Amsterdam, 24 February 2022
EMA/495654/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

M-M-RvaxPro

measles, mumps and rubella vaccine (live)

Procedure no: EMEA/H/C/000604/P46/039

Note

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

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1. Introduction

On 23-Nov-2021, the MAH submitted a completed paediatric study for M-M-RVAXPRO (referred to as V114 in this assessment report), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. The purpose of the Study V114-P029 was to evaluate the safety and the immunogenicity of a 4-dose regimen of V114 compared with Prevnar 13TM in Healthy Infants.

This was a randomized, active comparator-controlled, parallel-group, multi-site, double-blind study of V114 in healthy infants enrolled at approximately 2 months of age (from 42 to 90 days, inclusive). V114 or Prevnar 13 was administered at approximately 2, 4, 6, and 12 to 15 months of age. Participants also received the following pediatric vaccines: RotaTeq, Pentacel, RECOMBIVAX HB, VAQTA, M-M-R II, VARIVAX, and HIBERIX.

This study was part of the US initial pediatric study plan for V114.The MAH does not propose any revisions to the RMP or risk-benefit analysis for M-M-RvaxPro. As Vaxneuvance (V114) is not yet approved for use in the paediatric population, the MAH does not propose any changes to the current Product Information.

The study V114-029 will be also assessed into the upcoming EoI of the Vaxneuvance product.

2. Scientific discussion

2.1. Information on the development program

Study V114-P029 was a phase 3, multicenter, randomized, double-blind, active-comparator-controlled study to evaluate the safety, tolerability, and immunogenicity of a 4-dose regimen of V114 in healthy infants (PNEU-PED).Healthy infants approximately 2 months (42 to 90 days, inclusive) of age, without a history of invasive pneumococcal disease or prior administration of any pneumococcal vaccine.

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 2.5- pedspneumo: 1)

Intervention Group Name	Vaccine	Dose Strength	Dose Frequency	Route of Admin.	Vaccination Regimen	Use
V114	V114	Refer to IB	4 doses	IM	Single dose at Visits 1, 2, 3, and 5 (~2, 4, 6, and 12 to 15 months of age, respectively)	Experimental
Prevnar 13™	Prevnar 13™	Refer to product labeling	4 doses	IM	Single dose at Visits 1, 2, 3, and 5 (~2, 4, 6, and 12 to 15 months of age, respectively)	Experimental

Admin.=administration; IB=Investigator's Brochure; IM=intramuscular.
Note: All participants also received other pediatric vaccines, including RotaTeq™, Pentacel™, RECOMBIVAX HB™, VAQTA™, M-M-R™II, VARIVAX™, and HIBERIX™. Tradenames for licensed vaccines varied depending on where clinical supplies were sourced by the Sponsor.

Assessor`s comment:

Please note that the study for M-M-RVAXPRO is referred to as V114 study in this assessment report. The US vaccine Prevnar13 is licensed under the name Prevenar13 in the EU.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

• Protocol V114-P029 was a phase 3, multicenter, randomized, double-blind, active-comparator-controlled study to evaluate the safety, tolerability, and immunogenicity of a 4-dose regimen of V114 in healthy infants (PNEU-PED).Healthy infants approximately 2 months (42 to 90 days, inclusive) of age, without a history of invasive pneumococcal disease or prior administration of any pneumococcal vaccine.

2.3.2. Clinical study

Protocol V114-P029: a phase 3, multicenter, randomized, double-blind, active-comparator-controlled study to evaluate the safety, tolerability, and immunogenicity of a 4-dose regimen of V114 in healthy infants.

Description

Study V114-P029 was a phase 3, multicenter, randomized, double-blind, active-comparator-controlled study to evaluate the safety, tolerability, and immunogenicity of a 4-dose regimen of V114 in healthy infants (PNEU-PED).Healthy infants approximately 2 months (42 to 90 days, inclusive) of age, without a history of invasive pneumococcal disease or prior administration of any pneumococcal vaccine. In healthy infants and toddlers, V114 is well tolerated with a safety profile generally comparable to Prevnar 13. V114 elicits serotype-specific immune responses (IgG and OPA) to all 15 serotypes contained in the vaccine in healthy infants and toddlers. V114 can also be administered concomitantly with licensed pediatric vaccines, including Pentacel, VAQTA, M-M-R II, VARIVAX, and HIBERIX. Table 2 summarized the concomitant vaccines at the corresponding visits within the study.

Table 2. V114-029 Concomitant Vaccine Dosing Schedule
(Source: Table 2.5- pedspneumo: 2)

Vaccine 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	
VAQTA™ (Hepatitis A Vaccine, Inactivated)	Prevention of hepatitis A virus infection				X
M-M-R™ II (Measles, Mumps, and Rubella Virus Vaccine Live)	Prevention of measles, mumps, and rubella				X
VARIVAX™ (Varicella Virus Vaccine Live)	Prevention of varicella				X
HIBERIX™ (Haemophilus b Conjugate Vaccine [Tetanus Toxoid Conjugate])	Prevention of invasive disease caused by *Haemophilus influenzae* type b				X

[a] Tradenames for licensed vaccines varied depending on where clinical supplies were sourced by the Sponsor.
[b] RotaTeq™ was administered orally and was given before V114 or Prevnar 13™ and other concomitant vaccines. Injectable vaccines administered in the study were given after V114 or Prevnar 13™.
[c] For participants who received the first dose of hepatitis B vaccine before enrollment, RECOMBIVAX HB™ was administered at ~2 and 6 months of age.
Note: Pentacel™, VAQTA™, M-M-R™ II, VARIVAX™, and HIBERIX™ were evaluated as part of V114-029.

Methods

Objective(s)

Primary objective:

- To evaluate the safety and tolerability of V114 with respect to the proportion of participants with adverse events (AEs).

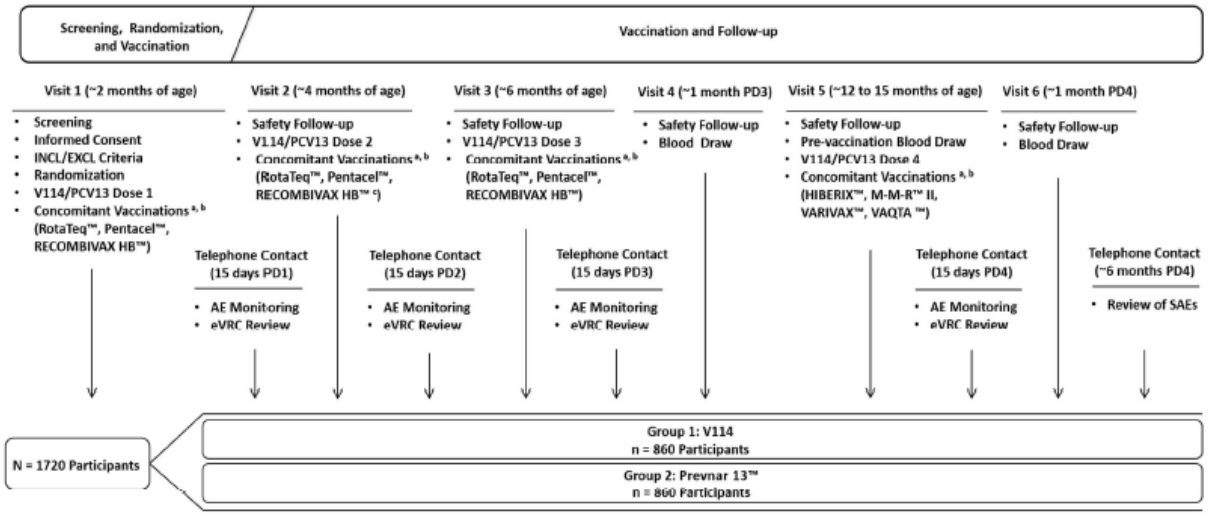
Secondary objectives:

- To compare the antigen-specific response rate to each antigen and the antigen-specific GMCs for the pertussis antigens included in Pentacel at 30 days following Dose 3 for participants administered V114 concomitantly with Pentacel versus participants administered Prevnar 13 concomitantly with Pentacel.
- The same comparison to be done also for VAQTA, MMR II, VARIVAX and HIBERIX at 30 days following Dose 4 in both two groups (V114 and Prevnar 13).

Study design

Study V114-P029 was a multicenter, randomized, double-blind, active-comparator-controlled study to evaluate the safety, tolerability, and immunogenicity of a 4-dose regimen of V114 in healthy infants (PNEU-PED).Healthy infants approximately 2 months (42 to 90 days, inclusive) of age, without a history of invasive pneumococcal disease or prior administration of any pneumococcal vaccine. Figure 1 summarized the study design.

Figure 1. V114-029 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] Tradenames for the licensed vaccines may vary depending on where clinical supplies are sourced by the Sponsor.

[b] RotaTeq™ is administered orally and should be given before V114 or Prevnar 13™ and other concomitant vaccines. Injectable vaccines (Pentacel ™, RECOMBIVAX HB™, HIBERIX™, M-M-R™ II, VARIVAX™, VAQTA ™) should be given after V114 or Prevnar 13™.

[c] 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.

Source: [Ref. 5.3.5.1: P029V114: 16.1.1]

Study population /Sample size

Eligible subjects were healthy infants approximately 2 months (42 to 90 days, inclusive) of age, without a history of invasive pneumococcal disease or prior administration of any pneumococcal vaccine. This study was conducted at 82 centers in 3 countries: Thailand, Turkey, and the USA, including Puerto Rico.

1713 vaccinated participants (V114: 858 participants; Prevnar 13: 855 participants).

Treatments

Study subjects were challenged to receive either V114 or Prevnar 13 at approximately 2, 4, 6, and 12 to 15 months of age in this study as follows:

Table 3. Study Intervention (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
V114	Experimental	V114	Biological/ Vaccine	Sterile Suspension	Refer to IB	0.5 mL	IM	Single dose at Visits 1, 2, 3, and 5	Experimental	IMP	Central
V114	Experimental	RotaTeq™	Biological/ Vaccine	Sterile Solution	Refer to product labeling	2 mL	Oral	Single dose at Visits 1, 2, and 3	Background Treatment	NIMP	Central or Local
V114	Experimental	Pentacel™	Biological/ Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	IM	Single dose at Visits 1, 2, and 3	Experimental	IMP	Central or Local
V114	Experimental	RECOMBIVAX HB™*	Biological/ Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	IM	Single dose at Visits 1, 2, and 3	Background Treatment	NIMP	Central or Local
V114	Experimental	VAQTA™	Biological/ Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	IM	Single dose at Visit 5	Experimental	IMP	Central or Local
V114	Experimental	M-M-R™II	Biological/ Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	SC	Single dose at Visit 5	Experimental	IMP	Central or Local
V114	Experimental	VARIVAX™	Biological/ Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	SC	Single dose at Visit 5	Experimental	IMP	Central or Local
V114	Experimental	HIBERIX™	Biological/ Vaccine	Sterile Solution	Refer to product labeling	0.5 mL	IM	Single dose at Visit 5	Experimental	IMP	Central or Local
Prevnar 13™	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	Experimental	IMP	Central
Prevnar 13™	Active Comparator	RotaTeq™	Biological/ Vaccine	Sterile Solution	Refer to product labeling	2 mL	Oral	Single dose at Visits 1, 2, and 3	Background Treatment	NIMP	Central or Local
Prevnar 13™	Active Comparator	Pentacel™	Biological/ Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	IM	Single dose at Visits 1, 2, and 3	Experimental	IMP	Central or Local
Prevnar 13™	Active Comparator	RECOMBIVAX HB™*	Biological/ Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	IM	Single dose at Visits 1, 2, and 3	Background Treatment	NIMP	Central or Local
Prevnar 13™	Active Comparator	VAQTA™	Biological/ Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	IM	Single dose at Visit 5	Experimental	IMP	Central or Local
Prevnar 13™	Active Comparator	M-M-R™II	Biological/ Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	SC	Single dose at Visit 5	Experimental	IMP	Central or Local
Prevnar 13™	Active Comparator	VARIVAX™	Biological/ Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	SC	Single dose at Visit 5	Experimental	IMP	Central or Local
Prevnar 13™	Active Comparator	HIBERIX™	Biological/ Vaccine	Sterile Solution	Refer to product labeling	0.5 mL	IM	Single dose at Visit 5	Experimental	IMP	Central or Local

Admin=administration; IB=Investigator's Brochure; IM=intramuscular; IMP=investigational medicinal product; NIMP=non-investigational medicinal product; SC=subcutaneous.
Definition: Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (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.
*For participants who received the first dose of hepatitis B vaccine before enrollment, RECOMBIVAX HB™ was administered at Visits 1 and 3.

Outcomes/endpoints

Primary safety endpoints

Following any vaccination with V114:

- 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

Primary immunogenicity endpoints

Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days Postdose 3 (PD3)

Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days Postdose 4 (PD4)

Secondary immunogenicity endpoints:

Antibody responses to:
• diphtheria toxoid
• tetanus toxoid
• pertussis toxin (PT)Primn
• pertussis filamentous hemagglutinin(FHA)
• pertussis fimbrae types 2/3 (FIM 2/3)
• pertussis pertactin (PRN)
• poliovirus serotypes 1, 2 and 3
• *Haemophilus influenzae* type b polyribosylribitol phosphate (Hib-PRP) at 30 days PD3 of V114 or Prevnar 13.

Antibody responses to:

- Hepatitis A antigen
- Measles, mumps, and rubella virus
- Varicella Zoster Virus (VZV)
- PRP

at 30 days PD4 of V114 or Prevnar 13.

Safety endpoint:

- Safety was monitored by collecting vaccine-related AEs and SAEs comparable between intervention groups.

Statistical methods

Immunogenicity analyses

The primary immunogenicity objective was calculated by evaluating the non-inferiority of serotype-specific IgG GMCs at 30 days PD3 and 30 days PD4, the between-treatment comparison was made based on serotype-specific IgG GMCs for the 13 shared serotypes and the 2 unique serotypes. The estimation of the IgG GMC ratios and the 95% confidence interval (CI) were calculated using the t-distribution with the variance estimate from a linear model utilizing the log-transformed antibody concentration as the response and a single term for vaccination group.

Similar statistical approaches were used to evaluate the non-inferiority of the concomitant vaccines, the superiority of the 2 unique V114 serotypes, and the superiority of serotype 3 at 30 days PD3 and 30 days PD4 in the secondary objectives.

Safety analyses

Safety and tolerability were assessed by reviewing all relevant parameters including AEs and post-vaccination temperature measurements following any vaccination with V114 or Prevnar 13. The analysis of safety results followed a tiered approach. P-values (Tier 1 endpoints) and 95% CIs (Tier 1 and 2 endpoints) were provided for between-vaccination group differences in the percentage of participants with events; these analyses were performed using the M&N method.

Analysis sets

Immunogenicity

The per protocol (PP) population was the primary population for the analysis of immunogenicity data in this study. This population consisted of all the randomized subjects without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint.

The percentages of the randomized participants included in the PP population at each timepoint were as per below:

- The majority (>79%) of randomized participants were included for pneumococcal IgG analyses (CSR Table 10-3).
- Most (>96%) of randomized participants in the OPA subset were included for pneumococcal OPA analysis (CSR Table 10-4).
- The majority of participants were included in the PP populations for the Pentacel, VAQTA, M-M-R II, VARIVAX, and HIBERIX analyses (CSR Table 14.1-12).

The reasons for exclusion from the PP population were generally comparable between intervention groups. Potential deviations that could lead to the exclusion of a subject from the PP population for all immunogenicity analyses included:

- Missing serology results
- Blood draw out of window
- Missed at least one vaccination of PCV at Vaccination 1, 2, 3 or 4
- Failure to receive study vaccine(s) per randomization schedule

Safety

Safety analyses were based on the (APaT) population, which included 1713 randomized participants (V114: 858 participants; Prevnar 13: 855 participants) who received at least 1 dose of study intervention for the time point of interest. One participant in the Prevnar 13 group inadvertently received both V114 and Prevnar 13 and was excluded from the APaT population.

Sample size and power

Approximately 1720 participants were planned for enrollment (860 in V114 group, 860 in Prevnar 13 group).

Immunogenicity

Immunogenicity endpoints related to concomitant vaccines and the corresponding results were not in the scope of this submission, as the results pertain to the investigational medicinal product V114. After the conclusion of the ongoing review of the V114 MAA in the adult population, the applicant will evaluate the need to include these results in the product information of VAQTA, M-M-R II, and VARIVAX for concomitant use with V114.

Safety

The proportions of participants with AEs, including injection-site, systemic, and vaccine related AEs, and SAEs were generally comparable between intervention groups. AEs were reported for the majority (>92%) of participants in both intervention groups. Solicited events accounted for the majority of all AEs and vaccine-related AEs (CSR Table 12-1). SAEs were reported for approximately 10% of participants; none were considered by the investigator to be related to study intervention. No participant discontinued study intervention due to an AE. Two participants died during the study (1 participant in the V114 group and 1 participant in the Prevnar 13 group); both deaths were assessed by the investigator to be not related to the study vaccine (CRS Table 14.3-79).The proportions of participants with AEs and SAEs following each dose of study intervention were generally comparable between intervention groups.

Results

Recruitment / number analysed

A total of 1720 participants were randomized (1713 were vaccinated) across 75 study sites in 3 countries. The majority (>88%) of participants received all doses of PCVs and one dose of the concomitant vaccines, VAQTA, M-M-R II, and VARIVAX. The majority (>86%) of participants completed the study. The most common reasons for discontinuing study intervention were withdrawal by parent/guardian (8.4%) and lost to follow-up (3.5%).

Table 4. Disposition of Participants (All Randomized Participants)
(Source: Table 2.5- pedspneumo: 2)

	V114		Prevnar 13™		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	860		860		1,720	
Vaccinated at ~2 months of age with						
PCV	858	(99.8)	856	(99.5)	1,714	(99.7)
Pentacel™	858	(99.8)	856	(99.5)	1,714	(99.7)
RECOMBIVAX HB™	858	(99.8)	856	(99.5)	1,714	(99.7)
RotaTeq™	858	(99.8)	856	(99.5)	1,714	(99.7)
Vaccinated at ~4 months of age with						
PCV	836	(97.2)	820	(95.3)	1,656	(96.3)
Pentacel™	836	(97.2)	820	(95.3)	1,656	(96.3)
RECOMBIVAX HB™	14	(1.6)	14	(1.6)	28	(1.6)
RotaTeq™	836	(97.2)	820	(95.3)	1,656	(96.3)
Vaccinated at ~6 months of age with						
PCV	810	(94.2)	786	(91.4)	1,596	(92.8)
Pentacel™	810	(94.2)	786	(91.4)	1,596	(92.8)
RECOMBIVAX HB™	810	(94.2)	786	(91.4)	1,596	(92.8)
RotaTeq™	810	(94.2)	785	(91.3)	1,595	(92.7)
Vaccinated at ~12 to 15 months of age with						
PCV	781	(90.8)	750	(87.2)	1,531	(89.0)
VAQTA™	781	(90.8)	749	(87.1)	1,530	(89.0)
M-M-R™ II	780	(90.7)	748	(87.0)	1,528	(88.8)
VARIVAX™	780	(90.7)	748	(87.0)	1,528	(88.8)
HIBERIX™	780	(90.7)	750	(87.2)	1,530	(89.0)
Trial Disposition						
Completed	758	(88.1)	734	(85.3)	1,492	(86.7)
Discontinued	102	(11.9)	126	(14.7)	228	(13.3)
Death	1	(0.1)	0	(0.0)	1	(0.1)
Lost To Follow-Up	34	(4.0)	27	(3.1)	61	(3.5)
Physician Decision	8	(0.9)	14	(1.6)	22	(1.3)
Withdrawal By Parent/Guardian	59	(6.9)	85	(9.9)	144	(8.4)
Each participant is counted once for Trial Disposition based on the latest corresponding disposition record. PCV=pneumococcal conjugate vaccine (V114 or Prevnar 13™).						

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 participant's rights, safety, or well-being; or not important. Important protocol deviations were further classified as either 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 477 (27.7%) subjects in this study (CSR Table 14.1-4). Of them, 239 (13.9%) subjects had important protocol deviations that were considered to be clinically important were excluded from the immunogenicity analyses. These were related to trial

procedures (eg, study vaccination administered outside the protocol-defined window). The protocol deviations were comparably distributed between intervention groups. These were important protocol deviations but were not considered to be clinically important (CRS Table 14.1-6).
No important protocol deviations were classified as a serious GCP noncompliance issue.

Important and not important protocol deviations associated with the COVID-19 pandemic were reported for 156 (9.1%) participants (CSR Table 14.1-8). Ninety-three (5.4%) participants had deviations associated with the pandemic that were considered clinically important; immunogenicity blood sample drawn outside the protocol-defined window was the most frequently reported deviation.

Changes in the conduct of the study: Per protocol, a single dose of the M-M-R II vaccine was to be administered at Visit 5 (~12 to 15 months of age). Due to a measles outbreak in Turkey, mandatory M-M-R II vaccination at 9 months of age was implemented by the Turkish Ministry of Health, which led to the majority of participants in Turkey receiving the M-M-R II vaccine prior to the time point specified in the protocol. These participants were excluded from the PP population for the M-M-R II analysis.

Assessor's comment:
Although part of this study was conducted during Covid- 19 pandemic the sponsor has followed the SOPs for study conduct to ensure the safety of the study participants and to all the other staff included in the study. The changes of the study conduct were implemented by protocol amendment (Table 5). There were no changes in the planned analyses of the study.

Table 5. Changes in the Conduct of the Study (Source: Amendment V114-029-02, pg 61 CSR)

Amendment	Date of Issue	Overall Rationale
V114-029-02	16-MAR-2021	Amendment to expand the visit windows for Visit 3 (Dose 3 vaccination), Visit 4 (postdose 3 blood draw) and Visit 6 (postdose 4 blood draw) to allow inclusion of more participants in the immunogenicity analysis based on the per-protocol population. This change is being made in response to the COVID-19 global pandemic which impacted the ability of many participants to attend study visits within the prescribed visit windows due to local conditions and travel restrictions. This amendment also includes the addition of 3 secondary hypotheses relating to the demonstration of superiority for serotype 3 immune responses.
V114-029-01	28-FEB-2020	Amendment to incorporate changes to the statistical analyses for the evaluation of the 2 unique V114 serotypes compared with Prevnar 13™

Baseline data

1713 randomized participants (V114: 858 participants; Prevnar 13: 855 participants) were enrolled in this study. Of them, 52% of the participants were male; 55% were white, and 26% were Asian. The majority (>74%) of participants were of non-Hispanic or Latino ethnicity. Approximately 9% of participants were preterm infants (gestational age <37 weeks).

Table 6. Subjects characteristics (All vaccinated subjects) (Source Table 10-2 CSR)

	V114		Prevnar 13™		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	858		856		1,714	
Sex						
Male	461	(53.7)	429	(50.1)	890	(51.9)
Female	397	(46.3)	427	(49.9)	824	(48.1)
Age (Weeks)						
6 weeks	75	(8.7)	80	(9.3)	155	(9.0)
7 weeks	100	(11.7)	98	(11.4)	198	(11.6)
8 weeks	276	(32.2)	252	(29.4)	528	(30.8)
9 weeks	281	(32.8)	289	(33.8)	570	(33.3)
10 weeks	90	(10.5)	96	(11.2)	186	(10.9)
11 weeks	28	(3.3)	32	(3.7)	60	(3.5)
12 weeks	8	(0.9)	9	(1.1)	17	(1.0)
Mean	8.4		8.4		8.4	
SD	1.2		1.3		1.2	
Median	8.0		8.0		8.0	
Range	6 to 12		6 to 12		6 to 12	
Race						
American Indian Or Alaska Native	6	(0.7)	13	(1.5)	19	(1.1)
Asian	223	(26.0)	226	(26.4)	449	(26.2)
Black Or African American	52	(6.1)	53	(6.2)	105	(6.1)
Multiple	98	(11.4)	80	(9.3)	178	(10.4)
American Indian Or Alaska Native, Asian	0	(0.0)	2	(0.2)	2	(0.1)
American Indian Or Alaska Native, Black Or African American	1	(0.1)	1	(0.1)	2	(0.1)
American Indian Or Alaska Native, Black Or African American, White	3	(0.3)	1	(0.1)	4	(0.2)
American Indian Or Alaska Native, White	7	(0.8)	5	(0.6)	12	(0.7)
Black Or African American, Asian	1	(0.1)	1	(0.1)	2	(0.1)
Black Or African American, Native Hawaiian Or Other Pacific Islander, White	1	(0.1)	0	(0.0)	1	(0.1)
Black Or African American, White	71	(8.3)	59	(6.9)	130	(7.6)
Black Or African American, White, Asian	1	(0.1)	1	(0.1)	2	(0.1)
Native Hawaiian Or Other Pacific Islander, Asian	1	(0.1)	1	(0.1)	2	(0.1)
Native Hawaiian Or Other Pacific Islander, White	0	(0.0)	2	(0.2)	2	(0.1)
White, Asian	12	(1.4)	7	(0.8)	19	(1.1)
Native Hawaiian Or Other Pacific Islander	6	(0.7)	4	(0.5)	10	(0.6)
White	472	(55.0)	480	(56.1)	952	(55.5)
Missing	1	(0.1)	0	(0.0)	1	(0.1)
Ethnicity						
Hispanic Or Latino	206	(24.0)	203	(23.7)	409	(23.9)
Not Hispanic Or Latino	639	(74.5)	643	(75.1)	1,282	(74.8)
Not Reported	11	(1.3)	5	(0.6)	16	(0.9)
Unknown	2	(0.2)	5	(0.6)	7	(0.4)
Gestational Age (Weeks)						
<37	74	(8.6)	76	(8.9)	150	(8.8)
≥37	784	(91.4)	780	(91.1)	1,564	(91.2)

SD=standard deviation.

Medical history and concurrent illnesses

The top three most frequently medical conditions reported by preferred term were: jaundice neonatal (22.1%), vaccination site scar (14.7%), and ankyloglossia congenital (13.4%) (Source: CSR Table 14.1-5).

Prior and concomitant medications/treatments/vaccines

Prior medications were reported for 33.5% of participants; the most frequently reported were vitamin D not otherwise specified (9.9%), cholecalciferol (8.0%), and simethicone (3.0%). One participant received a prior vaccination (hepatitis B) within the 30 days before receiving the first study vaccination. Concomitant medications were reported for 86.2% of participants; the most frequently reported were paracetamol (67.0%), ibuprofen (17.9%), and amoxicillin (16.3%). Concomitant receipt of non-study vaccine was reported for 58.8% of participants; the top 3 most frequently reported concomitant non-study vaccinations were influenza vaccine (31.0%), influenza vaccine inactivated split 4V(12.8%), and Japanese encephalitis vaccine (11.8%).

Immunogenicity

Immunogenicity analysis population

The primary immunogenicity analyses were conducted using the PP population which was defined as all randomized participants without protocol deviations that could have substantially impacted the results of the immunogenicity analyses. The majority (>79%) of randomized participants were included in the PP population for pneumococcal IgG analyses at each time point. Most (>96%) randomized participants in the OPA subset were included in the PP population for pneumococcal OPA analysis at each time point. The reasons for exclusion from the PP populations for these analyses were generally comparable between intervention groups.

Primary immunogenicity endpoint – Serotype-specific IgG Response Rates at 30 Days Postdose 3 and Postdose 4

V114 elicited immune responses that were comparable to Prevnar 13 for 13 shared serotypes. For the 2 unique serotypes, V114 elicited immune responses that were comparable to the lowest immune response elicited by Prevnar 13 for any of the shared serotypes (excluding serotype 3) (CSR Table 11.1-2, Figure 14.2-4)

Table 7. Analysis of the Proportions of Participants with IgG **≥0.35 µ**g/mL For the 13 Shared Serotypes at 30 Days Postdose 3 (PP) (Source: Table 11-1 CSR)

Pneumococcal Serotype	V114 (N=858)	Prevnar 13™ (N=856)	Percentage Point Difference (V114 - Prevnar 13™)	
	Observed Response Percentage (m/n)	Observed Response Percentage (m/n)	Estimate (95% CI)[ab]	p-value[ab] (1-sided)
13 Shared Serotypes (Non-inferiority)				
1	95.7 (672/702)	99.1 (659/665)	-3.4 (-5.2, -1.8)	<0.001
3	94.7 (662/699)	79.2 (524/662)	15.6 (12.1, 19.2)	<0.001
4	96.4 (674/699)	98.6 (654/663)	-2.2 (-4.0, -0.6)	<0.001
5	95.3 (669/702)	97.4 (647/664)	-2.1 (-4.2, -0.2)	<0.001
6A	93.7 (658/702)	98.6 (654/663)	-4.9 (-7.1, -3.0)	<0.001
6B	88.6 (619/699)	92.0 (609/662)	-3.4 (-6.6, -0.3)	<0.001
7F	99.0 (694/701)	99.8 (664/665)	-0.8 (-1.9, -0.1)	<0.001
9V	97.1 (680/700)	98.2 (649/661)	-1.0 (-2.8, 0.6)	<0.001
14	97.9 (685/700)	97.9 (647/661)	-0.0 (-1.6, 1.6)	<0.001
18C	97.4 (682/700)	98.3 (651/662)	-0.9 (-2.6, 0.7)	<0.001
19A	97.9 (687/702)	99.7 (663/665)	-1.8 (-3.2, -0.8)	<0.001
19F	99.0 (693/700)	100.0 (663/663)	-1.0 (-2.1, -0.4)	<0.001
23F	91.5 (639/698)	91.8 (607/661)	-0.3 (-3.2, 2.7)	<0.001

[a] Estimated difference, CI, and p-value are based on the Miettinen & Nurminen method.
[b] A conclusion of non-inferiority of V114 to Prevnar 13™ is based on the lower bound of the 2-sided 95% CI for the difference in percentages (V114 - Prevnar 13™) 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.
CI=confidence interval; IgG=immunoglobulin G.

Source: [P029V114: adam-adsl; adimm]

Table 8. Analysis of the Proportions of Participants with IgG **≥0.35 µ**g/mL For the 2 Serotypes Unique to V114 at 30 Days Postdose 3 (Source: Table 11-2 CSR)

Pneumococcal Serotype in V114	V114 (N=858)	Pneumococcal Serotype in Prevnar 13™	Prevnar 13™ (N=856)	Percentage Point Difference (V114 - Prevnar 13™)	
	Observed Response Percentage (m/n)		Observed Response Percentage (m/n)	Estimate (95% CI)[ab]	p-value[ab] (1-sided)
22F	98.6 (691/701)	23F	91.8 (607/661)	6.7 (4.6, 9.2)	<0.001
33F	87.3 (613/702)	23F	91.8 (607/661)	-4.5 (-7.8, -1.3)	<0.001

[a] Estimated difference, CI, and p-value are based on the Miettinen & Nurminen method.
[b] A conclusion of non-inferiority of V114 to Prevnar 13™ is based on the lower bound of the 2-sided 95% CI for the difference in percentages (V114 - Prevnar 13™) 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.
The pneumococcal serotype in Prevnar 13™ selected for comparison in this table is the serotype with the lowest observed response rate among the 13 serotypes in Prevnar 13™, excluding serotype 3.
Note: Per protocol, dose 3 was administered at ~6 months of age.
CI=confidence interval; IgG=immunoglobulin G.

Assessor's comment:
V114 immune responses were also non-inferior to Prevnar 13 for 14 of the 15 serotypes, assessed by IgG GMCs at 30 days PD3, but narrowly missing the non-inferiority margin for serotype 6A (lower bound of the CI 0.48 versus >0.5).The failure to meet the protocol pre-specified non-inferiority

criterion for serotype 6A based on IgG GMCs at 30 days PD3 is not likely clinically significant when considering the totality of immunogenicity data of the study.

As outlined in WHO guidelines for evaluation of next generation PCVs and established by Prevnar and Prevnar 13, an important aspect of PCVs is the generation of immune memory in an infant population.

Secondary immunogenicity endpoint – Concomitant Vaccines

Immune responses to licensed vaccines, including Pentacel, VAQTA, M-M-RTMII, VARIVAX, and HIBERIX, administered concomitantly with PCV were comparable in the V114 and Prevnar 13 groups as per below:

1. Immune responses to Pentacel administered concomitantly with V114 met non-inferiority criteria as assessed by the proportions of participants meeting specified antibody responses to antigens included in Pentacel (response rates) at 30 days PD3.

Table 9. Pentacel Antigen Responses at 30 Days Postdose 3 (Per-Protocol Population) (Source: Table 11-7 CSR)

Antigen	Endpoint	Non-inferiority Margin	V114 (N=858)	Prevnar 13™ (N=856)	Percentage Point Difference (V114 - Prevnar 13™)	
			Observed Response Percentage (m/n)	Observed Response Percentage (m/n)	Estimate (95% CI)[ab]	p-value[ab] (1-sided)
Diphtheria toxoid	% ≥0.1 IU/mL	-10%	96.9 (681/703)	97.6 (650/666)	-0.7 (-2.6, 1.1)	<0.001
Tetanus toxoid	% ≥0.1 IU/mL	-5%	100.0 (703/703)	99.8 (665/666)	0.2 (-0.4, 0.8)	<0.001
Pertussis - PT	% ≥5 EU/mL	-10%	99.0 (696/703)	98.5 (656/666)	0.5 (-0.7, 1.9)	<0.001
Pertussis - FHA	% ≥5 EU/mL	-10%	99.1 (697/703)	99.4 (662/666)	-0.3 (-1.3, 0.8)	<0.001
Pertussis - FIM 2/3	% ≥20 EU/mL	-10%	63.7 (448/703)	61.7 (411/666)	2.0 (-3.1, 7.1)	<0.001
Pertussis - PRN	% ≥5 EU/mL	-10%	67.3 (473/703)	65.5 (436/666)	1.8 (-3.2, 6.8)	<0.001
Poliovirus 1	% with NAb≥1:8 dilution	-5%	99.8 (661/662)	99.8 (618/619)	0.0 (-0.7, 0.8)	<0.001
Poliovirus 2	% with NAb≥1:8 dilution	-5%	100.0 (648/648)	100.0 (614/614)	0.0 (-0.6, 0.6)	<0.001
Poliovirus 3	% with NAb≥1:8 dilution	-5%	100.0 (650/650)	100.0 (607/607)	0.0 (-0.6, 0.6)	<0.001
Hib-PRP	% ≥0.15 µg/mL	-10%	92.1 (597/648)	93.5 (575/615)	-1.4 (-4.3, 1.5)	<0.001

[a] Estimated difference, CI, and p-value are based on the Miettinen & Nurminen method.

[b] A conclusion of non-inferiority of Pentacel™ administered concomitantly with V114 to Pentacel™ administered concomitantly with Prevnar 13™ is based on the lower bound of the 2-sided 95% CI for the difference in percentages (V114 - Prevnar 13™) being greater than the specified non-inferiority margin (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.

CI=confidence interval; EU=endotoxin unit; FHA=filamentous hemagglutinin; FIM 2/3=fimbriae types 2 and 3; Hib=Haemophilus influenzae type b; IU=international unit; Nab=neutralizing antibodies; PRN=pertactin; PRP=polyribosylribitol phosphate; PT=pertussis toxin.

2. Immune responses to VAQTA administered concomitantly with V114 met non-inferiority criteria as assessed by the proportions of participants with antibody concentration ≥10 mIU/mL to anti-hepatitis antigen (response rates) at 30 days PD4.

Table 10. VAQTA Antigen Responses at 30 Days Postdose 4(PP) (Source CSR Table 11-9)

Antigen	Endpoint	Non-inferiority Margin	V114 (N=858)	Prevnar 13™ (N=856)	Percentage Point Difference (V114 - Prevnar 13™)	
			Observed Response Percentage (m/n)	Observed Response Percentage (m/n)	Estimate (95% CI)[ab]	p-value[ab] (1-sided)
Hepatitis A	% ≥10 mIU/mL	-10%	97.4 (632/649)	97.1 (608/626)	0.3 (-1.6, 2.2)	<0.001

[a] Estimated difference, CI, and p-value are based on the Miettinen & Nurminen method.

[b] A conclusion of non-inferiority of VAQTA™ administered concomitantly with V114 to VAQTA™ administered concomitantly with Prevnar 13™ is based on the lower bound of the 2-sided 95% CI for the difference in percentages (V114 - Prevnar 13™) being greater than the specified non-inferiority margin (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 4 was administered at ~12 to 15 months of age.

CI=confidence interval; IU=international unit.

3. Immune responses to M-M-R II administered concomitantly with V114 met non-inferiority criteria as assessed by the proportions of participants meeting specified antibody responses to M-M-R II antigens (response rates) at 30 days PD4.

Table 11. MMR II Antigen Responses at 30 Days Postdose 4 (PP) (Source CSR Table 11-10)

Antigen	Endpoint	Non-inferiority Margin	V114 (N=858)	Prevnar 13™ (N=856)	Percentage Point Difference (V114 - Prevnar 13™)	
			Observed Response Percentage (m/n)	Observed Response Percentage (m/n)	Estimate (95% CI)[ab]	p-value[ab] (1-sided)
Measles	% ≥255 mIU/mL	-5%	98.1 (657/670)	98.3 (637/648)	-0.2 (-1.8, 1.3)	<0.001
Mumps	% ≥10 mumps Ab units/mL	-5%	95.8 (642/670)	97.5 (632/648)	-1.7 (-3.8, 0.2)	0.001
Rubella	% ≥10 IU/mL	-5%	98.1 (657/670)	98.9 (641/648)	-0.9 (-2.3, 0.5)	<0.001

[a] Estimated difference, CI, and p-value are based on the Miettinen & Nurminen method.

[b] A conclusion of non-inferiority of M-M-R™ II administered concomitantly with V114 to M-M-R™ II administered concomitantly with Prevnar 13™ is based on the lower bound of the 2-sided 95% CI for the difference in percentages (V114 - Prevnar 13™) being greater than the specified non-inferiority margin (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 4 was administered at ~12 to 15 months of age.

Ab=antibody; CI=confidence interval; IU=international unit.

4. Immune responses to VARIVAX administered concomitantly with V114 met non-inferiority criteria as assessed by the proportions of participants with antibody concentration ≥5 gpELISA units/ml to anti-varicella antigen (response rates) at 30 days PD4.

Table 12. VARIVAX Antigen Responses at 30 Days Postdose 4 (PP)
(Source CSR Table 11-11)

Antigen	Endpoint	Non-inferiority Margin	V114 (N=858)	Prevnar 13™ (N=856)	Percentage Point Difference (V114 - Prevnar 13™)	
			Observed Response Percentage (m/n)	Observed Response Percentage (m/n)	Estimate (95% CI)[ab]	p-value[ab] (1-sided)
VZV	% ≥5 gpELISA units/ml	-10%	96.4 (689/715)	97.7 (669/685)	-1.3 (-3.2, 0.5)	<0.001

[a] Estimated difference, CI, and p-value are based on the Miettinen & Nurminen method.
[b] A conclusion of non-inferiority of VARIVAX™ administered concomitantly with V114 to VARIVAX™ administered concomitantly with Prevnar 13™ is based on the lower bound of the 2-sided 95% CI for the difference in percentages (V114 - Prevnar 13™) being greater than the specified non-inferiority margin (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 4 was administered at ~12 to 15 months of age.
CI=confidence interval; gpELISA=glycoprotein enzyme-linked immunosorbent assay; VZV=varicella-zoster virus.

5. Immune responses to HIBERIX administered concomitantly with V114 met non-inferiority criteria as assessed by the proportions of participants with antibody concentration ≥0.15 µg/mL to anti-PRP antigen (response rates) at 30 days PD4

Table 13. HIBERIX Antigen Responses at 30 Days Postdose 4 (PP)
(Source CSR Table 11-12)

Antigen	Endpoint	Non-inferiority Margin	V114 (N=858)	Prevnar 13™ (N=856)	Percentage Point Difference (V114 - Prevnar 13™)	
			Observed Response Percentage (m/n)	Observed Response Percentage (m/n)	Estimate (95% CI)[ab]	p-value[ab] (1-sided)
Hib-PRP	% ≥0.15 µg/mL	-10%	98.9 (643/650)	100.0 (626/626)	-1.1 (-2.2, -0.5)	<0.001

[a] Estimated difference, CI, and p-value are based on the Miettinen & Nurminen method.
[b] A conclusion of non-inferiority of HIBERIX™ administered concomitantly with V114 to HIBERIX™ administered concomitantly with Prevnar 13™ is based on the lower bound of the 2-sided 95% CI for the difference in percentages (V114 - Prevnar 13™) being greater than the specified non-inferiority margin (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 4 was administered at ~12 to 15 months of age.
CI=confidence interval; Hib=haemophilus influenzae type b; PRP=polyribosylribitol phosphate.

Assessor's comment:

All primary and secondary immunogenicity endpoints were met.

Safety results

The proportions of participants with AEs, including injection-site, systemic, and vaccine related AEs, and SAEs were generally comparable between intervention groups. AEs were reported for the majority (>92%) of participants in both intervention groups. The 3 most frequently reported AEs were irritability, somnolence, and injection-site pain. SAEs were reported for approximately 10% of participants and the proportions of participants with SAEs were comparable between intervention

groups. Respiratory syncytial virus bronchiolitis (1.1%) participants, gastroenteritis (1.0%) participants, and bronchiolitis (1.0%) participants were the top 3 most frequently reported SAEs overall. None of the SAEs were assessed by the investigator to be related to the study intervention. No participant discontinued study intervention due to an AE.

Two participants died during the study: one participant (V114 group) died on Day 2 relative to dose 3, secondary to complications from congenital heart disease. The other participant (Prevnar 13 group) experienced a serious head injury on Day 21 relative to dose 2 and was hospitalized. Five days after discontinuation from the study, the participant died (on Day 185) from complications of head injury and septic shock. Neither death was considered to be related to the study intervention.

The distribution of maximum body temperature measurements was generally comparable between intervention groups. The analysis of adverse event summary is described in table 14.

Table 14. Analysis of Adverse Event Summary (All Participants as Treated Population) (Following Any Dose) (Source: Table 14.3-1 CSR)

	V114		Prevnar 13™	
	n	(%)	n	(%)
Participants in population	858		855	
with one or more adverse events	805	(93.8)	790	(92.4)
injection-site	598	(69.7)	595	(69.6)
systemic	785	(91.5)	766	(89.6)
with no adverse event	53	(6.2)	65	(7.6)
with vaccine-related[a] adverse events	758	(88.3)	740	(86.5)
injection-site	595	(69.3)	593	(69.4)
systemic	651	(75.9)	646	(75.6)
with serious adverse events	88	(10.3)	81	(9.5)
with serious vaccine-related adverse events	0	(0.0)	0	(0.0)
who died	1	(0.1)	1	(0.1)
discontinued vaccine due to an adverse event	0	(0.0)	0	(0.0)
discontinued vaccine due to a vaccine-related adverse event	0	(0.0)	0	(0.0)
discontinued vaccine due to a serious adverse event	0	(0.0)	0	(0.0)
discontinued vaccine due to a serious vaccine-related adverse event	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.

Subgroup analyses

An overall summary of AEs and a summary of solicited AEs following any vaccination from a subgroup are shown if there were ≥5% of the total number of randomized participants in each vaccination group within that subgroup. Safety results observed within each subgroup analyzed were generally consistent with those in the overall population.

2.3.3. Discussion on clinical aspects

V114-029 was developed with input from US Food and Drug Administration Center for Biologics Evaluation and Research to evaluate immunogenicity, safety, and tolerability of 4-dose vaccination regimen in infants (US pivotal study). This study was part of the US initial pediatric study plan for V114.

This clinical study was conducted to evaluate the safety and immunogenicity of V114 administered at 2, 4, 6, and 12 to 15 months of age compared with Prevnar 13. The 3+1 PCV immunization schedule is currently recommended by the US ACIP.

This study also evaluated concomitant administration of V114 and licensed pediatric vaccines, Pentacel, VAQTA, HIBERIX, M-M-RII, and VARIVAX. It was a randomized, active comparator-controlled, parallel-group, multi-site, double-blind study of V114 in healthy infants enrolled at approximately 2 months of age (from 42 to 90 days, inclusive).

The objectives of the study were to evaluate the safety and tolerability of V114 with respect to the proportion of participants with adverse events (AEs). Also to compare the antigen-specific response rate to each antigen and the antigen-specific GMCs for the pertussis antigens included in Pentacel at 30 days following Dose 3 for participants administered V114 concomitantly with Pentacel versus participants administered Prevnar 13 concomitantly with Pentacel. The same comparison also have been done for VAQTA, MMR II, VARIVAX and HIBERIX at 30 days following Dose 4 in both two groups (V114 and Prevnar 13).

A total of 1720 participants were randomized (1713 were vaccinated) across 75 study sites in 3 countries. One participant in the Prevnar 13 group inadvertently received both V114 and Prevnar 13 and was excluded from the APaT population. The majority (>88%) of participants received all doses of PCVs and one dose of the concomitant vaccines, VAQTA, M-M-RII, and VARIVAX. The majority (>86%) of participants completed the study, the most common reasons for discontinuing study intervention were withdrawal by parent/guardian (8.4%) and lost to follow-up (3.5%).Prior medications and concomitant medications were reported for the participants (33.5% and 86.2%). Concomitant non-study vaccines were influenza vaccine (31.0%), influenza vaccine inactivated split 4V (12.8%), and Japanese encephalitis vaccine (11.8%).

The majority (>79%) of randomized participants were included in the PP population for pneumococcal IgG and most (>96%) randomized participants in the OPA subset were included in the PP population for pneumococcal OPA analysis at each time point. Immune responses to licensed vaccines, including Pentacel, VAQTA, M-M-RTMII, VARIVAX, and HIBERIX, administered concomitantly with PCV were comparable in the V114 and Prevnar 13 groups.

The V114 safety profile was generally comparable to that of Prevnar 13; most AEs were transient, and mild or moderate in intensity in both groups. The proportions of participants with solicited systemic and injection-site AEs were generally comparable between intervention groups. There were no vaccine-related SAEs or discontinuations due to vaccine related AEs. There were 2 deaths; 1 in each intervention group, neither were considered vaccine-related.

V114 elicited immune responses were comparable to Prevnar 13 for 13 shared serotypes, they met the non- inferiority criteria, assessed by IgG GMCs at 30 days PD3.V114 immune responses were also non-inferior to Prevnar 13 for 14 of the 15 serotypes, narrowly missing the non-inferiority margin for serotype 6A. The failure to meet the protocol pre-specified non-inferiority criterion for serotype 6A based on IgG GMCs at 30 days PD3 is not likely clinically significant when considering the totality of immunogenicity data of the study. This study showed that V114 elicits comparable immune responses to the 13 shared serotypes and higher responses to the 2 unique serotypes, with a safety profile that is comparable to Prevnar 13. As outlined in WHO guidelines for evaluation of next generation PCVs and

established by Prevnar and Prevnar 13, an important aspect of PCVs is the generation of immune memory in an infant population.

Based on the safety results from study V114-029, the following conclusion can be made: When administered concomitantly with licensed pediatric vaccines, VAQTA, M-M-R II, and VARIVAX, V114 is well tolerated with a safety profile generally comparable to Prevnar 13 in healthy infants and toddlers.

3. Rapporteur's overall conclusion and recommendation

No regulatory guidance specific to the V114-029 clinical study has been obtained from CHMP/EMA prior to this clinical overview submission per Article 46 Regulation (EC) No. 1901/2006 requirements.

The clinical overview fulfils the requirements of Article 46 Regulation (EC) No. 1901/2006 for study V114-029. The results from this clinical study support the immunogenicity and safety of the concomitant administration of V114 with hepatitis A virus vaccine; measles, mumps, and rubella virus vaccine; and varicella virus vaccine.

No changes to the current EU product information for either VAQTA, M-M-R II, and VARIVAX are proposed based on the results of study V114-029.

No modifications to the EU product information (SmPC, package leaflet, or texts of outer or immediate packaging) are proposed.

The study V114-029 will be also assessed into the upcoming EoI of the Vaxneuvance product.

☒ Fulfilled:

No regulatory action required.

4. Additional clarification requested

The results of study V114-029 provided no new information impacting the current label recommendations of the concomitantly VAQTA, M-M-R II, and VARIVAX administered vaccines.