2 SYNOPSIS

SPONSOR: Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc., NJ, USA (MSD)

COMPOUND NAME: V114

PROTOCOL TITLE: A Phase 3, Multicenter, Randomized, Double-blind Study to Evaluate the Interchangeability of V114 and Prevnar 13™ with Respect to Safety, Tolerability, and Immunogenicity in Healthy Infants (PNEU-DIRECTION)

STUDY IDENTIFIERS:

IND: 14115	EudraCT: 2018-001151-12

STUDY PHASE: 3

INDICATION: Pneumococcal disease

STUDY CENTERS: This study was conducted at 34 centers in 3 countries.

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

First Patient, First Visit	Last Patient, Last Visit	Database Lock Date
18-OCT-2018	14-DEC-2020	27-JAN-2021

NOTE: Patient = Participant

METHODOLOGY:

This was a multicenter, randomized, active-controlled, parallel-group, double-blind interchangeability study to evaluate the safety, tolerability, and immunogenicity of mixed pneumococcal conjugate vaccine (PCV) regimens in infants approximately 2 months of age. In 2 intervention groups, infants received a 4-dose series of either Prevnar 13™ (Group 1) or V114 (Group 5). In 3 other intervention groups, the immunization series was initiated with Prevnar 13™ and changed to V114 at Dose 2, 3 or 4 (Groups 4, 3, and 2, respectively). Infants also received other licensed pediatric vaccines administered concomitantly with the PCV, including RECOMBIVAX HB™ and RotaTeq™.

Part of this study was conducted during the COVID-19 pandemic. The Sponsor continued to follow the Standard Operating Procedures for study conduct, monitoring, and oversight during the pandemic and employed a risk-based approach to assess and mitigate impact on study conduct.

Eligible participants were randomly assigned in a 1:1:1:1:1 ratio to 1 of 5 intervention groups.

V114/Prevnar 13™ Dosing Schedule

Intervention Group Name	Dose 1 (Visit 1, ~2 months of age) ≥42 days of age to ≤90 days of age	Dose 2 (Visit 2, ~4 months of age) 4 months of age to 1 day prior to 5 months of age	Dose 3 (Visit 3, ~6 months of age) 6 months of age to 1 day prior to 7 months of age	Dose 4 (Visit 5, ~12 to 15 months of age) 12 months of age to 1 day prior to 16 months of age
Group 1	Prevnar 13™	Prevnar 13™	Prevnar 13™	Prevnar 13™
Group 2	Prevnar 13™	Prevnar 13™	Prevnar 13™	V114
Group 3	Prevnar 13™	Prevnar 13™	V114	V114
Group 4	Prevnar 13™	V114	V114	V114
Group 5	V114	V114	V114	V114

ELIGIBILITY CRITERIA: Eligible participants were healthy male or female infants approximately 2 months of age (42 to 90 days, inclusive) without a history of invasive pneumococcal disease or prior administration of any pneumococcal vaccine.

OBJECTIVES AND ENDPOINTS:

Primary Objectives	Primary Endpoints
To evaluate the safety and tolerability of complete V114 (Group 5) and mixed Prevnar 13™/V114 dosing schedules (Groups 2, 3, and 4) compared with a complete dosing schedule of Prevnar 13™ (Group 1) with respect to the proportion of participants with adverse events (AEs).	Following any vaccination with V114 or Prevnar 13™: • Solicited injection-site AEs from Day 1 through Day 14 postvaccination • Solicited systemic AEs from Day 1 through Day 14 postvaccination • Vaccine-related serious adverse events (SAEs) through completion of study participation
To evaluate the anti-pneumococcal polysaccharide (PnPs) serotype-specific Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) at 30 days following Dose 4 for participants administered mixed dosing schedules of Prevnar 13™/V114 (Groups 2, 3, and 4) compared with participants administered a complete dosing schedule of Prevnar 13™ (Group 1).	Anti-PnPs serotype-specific IgG responses for the 13 shared serotypes contained in V114 and Prevnar 13™ at 30 days postdose 4 (PD4)

Secondary Objectives	Secondary Endpoints
To compare the proportion of participants with anti-hepatitis B surface antigen (HBsAg) concentration ≥10 mIU/mL at 30 days following Dose 3 for participants administered a complete primary infant series dosing schedule of V114 (Group 5) concomitantly with RECOMBIVAX HB™ versus participants administered a complete primary infant series dosing schedule of Prevnar 13™ (Groups 1 and 2) concomitantly with RECOMBIVAX HB™.	Anti-HBsAg response at 30 days postdose 3 (PD3) of V114 or Prevnar 13™
To compare the anti-rotavirus Immunoglobulin A (IgA) Geometric Mean Titer (GMT) at 30 days following Dose 3 for participants administered a complete primary infant series dosing schedule of V114 (Group 5) concomitantly with RotaTeq™ versus participants administered a complete primary infant series dosing schedule of Prevnar 13™ (Groups 1 and 2) concomitantly with RotaTeq™.	Anti-rotavirus IgA response at 30 days PD3 of V114 or Prevnar 13™
To evaluate the anti-PnPs serotype-specific IgG GMCs and the anti-PnPs serotype-specific IgG response rates (proportion of participants meeting serotype-specific IgG threshold value of ≥0.35 µg/mL) at 30 days following Dose 3 separately for each vaccination group (Groups 1, 2, 3, 4, and 5).	Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days PD3
To evaluate the anti-PnPs serotype-specific IgG GMCs at 30 days following Dose 4 for participants administered a complete dosing schedule of V114 (Group 5) compared with participants administered a complete dosing schedule of Prevnar 13™ (Group 1).	Anti-PnPs serotype-specific IgG responses for the 13 shared serotypes contained in V114 and Prevnar 13™ at 30 days PD4

NUMBER OF PARTICIPANTS (planned and analyzed): The planned enrollment total was 900 participants. As of the data cutoff date for this report, 900 participants were randomized (179 in Group 1, 181 in Group 2, 180 in Group 3, 180 in Group 4 and 180 in Group 5).

STATISTICAL ANALYSIS METHODS:

The primary immunogenicity objective was descriptive without formal hypothesis testing. The serotype-specific IgG GMCs for 13 shared serotypes contained in V114 and Prevnar 13™ at 30 days PD4 were compared between groups through the estimation of serotype-specific IgG GMC ratios for each serotype. Estimation of the IgG GMC ratios and computation of the corresponding 95% confidence intervals (CIs) were calculated using an analysis of covariance (ANCOVA) model with vaccination group and stratification factor

(hepatitis B vaccination status before enrollment = Yes, No) as covariates. The pairwise comparisons included Group 2 vs Group 1; Group 3 vs Group 1; and Group 4 vs Group 1.

For the secondary objective of the noninferiority evaluation of immunogenicity of RECOMBIVAX HB™ when given concomitantly with V114 or Prevnar 13™, the proportions of participants with anti-HBsAg concentration ≥10 mIU/mL at 30 days PD3 of V114 or Prevnar 13™ were compared between groups. The between-treatment difference based on the proportions of participants with anti-HBsAg concentration ≥10 mIU/mL [V114 (Group 5) minus Prevnar 13™ (Group 1 + Group 2)] and its 95% CI were calculated using stratified Miettinen and Nurminen method.

For the secondary objective of the noninferiority evaluation of immunogenicity of RotaTeq™ when given concomitantly with V114 or Prevnar 13™, the anti-rotavirus IgA GMT at 30 days PD3 of V114 or Prevnar 13™ was compared between groups through the estimation of anti-rotavirus IgA GMT ratios. Estimation of the anti-rotavirus IgA GMT ratio [V114 (Group 5)/Prevnar 13™ (Group 1 + Group 2)] and the corresponding 95% CIs were calculated using ANCOVA with vaccination group and stratification factor (hepatitis B vaccination status before enrollment = Yes, No) as covariates.

Safety and tolerability were assessed by clinical review of all relevant parameters including AEs and postvaccination temperature measurements. P-values (Tier 1 endpoints) and 95% CIs (Tier 1 and Tier 2 endpoints) were provided for between-vaccination group differences in the percentage of participants with prespecified events.

RESULTS:

Disposition and Demographics:

Number of Participants Randomized/Treated/Completed/Discontinued:

Group 1: 179 randomized / 179 vaccinated[a] / 164 completed / 15 discontinued
Group 2: 181 randomized / 181 vaccinated[a] / 167 completed / 14 discontinued
Group 3: 180 randomized / 178 vaccinated[a] / 147 completed / 33 discontinued
Group 4: 180 randomized / 179 vaccinated[a] / 160 completed / 20 discontinued
Group 5: 180 randomized / 179 vaccinated[a] / 167 completed / 13 discontinued
TOTAL: 900 randomized / 896 vaccinated[a] / 805 completed / 95 discontinued
[a] Vaccinated with at least 1 dose of PCV

Among the vaccinated participants (n=896):
Overall Median Age (range): 9.0 weeks (6 to 12 weeks)

Sex: 473 (52.8%) male, 423 (47.2%) female

Ethnicity: 683 (76.2%) not Hispanic or Latino, 212 (23.7%) Hispanic or Latino, 1 (0.1%) unknown

Race: 550 (61.4%) white, 177 (19.8%) Asian, 132 (14.7%) Multiple, 34 (3.8%) black or African-American, 2 (0.2%) Native Hawaiian or Other Pacific Islander, 1 (0.1%) American Indian or Alaska Native

Gestational Age: 91 (10.2%) <37 weeks, 805 (89.8%) ≥37 weeks

Hepatitis B Vaccination Status Before Enrollment: 876 (97.8%) yes, 20 (2.2%) no

Immunogenicity:

Primary Immunogenicity Endpoint

- Serotype-specific IgG GMCs at 30 days PD4 for the 13 shared serotypes were generally comparable for participants administered mixed regimens and for participants administered a complete dosing regimen of Prevnar 13™ as assessed by IgG GMC ratios.

Secondary Immunogenicity Endpoints

- Responses to RECOMBIVAX HB™ administered concomitantly with V114 met noninferiority criteria as assessed by the proportions of participants with anti-HBsAg concentration ≥10 mIU/mL at 30 days PD3.
- Responses to RotaTeq™ administered concomitantly with V114 met noninferiority criteria as assessed by anti-rotavirus IgA GMTs at 30 days PD3.
- Serotype-specific immune responses at 30 days PD3 for the 13 shared serotypes were generally comparable across intervention groups as assessed by the proportions of participants meeting the IgG threshold value of ≥0.35 µg/mL (response rates) and IgG GMCs.
- Serotype-specific immune responses at 30 days PD3 for serotype 22F were higher after 1 dose of V114 in the infant series (Group 3); similar responses were observed in Groups 4 and 5, which received additional V114 doses in the infant series as assessed by response rates and IgG GMCs.
- Serotype-specific immune responses at 30 days PD3 for serotype 33F were higher after 1 dose of V114 in the infant series (Group 3) and increased incrementally with additional V114 primary series doses administered (Groups 4 and 5) as assessed by response rates and IgG GMCs.
- Serotype-specific IgG GMCs at 30 days PD4 for the 13 shared serotypes were generally comparable for participants administered a complete 4-dose regimen of V114 and for participants administered a complete 4-dose regimen of Prevnar 13™ as assessed by serotype-specific IgG GMC ratios.

Safety:

Adverse Event Summary
(All Participants as Treated Population)
(Following Any Dose)

	Group 1		Group 2		Group 3		Group 4		Group 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	179		181		178		179		179	
with one or more adverse events	168	(93.9)	165	(91.2)	165	(92.7)	167	(93.3)	163	(91.1)
injection-site	128	(71.5)	114	(63.0)	123	(69.1)	121	(67.6)	127	(70.9)
systemic	161	(89.9)	160	(88.4)	156	(87.6)	161	(89.9)	156	(87.2)
with no adverse event	11	(6.1)	16	(8.8)	13	(7.3)	12	(6.7)	16	(8.9)
with vaccine-related[a] adverse events	150	(83.8)	149	(82.3)	149	(83.7)	151	(84.4)	153	(85.5)
injection-site	128	(71.5)	114	(63.0)	123	(69.1)	121	(67.6)	127	(70.9)
systemic	110	(61.5)	110	(60.8)	108	(60.7)	118	(65.9)	113	(63.1)
with serious adverse events	21	(11.7)	24	(13.3)	15	(8.4)	18	(10.1)	21	(11.7)
with serious vaccine-related adverse events	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued vaccine due to an adverse event	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)
discontinued vaccine due to a vaccine-related adverse event	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)
discontinued vaccine due to a serious adverse event	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)
discontinued vaccine due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the vaccine.

Reported adverse events include nonserious adverse events that occurred within 14 days of any vaccination and serious adverse events that occurred from ~2 months of age (following dose 1) through completion of study participation.

Group 1: Prevnar 13™ → Prevnar 13™ → Prevnar 13™ → Prevnar 13™

Group 2: Prevnar 13™ → Prevnar 13™ → Prevnar 13™ → V114

Group 3: Prevnar 13™ → Prevnar 13™ → V114 → V114

Group 4: Prevnar 13™ → V114 → V114 → V114

Group 5: V114 → V114 → V114 → V114

CONCLUSIONS:

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

In healthy infants and toddlers:

- Following a toddler dose administered at ~12 to 15 months of age, mixed dosing regimens of V114 and Prevnar 13™ elicit generally comparable immune responses to a complete 4-dose regimen of Prevnar 13™ for the 13 shared serotypes as assessed by serotype-specific IgG GMCs and IgG GMC ratios at 30 days postvaccination.
- Following 3 doses in the infant primary series, RECOMBIVAX HB™ administered concomitantly with V114 is noninferior to RECOMBIVAX HB™ administered concomitantly with Prevnar 13™ as measured by the proportion of patients with anti-HBsAg concentration ≥10 mIU/mL at 30 days postvaccination.
- Following 3 doses in the infant primary series, RotaTeq™ administered concomitantly with V114 is noninferior to RotaTeq™ administered concomitantly with Prevnar 13™ as measured by anti-rotavirus IgA GMT at 30 days postvaccination.
- Complete V114 and mixed Prevnar 13™ and V114 dosing regimens are generally well-tolerated with safety profiles generally comparable to a complete dosing regimen of Prevnar 13™.

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

REPORT DATE: 25-MAY-2021