Amsterdam, 17 August 2023
EMA/429416/2023
Human Medicines Division

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

Vaxneuvance

pneumococcal polysaccharide conjugate vaccine (15 valent, adsorbed)

Procedure no: EMEA/H/C/005477/P46/003

Note

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

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1. Introduction

On 25 May 2023, the MAH submitted a completed paediatric study for Vaxneuvance, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study V114-036, a Phase 3, Single-Arm, Open-label Clinical Study to Evaluate the Safety and Immunogenicity of 4 doses of V114 administered to Healthy Infants in South Korea, is a stand alone study.

V114-036 was designed to evaluate the safety and immunogenicity of Vaxneuvance (V114) when administered as a 4-dose regimen (3-dose infant primary series followed by a toddler dose) in healthy South Korean infants at approximately 2, 4, 6 and 12 to 15 months of age. Study V114-036 was conducted to support the registration of V114 in South Korea.

2.2. Information on the pharmaceutical formulation used in the study

Vaxneuvance is a 0.5-mL dose. The manufacturing lots used were 0001069325 and 0001335215.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- V114-036: A Phase 3, Single-Arm, Open-label Clinical Study to Evaluate the Safety and Immunogenicity of 4 doses of V114 Administered to Healthy Infants in South Korea

2.3.2. Clinical study

V114-036

Description

V114-036 was an open-label, single-group, multicentre clinical study designed to evaluate the safety and immunogenicity of V114 when administered as a 4-dose regimen in healthy infants beginning at approximately 2 months of age (42 to 90 days of age, inclusive).

Study design is presented in Figure 1.

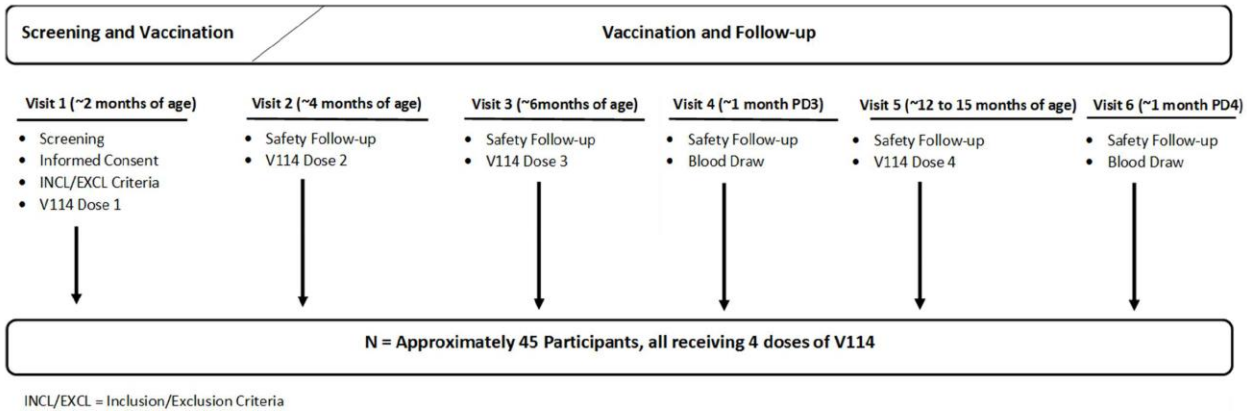

Figure 1 Design of study V114-036

CHMP´s comment:

As this study evaluated administration of Vaxneuvance using an already approved regimen (3 dose primary series + toddler booster dose) in an approved population (infants ≥6 weeks of age), limited new information can be expected from this study. This is in line with the goal of the study to support registration of Vaxneuvance in South Korea.

Methods

Study participants

Healthy male and female South Korean infants approximately 2 months of age, from 42 to 90 days (inclusive) and whose parent(s)/legally acceptable representative (LAR(s)) who could provide written informed consent were enrolled in this study.

Key exclusion criteria included prior administration of any pneumococcal vaccine and a history of pneumococcal disease.

CHMP's comment

The in- and exclusion criteria are deemed appropriate. The population consists of healthy infants approximately 2 months of age, which is consistent with the population for which Vaxneuvance is approved (individuals ≥6 weeks of age). The study was performed to support licensure in South Korea, therefore inclusion of South Korean infants only is appropriate.

Treatments

A 0.5-mL intramuscular dose of study vaccine will be administered to healthy South Korean infants at approximately 2, 4, 6, and 12 to 15 months of age. It is recommended that the study vaccines are administered intramuscularly in the right thigh.

CHMP's comment

Subjects received an in the SmPC recommended dosing regimen, consisting of 4 doses of Vaxneuvance of 0.5 mL. The primary series consisted of 3 doses administered at an interval of 4 to 8 weeks and a fourth dose administered when the subjects were between 11 and 15 months of age and at least 2 months after the third dose.

Objectives and Endpoints

The following objectives and endpoints will be evaluated in healthy infants enrolled at approximately 2 months of age (from 42 to 90 days [inclusive]) administered V114.

Objectives	**Endpoints**
Primary	
• Objective 1: To evaluate the safety and tolerability of V114 with respect to the proportion of participants with adverse events (AEs).	• Solicited injection-site AEs from Day 1 through Day 7 postvaccination. • Solicited systemic AEs from Day 1 through Day 7 postvaccination. • Vaccine-related serious adverse events (SAEs) through completion of study participation.
• Objective: To evaluate the anti- pneumococcal polysaccharide (PnPs) serotype-specific Immunoglobulin G (IgG) response rates (proportion of participants meeting serotype-specific IgG threshold value of ≥0.35 µg/mL) at 30 days after Dose 3. • Objective: To evaluate the anti-PnPs serotype-specific IgG Geometric Mean Concentrations (GMCs) at 30 days after Dose 3.	• Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days Postdose 3 (PD3).
Secondary	
• Objective: To evaluate the anti-PnPs serotype-specific IgG GMCs at 30 days after Dose 4.	• Anti-PnP serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days Postdose 4 (PD4).

CHMP's comment

The immune response induced by Vaxneuvance will be described in terms of percentage of participants achieving an serotype specific IgG titre ≥ 0.35µg (which is considered a correlate of protection at population level) for the 15 serotypes in the vaccine and serotype specific IgG geometric mean concentrations (GMCs) 1 month after primary series and 1 month after the toddler dose. This information is considered limited, however the most clinically relevant information is provided.

The safety information is limited, as unsolicited AEs are only recorded up to 14 days after vaccination.

Sample size

This is a descriptive study.

This study planned to allocate approximately 45 participants to V114. It is assumed that approximately 38 participants will be evaluable for immunogenicity analyses at 30 days post dose 3 (PD3) (85% evaluability rate), and approximately 36 participants will be evaluable for immunogenicity analyses at 30 days post dose 4 (PD4) (80% evaluability rate).

CHMP's comment

No hypothesis testing was underlying the sample size determination. The sample size was originally planned to enrol 100 subjects, however, due to enrolment challenges related to COVID-19, this was reduced to 45. The reduction in sample size will only impact variability around the point estimate for the immune responses measured.

Due to the limited number of participants, the probability of observing an adverse event is very low, with only the most common AEs being able to be detected.

Randomisation and blinding (masking)

This is a single-arm, open-label study. There is no randomisation or blinding for this study.

Statistical Methods

Immunogenicity analyses were conducted for each of the 15 pneumococcal serotypes in V114 separately. To address the primary immunogenicity objectives, evaluation of the IgG response rates and IgG GMCs at 30 days after the third dose of V114 included descriptive summaries and 95% confidence intervals (CIs). For IgG response rates, the CIs were calculated based on the exact binomial method proposed by Clopper and Pearson. For IgG GMCs, point estimates were calculated by exponentiating the estimates of the mean of the natural log values. The CIs were derived by exponentiating the CIs of the mean of the natural log values based on the t-distribution.

To address the secondary immunogenicity objective, evaluation of the IgG GMCs conducted at 30 days after the fourth dose of V114 included descriptive summaries and 95% CIs, which were calculated using the same methodology as the primary objective.

Safety parameters were summarized for participants separately via descriptive statistics. In addition, for select safety parameters, 95% CIs were provided.

CHMP's comment

No hypothesis testing was predefined. The results will be presented descriptively.

Results

Participant flow

A total of 58 participants were enrolled and 57 participants were vaccinated. One participant was enrolled in error (participant had received previous administration of Prevenar 13™) and was discontinued from the study without receipt of V114.

All but 1 enrolled participant received at least 1 V114 dose, and 50 (86.2%) participants received all subsequent V114 doses and completed the study Table 1.

The most common reason for study discontinuation was "Withdrawal by Parent/Guardian" (6.9%) Table 1.

Table 1 Disposition of Participants (All Randomized Participants)

	V114	
	n	(%)
Participants in population	58	
Vaccinated with		
PCV (~2 months of age)	57	(98.3)
PCV (~4 months of age)	56	(96.6)
PCV (~6 months of age)	55	(94.8)
PCV (~12 to 15 months of age)	50	(86.2)
Trial Disposition		
Completed	53	(91.4)
Discontinued	5	(8.6)
Randomized By Mistake Without Study Treatment	1	(1.7)
Withdrawal By Parent/Guardian	4	(6.9)

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

CHMP's comment

In total 58 participants were enrolled, with 1 participant not receiving V114 as this participant was enrolled in error. Of the 57 participants (98.3%) who received the first dose of V114, 56 (96.6%) received the 2nd dose, 55 (94.8%) received the 3rd dose and 50 (86.2%) received the 4th dose.

In total 5 participants discontinued the study, with the main reason for withdrawal being withdrawal by parent/guardian.

Due to the low number of participants receiving Vaxneuvance, any immunogenicity or safety data obtained is limited.

Recruitment

The study was conducted at 13 centres in 1 country, South Korea. Study period was between 10-FEB-2021 until 04-NOV-2022, with a database lock at 13-DEC-2022.

Baseline data

Approximately half of the participants were female (56.1%). The median age at enrolment was 9.0 weeks, with a majority (64.9%) of participants enrolled at 8 or 9 weeks. Approximately 9% of participants were preterm infants (gestational age <37 weeks).

Table 2 Participant Characteristics (All Vaccinated Participants)

	V114	
	n	(%)
Participants in population	57	
Sex		
Male	25	(43.9)
Female	32	(56.1)
Age (Weeks)		
6	1	(1.8)
7	6	(10.5)
8	20	(35.1)
9	17	(29.8)
10	8	(14.0)
11	5	(8.8)
Mean	8.7	
SD	1.2	
Median	9.0	
Range	6 to 11	
Race		
Asian	57	(100.0)
Ethnicity		
Not Hispanic Or Latino	56	(98.2)
Not Reported	1	(1.8)
Gestational Age (Weeks)		
<37	5	(8.8)
≥37	52	(91.2)

SD=standard deviation.

CHMP's comment

The mean age of the study participants was 8.7 weeks (range: 6-11 weeks) at baseline. All participants were Asian and representative for both genders (43.9% male and 56.1% female).

Number analysed

The primary and secondary immunogenicity analyses were conducted using the PP population, defined as all randomized participants without deviations from the protocol that may have substantially affected the results of the immunogenicity endpoints.

For the primary endpoint, the majority (81.0%) of enrolled participants were included in the IgG analyses at 30 days PD3 (Table 3). For the secondary endpoint, the majority (84.5%) of enrolled participants were included in the IgG analysis at 30 days PD4 (Table 3).

The most common reason for exclusion from analyses of the PP population at 30 Days PD3 was receipt of prohibited concomitant medication(s) and/or vaccination(s) (6 [10.3%] participants). At 30 days PD4, the most common reason for exclusion from analysis of the PP population was missing serology results (4 [6.9%] participants) (Table 3).

Supportive immunogenicity analyses were conducted using the FAS, defined as all enrolled participants who received at least 1 study vaccination and have at least 1 serology result.

Table 3 Participant Accounting for IgG Analyses of the Per-Protocol Population (All Randomized Participants)

	V114	
	n	**(%)**
Participants randomized	58	
Participants included in analyses by timepoint		
30 Days Postdose 3	47	(81.0)
30 Days Postdose 4	49	(84.5)
Reasons for exclusions from analyses[a]		
Participant-level exclusions[b]	**1**	**(1.7)**
Randomized but not vaccinated	1	(1.7)
Prior pneumococcal vaccine	1	(1.7)
Visit-level exclusions - 30 Days Postdose 3	**10**	**(17.2)**
Blood draw out of window	1	(1.7)
Missing serology results[c]	2	(3.4)
Prohibited concomitant medication or vaccination	6	(10.3)
Vaccination out of window	2	(3.4)
Visit-level exclusions - 30 Days Postdose 4	**8**	**(13.8)**
Blood draw out of window	1	(1.7)
Missing serology results[c]	4	(6.9)
Prohibited concomitant medication or vaccination	3	(5.2)

Percentages are calculated based on the number of participants randomized.
[a] Participants may have more than one reason for exclusion. Participants are displayed in all applicable categories.
[b] Participant-level exclusions result in exclusion from analyses at all timepoints. These participants do not also appear in the Visit-level exclusions rows.
[c] Missing serology results for all 15 serotypes, 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, and dose 4 was administered at ~12 to 15 months of age. IgG=Immunoglobulin G.
Source: [P036V114: adam-adsl; adpdev; adimm]

CHMP's comment

The most common reason for exclusion from the PP analysis set was prohibited concomitant medication or vaccination followed by missing serology result and vaccination out of window at 30 days PD3 and missing serology results followed by prohibited concomitant medication or vaccination at 30 days PD4.

As >10% of participants visits were excluded from the PP analysis , and overall 1.7 % of the participants were excluded, a supportive analysis in the FAS is appreciated.

Due to the low number of participants receiving Vaxneuvance, any immunogenicity data obtained is limited.

Efficacy (Immunogenicity) results

For the primary immunogenicity endpoint, V114 was immunogenic for all 15 serotypes contained in the vaccine as assessed by the proportion of participants meeting the serotype-specific IgG threshold value of ≥0.35 µg/mL (response rate) at 30 days PD3. IgG response rates were >95% for all 15 serotypes [Table 4]. Results in the FAS population were consistent with those observed in the PP population.

Table 4 Summary of the Proportions of Participants With IgG ≥0.35 µg/mL at 30 Days Postdose 3 (Per-Protocol Population)

Pneumococcal Serotype	V114 (N = 57)	
	Observed Response Percentage (m/n)	95% CI[a]
1	100.0 (47/47)	(92.5, 100.0)
3	100.0 (47/47)	(92.5, 100.0)
4	100.0 (47/47)	(92.5, 100.0)
5	100.0 (47/47)	(92.5, 100.0)
6A	100.0 (47/47)	(92.5, 100.0)
6B	95.7 (45/47)	(85.5, 99.5)
7F	100.0 (47/47)	(92.5, 100.0)
9V	100.0 (47/47)	(92.5, 100.0)
14	100.0 (47/47)	(92.5, 100.0)
18C	97.9 (46/47)	(88.7, 99.9)
19A	97.9 (46/47)	(88.7, 99.9)
19F	100.0 (47/47)	(92.5, 100.0)
22F	100.0 (47/47)	(92.5, 100.0)
23F	100.0 (47/47)	(92.5, 100.0)
33F	97.9 (46/47)	(88.7, 99.9)

[a] The within-group CIs are based on the exact binomial method proposed by Clopper and Pearson.
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: [P036V114: adam-adsl; adimm]

Second primary immunogenicity endpoint, V114 was immunogenic for all 15 serotypes contained in the vaccine as assessed by serotype-specific IgG GMCs at 30 days PD3 [Table 5]. Secondary immunogenicity endpoint, serotype-specific IgG GMCs at 30 days PD4 were generally higher than serotype-specific IgG GMCs at 30 days PD3 [Table 5]. Results in the FAS population were consistent with those observed in the PP population

Table 5 Summary of IgG GMCs at 30 Days Postdose 3 and 4 (Per-Protocol Population)

Pneumococcal Serotype	IgG GMCs at 30 days postdose 3 V114 (N = 57)			IgG GMCs at 30 days postdose 4 V114 (N = 57)		
	n	Observed GMC	95% CIa	n	Observed GMC	95% CIa
1	47	1.69	(1.46, 1.94)	49	2.24	(1.77, 2.83)
3	47	1.70	(1.41, 2.06)	49	1.32	(1.07, 1.62)

Pneumococcal Serotype	IgG GMCs at 30 days postdose 3 V114 (N = 57)			IgG GMCs at 30 days postdose 4 V114 (N = 57)		
	n	Observed GMC	95% CIa	n	Observed GMC	95% CIa
4	47	1.87	(1.49, 2.34)	49	1.86	(1.39, 2.49)
5	47	2.14	(1.74, 2.63)	49	3.27	(2.57, 4.17)
6A	47	2.16	(1.74, 2.67)	49	5.77	(4.38, 7.60)
6B	47	2.53	(1.93, 3.32)	49	6.80	(5.28, 8.76)
7F	47	2.80	(2.35, 3.32)	49	5.17	(3.92, 6.81)
9V	47	2.01	(1.63, 2.47)	49	3.27	(2.50, 4.28)
14	47	7.47	(5.98, 9.32)	49	9.04	(7.22, 11.31)
18C	47	1.90	(1.47, 2.46)	49	3.81	(2.97, 4.88)
19A	47	2.20	(1.76, 2.76)	49	4.91	(4.03, 5.97)
19F	47	3.04	(2.55, 3.63)	49	5.41	(4.40, 6.65)
22F	47	5.97	(4.83, 7.37)	49	9.20	(7.19, 11.79)
23F	47	1.71	(1.37, 2.15)	49	2.82	(2.14, 3.73)
33F	47	2.41	(1.84, 3.15)	49	6.21	(5.05, 7.63)

a The within-group 95% 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 and dose 4 was administered at ~12 to 15 months of age.
CI=confidence interval; GMC=geometric mean concentration (µg/mL); IgG=Immunoglobulin G.

In the subgroup analysis by sex, immune responses in both male and female participants were consistent with the results observed in the overall population.

CHMP's comment

At 30 days post-dose 3, the vast majority of participants achieved the surrogate of protection, a serotype-specific IgG threshold titre of ≥0.35 µg/mL, for all of the 15 serotypes included in the vaccine. This indicates a good level of protection against IPD.

At 30 days post-dose 3 the IgG GMCs ranged from 1.69 (serotype 1) to 7.47 (serotype 14). The IgG GMCs increased for the majority of serotype post-dose 4 and ranged from 1.32 (serotype 3) to 9.20 (serotype 22F).

V114 was shown to be immunogenic in both male and female participants. Although slight differences could be observed, no clear trend was seen.

Analysis performed using the FAS population, provided similar results to the analysis performed on the PP population, indicating robustness of the results.

The results are in line with the immunogenicity results already presented in the SmPC. No new information is derived from this study.

Safety results

Safety evaluation methods

All participants were observed for at least 15 minutes after each vaccination for any immediate reactions. The observation period could be extended if clinically indicated.

Participant's parent or legally acceptable representative will use the paper vaccine report card (VRC) to document the following information:

- Rectal/axial temperatures measured Day 1 (day of vaccination) through Day 7 after each vaccination
- Solicited injection-site AEs (swelling, redness, pain or tenderness, and hard lump) Day 1 through Day 7 postvaccination

- Solicited systemic AEs (irritability, drowsiness, appetite lost, and hives or welts) Day 1 through Day 7 postvaccination
- Any other unsolicited injection-site or systemic AEs Day 1 through Day 14 postvaccination
- Use of any analgesic or antipyretic on the day of vaccination
- Concomitant medications and non-study vaccinations Day 1 to Day 14 postvaccination

Nonserious AEs are to be reported from Days 1 through 14 after each vaccination. SAEs and deaths are to be reported throughout the duration of an individual's study participation

CHMP's comment

In general methods to assess the reactogenicity and safety of V114 are acceptable. Reactogenicity was followed for 7 days when concerning solicited local and systemic reactions, which is acceptable (see Guideline on clinical evaluation of vaccines). Noteworthy is the short follow-up time after dose 4, as the follow-up after vaccination 4 (toddler dose) appears to be only approximately 28 days.

Exposure

All but 1 enrolled participant received V114 on Day 1. Most (94.8%) participants received all 3 doses of the V114 infant primary series and most (86.2%) received the fourth V114 dose, see Table 1.

CHMP's comment

In total 57 participants received at least 1 dose of V114 and were included in the safety analysis set.

Based on the number of participants, only frequently occurring adverse events are expected to be observed and assessable.

Adverse Reactions

AEs and vaccine-related AEs were reported for all but 1 participant (56 [98.2%]) following any V114 dose [Table 6].

SAEs were reported for 4 (7.0%) participants, none of which were considered by the investigator to be related to V114. No participants discontinued study intervention due to an AE, and no participants died during the study.

Table 6 Summary of Adverse Events (All Participants as Treated Population) (Following Any Dose)

	V114		
	n	(%)	95% CI[b]
Participants in population	57		
with one or more adverse events	56	(98.2)	(90.6, 100.0)
injection-site	42	(73.7)	
systemic	55	(96.5)	
with no adverse event	1	(1.8)	
with vaccine-related[a] adverse events	56	(98.2)	(90.6, 100.0)
injection-site	42	(73.7)	
systemic	47	(82.5)	
with serious adverse events	4	(7.0)	(1.9, 17.0)
with serious vaccine-related adverse events	0	(0.0)	(0.0, 6.3)
who died	0	(0.0)	(0.0, 6.3)
discontinued vaccine due to an adverse event	0	(0.0)	(0.0, 6.3)
discontinued vaccine due to a vaccine-related adverse event	0	(0.0)	(0.0, 6.3)
discontinued vaccine due to a serious adverse event	0	(0.0)	(0.0, 6.3)
discontinued vaccine due to a serious vaccine-related adverse event	0	(0.0)	(0.0, 6.3)

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

[b] Estimated CIs are calculated based on the exact binomial method proposed by Clopper and Pearson and are provided in accordance with the statistical analysis plan.

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.

CI=confidence interval.

Source: [P036V114: adam-adsl; adae]

CHMP's comment

Vaxneuvance is a reactogenic vaccine, with all but 1 participant experiencing a vaccine-related AE. None of the participants experienced a vaccine-related SAE, died or discontinued due to an AE.

Solicited Adverse Events

All but 1 participant reported 1 or more solicited AEs following any V114 dose [Table 7]. Results following each V114 dose were similar to those observed after any V114 dose.

The most frequently reported AEs following any V114 dose were irritability (89.5%), somnolence (82.5%), and decreased appetite (71.9%) [Table 7].

Of the participants with AEs graded by intensity (solicited and unsolicited), the majority had events with a maximum intensity of mild or moderate following any V114 dose. Of the participants with the solicited injection-site AEs of erythema, induration and swelling, the majority had events with a maximum size of ≤1 inch (smallest size).

Of the participants with solicited AEs, the majority had events with a maximum duration of ≤3 days except for injection site induration, for which the majority of participants had events with a maximum duration of ≤5 days following any V114 dose

Table 7 Participants With Solicited Adverse Events (Incidence > 0%) (All Participants as Treated Population) (Following Any Dose)

	V114	
	n	(%)
Participants in population	57	
with one or more solicited adverse events	56	(98.2)
with no solicited adverse events	1	(1.8)
Solicited injection site adverse events	**42**	**(73.7)**
Injection site erythema	31	(54.4)
Injection site induration	33	(57.9)
Injection site pain	29	(50.9)
Injection site swelling	34	(59.6)
Solicited systemic adverse events	**54**	**(94.7)**
Decreased appetite	41	(71.9)
Irritability	51	(89.5)
Somnolence	47	(82.5)
Urticaria	5	(8.8)

Every participant is counted a single time for each applicable row and column.
Injection site erythema, injection site induration, injection site pain, injection site swelling, decreased appetite, irritability, somnolence, and urticaria were solicited from Day 1 through Day 7 following each vaccination.
MedDRA version 25.1 was used in the reporting of this study.

Source: [P036V114: adam-adsl; adae]

CHMP's comment

The reactogenicity profile is largely comparable to the profile observed for previous studies used for licensure.

The vast majority of participants experienced a solicited adverse event, which were mostly mild to moderate in intensity. Duration of the solicited adverse events appears to be slightly longer in the current study compared to the studies included in the submission for licensure. However, this is not considered to be clinically relevant, as the majority of solicited adverse events had a duration of ≤5 days instead of ≤3 days. This slight difference could be due to small number of participants in the current study.

Related adverse events

All injection-site AEs were considered vaccine-related. An overview of vaccine-related systemic events is presented in Table 8. The most frequently reported vaccine-related systemic AE was the solicited systemic AE of irritability [Table 8].

Results following each V114 dose were similar to those observed after any V114 dose

Table 8 Participants with systemic adverse events related to study vaccine (Incidence >0%) (All Participants as Treated Population) (Following Any Dose)

	V114	
	n	(%)
Participants in population	57	
with one or more systemic adverse events related to study vaccine	47	(82.5)
with no systemic adverse events related to study vaccine	10	(17.5)
Gastrointestinal disorders	**3**	**(5.3)**
Diarrhoea	2	(3.5)
Vomiting	1	(1.8)
General disorders and administration site conditions	**18**	**(31.6)**
Pyrexia	18	(31.6)
Metabolism and nutrition disorders	**32**	**(56.1)**
Decreased appetite[a]	32	(56.1)
Nervous system disorders	**39**	**(68.4)**
Somnolence[a]	39	(68.4)
Psychiatric disorders	**41**	**(71.9)**
Irritability[a]	41	(71.9)
Skin and subcutaneous tissue disorders	**5**	**(8.8)**
Urticaria[a]	5	(8.8)

Every participant is counted a single time for each applicable row and column.
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.
[a] Decreased appetite, irritability, somnolence, and urticaria were solicited from Day 1 through Day 7 following each vaccination.
Relatedness to study vaccine was determined by the investigator.
MedDRA version 25.1 was used in the reporting of this study.

Source: [P036V114: adam-adsl; adae]

Body temperature increased

The majority of participants had maximum body temperatures <39.0°C (102.2°F) following any dose. Few participants reported a maximum body temperature ≥40.0°C (104.0°F)[Table 9].

Table 9 Summary of Maximum Temperatures by Brighton Collaboration Cut Points (All Participants as Treated Population) (Following Any Dose)

	V114	
	n	(%)
Participants in population	57	
without temperature data (Day 1 through Day 7)[a]	0	(0.0)
with temperature data (Day 1 through Day 7)	57	(100.0)
Maximum Temperature (Rectal or Rectal Equivalent)		
<100.4 °F (38.0 °C)	3	(5.3)
≥100.4 °F (38.0 °C) and <101.3 °F (38.5 °C)	21	(36.8)
≥101.3 °F (38.5 °C) and <102.2 °F (39.0 °C)	11	(19.3)
≥102.2 °F (39.0 °C) and <103.1 °F (39.5 °C)	12	(21.1)
≥103.1 °F (39.5 °C) and <104.0 °F (40.0 °C)	6	(10.5)
≥104.0 °F (40.0 °C) and <104.9 °F (40.5 °C)	3	(5.3)
≥104.9 °F (40.5 °C) and <105.8 °F (41.0 °C)	1	(1.8)
≥105.8 °F (41.0 °C)	0	(0.0)

[a] Includes participants whose temperature methods were unreported or unable to be converted to rectal equivalent for Day 1 through Day 7 following all vaccinations.

Percentages for the maximum temperature categories are calculated based on the number of participants with temperature data.

Multiple occurrences of maximum temperature are counted only once.

Non-rectal temperatures have been converted to rectal equivalent.

Source: [P036V114: adam-adsl; advstemp]

CHMP's comment

Unsolicited AEs were recorded for 14 days after each vaccination. The most frequently reported vaccine related AEs, were the solicited AEs of irritability, somnolence and decreased appetite.

In addition to the solicited AEs, pyrexia, diarrhoea and vomiting were reported as related AEs. These related AEs have been observed in the studies used for licensure.

The proportion of participants with the maximum body temperature ≥40.0°C (104.0°F) is 7%. This is higher compared to the previous studies used for licensure where this proportion was <2%, however, it is still in line with the frequency category listed in the SmPC.

No new safety signals were observed.

SAEs and deaths

There were no deaths due to AEs reported for this study.

One or more SAEs were reported for 4 (7.0%) participants, see Table 10.

Table 10 Participants With Serious Adverse Events (Incidence > 0%) (All Participants as Treated Population) (Following Any Dose)

	V114	
	n	(%)
Participants in population	57	
with one or more serious adverse events	4	(7.0)
with no serious adverse events	53	(93.0)
General disorders and administration site conditions	**1**	**(1.8)**
Pyrexia	1	(1.8)
Infections and infestations	**3**	**(5.3)**
Asymptomatic COVID-19	1	(1.8)
Gastroenteritis norovirus	1	(1.8)
Urinary tract infection	1	(1.8)
Urinary tract infection bacterial	1	(1.8)

Every participant is counted a single time for each applicable row and column.
Reported serious adverse events occurred from ~2 months of age (following dose 1) through completion of study participation.
MedDRA version 25.1 was used in the reporting of this study.
COVID-19=coronavirus disease 2019.

Source: [P036V114: adam-adsl; adae]

CHMP's comment

None of the participants in the study died.

SAEs were experienced by a low number of participants (n=4, 0.7%). Based on the narratives it can be agreed that none of the SAEs were related to the investigational vaccine. For the SAE of pyrexia, TTO was day 5 after vaccination 1, however, a history of UTI diagnosed on Day -37 and Day -13 and urine culture positive for E coli offer a plausible other aetiology. Therefore a clear causal relation to the vaccine cannot be made.

No new safety signal was observed.

Discontinuations due to Adverse Events

No participants discontinued from study vaccine due to an AE.

2.3.3. Discussion on clinical aspects

V114-036 was designed to evaluate the safety and immunogenicity of Vaxneuvance (V114) when administered as a 4-dose regimen (3-dose infant primary series followed by a toddler dose) in healthy South Korean infants at approximately 2, 4, 6 and 12 to 15 months of age. Study V114-036 was conducted to support the registration of V114 in South Korea. Due to the limited number of participants, n=57, the study provides limited data on immunogenicity and safety.

The study showed that V114 induces an immune response to all 15 serotypes contained within the vaccine. The response rate at 30 days post dose 3, defined as the proportion of participants achieving IgG of ≥0.35 µg/mL, was ≥95% for all serotypes. At 30 days post dose 3 and post dose 4 the IgG GMCs for all serotypes were well above the threshold of 0.35 µg/mL. These results indicate that V114 induced a substantial immune response that is likely to offer protection against IPD. These results are in line with the results presented in the SmPC.

The safety profile of V114 is characterised by AEs that are mainly mild to moderate in intensity and of short duration. V114 is overall well tolerated. No new safety signals were observed.

Overall, the results of study V114-036 in 57 South Korean infants add no new information to what was already known for V114 and do not need to be reflected in the SmPC.

3. Rapporteur's overall conclusion and recommendation

The results from Study V114-036, a Phase 3, Single-Arm, Open-label Clinical Study to Evaluate the Safety and Immunogenicity of 4 doses of V114 administered to Healthy Infants in South Korea, do not change the benefit-risk profile of Vaxneuvance. The results of this study do not change the opinion on immunogenicity and indicate no new safety concern.

☒ Fulfilled:

No regulatory action required.