Safety and Immunogenicity of V114 Administered Concomitantly With Influenza Vaccine (PNEU-FLU)

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Background

- *Streptococcus pneumoniae* and influenza virus are significant causes of disease worldwide
  - Clinical manifestations of *S pneumoniae* include pneumonia, meningitis, otitis media, sinusitis, and sepsis
  - Adults ≥50 years of age are at elevated risk for pneumococcal disease and associated morbidity and mortality
  - Pneumococcal pneumonia is a frequent complication of influenza
  - Simultaneous vaccination against both influenza virus and *S pneumoniae* in at-risk individuals has been shown to reduce rates of hospitalization and mortality
- V114 (Merck & Co., Inc., Kenilworth, NJ, USA)
  - Investigational 15-valent PCV
  - *S pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, plus 22F and 33F
- Quadrivalent influenza vaccine (QIV) (GlaxoSmithKline, Research Triangle Park, NC, USA)
  - Antigens from influenza A (H1N1) virus, influenza A (H3N2) virus, influenza B/Victoria virus, and influenza B/Yamagata virus
- This phase 3 trial evaluated safety and immunogenicity of concomitant and nonconcomitant administration of V114 and QIV in adults aged ≥50 years, with or without prior history of 23-valent pneumococcal polysaccharide vaccine (PPSV23; Merck & Co., Inc., Kenilworth, NJ, USA) administration

Study Methods

- **Setting:** Multicenter, randomized, double-blind trial to evaluate the safety and immunogenicity of V114 administered concomitantly vs nonconcomitantly with QIV (PNEU-FLU)
- **Enrollment:** Overall, 1,200 healthy adults ≥50 years old randomized to receive V114 concomitantly (n=600) or nonconcomitantly (n=600) with QIV
  - Randomization stratified by age (50 to 64, 65 to 74, and ≥75 years) and by history (yes/no) of prior PPSV23 vaccination
- **Dose Regimen:** 0.5 mL intramuscular dose of study vaccine administered to healthy adults at Day 1 (V114 or placebo, plus QIV) and Day 30 (V114 or placebo)
- **Concomitant Group:** QIV + V114 on Day 1; placebo on Day 30
- **Nonconcomitant Group:** QIV + placebo on Day 1; V114 on Day 30
- **Blood Draws:** Blood samples for immunogenicity assays were obtained prior to any procedures/vaccinations at Day 1 (Visit 1), Day 30 (Visit 2), and Day 60 (Visit 3)

Primary Study Objectives

Primary Safety

- To evaluate the safety and tolerability of V114 and QIV when administered concomitantly compared with V114 and QIV when administered nonconcomitantly with respect to the proportion of participants with adverse events (AE)

Primary Immunogenicity

- To demonstrate noninferiority of pneumococcal serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMT) at 30 days postvaccination with V114 administered concomitantly with QIV vs V114 administered nonconcomitantly with QIV
- To demonstrate noninferiority of influenza strain-specific hemagglutination inhibition (HAI) GMTs at 30 days postvaccination with QIV administered concomitantly with V114 vs QIV administered nonconcomitantly with V114

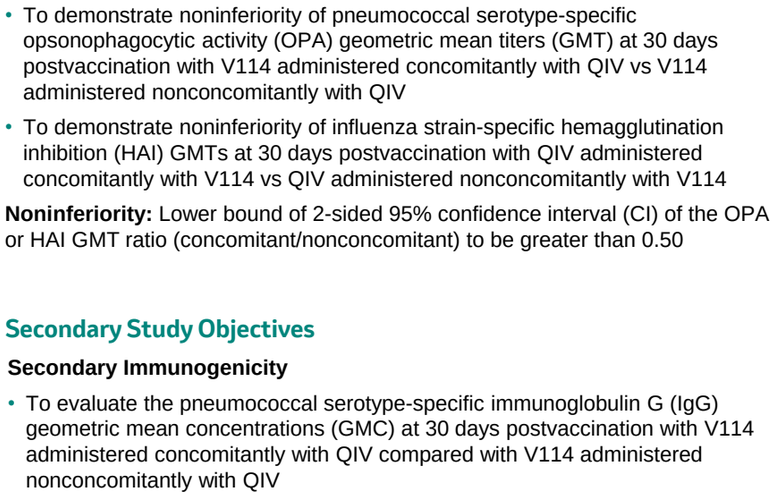
Noninferiority: Lower bound of 2-sided 95% confidence interval (CI) of the OPA or HAI GMT ratio (concomitant/nonconcomitant) to be greater than 0.50

Secondary Study Objectives

Secondary Immunogenicity

- To evaluate the pneumococcal serotype-specific immunoglobulin G (IgG) geometric mean concentrations (GMC) at 30 days postvaccination with V114 administered concomitantly with QIV compared with V114 administered nonconcomitantly with QIV
- Within each vaccination group, to evaluate the pneumococcal serotype-specific geometric mean fold rises (GMFR) and proportions of participants with a ≥4-fold rise from baseline (prevaccination with V114) to 30 days postvaccination with V114 for both OPA and IgG responses for participants administered V114 concomitantly with QIV and participants administered V114 nonconcomitantly with QIV
- Within each vaccination group, to evaluate the influenza strain-specific (1) GMFRs from baseline (prevaccination with QIV) to 30 days postvaccination with QIV, (2) proportions of participants with an HAI titer ≥1:40 at 30 days postvaccination with QIV, and (3) proportions of participants that seroconvert at 30 days postvaccination with QIV for participants administered QIV concomitantly with V114 and participants administered QIV nonconcomitantly with V114

Figure 1. Participant Disposition



[a]Two subjects were dispensed study intervention other than what was assigned in the allocation schedule. In the nonconcomitant group, 2 subjects received V114 at Vaccination 1 and 1 of the 2 subjects received placebo at Vaccination 2.

Table 1. Participant Demographics

	Concomitant Group		Nonconcomitant Group	
	n	(%)	n	(%)
Subjects in population	599		598	
Sex				
Male	269	(44.9)	256	(42.8)
Female	330	(55.1)	342	(57.2)
Age (years)				
50 to 64	299	(49.9)	298	(49.8)
65 to 74	236	(39.4)	236	(39.5)
≥75	64	(10.7)	64	(10.7)
Median (range)	65	50 to 98	65	50 to 98
Race				
White	493	(82.3)	495	(82.8)
Black	73	(12.2)	63	(10.5)
Asian	25	(4.2)	30	(5.0)
Other	8	(1.3)	10	(1.7)
Ethnicity				
Hispanic or Latino	120	(20.0)	119	(19.9)
Not Hispanic or Latino	471	(78.6)	472	(78.9)
History of Prior PPSV23				
With prior PPSV23	124	(20.7)	126	(21.1)
Without prior PPSV23	475	(79.3)	472	(78.9)

PPSV23 =PNEUMOVAX™23.
Other=American Indian, Alaska Native, native Hawaiian, Pacific Islander, Multiple, or Missing.

Table 2. Adverse Event Summary

	Concomitant		Nonconcomitant	
	n	(%)	n	(%)
Participants in Population	**600**		**596**	
Injection-Site AEs (Day 1 to 14 following vaccination)	**430**	**(71.1)**	**440**	**(73.8)**
Injection-site pain	413	(68.8)	424	(71.1)
Injection-site erythema	65	(10.8)	70	(11.7)
Injection-site swelling	86	(14.3)	99	(16.6)
Systemic AEs (Day 1 to 14 following vaccination)	**341**	**(56.8)**	**345**	**(57.9)**
Fatigue	163	(27.2)	179	(30.0)
Arthralgia	56	(9.3)	69	(11.6)
Myalgia	142	(23.7)	127	(21.3)
Headache	129	(21.5)	141	(23.7)
Serious AEs (duration of the study)	**22**	**(3.7)**	**14**	**(2.3)**
With vaccine-related[a] serious adverse events	0	(0.0)	0	(0.0)
Who died	1[b]	(0.2)	0	(0.0)
Discontinued due to an adverse event (serious or nonserious)	2[c,d]	(0.3)	1[e]	(0.2)
Maximum Body Temperature (Day 1 to 5 following vaccination)	**598**	**(99.7)**	**594**	**(99.7)**
<100.4°F (38.0°C)	589	(98.5)	586	(98.7)
≥100.4°F (38.0°C) and <102.2°F (39.0°C)	9	(0.2)	5	(0.1)
≥102.2°F (39.0°C)	0	(0.0)	3	(0.1)

[a]Determined by the investigator to be related to the vaccine.
[b]Myocardial infarction Day 10 following Visit 2 (placebo) resulting in death 2 days later; assessed as not related to vaccine by investigator.
[c]Cerebrovascular accident Day 20 Visit 1 (V114 + QIV) and lasted 3 days; assessed not related to vaccine by investigator.
[d]Sinusitis Day 4 following Visit 1 (V114 + QIV) and lasted for 1.58 months; assessed related to the vaccine by investigator.
[e]Upper abdominal pain Day 1, fatigue Day 1, nausea Day 1, arthralgia Day 2, rhinorrhea Day 2, and myalgia Day 5 following Visit 1 (QIV + placebo) and lasted for 4 days, 1.86 weeks, 3 days, 2 days, and 3 days, respectively; all assessed related to vaccine by investigator.

Figure 2. V114 Administered Concomitantly With QIV Is Noninferior to V114 Administered Nonconcomitantly With QIV as Assessed by Serotype-Specific OPA GMTs at 30 Days Postvaccination With V114

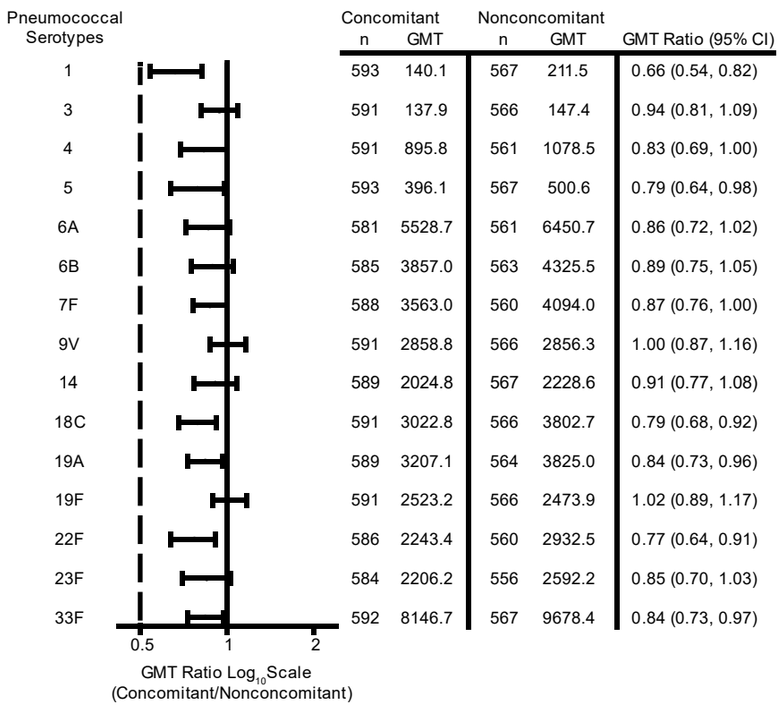


Figure 3. QIV Administered Concomitantly With V114 Is Noninferior to QIV Administered Nonconcomitantly With V114 as Assessed by Strain-Specific HAI GMTs at 30 Days Postvaccination With QIV

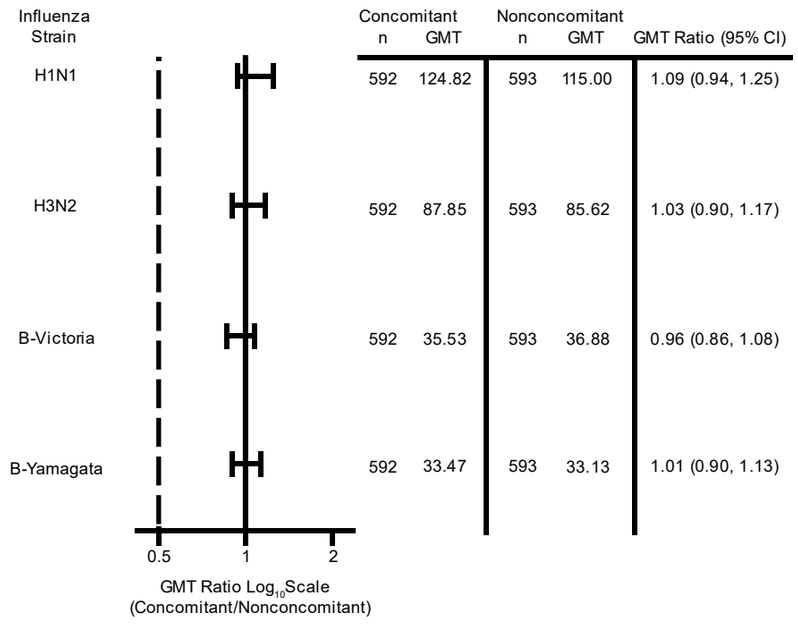
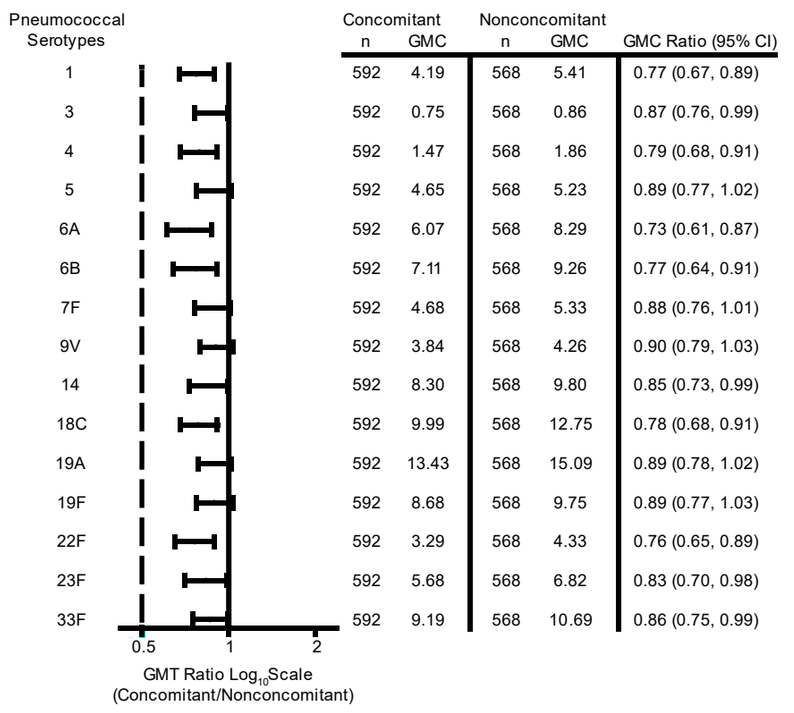


Figure 4. Between-Group Comparisons of IgG GMCs at 30 Days Postvaccination With V114 Are Consistent With the Primary Analysis of OPA GMTs



Summary

- Concomitant administration of V114 and QIV is generally well tolerated, with a safety profile that is comparable to nonconcomitant administration of V114 and QIV
- V114 administered concomitantly with QIV is noninferior to V114 administered nonconcomitantly with QIV based on the serotype-specific GMTs at 30 days postvaccination with V114, despite slightly lower GMTs
- QIV administered concomitantly with V114 is noninferior to QIV administered nonconcomitantly with V114 based on the strain-specific HAI GMTs at 30 days postvaccination with QIV
- The immunogenicity results were consistent in people with or without a history of previous PPV23 administration and across the age-groups studied
- Between-group comparisons of IgG GMCs at 30 days postvaccination with V114 are consistent with the between-group comparisons of OPA GMTs
- V114 can be administered concomitantly with inactivated QIV

Disclosures

This study was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (sponsor). In conjunction with the external investigators, this study was designed, executed, and analyzed by the sponsor. Although the sponsor formally reviewed a penultimate draft, the opinions expressed are those of the authorship and may not necessarily reflect those of the sponsor. All co-authors approved the final version of the presentation.

L Connor, J Li, A Pedley, J Hartzel, TM Sterling, KM Nolan, GM Tamms, LK Musey, and UK Buchwald were employees of the sponsor at the time of this study; employees may hold stock and/or stock options in the company. R Severance, H Schwartz, M Davis, and K Lesh have been investigators for the sponsor. R Dagan served as a member of the sponsor's scientific advisory committee for the V114 Phase III program.

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V114-021 Study Group

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