2 SYNOPSIS

Abbreviations are defined in the list of abbreviations located at the end of the Synopsis.

SPONSOR: Merck Sharp & Dohme LLC, Rahway, NJ, USA (hereafter called the Sponsor or MSD)

COMPOUND NAME: Pneumococcal Vaccine, Polyvalent (23-Valent) (V110)

PROTOCOL TITLE: A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of the Concomitant Administration of Either 23-Valent Pneumococcal Polysaccharide Vaccine or 15-Valent Pneumococcal Conjugate Vaccine with a Booster Dose of SARS-CoV-2 mRNA Vaccine in Healthy Adults 50 Years of Age or Older.

STUDY IDENTIFIERS:

IND: 00618 / 14977	EudraCT: 2021-003414-39	WHO/UTN: Not applicable	NCT: NCT05158140
	EU CT: Not applicable	JAPIC-CT: Not applicable	

STUDY PHASE: Phase 3

INDICATION: Pneumococcal infection

STUDY CENTERS: This study was conducted at 44 centers in 1 country (United States including Puerto Rico).

STUDY STATUS:
This study is complete; this report is based on the final analysis performed post final database lock.

First Participant First Visit	12-JAN-2022
Last Participant Last Visit	21-FEB-2023
Last Data Available	27-OCT-2023
Database Lock Date	31-OCT-2023

METHODOLOGY:

This was a randomized, placebo-controlled, parallel-group, multisite, double-blind study of a pneumococcal vaccine (V110 or V114) administered concomitantly or nonconcomitantly with a booster dose of SARS-CoV-2 vaccine (mRNA-1273) in adults 50 years of age and older who previously completed a 2-dose primary series of the mRNA-1273 SARS-CoV-2

vaccine ≥5 months before receipt of study vaccine at Visit 1. Participants may also have received a first booster dose of mRNA-1273 if given ≥4 months before receipt of study vaccine at Visit 1.

Participants were randomly assigned in a 1:1:1:1 ratio to receive either V110 or V114 with concomitant or nonconcomitant mRNA-1273. Randomization was stratified by age, history of pneumococcal vaccination (Yes, No), receipt of prior mRNA-1273 booster dose (Yes, No), and history of prior SARS-CoV-2 infection (Yes, No).

Study Interventions

Arm Name	Intervention Name	Unit Dose Strength	Dosage Level	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
V110 Concomitant Group	V110	Refer to product labeling	0.5 mL	IM	Single Dose at Visit 1 (Day 1)	Test product
V110 Concomitant Group	mRNA-1273	50 µg	0.25 mL	IM	Single Dose at Visit 1 (Day 1)	Test product
V110 Concomitant Group	Placebo (Sterile Saline)	N/A	0.5 mL	IM	Single Dose at Visit 3 (Day 30)	Placebo
V110 Nonconcomitant Group	Placebo (Sterile Saline)	N/A	0.5 mL	IM	Single Dose at Visit 1 (Day 1)	Placebo
V110 Nonconcomitant Group	mRNA-1273	50 µg	0.25 mL	IM	Single Dose at Visit 1 (Day 1)	Test product
V110 Nonconcomitant Group	V110	Refer to product labeling	0.5 mL	IM	Single Dose at Visit 3 (Day 30)	Test product
V114 Concomitant Group	V114	Refer to product labeling	0.5 mL	IM	Single Dose at Visit 1 (Day 1)	Test product
V114 Concomitant Group	mRNA-1273	50 µg	0.25 mL	IM	Single Dose at Visit 1 (Day 1)	Test product
V114 Concomitant Group	Placebo (Sterile Saline)	N/A	0.5 mL	IM	Single Dose at Visit 3 (Day 30)	Placebo
V114 Nonconcomitant Group	Placebo (Sterile Saline)	N/A	0.5 mL	IM	Single Dose at Visit 1 (Day 1)	Placebo

Arm Name	Intervention Name	Unit Dose Strength	Dosage Level	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
V114 Nonconcomitant Group	mRNA-1273	50 µg	0.25 mL	IM	Single Dose at Visit 1 (Day 1)	Test product
V114 Nonconcomitant Group	V114	Refer to product labeling	0.5 mL	IM	Single Dose at Visit 3 (Day 30)	Test product

IM=intramuscular; mRNA-1273=Moderna SARS-CoV-2 vaccine; N/A=not applicable; V110=PNEUMOVAX™23; V114=VAXNEUVANCE™.

This study was conducted during the COVID-19 pandemic. The Sponsor continued to follow its SOPs for study conduct, monitoring, and oversight during the pandemic and employed a risk-based approach to assess and mitigate the impact on study conduct.

ELIGIBILITY CRITERIA:

Eligible participants were adults, 50 years of age and older, who previously completed a 2-dose primary series of the mRNA-1273 SARS-CoV-2 vaccine ≥5 months before receipt of study vaccine at Visit 1, with or without a single booster dose of the mRNA-1273 SARS-CoV-2 vaccine ≥4 months before receipt of study vaccine at Visit 1. Participants with underlying chronic conditions were assessed to be in stable condition per the investigator's judgment. Participants were excluded from the study if they had a current SARS-CoV-2 infection or known history of SARS-CoV-2 infection <3 months before receipt of study vaccine at Visit 1. Participants were also excluded from the study if they had a history of myocarditis and/or pericarditis.

OBJECTIVES AND ENDPOINTS:

Objectives and endpoints were evaluated in adults ≥50 years of age who were administered V110 or V114 concomitantly or nonconcomitantly with a booster dose of mRNA-1273 SARS-CoV-2 vaccine.

Primary Objectives	Primary Endpoints
• To evaluate the safety and tolerability of V110 and mRNA-1273 when administered concomitantly or nonconcomitantly with respect to the proportion of participants with adverse events (AEs) within each vaccination group, separately	• Solicited injection-site AEs • Solicited systemic AEs • Vaccine-related serious adverse events (SAEs)
• To evaluate the safety and tolerability of V114 and mRNA-1273 when administered concomitantly or nonconcomitantly with respect to the	• Solicited injection-site AEs • Solicited systemic AEs

proportion of participants with AEs within each vaccination group, separately	• Vaccine-related SAEs
• To evaluate the serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) at 30 days postvaccination with V110 when administered concomitantly or nonconcomitantly with mRNA-1273 within each vaccination group, separately	• Serotype-specific OPA responses
• To evaluate the serotype-specific OPA GMTs at 30 days postvaccination with V114 when administered concomitantly or nonconcomitantly with mRNA-1273 within each vaccination group, separately	• Serotype-specific OPA responses
• To evaluate the SARS-CoV-2-specific binding antibody (bAb) GMTs at 30 days postvaccination when administered concomitantly or nonconcomitantly with V110 within each vaccination group, separately	• SARS-CoV-2-specific bAb responses
• To evaluate the SARS-CoV-2-specific bAb GMTs at 30 days postvaccination when administered concomitantly or nonconcomitantly with V114 within each vaccination group, separately	• SARS-CoV-2-specific bAb responses
Secondary Objectives	**Secondary Endpoints**
• To evaluate the serotype-specific geometric mean fold rises (GMFRs) and proportions of participants with a ≥4-fold rise from baseline (prevaccination with V110) to 30 days postvaccination with V110 for OPA responses for participants administered V110 concomitantly or nonconcomitantly with mRNA-1273 within each vaccination group, separately	• Serotype-specific OPA responses

• To evaluate the serotype-specific GMFRs and proportions of participants with a ≥4-fold rise from baseline (prevaccination with V114) to 30 days postvaccination with V114 for OPA responses for participants administered V114 concomitantly or nonconcomitantly with mRNA-1273 within each vaccination group, separately	• Serotypes-specific OPA responses
• To evaluate the GMFRs and proportions of participants with a ≥4-fold rise from baseline (prevaccination with mRNA-1273) to 30 days postvaccination with mRNA-1273 for SARS-CoV-2-specific bAb responses for participants administered mRNA-1273 concomitantly or nonconcomitantly with V110 within each vaccination group, separately	• SARS-CoV-2-specific bAb responses
• To evaluate the GMFRs and proportions of participants with a ≥4-fold rise from baseline (prevaccination with mRNA-1273) to 30 days postvaccination with mRNA-1273 for SARS-CoV-2-specific bAb responses for participants administered mRNA-1273 concomitantly or nonconcomitantly with V114 within each vaccination group, separately	• SARS-CoV-2-specific bAb responses

NUMBER OF PARTICIPANTS (planned and analyzed):

Approximately 1300 participants were to be enrolled in this study. Enrollment was closed on 31-AUG-2022 following EUA of the bivalent COVID-19 vaccine boosters and revocation of the EUA for the monovalent COVID-19 vaccine boosters. At the time enrollment was closed, 850 participants were enrolled. As of the final database lock, 850 participants were randomized (214 in the V110 concomitant group, 212 in the V110 nonconcomitant group, 214 in the V114 concomitant group, and 210 in the V114 nonconcomitant group).

STATISTICAL AND ANALYSIS METHODS:

Immunogenicity analyses were conducted separately for 14 of 23 pneumococcal serotypes in V110, each of the 15 serotypes in V114, and SARS-CoV-2 spike protein for mRNA-1273.

To address the primary immunogenicity objective, evaluation of the OPA GMTs and the bAb GMTs at 30 days postvaccination with V110 or V114, when administered concomitantly or nonconcomitantly with mRNA-1273, included descriptive summaries and within-group 95% CIs for each vaccination group. The point estimates were calculated by exponentiating the estimates of the mean of the natural log values, and the within-group CIs were derived by exponentiating the CIs of the mean of the natural log values based on the t-distribution.

Separate safety summaries were provided for the V110 concomitant and nonconcomitant groups and for the V114 concomitant and nonconcomitant groups. The analysis of safety followed a tiered approach. Point estimates with the corresponding within-group 95% CIs based on the exact binomial method proposed by Clopper and Pearson were provided for the proportions of participants with events following any vaccination.

RESULTS:

Participant Disposition:

- V110 Concomitant Group: 214 randomized, 214 vaccinated with mRNA-1273 and 213 vaccinated with V110 at Visit 1, 206 vaccinated with placebo at Visit 3, 208 completed study, 6 discontinued study.
- V110 Nonconcomitant Group: 212 randomized, 211 vaccinated with mRNA-1273 and 211 vaccinated with placebo at Visit 1, 203 vaccinated with V110 at Visit 3, 199 completed study, 13 discontinued study.
- V114 Concomitant Group: 214 randomized, 210 vaccinated with mRNA-1273 and 209 vaccinated with V114 at Visit 1, 205 vaccinated with placebo at Visit 3, 203 completed study, 11 discontinued study.
- V114 Nonconcomitant Group: 210 randomized, 208 vaccinated with mRNA-1273 and 208 vaccinated with placebo at Visit 1, 199 vaccinated with V114 at Visit 3, 198 completed study, 12 discontinued study.

Demographics and Baseline Characteristics:

Demographics and baseline characteristics were generally comparable between intervention groups.
The data presented below are based on all vaccinated participants (843 participants).

- **Overall Mean Age (Standard Deviation):** 60.4 years (8.1 years)
- **Sex:** 480 (56.9%) female, 363 (43.1%) male
- **Race:** 657 (77.9%) White, 149 (17.7%) Black or African American, 18 (2.1%) Asian, 16 (1.9%) multiple, 3 (0.4%) American Indian or Alaska Native
- **Ethnicity:** 476 (56.5%) not Hispanic or Latino, 364 (43.2%) Hispanic or Latino, 3 (0.4%) not reported

Immunogenicity:

Primary Immunogenicity Endpoints (V110)

- Serotype-specific OPA GMTs at 30 days postvaccination were generally comparable when V110 was administered concomitantly or nonconcomitantly with mRNA-1273.
- SARS-CoV-2-specific bAb GMTs at 30 days postvaccination with mRNA-1273 were lower when mRNA-1273 was administered concomitantly with V110 compared with mRNA-1273 administered with placebo.

Primary Immunogenicity Endpoints (V114)

- Serotype-specific OPA GMTs at 30 days postvaccination were generally comparable when V114 was administered concomitantly or nonconcomitantly with mRNA-1273.
- SARS-CoV-2-specific bAb GMTs at 30 days postvaccination with mRNA-1273 were lower when mRNA-1273 was administered concomitantly with V114 compared with mRNA-1273 administered with placebo.

Secondary Immunogenicity Endpoints (V110)

- The observed serotype-specific GMFRs and the proportion of participants with ≥4-fold rise from baseline to 30 days postvaccination with V110, were generally comparable for most serotypes when V110 was administered concomitantly with mRNA-1273 compared with V110 administered alone.
- The observed SARS-Cov-2 specific bAb GMFRs and the proportion of participants with ≥4-fold rise from baseline to 30 days postvaccination with mRNA-1273, were generally comparable when mRNA-1273 was administered concomitantly with V110 compared with mRNA-1273 administered with placebo.

Secondary Immunogenicity Endpoints (V114)

- The observed serotype-specific GMFRs and the proportion of participants with ≥4-fold rise from baseline to 30 days postvaccination with V114, were generally comparable for most serotypes when V114 was administered concomitantly with mRNA-1273 compared with V114 administered alone.
- The observed SARS-Cov-2 specific bAb GMFRs and the proportion of participants with ≥4-fold rise from baseline to 30 days postvaccination with mRNA-1273, were generally comparable when mRNA-1273 was administered concomitantly with V114 compared with mRNA-1273 administered with placebo.

Safety:

Safety Results Summary (V110)

- The proportions of participants with AEs, including injection-site AEs, systemic AEs, vaccine-related AEs, and SAEs were generally comparable in the V110 concomitant and nonconcomitant groups.
- In both V110 intervention groups, the most frequently reported AEs (>20% overall) were the solicited AEs of injection-site pain (74.6%), fatigue (39.1%), headache (32.2%), injection-site swelling (24.9%), myalgia (22.1%), and lymphadenopathy (21.2%). The proportions of participants with solicited AEs were generally comparable between V110 intervention groups.
- Of the participants with solicited AEs , the majority had events that were mild to moderate intensity in both V110 intervention groups.
- The proportions of participants with SAEs were low (<1%) in both V110 intervention groups. None of the SAEs were considered to be related to study vaccine by the investigator.
- One participant was discontinued from the V110 concomitant group due to an AE of injection-site induration, which was considered by the investigator to be vaccine related.
- There were no deaths due to AEs in the V110 intervention groups.

Adverse Event Summary
(All Participants As Treated Population)
(Following Any Vaccination)
(V110 Group)

	Concomitant Group		Nonconcomitant Group		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	214		211		425	
with one or more adverse events	175	(81.8)	171	(81.0)	346	(81.4)
injection-site	164	(76.6)	162	(76.8)	326	(76.7)
systemic	132	(61.7)	123	(58.3)	255	(60.0)
with no adverse event	39	(18.2)	40	(19.0)	79	(18.6)
with vaccine-related[a] adverse events	171	(79.9)	170	(80.6)	341	(80.2)
injection-site	164	(76.6)	162	(76.8)	326	(76.7)
systemic	119	(55.6)	108	(51.2)	227	(53.4)
with serious adverse events	2	(0.9)	2	(0.9)	4	(0.9)
with serious vaccine-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)
discontinued vaccine due to an adverse event	1	(0.5)	0	(0.0)	1	(0.2)
discontinued vaccine due to a vaccine-related adverse event	1	(0.5)	0	(0.0)	1	(0.2)
discontinued vaccine due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued vaccine due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the vaccine.
Non-serious adverse events were collected from Day 1 to Day 28 following vaccination. Serious adverse events and AESIs were reported throughout the duration of the study.

Source: [P911V110: adam-adsl; adaece]

Safety Results Summary (V114)

- The proportions of participants with AEs, including injection-site AEs, systemic AEs, vaccine-related AEs, and SAEs were generally comparable in the V114 concomitant and nonconcomitant groups.
- In both V114 intervention groups, the most frequently reported (>20%) AEs were the solicited AEs of injection-site pain (73.9%), fatigue (44.4%), headache (33.8%), injection-site swelling (24.9%), myalgia (24.2%) and lymphadenopathy (21.6%). The proportions of participants with solicited AEs were generally comparable between V114 intervention groups.
- Of the participants with solicited AEs , the majority had events that were mild to moderate intensity in both V114 intervention groups.
- The proportions of participants with SAEs were low (<3%) in both V114 intervention groups. None of the SAEs were considered to be related to study vaccine by the investigator.
- Two (0.5%) participants were discontinued (both from the V114 nonconcomitant group) due to SAEs, which were not considered by the investigator to be vaccine related. One of these participants had an SAE of pancreatic carcinoma. The other participant had an SAE of cardiac arrest resulting in death.
- There was 1 death in the V114 nonconcomitant group due to an AE of cardiac arrest (Day 8), which was not considered by the investigator to be vaccine related.

Adverse Event Summary
(All Participants As Treated Population)
(Following Any Vaccination)
(V114 Group)

	Concomitant Group		Nonconcomitant Group		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	209		208		417	
with one or more adverse events	164	(78.5)	174	(83.7)	338	(81.1)
injection-site	154	(73.7)	164	(78.8)	318	(76.3)
systemic	121	(57.9)	132	(63.5)	253	(60.7)
with no adverse event	45	(21.5)	34	(16.3)	79	(18.9)
with vaccine-related[a] adverse events	164	(78.5)	172	(82.7)	336	(80.6)
injection-site	154	(73.7)	164	(78.8)	318	(76.3)
systemic	111	(53.1)	124	(59.6)	235	(56.4)
with serious adverse events	6	(2.9)	4	(1.9)	10	(2.4)
with serious vaccine-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	1	(0.5)	1	(0.2)
discontinued vaccine due to an adverse event	0	(0.0)	2	(1.0)	2	(0.5)
discontinued vaccine due to a vaccine-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued vaccine due to a serious adverse event	0	(0.0)	2	(1.0)	2	(0.5)
discontinued vaccine due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the vaccine.
Non-serious adverse events were collected from Day 1 to Day 28 following vaccination. Serious adverse events and AESIs were reported throughout the duration of the study.

Source: [P911V110: adam-adsl; adaece]

CONCLUSIONS:

Immunogenicity for V110

The following key immunogenicity results were observed:

- Serotype-specific OPA GMTs at 30 days postvaccination with V110 were generally comparable when V110 was administered concomitantly or nonconcomitantly with mRNA-1273.
- SARS-CoV-2-specific bAb GMTs at 30 days postvaccination with mRNA-1273 were lower when mRNA-1273 was administered concomitantly with V110 compared with mRNA-1273 administered with placebo.

Immunogenicity for V114

- Serotype-specific OPA GMTs at 30 days postvaccination with V114 were generally comparable when V114 was administered concomitantly or nonconcomitantly with mRNA-1273.
- SARS-CoV-2-specific bAb GMTs at 30 days postvaccination with mRNA-1273 were lower when mRNA-1273 was administered concomitantly with V114 compared with mRNA-1273 administered with placebo.

Safety

Based on the results from this study, the following safety conclusions can be made:

- Concomitant administration of either V110 or V114 with mRNA-1273 is generally well tolerated, with a safety profile comparable to V110 or V114 alone.

LIST OF ABBREVIATIONS:

Abbreviation/Term	Definition
AE	adverse event
APaT	all participants as treated
bAb	SARS-CoV-2-specific binding antibody
CI	confidence interval
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
EUA	Emergency use authorization
GCP	Good Clinical Practice

Abbreviation/Term	Definition
GMFR	geometric mean fold rise
GMT	geometric mean titer
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
mRNA	messenger ribonucleic acid
mRNA-1273	nucleoside-modified mRNA vaccine 1273 (Moderna Inc.)
OPA	opsonophagocytic activity
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
V110	PNEUMOVAX™23 (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F)
V114	VAXNEUVANCE™ (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F)

PUBLICATION(S): As of the date of this report, there are no publications based on this study.

REPORT DATE: 01-FEB-2024

REVISED REPORT DATE: Not applicable