 elicited OPA geometric mean titers (GMT) to the common serotypes at day 30 that were generally comparable to PPSV23 (Figure 5)
- OPA GMTs to the unique serotypes were higher in the V116-1 and V116-2 groups as compared to the PPSV23 group (Figure 6)
- While a direct comparison of V116-1 and V116-2 was not an objective of the study, V116-2 elicited higher OPA GMT responses at day 30 than V116-1 for all serotypes, except 9N
- The lower bound of the 95% CI for the OPA GMT ratio (V116-2/PPSV23) was >0.5 for all 12 common serotypes and >1.0 for all of the 9 unique serotypes (Figures 5, 6)
- Percentage of participants with a ≥4-fold rise in OPA 30 days post-vaccination were generally comparable across intervention groups for the common serotypes and higher in the V116-1 and V116-2 groups for the unique serotypes (Figure 7)
- Immune responses were assessed for serotypes 6C and 15B, based on the expectation of cross-reactive immune response from 6A and 15C, respectively. The proportion of participants with a ≥4-fold rise in serotype 6C- and 15B-specific OPA from pre-vaccination to day 30 are shown in Figure 7
- IgG GMC data were generally comparable to the OPA results (data not shown)

Disclosures

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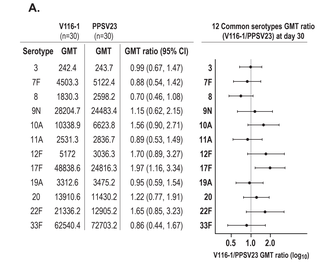
HP, DF, NG, AS, AP, LH, GT, HS, JJ, RM are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, or were at the time of the study and may hold stock and/or stock options in Merck & Co., Inc., Rahway, NJ, USA. JS and LM are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, may hold stock and/or stock options in Merck & Co., Inc., Rahway, NJ, USA, and hold a patent related to V116 vaccine.

Figure 5. Estimated OPA GMT 30 days post-vaccination, serotypes common to V116 and PPSV23

A.

Serotype	V116-1 (n=30) GMT	PPSV23 (n=30) GMT	GMT ratio (95% CI)
3	242.4	243.7	0.99 (0.67, 1.47)
7F	4503.3	5122.4	0.88 (0.54, 1.42)
8	1830.3	2598.2	0.70 (0.46, 1.08)
9N	28204.7	24483.4	1.15 (0.62, 2.15)
10A	10338.9	6623.8	1.56 (0.90, 2.71)
11A	2531.3	2836.7	0.89 (0.53, 1.49)
12F	5172	3036.3	1.70 (0.89, 3.27)
17F	48838.6	24816.3	1.97 (1.16, 3.34)
19A	3312.6	3475.2	0.95 (0.59, 1.54)
20	13910.6	11430.2	1.22 (0.77, 1.91)
22F	21336.2	12905.2	1.65 (0.85, 3.23)
33F	62540.4	72703.2	0.86 (0.44, 1.67)



B.

Serotype	V116-2 (n=29) GMT	PPSV23 (n=30) GMT	GMT ratio (95% CI)
3	259.2	243.7	1.06 (0.72, 1.57)
7F	5672.1	5122.4	1.11 (0.68, 1.80)
8	2321.2	2598.2	0.89 (0.58, 1.38)
9N	26659.1	24483.4	1.09 (0.58, 2.04)
10A	12377.5	6623.8	1.87 (1.08, 3.23)
11A	3152.1	2836.7	1.11 (0.66, 1.87)
12F	7279.6	3036.3	2.40 (1.24, 4.62)
17F	51153.0	24816.3	2.06 (1.21, 3.51)
19A	4595.6	3475.2	1.32 (0.81, 2.15)
20	17799.3	11430.2	1.56 (0.99, 2.45)
22F	26004.0	12905.3	2.01 (1.03, 3.96)
33F	137389.7	72703.2	1.89 (0.97, 3.69)

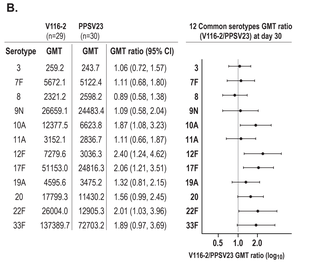
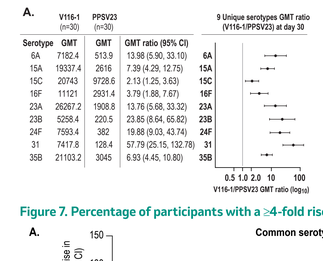


Figure 6. Estimated OPA GMT 30 days post-vaccination, serotypes unique to V116, not in PPSV23

A.

Serotype	V116-1 (n=30) GMT	PPSV23 (n=30) GMT	GMT ratio (95% CI)
6A	7182.4	513.9	13.98 (5.90, 33.10)
15A	19337.4	2616	7.39 (4.29, 12.75)
15C	20743	9728.6	2.13 (1.25, 3.63)
16F	11121	2931.4	3.79 (1.88, 7.67)
23A	26267.2	1908.8	13.76 (5.68, 33.32)
23B	5258.4	220.5	23.85 (8.64, 65.82)
24F	7593.4	382	19.88 (9.03, 43.74)
31	7417.8	128.4	57.79 (25.15, 132.78)
35B	21103.2	3045	6.93 (4.45, 10.80)



B.

Serotype	V116-2 (n=29) GMT	PPSV23 (n=30) GMT	GMT ratio (95% CI)
6A	7407.7	513.9	14.42 (6.05, 34.35)
15A	24580.5	2616	9.40 (5.42, 16.28)
15C	27242.1	9728.6	2.80 (1.64, 4.79)
16F	17201.7	2931.4	5.87 (2.88, 11.94)
23A	36793.1	1908.8	19.28 (7.91, 47.00)
23B	8684.8	220.5	39.39 (14.15, 109.65)
24F	11867.2	382	31.07 (13.98, 69.03)
31	7453.5	128.4	58.07 (25.10, 134.33)
35B	23826.5	3045	7.82 (5.00, 12.24)

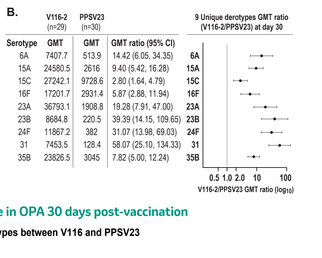
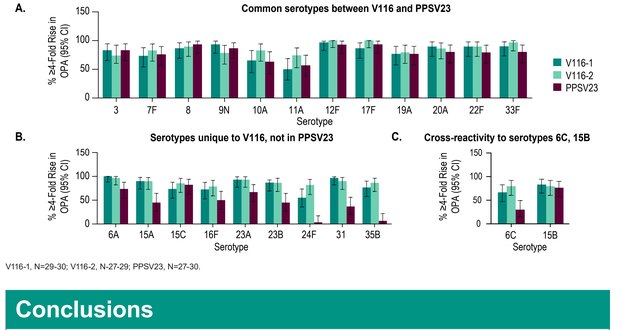


Figure 7. Percentage of participants with a ≥4-fold rise in OPA 30 days post-vaccination



V116-1, N=29-30; V116-2, N-27-29; PPSV23, N=27-30.

Conclusions

In adults aged 18-49 years of age:

- V116-1 and V116-2 were well tolerated with an overall safety profile generally comparable to PPSV23 and consistent with reported data for licensed PCVs
- Both V116-1 and V116-2 elicited functional antibody response (OPA) to all serotypes in the vaccine, and a dose-response trend was observed, with higher OPA GMTs in the V116-2 group for most vaccine serotypes
- OPA GMT responses in the V116-1 and V116-2 groups at day 30 were:
  - Generally comparable to PPSV23 for the 12 common serotypes
  - Higher than PPSV23 for the 9 serotypes unique to V116
- The results of this study support the continued development of the 4 µg/PnPS dose of V116 for the prevention of pneumococcal disease in adults
- V116 has the potential to address the unmet medical need due to the residual pneumococcal disease burden in adults

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