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Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

HBVAXPRO

hepatitis b vaccine (rdna)

Procedure no: EMEA/H/C/000373/P46/060

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 04 June 2021, the MAH submitted a completed paediatric study for HBVAXPRO in accordance with Article 46 of Regulation (EC) No1901/2006 as amended. This study is part of the PIP agreed for V114 (P/0339/2017).

A short critical expert overview has also been provided.

V114 is a pneumococcal 15-valent conjugate vaccine [CRM197 protein, adsorbed] undergoing review as part of a centralised marketing authorisation application under procedure EMEA/H/C/005477/0000. The vaccine aims to prevent pneumococcal disease caused by the serotypes included in the vaccine. V114 contains the 13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) present in Prevnar 13 and 2 additional serotypes: 22F and 33F.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that V114-027 is a stand-alone study.

Study V114-027 was a phase 3, multicentre, randomised, double-blind study to evaluate the safety, tolerability, and immunogenicity of mixed pneumococcal conjugated vaccines regimens in infants of approximately 2 months of age. It evaluated a 4-dose regimen, eg 3 infant primary series followed by 1 toddler dose, when changing from Prevnar 13 to V114 at Doses 2, 3, or 4 during the immunisation dosing regimen. In 2 intervention groups, the infants received a 4-dose series of Prevnar 13 (Group 1) or V114 (Group 5). In the other 3 intervention groups, the immunisation series was initiated with Prevnar 13 and changed to V114 at Dose 2, 3, or 4 (Groups 4, 3, and 2). All the subjects in V114-027 received licensed paediatric vaccines administered concomitantly according to the recommended schedule by the US ACIP. These included RotaTeq, Pentacel, RECOMBIVAX HB (approved under the name HBVAXPRO® in the EEA and United Kingdom), M-M-R II, and VARIVAX. This study only evaluated the concomitant administration of V114 with RECOMBIVAX HB and RotaTeq; the other licensed vaccines were administered as part of standard of care and will be evaluated in other studies as part of the V114 development program.

2.2. Information on the pharmaceutical formulation used in the study

Table 1 summarises the study interventions used in this study, including formulation, strength, dose, and route of administration.

Table 1 Study interventions [Source: Table 9-1 CSR]

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin	Vaccination Regimen	Use	IMP/NIMP	Sourcing
1	Active Comparator	Prevnar 13™	Biological/ Vaccine	Sterile suspension	Refer to product labeling	0.5 mL	IM	Single dose at Visits 1, 2, 3, and 5 (~2, 4, 6, and 12 to 15 months of age, respectively)	Experimental	IMP	Central
2	Experimental	Prevnar 13™	Biological/ Vaccine	Sterile suspension	Refer to product labeling	0.5 mL	IM	Single dose at Visits 1, 2, and 3 (~2, 4, and 6 months of age, respectively)	Experimental	IMP	Central
		V114	Biological/ Vaccine	Sterile suspension	Refer to IB	0.5 mL	IM	Single dose at Visit 5 (~12 to 15 months of age)	Experimental	IMP	Central
3	Experimental	Prevnar 13™	Biological/ Vaccine	Sterile suspension	Refer to product labeling	0.5 mL	IM	Single dose at Visits 1 and 2 (~2 and 4 months of age, respectively)	Experimental	IMP	Central
		V114	Biological/ Vaccine	Sterile suspension	Refer to IB	0.5 mL	IM	Single dose at Visits 3 and 5 (~6 and 12 to 15 months of age, respectively)	Experimental	IMP	Central
4	Experimental	Prevnar 13™	Biological/ Vaccine	Sterile suspension	Refer to product labeling	0.5 mL	IM	Single dose at Visit 1 (~2 months of age)	Experimental	IMP	Central
		V114	Biological/ Vaccine	Sterile suspension	Refer to IB	0.5 mL	IM	Single dose at Visits 2, 3, and 5 (~4, 6, and 12 to 15 months of age, respectively)	Experimental	IMP	Central
5	Experimental	V114	Biological/ Vaccine	Sterile suspension	Refer to IB	0.5 mL	IM	Single dose at Visits 1, 2, 3, and 5 (~2, 4, 6, and 12 to 15 months of age, respectively)	Experimental	IMP	Central

Admin = administration; IB = Investigator's Brochure; IM = intramuscular; IMP = investigational medicinal product; NIMP = non-investigational medicinal product
The definition of IMP and NIMP is based on guidance issued by the European Commission. Regional and/or country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- P027V114: a Phase 3, multicentre, randomised, double-blind study to evaluate the interchangeability of V114 and Prevnar 13 with respect to safety, tolerability, and immunogenicity in healthy infants (PNEU-DIRECTION)

2.3.2. Clinical study

2.4. P027V114

A Phase 3, multicentre, randomised, double-blind study to evaluate the interchangeability of V114 and Prevnar 13 with respect to safety, tolerability, and immunogenicity in healthy infants (PNEU-DIRECTION)

Description

Study V114-027 was designed to evaluate the safety, tolerability, and immunogenicity of mixed pneumococcal conjugated vaccines regimens in infants of approximately 2 months of age. In 2 intervention groups, infants received a 4-dose series of 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). All participants in this study received licensed paediatric vaccines administered concomitantly, according to the recommended schedule by the US ACIP. This study only evaluated the concomitant administration of V114 with RECOMBIVAX HB and RotaTeq.

Methods

Objective(s)

Primary objectives:

- 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 subjects with adverse events (AEs)
- To evaluate the anti-pneumococcal polysaccharide (PnPs) serotype-specific immunoglobulin G (IgG) geometric mean concentrations (GMCs) at 30 days following Dose 4 for subjects administered mixed dosing schedules of Prevnar 13/V114 (Groups 2, 3, and 4) compared with subjects administered a complete dosing schedule of Prevnar 13 (Group 1)

Secondary objectives:

- To compare the proportion of subjects 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 subjects administered a complete primary infant series dosing schedule of Prevnar 13 (Groups 1 and 2) concomitantly with RECOMBIVAX HB

  Hypothesis (H1): RECOMBIVAX HB administered concomitantly with V114 is non-inferior to RECOMBIVAX HB administered concomitantly with Prevnar 13 as measured by the proportion of subjects with anti-HBsAg concentration ≥10 mIU/mL at 30 days following Dose 3.

  The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI of the difference in proportions of subjects with anti-HBsAg concentration ≥10 mIU/mL [V114 minus Prevnar 13] to be greater than -0.10.

- To compare the anti-rotavirus immunoglobulin A (IgA) geometric mean titre (GMT) at 30 days following Dose 3 for subjects administered a complete primary infant series dosing schedule of V114 (Group 5) concomitantly with RotaTeq versus subjects administered a complete primary infant series dosing schedule of Prevnar 13 (Groups 1 and 2) concomitantly with RotaTeq

  Hypothesis (H2): RotaTeq administered concomitantly with V114 is non-inferior to RotaTeq administered concomitantly with Prevnar 13 as measured by anti-rotavirus IgA GMT at 30 days following Dose 3.

  The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI of the anti-rotavirus IgA GMT ratio [V114/Prevnar 13] to be greater than 0.50.

- To evaluate the anti-PnPs serotype-specific IgG GMCs and the anti-PnPs serotype-specific IgG response rates (proportion of subjects 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)
- To evaluate the anti-PnPs serotype-specific IgG GMCs at 30 days following Dose 4 for subjects administered a complete dosing schedule of V114 (Group 5) compared with subjects administered a complete dosing schedule of Prevnar 13 (Group 1)

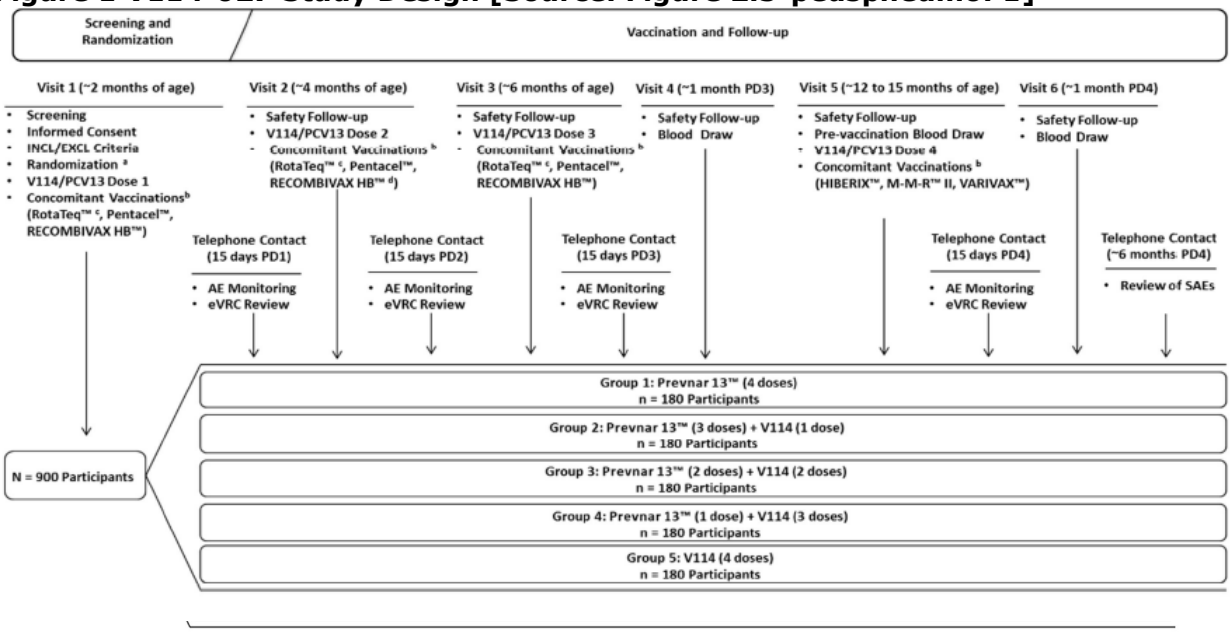
Tertiary/Exploratory objectives

- To evaluate the anti-PnPs serotype-specific IgG GMCs prior to Dose 4 separately for each vaccination group (Groups 1, 2, 3, 4, and 5)

- To evaluate the anti-HBsAg GMCs at 30 days following Dose 3 for subjects administered a complete primary infant series dosing schedule of V114 (Group 5) concomitantly with RECOMBIVAX HB versus subjects administered a complete primary infant series dosing schedule of Prevnar 13 (Groups 1 and 2) concomitantly with RECOMBIVAX HB

Study design

Figure 1 V114-027 Study Design [Source: Figure 2.5-pedspneumo: 1]



AE = adverse event; eVRC = electronic Vaccination Report Card; INCL/EXCL = Inclusion/Exclusion Criteria; PCV13 = Prevnar 13™; PD = postdose; SAE = serious adverse event

[a] Randomization will be stratified by previous hepatitis B vaccination status.

[b] Tradenames for the concomitant vaccines may vary depending on where clinical supplies are sourced by the Sponsor.

[c] RotaTeq™ is administered orally and should be given before V114 or Prevnar 13™ and other injectable concomitant vaccines.

[d] For participants who received the first dose of hepatitis B vaccine before enrollment, RECOMBIVAX HB™ will be administered at ~2 and 6 months of age and not at ~4 months of age.

Study population /Sample size

Healthy male or female infants of approximately 2 months of age (42 to 90 days inclusive) without a history of invasive pneumococcal disease or prior administration of any pneumococcal vaccine were eligible for enrolment.

900 participants were planned and randomised as follows: Group 1: 179, Group 2: 181, Group 3:180, Group 4: 180, and Group 5: 180.

Treatments

Table 2 summarises the treatment schedule for Prevnar 13 or V114 and Table 3 the concomitant vaccine dosing schedule.

Table 2 V114-027 Pneumococcal conjugated vaccine dosing schedule [Source: Table 2.5-pedspneumo: 1]

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
PCV=pneumococcal conjugate vaccine				

Source: [Ref. 5.3.5.1: P027V114: 16.1.1]

Table 3 V114-027 Concomitant vaccine dosing schedule [Source: Table 2.5-pedspneumo: 2]

Vaccine US Tradename[a] (Generic Name)	Indication	Visit 1 (~2 months of age)	Visit 2 (~4 months of age)	Visit 3 (~6 months of age)	Visit 5 (~12 to 15 months of age)
RotaTeq™[b] (Rotavirus Vaccine, Live, Oral, Pentavalent)	Prevention of rotavirus gastroenteritis	X	X	X	
Pentacel™ (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate [Tetanus Toxoid Conjugate] Vaccine)	Prevention of diphtheria, tetanus, pertussis, poliomyelitis, and invasive disease due to *Haemophilus influenzae* type b	X	X	X	
RECOMBIVAX HB™ (Hepatitis B Vaccine [Recombinant])	Prevention of hepatitis B virus infection	X	X[c]	X	
HIBERIX™ (Haemophilus b Conjugate Vaccine [Tetanus Toxoid Conjugate])	Prevention of invasive disease caused by *Haemophilus influenzae* type b				X
M-M-R™ II (Measles, Mumps, and Rubella Virus Vaccine Live)	Simultaneous vaccination against measles, mumps, and rubella				X
VARIVAX™ (Varicella Virus Vaccine Live)	Prevention of varicella				X

[a] Tradenames for concomitant vaccines varied depending on where clinical supplies were sourced by the Sponsor.
[b] RotaTeq™ was administered orally and was to be given before V114 or Prevnar 13™ and other injectable concomitant vaccines.
[c] For participants who received the first dose of hepatitis B vaccine before enrollment, RECOMBIVAX HB™ was to be administered at ~2 and 6 months of age, and not at ~4 months of age.
Note: Only RotaTeq™ and RECOMBIVAX HB™ were evaluated as part of V114-027.

Source: [Ref. 5.3.5.1: P027V114: 16.1.1]

Outcomes/endpoints

Primary endpoints:

Safety

Following any vaccination with V114 or with Prevnar 13:

- Solicited injection-site AEs from Day 1 through Day 14 post-vaccination
- Solicited systemic AEs from Day 1 through Day 14 post-vaccination
- Vaccine-related serious adverse events (SAEs) through completion of study participation

Immunogenicity

- Anti-PnPs serotype-specific IgG responses for the 13 shared serotypes contained in V114 and Prevnar 13 at 30 days post-dose 4 (PD4)

Secondary endpoints:

- Anti-HBsAg response at 30 days post-dose 3 (PD3) of V114 or Prevnar 13
- Anti-rotavirus IgA response at 30 days PD3 of V114 or Prevnar 13
- Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days PD3
- Anti-PnPs serotype-specific IgG responses for the 13 shared serotypes contained in V114 and Prevnar 13 at 30 days PD4

Statistical Methods

Analysis Sets

The **per-protocol (PP) population** was the primary population for the analysis of immunogenicity data in this study. It included all randomised subjects without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint(s). Potential deviations that could result in the exclusion of a subjects from the PP population for all immunogenicity analyses included:

- Failure to receive primary infant series vaccination (V114/Prevnar 13 Doses 1, 2, and 3) as per the randomisation schedule
- Receipt of prohibited medication or prohibited vaccine prior to study vaccination

Additional potential deviations that could result in the exclusion of a subject from this population for specific immunogenicity analyses (depending on the time point for analysis) included:

- Failure to receive the required study vaccine (V114, Prevnar 13, RECOMBIVAX HB, or RotaTeq) according to the vaccination schedule at the time point for the analysis
- Failure to receive the scheduled doses of V114 or Prevnar 13 (at least 28 days between Doses 1 and 2, and between Doses 2 and 3 [for PD3 and pre-dose 4 analysis], 12 months to 1 day prior to 16 months of age for Dose 4 [for PD4 PP analyses])
- Receipt of prohibited medication or prohibited vaccine prior to a blood sample collection
- Collection of blood sample at the time point for the analysis outside of the pre-specified window (as described in Section 1.3 of the protocol)

The **full analysis set (FAS) population** was used to perform a supportive analysis of the primary immunogenicity endpoints. This populations consisted of all the randomised subjects who received all study vaccinations required at the time point for the analysis, and had at least one serology result at

the time point for the analysis. Subjects were to be included in the vaccination group to which they were randomised for the analysis of immunogenicity data using the FAS population.

Safety analyses were conducted in the **all participants as treated (APaT) population**. This population consisted of all the randomised subjects [participants] who received at least 1 dose of study vaccination for the time point of interest. For safety analyses following any dose of pneumococcal conjugate vaccine (PCV), subjects vaccinated with PCV at any time point were to be included. For safety analyses following each dose of PCV, subjects vaccinated with PCV at that dose were to be included. Subjects who received Prevnar 13 following V114 during the study were to be excluded from the analyses, and were only to be included in a separate AE listing. Subjects were to be included in the group corresponding to the study vaccination they actually received for the analysis of safety data using the APaT population. That is, the group to which they were randomised except for those who received the incorrect study vaccination. The latter were to be included in the vaccination group corresponding to the vaccination they received. At least 1 temperature measurement obtained subsequent to study intervention was required for inclusion in the analysis of temperature.

Sample Size and Power

Immunogenicity

The primary immunogenicity objective of the study was descriptive. The study randomised subjects in a 1:1:1:1:1 ratio into the 5 vaccination groups. The overall sample size was to be approximately 900, 180 participants were to be included in each of the 5 vaccination groups. It was assumed that about 135 participants per vaccination group were to be evaluable for PP immunogenicity analyses at 30 days PD4 (based on a 75% evaluability rate). For the descriptive primary endpoint IgG GMC, the width of the 95% CIs for the serotype-specific IgG GMC ratios depended on the sample size, variability of the natural log concentrations, and the magnitude of the IgG GMC ratio. The 95% CIs for various hypothetical IgG GMC ratios at 30 days PD4 and standard deviation (SD) estimates for the natural log titers are displayed in Table 5 in the supplementary statistical analysis plan.

For the secondary endpoints, the power was ~96% and ~98% for each of the 2 non-inferiority hypotheses when RECOMBIVAX HB or RotaTeq were administered concomitantly with V114 or Prevnar 13.

For the secondary endpoint #1/hypothesis (H1), the study had ~96% power at a 1-sided 2.5% alpha-level to demonstrate that RECOMBIVAX HB administered concomitantly with V114 was non-inferior to RECOMBIVAX HB administered concomitantly with Prevnar 13. This was based on the proportion of subjects with anti-HBsAg concentration ≥10 mIU/mL 30 days PD3 based on the following assumptions: (1) an approximately 80% evaluability rate at PD3 as observed in the V114-008 paediatric study; (2) a non-inferiority margin of -0.10 for the difference (Group 5 – [Group 1 + Group 2]); and (3) an underlying response rate (proportion of subjects with anti-HBsAg concentration ≥10 mIU/mL 30 days PD3 of V114 or Prevnar 13) of 95% for the Prevnar 13 group as observed in a previous MSD study.

For the secondary endpoint #2/hypothesis (H2), the study had ~98% power at a 1-sided 2.5% alpha-level to demonstrate that RotaTeq administered concomitantly with V114 was non-inferior to RotaTeq administered concomitantly with Prevnar 13 as measured by the anti-rotavirus IgA GMT at 30 days PD3 based on the following assumptions: (1) an approximately 80% evaluability rate at PD3 as observed in the V114-008 paediatric study; (2) a non-inferiority margin of 2-fold; (3) SD of anti-rotavirus IgA responses in log scale was 1.7 as those observed in a previous MDS study, and (4) the true GMT ratio (Group 5/[Group 1 +Group 2]) for anti-rotavirus IgA responses was 1.0.

Safety

The probability of observing at least 1 SAE in the study depended on the number of subjects vaccinated, and the underlying incidence of subjects with an SAE in the study population. The calculations given in Table 6 of the supplementary statistical analysis plan assumed that 100% of the randomised subjects were to be evaluable for the safety analyses. There was an 80% chance of observing at least one SAE among 180 subjects in each of the complete and mixed dosing regimens of V114 and Prevnar 13 if the underlying incidence of an SAE was 0.89% (1 of every 112 subjects receiving the vaccine). There was a 50% chance of observing at least one SAE among 180 subjects in the complete and mixed dosing regimens of V114 and Prevnar 13 group if the underlying incidence of an SAE was 0.38% (1 of every 260 subjects receiving the vaccine). If no SAEs were observed among 180 subjects, the study was to provide 97.5% confidence that the underlying percentage of subjects with an SAE was <2.03% (one in every 49 subjects).

Results

Recruitment/ Number analysed

900 subjects were randomised; of these, 896 were vaccinated. The trial was conducted in 31 study sites in Thailand, Turkey, and the USA including Puerto Rico. More than 99% of subjects received the first dose of all protocol-specified study interventions, including RECOMBIVAX HB and RotaTeq. The majority (>90%) received all subsequent doses. Per protocol, subjects who received the first dose of hepatitis B vaccine before enrolment did not receive RECOMBIVAX HB at ~4 months of age. The majority of subjects (~89%) in each intervention group completed the study. The most common reason for discontinuation was withdrawal by parent/guardian. Patient disposition is given in Table 4 for all randomised subjects.

Table 4 Subjects disposition (All randomized subjects) [Source: Table 10-1 CSR]

	Group 1		Group 2		Group 3		Group 4		Group 5		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	179		181		180		180		180		900	
Vaccinated at ~2 months of age with												
PCV	179	(100.0)	181	(100.0)	178	(98.9)	179	(99.4)	179	(99.4)	896	(99.6)
Pentacel™	179	(100.0)	181	(100.0)	178	(98.9)	179	(99.4)	179	(99.4)	896	(99.6)
RECOMBIVAX HB™	179	(100.0)	181	(100.0)	178	(98.9)	179	(99.4)	179	(99.4)	896	(99.6)
RotaTeq™	179	(100.0)	181	(100.0)	178	(98.9)	179	(99.4)	179	(99.4)	896	(99.6)
Vaccinated at ~4 months of age with												
PCV	176	(98.3)	175	(96.7)	166	(92.2)	169	(93.9)	173	(96.1)	859	(95.4)
Pentacel™	176	(98.3)	175	(96.7)	165	(91.7)	168	(93.3)	173	(96.1)	857	(95.2)
RECOMBIVAX HB™	3	(1.7)	5	(2.8)	5	(2.8)	4	(2.2)	3	(1.7)	20	(2.2)
RotaTeq™	176	(98.3)	175	(96.7)	166	(92.2)	169	(93.9)	173	(96.1)	859	(95.4)
Vaccinated at ~6 months of age with												
PCV	175	(97.8)	174	(96.1)	161	(89.4)	167	(92.8)	173	(96.1)	850	(94.4)
Pentacel™	175	(97.8)	174	(96.1)	161	(89.4)	167	(92.8)	173	(96.1)	850	(94.4)
RECOMBIVAX HB™	175	(97.8)	174	(96.1)	161	(89.4)	167	(92.8)	173	(96.1)	850	(94.4)
RotaTeq™	175	(97.8)	174	(96.1)	161	(89.4)	167	(92.8)	173	(96.1)	850	(94.4)
Vaccinated at ~12 to 15 months of age with												
PCV	165	(92.2)	168	(92.8)	150	(83.3)	162	(90.0)	168	(93.3)	813	(90.3)
HIBERIX™	165	(92.2)	168	(92.8)	150	(83.3)	162	(90.0)	168	(93.3)	813	(90.3)
M-M-R™ II	165	(92.2)	168	(92.8)	150	(83.3)	162	(90.0)	168	(93.3)	813	(90.3)
VARIVAX™	165	(92.2)	168	(92.8)	149	(82.8)	161	(89.4)	168	(93.3)	811	(90.1)

	Group 1		Group 2		Group 3		Group 4		Group 5		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Trial Disposition												
Completed	164	(91.6)	167	(92.3)	147	(81.7)	160	(88.9)	167	(92.8)	805	(89.4)
Discontinued	15	(8.4)	14	(7.7)	33	(18.3)	20	(11.1)	13	(7.2)	95	(10.6)
Lost To Follow-Up	2	(1.1)	6	(3.3)	7	(3.9)	3	(1.7)	2	(1.1)	20	(2.2)
Physician Decision	4	(2.2)	0	(0.0)	1	(0.6)	0	(0.0)	2	(1.1)	7	(0.8)
Withdrawal By Parent/Guardian	9	(5.0)	8	(4.4)	25	(13.9)	17	(9.4)	9	(5.0)	68	(7.6)

Each participant is counted once for Trial Disposition based on the latest corresponding disposition record.
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
PCV=pneumococcal conjugate vaccine (V114 or Prevnar 13™).

Source: [P027V114: adam-adsl; adex]

RECOMBIVAX HB and RotaTeq

More than 75% of the subjects were included in the PP populations for RECOMBIVAX HB and RotaTeq analyses. The main reason for exclusion across intervention groups was missing serology results (

Table 5 and Table 6).

Table 5 Subject accounting for RECOMBIVAX HB analyses of the per-protocol population (All randomized subjects) [Source: Table 2.5-pedspneumo: 5]

	Group 1		Group 2		Group 3		Group 4		Group 5		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants randomized	179		181		180		180		180		900	
Participants included in analyses by timepoint												
30 Days Postdose 3	142	(79.3)	142	(78.5)	136	(75.6)	141	(78.3)	153	(85.0)	714	(79.3)
Reasons for exclusions from analyses[a]												
Missed at least one vaccination of PCV at Vaccination 1, 2, 3[b]	4	(2.2)	7	(3.9)	19	(10.6)	13	(7.2)	7	(3.9)	50	(5.6)
No initial consent	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Blood draw out of window	7	(3.9)	5	(2.8)	8	(4.4)	6	(3.3)	3	(1.7)	29	(3.2)
Missing serology results[c]	25	(14.0)	26	(14.4)	17	(9.4)	19	(10.6)	16	(8.9)	103	(11.4)
Prohibited concomitant medication or vaccination	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)	1	(0.1)
Vaccination out of window	3	(1.7)	2	(1.1)	0	(0.0)	0	(0.0)	1	(0.6)	6	(0.7)

Percentages are calculated based on the number of participants randomized.
[a] Participants may have more than one reason for exclusion.
[b] Includes participants who discontinued the study. These participants do not also appear in the other reasons for exclusions from analyses rows.
[c] Missing serology results for all antigen(s) included in the concomitant vaccine, which may be due to discontinuation prior to serum sample collection, failure to provide a serum sample, and serum sample lost or damaged.
Per protocol, dose 3 was administered at ~6 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
PCV=pneumococcal conjugate vaccine (V114 or Prevnar 13™).

Source: [P027V114: adam-adsl; adpdev; adimm]

Table 6 Subject accounting for RotaTeq analyses of the per-protocol population (All randomized subjects) [Source: Table 2.5-pedspneumo: 6]

	Group 1		Group 2		Group 3		Group 4		Group 5		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants randomized	179		181		180		180		180		900	
Participants included in analyses by timepoint												
30 Days Postdose 3	147	(82.1)	143	(79.0)	136	(75.6)	143	(79.4)	152	(84.4)	721	(80.1)
Reasons for exclusions from analyses[a]												
Missed at least one vaccination of PCV at Vaccination 1, 2, 3[b]	4	(2.2)	7	(3.9)	19	(10.6)	13	(7.2)	7	(3.9)	50	(5.6)
No initial consent	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Blood draw out of window	9	(5.0)	5	(2.8)	8	(4.4)	5	(2.8)	4	(2.2)	31	(3.4)
Missing serology results[c]	18	(10.1)	25	(13.8)	17	(9.4)	19	(10.6)	16	(8.9)	95	(10.6)
Vaccination out of window	3	(1.7)	2	(1.1)	0	(0.0)	0	(0.0)	1	(0.6)	6	(0.7)

Percentages are calculated based on the number of participants randomized.
[a] Participants may have more than one reason for exclusion.
[b] Includes participants who discontinued the study. These participants do not also appear in the other reasons for exclusions from analyses rows.
[c] Missing serology results for all antigen(s) included in the concomitant vaccine, which may be due to discontinuation prior to serum sample collection, failure to provide a serum sample, and serum sample lost or damaged.
Per protocol, dose 3 was administered at ~6 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
PCV=pneumococcal conjugate vaccine (V114 or Prevnar 13™).

Source: [P027V114: adam-adsl; adpdev; adimm]

Protocol deviations

The Sponsor followed the definition from ICHE3 to classify protocol deviations as important, eg those that may significantly impact the quality or integrity of key study data or that may significantly affect a subject's rights, safety, or well-being; or not important. Important protocol deviations were further classified as clinically important, eg deviations that may compromise critical data analyses pertaining to primary efficacy and/or safety endpoints or the participant's safety, or not clinically important.

Important protocol deviations were reported for 210 (23.3%) subjects. Of them, 138 (15.3%) subjects had important protocol deviations considered clinically important. The most frequently reported clinically important protocol deviations were related to trial procedures, eg immunogenicity blood samples drawn outside protocol-defined windows. The protocol deviations were comparably across intervention groups (CSR Table 10-2).There were no important protocol deviations classified as serious GCP non-compliance issues.

Protocol deviations associated with the covid-19 pandemic

Protocol deviations associated with the pandemic were reported for 41 (4.6%) subjects. 35 (3.9%) subjects had important deviations considered to be clinically important (CSR Table 14.1-8). Data from 23 (2.6%) subjects were excluded from pneumococcal IgG analyses due to protocol deviations, eg PD4 blood draw out of window, associated with the COVID-19 pandemic (CSR Table 14.1-9).

Baseline data

Demographic and baseline characteristics were comparable across intervention groups. The subjects' median age at the time of consent was 9.0 weeks (range: 6-12 weeks). The majority was male, white, and of non-Hispanic or Latino ethnicity. Approximately 10% of subjects were preterm infants (gestational age <37 weeks). Most of the subjects (97.8%) received hepatitis B vaccination before study enrolment (CSR Table 10-6).

Efficacy results

Immunogenicity - Primary immunogenicity endpoint

Serotype-specific IgG GMCs at 30 days PD4 for the 13 shared serotypes were comparable for subjects who received mixed regimens (Prevnar 13/V114), and for those who received a complete dosing regimen of Prevnar 13 as assessed by IgG GMC ratios (Table 7 and Table 8).

The results shown by reverse cumulative distribution curves (RCDCs) and those performed in the FAS population were also consistent with those presented in Table 7 and Table 8 (CSR Figure 14.2-1 to Figure 14.2-4, and Tables 14.2-3 and 14.2-4).

Table 7 Analysis of IgG GMCs for the 13 shared serotypes at 30 days post-dose 4 Groups 4, 3, and 2 versus Group 1 (Per-Protocol Population) [Source: Table 11-1 CSR]

Pneumococcal Serotype	Vaccination Group				GMC Ratio[a] (Group 4, 3, 2 / Group 1)
		N	n	GMC[a]	Estimate (95% CI)[a]
1	Group 4	179	139	1.67	0.83 (0.69, 1.00)
	Group 3	178	128	1.87	0.93 (0.77, 1.12)
	Group 2	181	151	1.67	0.83 (0.70, 1.00)
	Group 1	179	147	2.01	
3	Group 4	179	139	0.71	1.01 (0.86, 1.19)
	Group 3	178	128	0.66	0.94 (0.80, 1.12)
	Group 2	181	151	0.74	1.06 (0.90, 1.25)
	Group 1	179	148	0.70	
4	Group 4	179	139	1.44	0.81 (0.66, 1.00)
	Group 3	178	128	1.48	0.84 (0.68, 1.03)
	Group 2	181	151	1.56	0.88 (0.72, 1.08)
	Group 1	179	146	1.77	
5	Group 4	179	138	3.30	0.79 (0.64, 0.98)
	Group 3	178	128	4.34	1.04 (0.84, 1.29)
	Group 2	181	151	3.84	0.92 (0.75, 1.14)
	Group 1	179	147	4.16	
6A	Group 4	179	139	5.04	0.80 (0.66, 0.98)
	Group 3	178	128	6.97	1.11 (0.91, 1.37)
	Group 2	181	151	6.98	1.12 (0.92, 1.36)
	Group 1	179	146	6.26	
6B	Group 4	179	139	6.65	1.08 (0.88, 1.31)
	Group 3	178	128	6.67	1.08 (0.88, 1.32)
	Group 2	181	151	7.61	1.23 (1.02, 1.49)
	Group 1	179	146	6.18	

7F	Group 4	179	139	3.99	0.78 (0.64, 0.95)
	Group 3	178	128	5.07	0.99 (0.81, 1.21)
	Group 2	181	151	5.70	1.11 (0.92, 1.35)
	Group 1	179	146	5.11	
9V	Group 4	179	139	2.67	0.84 (0.70, 1.01)
	Group 3	178	128	2.78	0.88 (0.73, 1.06)
	Group 2	181	151	2.99	0.94 (0.79, 1.13)
	Group 1	179	147	3.18	
14	Group 4	179	139	7.69	1.03 (0.83, 1.28)
	Group 3	178	128	10.66	1.43 (1.15, 1.78)
	Group 2	181	151	10.34	1.39 (1.13, 1.71)
14	Group 1	179	146	7.44	
18C	Group 4	179	139	2.91	1.07 (0.88, 1.30)
	Group 3	178	128	3.90	1.44 (1.18, 1.76)
	Group 2	181	151	4.09	1.51 (1.25, 1.83)
	Group 1	179	147	2.71	
19A	Group 4	179	139	4.94	0.84 (0.69, 1.01)
	Group 3	178	128	5.19	0.88 (0.72, 1.07)
	Group 2	181	151	5.51	0.93 (0.77, 1.13)
	Group 1	179	148	5.91	
19F	Group 4	179	139	4.96	0.96 (0.81, 1.15)
	Group 3	178	128	5.42	1.05 (0.88, 1.26)
	Group 2	181	151	5.27	1.02 (0.86, 1.21)
	Group 1	179	148	5.17	
23F	Group 4	179	138	2.40	0.77 (0.61, 0.96)
	Group 3	178	127	2.47	0.79 (0.63, 0.99)
	Group 2	181	150	2.94	0.94 (0.76, 1.17)
	Group 1	179	146	3.12	

[a] GMC, GMC ratio, and CI are estimated from a serotype-specific ANCOVA model utilizing the natural log-transformed antibody concentration as the response and vaccination group and stratification factor (hepatitis B vaccination status before enrollment) as covariates.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Note: Per protocol, dose 4 was administered at ~12 to 15 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

ANCOVA=analysis of covariance; CI=confidence interval; GMC=geometric mean concentration (µg/mL); IgG=immunoglobulin G.

Table 8 Summary of IgG GMCs for the 13 shared serotypes at 30 days post-dose 4 (Per-Protocol Population) [Source: Table 11-2 CSR]

Pneumococcal Serotype	Group 1 (N = 179)			Group 2 (N = 181)			Group 3 (N = 178)			Group 4 (N = 179)			Group 5 (N = 179)		
	n	Observed Response	95% CI[a]	n	Observed Response	95% CI[a]	n	Observed Response	95% CI[a]	n	Observed Response	95% CI[a]	n	Observed Response	95% CI[a]
1	147	2.02	(1.78, 2.30)	151	1.69	(1.48, 1.93)	128	1.89	(1.63, 2.18)	139	1.68	(1.48, 1.91)	147	1.46	(1.30, 1.63)
3	148	0.72	(0.64, 0.82)	151	0.77	(0.68, 0.87)	128	0.68	(0.61, 0.77)	139	0.73	(0.66, 0.82)	147	0.89	(0.79, 0.99)
4	146	1.51	(1.30, 1.76)	151	1.33	(1.14, 1.56)	128	1.27	(1.10, 1.46)	139	1.23	(1.08, 1.41)	147	1.35	(1.17, 1.57)
5	147	3.66	(3.18, 4.20)	151	3.39	(2.91, 3.94)	128	3.82	(3.23, 4.51)	138	2.90	(2.50, 3.38)	147	2.90	(2.50, 3.35)
6A	146	6.42	(5.56, 7.42)	151	7.16	(6.30, 8.15)	128	7.16	(6.17, 8.30)	139	5.17	(4.43, 6.03)	147	4.43	(3.86, 5.09)
6B	146	6.15	(5.36, 7.07)	151	7.58	(6.61, 8.68)	128	6.64	(5.73, 7.69)	139	6.62	(5.75, 7.62)	147	5.83	(5.09, 6.68)
7F	146	5.10	(4.43, 5.88)	151	5.69	(4.93, 6.56)	128	5.06	(4.33, 5.92)	139	3.98	(3.47, 4.57)	147	3.43	(3.02, 3.91)
9V	147	2.93	(2.56, 3.34)	151	2.76	(2.41, 3.16)	128	2.57	(2.22, 2.97)	139	2.46	(2.19, 2.78)	147	2.89	(2.56, 3.26)
14	146	7.62	(6.55, 8.86)	151	10.59	(9.01, 12.44)	128	10.91	(9.29, 12.81)	139	7.87	(6.77, 9.16)	147	6.57	(5.73, 7.55)
18C	147	2.57	(2.21, 2.99)	151	3.88	(3.38, 4.45)	128	3.70	(3.20, 4.29)	139	2.76	(2.42, 3.15)	147	2.65	(2.34, 3.01)
19A	148	5.92	(5.15, 6.80)	151	5.52	(4.88, 6.25)	128	5.20	(4.42, 6.12)	139	4.95	(4.27, 5.73)	147	4.66	(4.15, 5.24)
19F	148	4.78	(4.22, 5.42)	151	4.88	(4.33, 5.51)	128	5.02	(4.40, 5.73)	139	4.60	(4.00, 5.28)	147	4.10	(3.66, 4.59)
23F	146	2.89	(2.42, 3.44)	150	2.72	(2.33, 3.18)	127	2.29	(1.93, 2.70)	138	2.22	(1.92, 2.56)	146	2.11	(1.81, 2.46)

[a] The within-group CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.
N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.
Note: Per protocol, dose 4 was administered at ~12 to 15 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
CI=confidence interval; GMC=geometric mean concentration (µg/mL); IgG=immunoglobulin G.

Source: [P027V114: adam-adsl; adimm]

Immunogenicity - Secondary immunogenicity endpoints related to RECOMBIVAX HB or RotaTeq

Anti-HBsAg response at 30 days post-dose 3

Following 3 doses of V114 (Group 5) or Prevnar 13 (Groups 1 and 2) in the infant primary series, RECOMBIVAX HB administered concomitantly with V114 elicited an immune response comparable to that of RECOMBIVAX HB administered concomitantly with Prevnar 13.

The concomitant administration of RECOMBIVAX HB and V114 met the non-inferiority criterion as assessed by the proportions of subjects with anti-HBsAg concentration ≥10 mIU/mL at 30 days PD3. The lower bound of the 2-sided 95% CI for the difference in proportions of subjects with anti-HBsAg concentration ≥10 mIU/mL (Group 5 minus [Group 1 + Group 2]) was greater than -10 percentage points (Table 9). Similar results were reported in the FAS population (CSR Table 14.2-6).

Table 9 Proportion of subjects with anti-HBsAg concentration ≥10 mIU/mL at 30 days post-dose 3 (Per-Protocol Population) [Source: Table 11-3 CSR]

Antigen	Group 5 (N=179)	Group 1+Group 2 (N=360)	Percentage Point Difference (Group 5 - Group 1+Group 2)	
	Observed Response Percentage (m/n)	Observed Response Percentage (m/n)	Estimate (95% CI)[ab]	p-value[ab] (1-sided)
Anti-HBsAg	98.7 (151/153)	98.9 (281/284)	-0.2 (-3.7, 2.0)	<0.001

[a] Estimated difference, CI, and p-value are based on the Miettinen & Nurminen method stratified by hepatitis B vaccination status before enrollment.

[b] A conclusion of non-inferiority of RECOMBIVAX™ HB administered concomitantly with V114 to RECOMBIVAX™ HB administered concomitantly with Prevnar 13™ is based on the lower bound of the 2-sided 95% CI for the difference in percentages (Group 5 - Group 1+Group 2) being >-10 percentage points (1-sided p-value <0.025).

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis; m=Number of participants with the indicated response.

Note: Per protocol, dose 3 was administered at ~6 months of age.

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

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

Group 5: V114 → V114 → V114 → V114

CI=confidence interval; HBsAg=hepatitis B surface antigen; IU=international unit.

Source: [P027V114: adam-adsl; adimm]

Anti-HBsAg GMCs at 30 days post-dose 3[1]

Following 3 doses of a PCV, anti-HBsAg GMCs were comparable for subjects receiving a complete series of V114 concomitantly with RECOMBIVAX HB (Group 5) to those receiving a complete series of Prevnar 13 together with RECOMBIVAX HB (Groups 1 and 2) (Table 10).

Table 10 Summary of anti-HBsAg GMCs at 30 days post-dose 3 (Per-Protocol Population) [Source: Table 2.5-pedspneumo: 10]

Antigen	Group 1 (N = 179)			Group 2 (N = 181)			Group 3 (N = 178)			Group 4 (N = 179)			Group 5 (N = 179)		
	n	Observed Response	95% CI[a]	n	Observed Response	95% CI[a]	n	Observed Response	95% CI[a]	n	Observed Response	95% CI[a]	n	Observed Response	95% CI[a]
Anti-HBsAg	142	548.9	(419.9, 717.4)	142	720.7	(584.4, 888.7)	136	714.0	(570.3, 894.0)	141	702.8	(539.7, 915.2)	153	697.6	(547.4, 889.1)

[a] The within-group CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Note: Per protocol, dose 3 was administered at ~6 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

CI=confidence interval; GMC=geometric mean concentration (mIU/mL); HBsAg=hepatitis B surface antigen; IU=international unit.

Source: [P027V114: adam-adsl; adimm]

Anti-rotavirus IgA response at 30 days post-dose 3

Following 3 doses of V114 (Group 5) or Prevnar 13 (Groups 1 and 2), the concomitant administration of RotaTeq with V114 elicited an immune response comparable to that of RotaTeq administered concomitantly with Prevnar 13. The concomitant administration of RotaTeq with V114 met the non-inferiority criterion as assessed by anti-rotavirus IgA GMTs at 30 days PD3. The lower bound of the 2-sided 95% CI of the anti-rotavirus IgA GMT ratio [Group 5/(Group 1 + Group 2)] was greater than

[1] This was defined as a tertiary/exploratory objective. It is presented in this section for completeness.

0.50 (Table 11). Similar responses were seen in the FAS population (CSR Table 14.2-9). Anti-rotavirus IgA GMTs at 30 days PD3 were comparable across intervention groups (Table 12).

Table 11 Analysis of anti-rotavirus IgA GMTs at 30 days post-dose 3 (Per-Protocol Population) [Source: Table 11-4 CSR]

Antigen	Group 5 (N=179)		Group 1+Group 2 (N=360)		GMT Ratio[a] (Group 5 / Group 1+Group 2)	
	n	GMT[a]	n	GMT[a]	Estimate (95% CI)[ab]	p-value[ab] (1-sided)
Rotavirus	152	283.1	290	291.4	0.97 (0.70, 1.34)	<0.001

[a] GMTs, GMT ratio, CI, and p-value are calculated using an ANCOVA model utilizing the natural log-transformed antibody titers as the response with vaccination group and hepatitis B vaccination status before enrollment as covariates.

[b] A conclusion of non-inferiority of RotaTeq™ administered concomitantly with V114 to RotaTeq™ administered concomitantly with Prevnar 13™ is based on the lower bound of the 2-sided 95% CI for the GMT ratio (Group 5/Group 1+Group 2) being >0.5 (1-sided p-value <0.025).

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Note: Per protocol, dose 3 was administered at ~6 months of age.

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

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

Group 5: V114 → V114 → V114 → V114

ANCOVA=analysis of covariance; CI=confidence interval; GMT=geometric mean titer (U/mL); IgA=immunoglobulin A; U=units.

Source: [P027V114: adam-adsl; adimm]

Table 12 Anti-rotavirus IgA GMTs at 30 days post-dose 3 (Per-Protocol Population) [Source: Table 2.5-pedspneumo: 12]

Antigen	Group 1 (N = 179)			Group 2 (N = 181)			Group 3 (N = 178)			Group 4 (N = 179)			Group 5 (N = 179)		
	n	Observed Response	95% CI[a]	n	Observed Response	95% CI[a]	n	Observed Response	95% CI[a]	n	Observed Response	95% CI[a]	n	Observed Response	95% CI[a]
Rotavirus	147	286.5	(218.1, 376.2)	143	329.5	(254.9, 426.1)	136	258.5	(195.3, 342.2)	143	322.4	(247.0, 420.8)	152	298.3	(228.2, 390.0)

[a] The within-group CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Note: Per protocol, dose 3 was administered at ~6 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

CI=confidence interval; GMT=geometric mean titer (U/mL); IgA=immunoglobulin A; U=units.

Source: [P027V114: adam-adsl; adimm]

See CSR section 11.1.2.3 for serotype-specific IgG responses for the 15 serotypes at 30 days post-dose 3, section 11.1.2.4 for serotype-specific IgG GMCs for the 13 shared serotypes at 30 days post-dose 4 (complete V114 compared with complete Prevnar 13 dosing regimen), and section 11.1.3 for exploratory immunogenicity endpoints.

Safety results

Listings of AEs by participant are provided in Appendices 16.2.7 and 16.4. The MedDRA version 23.1 was used to report AEs.

Summary of AEs

- AEs were reported for >90% of the subjects and solicited events accounted for the majority of all AEs and vaccine-related AEs (CSR Table 12-1). SAEs were reported for about 11% of

subjects; 1 subject had a vaccine-related SAE and discontinued from the study. There were no other discontinuations due to an AE. No deaths were reported during the study

- The proportions of subjects with AEs and SAEs following each dose of study intervention were comparable between intervention groups with complete V114 or mixed dosing regimens and those with a complete dosing regimen of Prevnar 13 (CSR Tables 14.3-2 to 14.3-5)

Most frequently reported AEs

- The 5 most frequently reported AEs following any dose of study intervention were irritability, somnolence, injection-site pain, injection-site erythema, and decreased appetite (CSR Table 12-2, Tables 14.3-7 and 14.3-8, Figure 14.3-1)
- The most frequently reported AEs following each dose were comparable to those observed after any dose (CSR Tables 14.3-9 to 14.3-20, Figures 14.3-2 to 14.3-5)
- Similar results were observed following a change from Prevnar 13 to V114 after any dose compared to intervention groups that received a 4-dose regimen of Prevnar 13 (Group 1) or V114 (Group 5) (CSR Tables 14.3-21 to 14.3-23)

Solicited AEs

- The proportions of subjects with solicited AEs following any dose of study intervention were comparable across intervention groups with complete or mixed V114 dosing regimens to those who received a complete dosing regimen of Prevnar 13 (CSR Table 12-3, Tables 14.3-25 to 14.3-28)
- The majority (>85%) of subjects across intervention groups had 1 or more solicited AEs (CSR Table 12-3)
- Between 63% and 72% of the subjects experienced solicited injection site AEs. Of them, the most commonly reported AEs were injection site erythema and injection site pain (38%-48% and 42%-48% of the subjects across treatment groups)
- After dose 3, the proportion of subjects who received a complete V114 regimen and experienced injection-site pain in Group 5 (25.4%) was statistically significantly higher (p-value = 0.043) than those who received a complete Prevnar 13 regimen in Group 1 (16.6%) (CSR Table 14.3-27)

Solicited AEs following a change from Prevnar 13 to V114

The proportion of subjects with solicited AEs immediately after the change from Prevnar 13 to V114 at Dose 4 for Group 2, Dose 3 for Group 3, and Dose 2 for Group 4 were comparable to those who received only V114 in Group 5 or Prevnar 13 in Group 1 (CSR Table 14.3-26[2], Table 14.3-27[3], and Table 14.3-28[4]).

- After dose 3, the proportion of subjects with injection-site pain was statistically significantly higher (p-value = 0.006) after changing from Prevnar 13 to V114 in Group 3 (29.2%)

[2] Analysis of Participants With Solicited Adverse Events (Incidence > 0% in One or More Vaccination Groups) (All Participants as Treated Population) (Following Dose 2)
[3] Analysis of Participants With Solicited Adverse Events (Incidence > 0% in One or More Vaccination Groups) (All Participants as Treated Population) (Following Dose 3)
[4] Analysis of Participants With Solicited Adverse Events (Incidence > 0% in One or More Vaccination Groups) (All Participants as Treated Population) (Following Dose 4)

compared with a third dose of Prevnar 13 in Group 1 (16.6%) (CSR Table 14.3-27). There was no similar trend in the other groups after changing from Prevnar 13 to V114

- After Dose 4, the proportion of subjects with injection-site pain was comparable between intervention groups with complete or mixed V114 dosing regimens with those that received a complete dosing regimen of Prevnar 13 (CSR Table 14.3-28)

AEs related to study intervention

All injection-site AEs were considered vaccine-related (CSR Table 12-1).

The proportion of subjects with solicited and unsolicited vaccine-related systemic AEs was comparable across intervention groups (CSR Table 12-4 and Table 14.3-35). The most commonly reported AEs were irritability, somnolence, and decreased appetite. Similar results were observed following each dose of study intervention (CSR Tables 14.3-36 to 14.3-43).

AEs by intensity

The proportion of subjects with solicited AEs in each maximum intensity category was comparable across intervention groups following any dose. The majority of the subjects had AEs that were mild or moderate in intensity (CSR Table 12-5). Similar results were observed following each dose of study intervention (CSR Tables 14.3-45 to 14.3-48), and in the evaluation of all solicited and unsolicited AEs (CSR Tables 14.3-49 to 14.3-53).

AEs by size

The proportion of subjects with injection-site AEs of erythema, induration, or swelling by maximum size was comparable across intervention groups following any dose. The majority of subjects who experienced solicited injection-site erythema, induration, or swelling had events with a maximum size of ≤2 inches (CSR Table 12-6). The proportion of subjects who had events with a maximum size >2 inches were low in each intervention group (CSR Table 12-6). Similar results were observed following each dose of study intervention (CSR Tables 14.3-60 to 14.3-63).

Duration of AEs

The proportion of subjects with solicited AEs by maximum duration were generally comparable across intervention groups. Of the subjects with solicited AEs, the majority had events of short duration (≤3 days) (CSR Table 12-7). Similar results were observed for solicited AEs following each dose of the study intervention (CSR Tables 14.3-70 to 14.3-73).

Serious AEs and deaths

There were no deaths due to AEs reported for this study (CSR Table 12-1).

The proportion of subjects with SAEs was comparable across intervention groups (CSR Table 12-8). Bronchiolitis (26 subjects) and respiratory syncytial virus bronchiolitis (11 subjects) were the most commonly reported SAEs. Similar results were observed following each dose of study intervention (CSR Tables 14.3-91 to 14.3-94).

In Group 3, one subject had an SAE of epilepsy considered to be related to study intervention following Dose 2: Prevnar 13 and concomitant vaccinations. This was the only subject who discontinued from the study due to an SAE (CSR Table 14.3-95). There were no other SAEs considered related to the study intervention. Narratives for all subjects with SAEs are provided in the CSR Appendix 16.2.7.2.

Summary of AEs related to the concomitant vaccines RECOMBIVAX HB and RotaTeq

- When administered concomitantly with RECOMBIVAX HB and RotaTeq, complete V114 and mixed Prevnar 13/V114 dosing regimens were well-tolerated with safety profiles comparable to a complete dosing regimen of Prevnar 13 (CSR Table 14.3-97[5] and Table 14.3-99[6])
- The proportions of subjects with systemic AEs related to PCV were comparable across intervention groups. The vaccine-related systemic AEs for the concomitant vaccines were consistent with those reported for PCV (Clinical overview Table 2.5-pedspneumo: 14; RECOMBIVAX HB: Table 2.5-pedspneumo: 15; RotaTeq: Table 2.5-pedspneumo: 16)
- There were no new safety issues identified for RECOMBIVAX HB or RotaTeq

2.4.1. Discussion on clinical aspects

The CSR for study V114-027 was submitted by MSD to fulfil the requirements of Article 46 Regulation (EC) No. 1901/2006.

The study was designed to evaluate the safety, tolerability, and immunogenicity of mixed pneumococcal conjugated vaccine regimens in infants of approximately 2 months of age. In Groups 1 and 5, the infants received a 4-dose series of Prevnar 13 or V114. In the other 3 intervention groups, the immunisation series was initiated with Prevnar 13 and changed to V114 at Dose 2, 3, or 4 (Groups 4, 3, and 2). The study also evaluated the concomitant administration of V114 with the licensed paediatric vaccines RECOMBIVAX HB and RotaTeq.

The study was conducted in 31 study sites in Thailand, Turkey, and the United States including Puerto Rico. 900 subjects were randomised; 179 to Group 1, 181 to Group 2, and 180 to Groups 3, 4, and 5. Of them, 896/900 were vaccinated. More than 99% of subjects received the first dose of all protocol-specified study interventions, including RECOMBIVAX HB and RotaTeq. The majority of subjects (~89%) in each intervention group completed the study. The most common reason for discontinuation was withdrawal by parent/guardian. Demographic and baseline characteristics were comparable across intervention groups.

The primary objectives of the study were to evaluate the safety and tolerability of V114 and mixed Prevnar 13/V114 dosing schedules with Prevnar 13, and to compare the immunological response based on IgG GMCs at 30 days post-vaccination 4 of subjects who received mixed schedules of Prevnar 13/V114 and Prevnar 13. The results show that serotype-specific IgG GMCs were comparable for subjects who received mixed pneumococcal vaccine regimens (Prevnar 13/V114) and Prevnar 13. Safety results show similar profiles in terms of AEs and SAEs for subjects with complete V114 regimen, mixed regimen (V114/Prevnar 13), and Prevnar 13.

The concomitant administration of V114 and RECOMBIVAX HB compared with the administration of Prevnar 13 and RECOMBIVAX HB was analysed as a secondary objective. The endpoint was based on the proportion of subjects with anti-HBsAg concentration ≥10 mIU/mL at 30 days following Dose 3 of V114 (Group 5) or Prevnar 13 (Group 1 plus Group 2). To show that the concomitant administration of RECOMBIVAX HB and V114 was not inferior to that of Prevnar 13 and RECOMBIVAX HB, the lower bound of the 2-sided 95% CI of the difference in proportions of subjects with anti-HBsAg concentration ≥10 mIU/mL [V114 minus Prevnar 13] had to be greater than -0.10. The results show that the

[5] Participants With Adverse Events Related to RotaTeq (Incidence > 0% in One or More Vaccination Groups) (All Participants as Treated Population) (Following Any Dose)
[6] Participants With Adverse Events Related to RECOMBIVAX HB (Incidence > 0% in One or More Vaccination Groups) (All Participants as Treated Population) (Following Any Dose)

concomitant administration of RECOMBIVAX HB with V114 or Prevnar 13 elicits a comparable immune response [98.7 and 98.9). The non-inferiority criterion was also met, the lower bound of the difference between Group 5 and the sum of Groups 1 and 2 was -0.2. Anti-HBsAg GMCs after dose 3 were also comparable in subjects receiving V114 and RECOMBIVAX HB (Group 5) and those receiving Prevnar 13 and RECOMBIVAX HB.

The concomitant administration of V114 with RotaTeq (Group 5) versus that of Prevnar 13 and RotaTeq (Groups 1 and 2) was also analysed as a secondary objective. The endpoint was anti-rotavirus IgA response at 30 days post-dose 3 of V114 or Prevnar 13. To show that the concomitant administration of RotaTeq with V114 was not inferior to that of RotaTeq with Prevnar 13, the lower bound of the 2-sided 95% CI of the anti-rotavirus IgA GMT ratio [V114/Prevnar 13] had to be greater than 0.50. The non-inferiority criterion was met. The GMT ratio of Group 5/Groups 1+2 was 0.97 (95% CI 0.70, 1.34). Anti-rotavirus IgA GMTs at 30 days post-dose 3 were comparable across intervention groups.

The safety profile of mixed PCV regimens (Prevnar 13/V114), and complete Prevnar 13 or V114 regimens was comparable. Most AEs were transient, and mild or moderate in intensity across intervention groups. The proportion of subjects with solicited systemic and injection-site AEs was comparable in intervention groups that changed from Prevnar 13 to V114, and in groups that received complete regimens of V114 or Prevnar 13. The exception was an increase in injection-site pain following a change from Prevnar 13 to V114 at dose 3 in Group 3. The safety profiles of RECOMBIVAX HB and RotaTeq when administered concomitantly with V114 or with mixed regimens were similar to those of RECOMBIVAX HB and RotaTeq administered concomitantly with Prevnar 13. There were no new safety issues identified for RECOMBIVAX HB and RotaTeq.

During review as part of a centralised marketing authorisation application under procedure EMEA/H/C/005477/0000 of V114 the concomitant use of RotaTeq and HBVaxPro with V114 should be mentioned in the SmPC section 4.5.

3. CHMP overall conclusion and recommendation

In conclusion, the concomitant administration of V114 and HBVaxPro or RotaTeq elicits an immunological response non-inferior to that of Prevnar 13 and HBVaxPro or RotaTeq, and the safety profile of the concomitant administration of either vaccine with V114 is comparable to that of Prevenar 13. Based on the results from this study, no changes to the current EU product information for HBVaxPro or RotaTeq are warranted, because V114 is not yet licensed.

☒ **Fulfilled**

No regulatory action required.