Clinical trial results:
A Phase II, observer-blind, randomized, controlled study to evaluate the immunogenicity and safety of a varicella vaccine at various potencies compared with Varivax, as a first dose, administered in healthy children in their second year of life

Summary

EudraCT number	2022-001910-21
Trial protocol	EE PL Outside EU/EEA
Global end of trial date	13 June 2024

Results information

Result version number	v1 (current)
This version publication date	26 December 2024
First version publication date	26 December 2024

Trial information

Trial identification

Sponsor protocol code	217212

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05084508
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	Rue de l'Institut, 89,, Rixensart, Belgium, 1330
Public contact	GSK Response Center, GlaxoSmithKline, 044 8664357343, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, GlaxoSmithKline, 044 8664357343, GSKClinicalSupportHD@gsk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 July 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 February 2024
Global end of trial reached?	Yes
Global end of trial date	13 June 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the immune response of VNS vaccine (formulated with different potencies) and VV vaccine in terms of geometric mean concentration at Day 43

Protection of trial subjects:

All participants were observed for 30 min after vaccination with appropriate medical treatment readily available. Vaccines were administered by qualified and trained personnel. Vaccines were administered only to eligible participants that have no contraindications to any components of the vaccines. Participants were followed-up for 180 days after the vaccination.
The burden of the study for the participant were minimized as much as possible. For taking blood samples, 3 attempts at most should be performed. If the investigator/designee was not successful after the third attempt, the investigator/designee made no further attempts. A local numbing cream or patch were offered at the discretion of the investigator prior to blood sampling, to minimize pain when blood samples were drawn.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 February 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Estonia: 100
Country: Number of subjects enrolled	Poland: 38
Country: Number of subjects enrolled	Taiwan: 10
Country: Number of subjects enrolled	United States: 652
Worldwide total number of subjects	800
EEA total number of subjects	138

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	800

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Out of 800 participants enrolled, 9 participants discontinued before receiving the vaccination and therefore only 791 participants were included in the Exposed Set and started the study.

Pre-assignment

Screening details:

The Prevnar 13 vaccine was administered only to participants enrolled in the US and in countries where pneumococcal conjugate vaccine is recommended at 12- 15 months as per national immunization schedule.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind[1]
Roles blinded	Data analyst, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	VNS_Low Group

Arm description:

Participants received 1 dose of an investigational varicella vaccine (VNS) of low potency, 1 dose of a measles, mumps, and rubella (MMR) vaccine, 1 dose of a hepatitis A vaccine (Havrix) and 1 dose of a13 valent pneumococcal conjugate vaccine (Prevnar 13) on Day 1.

Arm type	Experimental
Investigational medicinal product name	Investigational Varicella Vaccine (VNS vaccine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1 dose VNS vaccine (low potency) received on Day 1.

Investigational medicinal product name	Prevnar 13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

1 dose of 13 valent pneumococcal conjugate vaccine (Prevnar 13) on Day 1.

Investigational medicinal product name	Havrix
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

1 dose of a hepatitis A vaccine (Havrix) on Day 1.

Investigational medicinal product name	MMR (M-M-R II or M-M-RVaxPro) vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection

Routes of administration	Subcutaneous use

Dosage and administration details:

1 dose of a measles, mumps, and rubella (MMR) vaccine on Day 1.

Arm title	VNS_Med Group

Arm description:

Participants received 1 dose of VNS vaccine of medium potency, 1 dose of MMR vaccine, 1 dose of Havrix vaccine, and 1 dose of Prevnar 13 vaccine on Day 1.

Arm type	Experimental
Investigational medicinal product name	Investigational Varicella Vaccine (VNS vaccine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1 dose VNS vaccine (medium potency) received on Day 1.

Investigational medicinal product name	Prevnar 13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

1 dose of 13 valent pneumococcal conjugate vaccine (Prevnar 13) on Day 1.

Investigational medicinal product name	Havrix
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

1 dose of a hepatitis A vaccine (Havrix) on Day 1.

Investigational medicinal product name	MMR (M-M-R II or M-M-RVaxPro) vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1 dose of a measles, mumps, and rubella (MMR) vaccine on Day 1.

Arm title	VNS_High Group

Arm description:

Participants received 1 dose of VNS vaccine of high potency, 1 dose of MMR vaccine, 1 dose of Havrix vaccine, and 1 dose of Prevnar 13 vaccine on Day 1.

Arm type	Experimental
Investigational medicinal product name	Investigational Varicella Vaccine (VNS vaccine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1 dose VNS vaccine (high potency) received on Day 1.

Investigational medicinal product name	Prevnar 13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

1 dose of 13 valent pneumococcal conjugate vaccine (Prevnar 13) on Day 1.

Investigational medicinal product name	Havrix
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

1 dose of a hepatitis A vaccine (Havrix) on Day 1.

Investigational medicinal product name	MMR (M-M-R II or M-M-RVaxPro) vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1 dose of a measles, mumps, and rubella (MMR) vaccine on Day 1.

Arm title	VV_Lot1 and Lot2 Pooled Group

Arm description:

Participants received 1 dose of a licensed varicella vaccine (VV) of Lot 1 or 1 dose of a licensed vaccine (VV) of Lot 2, 1 dose of MMR vaccine, 1 dose of Havrix vaccine, and 1 dose of Prevnar 13 vaccine on Day 1.

Arm type	Active comparator
Investigational medicinal product name	VV Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1 dose of VV (comparator vaccine) received on Day 1.

Investigational medicinal product name	Prevnar 13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

1 dose of 13 valent pneumococcal conjugate vaccine (Prevnar 13) on Day 1.

Investigational medicinal product name	Havrix
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

1 dose of a hepatitis A vaccine (Havrix) on Day 1.

Investigational medicinal product name	MMR (M-M-R II or M-M-RVaxPro) vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection

Routes of administration	Subcutaneous use

Dosage and administration details:

1 dose of a measles, mumps, and rubella (MMR) vaccine on Day 1.

Notes:

[1] - The roles blinded appear to be inconsistent with a double blind trial.

Justification: This is an Observer-blind study.

Number of subjects in period 1[2]	VNS_Low Group	VNS_Med Group	VNS_High Group
Started	203	195	203
Completed	197	190	193
Not completed	6	5	10
Consent withdrawn by subject	-	2	3
Not specified	-	-	-
Lost to follow-up	6	3	7

Number of subjects in period 1[2]	VV_Lot1 and Lot2 Pooled Group
Started	190
Completed	185
Not completed	5
Consent withdrawn by subject	1
Not specified	1
Lost to follow-up	3

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Out of 800 participants enrolled, 9 participants discontinued before receiving the vaccination and therefore only 791 participants were included in the Exposed Set and started the study.

Baseline characteristics

Reporting groups	
Reporting group title	VNS_Low Group
Reporting group description:	
Participants received 1 dose of an investigational varicella vaccine (VNS) of low potency, 1 dose of a measles, mumps, and rubella (MMR) vaccine, 1 dose of a hepatitis A vaccine (Havrix) and 1 dose of a13 valent pneumococcal conjugate vaccine (Prevnar 13) on Day 1.	
Reporting group title	VNS_Med Group
Reporting group description:	
Participants received 1 dose of VNS vaccine of medium potency, 1 dose of MMR vaccine, 1 dose of Havrix vaccine, and 1 dose of Prevnar 13 vaccine on Day 1.	
Reporting group title	VNS_High Group
Reporting group description:	
Participants received 1 dose of VNS vaccine of high potency, 1 dose of MMR vaccine, 1 dose of Havrix vaccine, and 1 dose of Prevnar 13 vaccine on Day 1.	
Reporting group title	VV_Lot1 and Lot2 Pooled Group
Reporting group description:	
Participants received 1 dose of a licensed varicella vaccine (VV) of Lot 1 or 1 dose of a licensed vaccine (VV) of Lot 2, 1 dose of MMR vaccine, 1 dose of Havrix vaccine, and 1 dose of Prevnar 13 vaccine on Day 1.	

Reporting group values	VNS_Low Group	VNS_Med Group	VNS_High Group
Number of subjects	203	195	203
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	203	195	203
Age continuous Units: months			
arithmetic mean	12.4	12.4	12.3
standard deviation	± 0.7	± 0.7	± 0.7
Sex: Female, Male Units: Participants			
Male	89	93	102
Female	114	102	101
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	75	71	74
Not Hispanic nor Latino	128	124	128
Missing	0	0	1

Reporting group values	VV_Lot1 and Lot2 Pooled Group	Total	
Number of subjects	190	791	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	190	791	

Age continuous Units: months			
arithmetic mean	12.4		
standard deviation	± 0.7	-	
Sex: Female, Male Units: Participants			
Male	83	367	
Female	107	424	
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	73	293	
Not Hispanic nor Latino	117	497	
Missing	0	1	

End points

End points reporting groups

Reporting group title	VNS_Low Group
Reporting group description:	
Participants received 1 dose of an investigational varicella vaccine (VNS) of low potency, 1 dose of a measles, mumps, and rubella (MMR) vaccine, 1 dose of a hepatitis A vaccine (Havrix) and 1 dose of a13 valent pneumococcal conjugate vaccine (Prevnar 13) on Day 1.	
Reporting group title	VNS_Med Group
Reporting group description:	
Participants received 1 dose of VNS vaccine of medium potency, 1 dose of MMR vaccine, 1 dose of Havrix vaccine, and 1 dose of Prevnar 13 vaccine on Day 1.	
Reporting group title	VNS_High Group
Reporting group description:	
Participants received 1 dose of VNS vaccine of high potency, 1 dose of MMR vaccine, 1 dose of Havrix vaccine, and 1 dose of Prevnar 13 vaccine on Day 1.	
Reporting group title	VV_Lot1 and Lot2 Pooled Group
Reporting group description:	
Participants received 1 dose of a licensed varicella vaccine (VV) of Lot 1 or 1 dose of a licensed vaccine (VV) of Lot 2, 1 dose of MMR vaccine, 1 dose of Havrix vaccine, and 1 dose of Prevnar 13 vaccine on Day 1.	

Primary: Concentrations of anti-varicella zoster virus (VZV) glycoprotein E (gE) antibodies

End point title	Concentrations of anti-varicella zoster virus (VZV) glycoprotein E (gE) antibodies[1]
End point description:	
Concentrations of anti-VZV gE antibodies were presented as Geometric Mean Concentrations (GMCs) and expressed in milli-international units per milliliter (mIU/mL) for each group. The analysis was performed on the Per Protocol Set (PPS), which included participants who received all study interventions as per protocol, were not unblinded, had immunogenicity results post-dose, complied with blood draw intervals, without intercurrent medical conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination.	
End point type	Primary
End point timeframe:	
At Day 43	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The analysis of this primary endpoint was descriptive i.e. No statistical hypothesis test was performed.

End point values	VNS_Low Group	VNS_Med Group	VNS_High Group	VV_Lot1 and Lot2 Pooled Group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	171	159	158	161
Units: mlU/ml				
geometric mean (confidence interval 95%)	960 (843 to 1093)	1071 (952 to 1204)	1555 (1407 to 1718)	1284 (1136 to 1453)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with seroresponse to VZV gE

End point title	Percentage of participants with seroresponse to VZV gE

End point description:

Seroresponse was defined as the percentage of participants for whom the post-dose of anti VZV gE antibody concentration was greater than or equal to (>=) 300 mIU/mL for each group. The analysis was performed on the PPS, which included participants who received all study interventions as per protocol, were not unblinded, had immunogenicity results post-dose, complied with blood draw intervals, without intercurrent medical conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination.

End point type	Secondary

End point timeframe:

At Day 43

End point values	VNS_Low Group	VNS_Med Group	VNS_High Group	VV_Lot1 and Lot2 Pooled Group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	171	159	158	161
Units: Percentage of participants				
number (confidence interval 95%)	93.6 (88.78 to 96.75)	96.2 (91.97 to 98.60)	98.7 (95.50 to 99.85)	98.1 (94.65 to 99.61)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants reporting each solicited administration site events

End point title	Number of participants reporting each solicited administration site events

End point description:

Assessed solicited administration site events included injection site redness, pain, and swelling. The analysis was performed on the Exposed set (ES), which included all participants who received a study intervention. Analysis per group was based on the varicella intervention administered.

End point type	Secondary

End point timeframe:

Day 1 (post dose) to Day 4

End point values	VNS_Low Group	VNS_Med Group	VNS_High Group	VV_Lot1 and Lot2 Pooled Group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	203	195	203	190
Units: Participants				
Injection site pain	76	64	70	57
Redness at injection site	24	23	35	23
Swelling at injection site	14	11	15	12

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants reporting each solicited systemic events from Day 1 to Day 43

End point title	Number of participants reporting each solicited systemic events from Day 1 to Day 43

End point description:

Solicited systemic events included fever, varicella like rash (including injection site varicella-like rash), and general rash (not varicella-like) after the administration of all vaccines for each group. Fever was defined as temperature >= 38.0 °C (100.4°F) by any route (the preferred location for measuring temperature is the axilla). A typical varicella-like rash manifests as a rash/lesion that may appear within several weeks after the varicella vaccination. Lesions may contain spots, bumps, blisters, or crusts. Includes injection site varicella-like rash. The analysis was performed on the ES, which included all participants who received a study intervention. Analysis per group was based on the varicella intervention administered.

End point type	Secondary

End point timeframe:

Day 1 (post dose) to Day 43

End point values	VNS_Low Group	VNS_Med Group	VNS_High Group	VV_Lot1 and Lot2 Pooled Group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	203	195	203	190
Units: Participants				
Fever	49	48	59	44
Any varicella-like rash	33	31	35	29
Any general rash	66	51	68	59

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants reporting each solicited systemic events from Day 1 to Day 15

End point title	Number of participants reporting each solicited systemic events

	from Day 1 to Day 15

End point description:

Solicited systemic events included drowsiness, loss of appetite, and irritability after the administration of all vaccines for each group. The analysis was performed on the ES, which included all participants who received a study intervention. Analysis per group was based on the varicella intervention administered.

End point type	Secondary

End point timeframe:

Day 1 (post dose) to Day 15

End point values	VNS_Low Group	VNS_Med Group	VNS_High Group	VV_Lot1 and Lot2 Pooled Group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	203	195	203	190
Units: Participants				
Any drowsiness	86	68	93	80
Any loss of appetite	69	57	71	60
Any irritability	112	94	112	109

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants reporting unsolicited adverse events

End point title	Number of participants reporting unsolicited adverse events

End point description:

Unsolicited adverse events (AEs) included any AE reported in addition to solicited events during the study, or any "solicited" symptoms with onset outside of the specified period of follow-up for solicited symptoms; these were assessed for each group after the administration of all vaccines. Unsolicited AEs included both serious and non-serious AEs. The analysis was performed on the ES, which included all participants who received a study intervention. Analysis per group was based on the varicella intervention administered.

End point type	Secondary

End point timeframe:

Day 1 (post dose) to Day 43

End point values	VNS_Low Group	VNS_Med Group	VNS_High Group	VV_Lot1 and Lot2 Pooled Group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	203	195	203	190
Units: Participants	67	53	64	61

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants reporting serious adverse events (SAEs)

End point title	Number of participants reporting serious adverse events (SAEs)

End point description:

A SAE was defined as an AE which was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in disability/incapacity, or other situations that were considered serious per medical or scientific judgment. The analysis was performed on the ES, which included all participants who received a study intervention. Analysis per group was based on the varicella intervention administered.

End point type	Secondary

End point timeframe:

From Day 1 to Day 181 (Study end)

End point values	VNS_Low Group	VNS_Med Group	VNS_High Group	VV_Lot1 and Lot2 Pooled Group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	203	195	203	190
Units: Participants	2	4	4	6

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs were collected from Day 1 to Day 181 (Study end), solicited administration site events from Day 1 to Day 4, solicited systemic events from Day 1 to Day 15 & Day 1 to Day 43 and unsolicited AEs and general rash from Day 1 to Day 43

Assessment type	Systematic

Dictionary used

Dictionary name	v27.0
Dictionary version	27.0

Reporting groups

Reporting group title	VNS_Low Group

Reporting group description:

Participants received 1 dose of an investigational varicella vaccine (VNS) of low potency, 1 dose of a measles, mumps, and rubella (MMR) vaccine, 1 dose of a hepatitis A vaccine (Havrix) and 1 dose of a13 valent pneumococcal conjugate vaccine (Prevnar 13) on Day 1.

Reporting group title	VV_Lot1 and Lot2 Pooled Group

Reporting group description:

Participants received 1 dose of a licensed varicella vaccine (VV) of Lot 1 or 1 dose of a licensed vaccine (VV) of Lot 2, 1 dose of MMR vaccine, 1 dose of Havrix vaccine, and 1 dose of Prevnar 13 vaccine on Day 1.

Reporting group title	VNS_High Group

Reporting group description:

Participants received 1 dose of VNS vaccine of high potency, 1 dose of MMR vaccine, 1 dose of Havrix vaccine, and 1 dose of Prevnar 13 vaccine on Day 1.

Reporting group title	VNS_Med Group

Reporting group description:

Participants received 1 dose of VNS vaccine of medium potency, 1 dose of MMR vaccine, 1 dose of Havrix vaccine, and 1 dose of Prevnar 13 vaccine on Day 1.

Serious adverse events	VNS_Low Group	VV_Lot1 and Lot2 Pooled Group	VNS_High Group
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 203 (0.99%)	6 / 190 (3.16%)	4 / 203 (1.97%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Nervous system disorders			
Dyskinesia			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	1 / 203 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 203 (0.00%)	1 / 190 (0.53%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	0 / 203 (0.00%)	2 / 190 (1.05%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenovirus infection			
subjects affected / exposed	0 / 203 (0.00%)	1 / 190 (0.53%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	1 / 203 (0.49%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	1 / 203 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Croup infectious			
subjects affected / exposed	0 / 203 (0.00%)	1 / 190 (0.53%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			

subjects affected / exposed	1 / 203 (0.49%)	1 / 190 (0.53%)	1 / 203 (0.49%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 203 (0.49%)	0 / 190 (0.00%)	1 / 203 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 203 (0.00%)	1 / 190 (0.53%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 203 (0.00%)	1 / 190 (0.53%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	VNS_Med Group		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 195 (2.05%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Nervous system disorders			
Dyskinesia			
subjects affected / exposed	1 / 195 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 195 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoxia			

subjects affected / exposed	0 / 195 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	0 / 195 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Adenovirus infection			
subjects affected / exposed	0 / 195 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pharyngitis			
subjects affected / exposed	0 / 195 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	0 / 195 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Croup infectious			
subjects affected / exposed	0 / 195 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 195 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 195 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			

subjects affected / exposed	0 / 195 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	2 / 195 (1.03%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 195 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	VNS_Low Group	VV_Lot1 and Lot2 Pooled Group	VNS_High Group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	173 / 203 (85.22%)	158 / 190 (83.16%)	178 / 203 (87.68%)
General disorders and administration site conditions			
Administration site erythema			
subjects affected / exposed	24 / 203 (11.82%)	23 / 190 (12.11%)	35 / 203 (17.24%)
occurrences (all)	40	31	44
Administration site pain			
subjects affected / exposed	76 / 203 (37.44%)	57 / 190 (30.00%)	70 / 203 (34.48%)
occurrences (all)	103	67	87
Administration site swelling			
subjects affected / exposed	14 / 203 (6.90%)	12 / 190 (6.32%)	15 / 203 (7.39%)
occurrences (all)	21	14	18
Injection site bruising			
subjects affected / exposed	0 / 203 (0.00%)	1 / 190 (0.53%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	49 / 203 (24.14%)	44 / 190 (23.16%)	59 / 203 (29.06%)
occurrences (all)	99	87	145

Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Milk allergy			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Food allergy			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Seasonal allergy			
subjects affected / exposed	0 / 203 (0.00%)	2 / 190 (1.05%)	1 / 203 (0.49%)
occurrences (all)	0	2	1
Reproductive system and breast disorders			
Genital rash			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 203 (0.49%)	0 / 190 (0.00%)	1 / 203 (0.49%)
occurrences (all)	1	0	1
Wheezing			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	2 / 203 (0.99%)
occurrences (all)	0	0	2
Rhinorrhoea			
subjects affected / exposed	3 / 203 (1.48%)	1 / 190 (0.53%)	5 / 203 (2.46%)
occurrences (all)	4	1	5
Rhinitis allergic			
subjects affected / exposed	0 / 203 (0.00%)	1 / 190 (0.53%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Respiratory tract congestion			
subjects affected / exposed	1 / 203 (0.49%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Respiratory disorder			
subjects affected / exposed	1 / 203 (0.49%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0

Productive cough			
subjects affected / exposed	0 / 203 (0.00%)	1 / 190 (0.53%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Bronchial hyperreactivity			
subjects affected / exposed	1 / 203 (0.49%)	1 / 190 (0.53%)	0 / 203 (0.00%)
occurrences (all)	1	1	0
Cough			
subjects affected / exposed	4 / 203 (1.97%)	3 / 190 (1.58%)	2 / 203 (0.99%)
occurrences (all)	5	3	2
Epistaxis			
subjects affected / exposed	1 / 203 (0.49%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Nasal congestion			
subjects affected / exposed	1 / 203 (0.49%)	0 / 190 (0.00%)	1 / 203 (0.49%)
occurrences (all)	1	0	1
Psychiatric disorders			
Irritability			
subjects affected / exposed	113 / 203 (55.67%)	110 / 190 (57.89%)	112 / 203 (55.17%)
occurrences (all)	397	336	417
Investigations			
Influenza A virus test positive			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	2 / 203 (0.99%)	1 / 190 (0.53%)	2 / 203 (0.99%)
occurrences (all)	2	1	2
Contusion			
subjects affected / exposed	1 / 203 (0.49%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	1 / 203 (0.49%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0

Foot fracture			
subjects affected / exposed	0 / 203 (0.00%)	1 / 190 (0.53%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Head injury			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Torus fracture			
subjects affected / exposed	1 / 203 (0.49%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Somnolence			
subjects affected / exposed	87 / 203 (42.86%)	80 / 190 (42.11%)	93 / 203 (45.81%)
occurrences (all)	217	174	264
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Iron deficiency anaemia			
subjects affected / exposed	1 / 203 (0.49%)	0 / 190 (0.00%)	1 / 203 (0.49%)
occurrences (all)	1	0	1
Macrocytosis			
subjects affected / exposed	0 / 203 (0.00%)	1 / 190 (0.53%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Excessive cerumen production			
subjects affected / exposed	0 / 203 (0.00%)	1 / 190 (0.53%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Ear pain			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Cerumen impaction			
subjects affected / exposed	0 / 203 (0.00%)	1 / 190 (0.53%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Conjunctival hyperaemia			
subjects affected / exposed	1 / 203 (0.49%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0

Gastrointestinal disorders			
Abnormal faeces			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	2 / 203 (0.99%)	4 / 190 (2.11%)	0 / 203 (0.00%)
occurrences (all)	2	4	0
Diarrhoea			
subjects affected / exposed	4 / 203 (1.97%)	5 / 190 (2.63%)	2 / 203 (0.99%)
occurrences (all)	5	5	2
Flatulence			
subjects affected / exposed	1 / 203 (0.49%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Regurgitation			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Teething			
subjects affected / exposed	7 / 203 (3.45%)	5 / 190 (2.63%)	8 / 203 (3.94%)
occurrences (all)	7	5	9
Vomiting			
subjects affected / exposed	2 / 203 (0.99%)	5 / 190 (2.63%)	1 / 203 (0.49%)
occurrences (all)	2	8	1
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 203 (0.49%)	1 / 190 (0.53%)	1 / 203 (0.49%)
occurrences (all)	1	1	1
Dermatitis			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Idiopathic urticaria			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	2
Eczema			

subjects affected / exposed	0 / 203 (0.00%)	2 / 190 (1.05%)	0 / 203 (0.00%)
occurrences (all)	0	2	0
Dermatitis diaper			
subjects affected / exposed	7 / 203 (3.45%)	6 / 190 (3.16%)	5 / 203 (2.46%)
occurrences (all)	8	7	5
Dermatitis contact			
subjects affected / exposed	2 / 203 (0.99%)	2 / 190 (1.05%)	1 / 203 (0.49%)
occurrences (all)	3	2	1
Urticaria			
subjects affected / exposed	0 / 203 (0.00%)	1 / 190 (0.53%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Rashes, eruptions and exanthems NEC			
subjects affected / exposed	76 / 203 (37.44%)	72 / 190 (37.89%)	75 / 203 (36.95%)
occurrences (all)	443	350	514
Rash scarlatiniform			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	3 / 203 (1.48%)	1 / 190 (0.53%)	1 / 203 (0.49%)
occurrences (all)	3	1	1
Miliaria			
subjects affected / exposed	0 / 203 (0.00%)	1 / 190 (0.53%)	1 / 203 (0.49%)
occurrences (all)	0	1	1
Dermatitis atopic			
subjects affected / exposed	1 / 203 (0.49%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	3 / 203 (1.48%)	0 / 190 (0.00%)	2 / 203 (0.99%)
occurrences (all)	3	0	2
Cellulitis			
subjects affected / exposed	0 / 203 (0.00%)	1 / 190 (0.53%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Bronchitis			

subjects affected / exposed	3 / 203 (1.48%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	3	0	0
Bronchiolitis			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Acute sinusitis			
subjects affected / exposed	1 / 203 (0.49%)	2 / 190 (1.05%)	2 / 203 (0.99%)
occurrences (all)	1	2	2
Candida nappy rash			
subjects affected / exposed	3 / 203 (1.48%)	1 / 190 (0.53%)	0 / 203 (0.00%)
occurrences (all)	3	1	0
Herpangina			
subjects affected / exposed	1 / 203 (0.49%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	1 / 203 (0.49%)	0 / 190 (0.00%)	1 / 203 (0.49%)
occurrences (all)	1	0	1
Hand-foot-and-mouth disease			
subjects affected / exposed	1 / 203 (0.49%)	0 / 190 (0.00%)	4 / 203 (1.97%)
occurrences (all)	1	0	5
Gastroenteritis viral			
subjects affected / exposed	2 / 203 (0.99%)	1 / 190 (0.53%)	2 / 203 (0.99%)
occurrences (all)	2	1	2
Gastroenteritis			
subjects affected / exposed	2 / 203 (0.99%)	2 / 190 (1.05%)	2 / 203 (0.99%)
occurrences (all)	2	2	2
Exanthema subitum			
subjects affected / exposed	1 / 203 (0.49%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Ear infection			
subjects affected / exposed	0 / 203 (0.00%)	1 / 190 (0.53%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Croup infectious			
subjects affected / exposed	1 / 203 (0.49%)	1 / 190 (0.53%)	2 / 203 (0.99%)
occurrences (all)	1	1	2
COVID-19			

subjects affected / exposed	2 / 203 (0.99%)	0 / 190 (0.00%)	1 / 203 (0.49%)
occurrences (all)	2	0	1
Laryngitis			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis bacterial			
subjects affected / exposed	1 / 203 (0.49%)	3 / 190 (1.58%)	0 / 203 (0.00%)
occurrences (all)	1	3	0
Conjunctivitis viral			
subjects affected / exposed	0 / 203 (0.00%)	2 / 190 (1.05%)	0 / 203 (0.00%)
occurrences (all)	0	2	0
Laryngotracheitis obstructive			
subjects affected / exposed	1 / 203 (0.49%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Mastitis			
subjects affected / exposed	1 / 203 (0.49%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Mastoiditis			
subjects affected / exposed	1 / 203 (0.49%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Metapneumovirus infection			
subjects affected / exposed	0 / 203 (0.00%)	1 / 190 (0.53%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	2 / 203 (0.99%)	9 / 190 (4.74%)	4 / 203 (1.97%)
occurrences (all)	2	11	4
Otitis externa			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Otitis media			
subjects affected / exposed	7 / 203 (3.45%)	5 / 190 (2.63%)	2 / 203 (0.99%)
occurrences (all)	7	5	2
Otitis media acute			
subjects affected / exposed	9 / 203 (4.43%)	6 / 190 (3.16%)	2 / 203 (0.99%)
occurrences (all)	10	7	2
Otitis media chronic			

subjects affected / exposed	0 / 203 (0.00%)	1 / 190 (0.53%)	1 / 203 (0.49%)
occurrences (all)	0	1	1
Parainfluenzae virus infection			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	4 / 203 (1.97%)	1 / 190 (0.53%)	1 / 203 (0.49%)
occurrences (all)	4	1	1
Pharyngitis streptococcal			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Pneumonia viral			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	1 / 203 (0.49%)	1 / 190 (0.53%)	0 / 203 (0.00%)
occurrences (all)	1	1	0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Respiratory tract infection viral			
subjects affected / exposed	2 / 203 (0.99%)	0 / 190 (0.00%)	1 / 203 (0.49%)
occurrences (all)	2	0	1
Rhinitis			
subjects affected / exposed	1 / 203 (0.49%)	2 / 190 (1.05%)	1 / 203 (0.49%)
occurrences (all)	1	2	1
Rhinovirus infection			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Skin candida			
subjects affected / exposed	1 / 203 (0.49%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0

Sinusitis			
subjects affected / exposed	0 / 203 (0.00%)	1 / 190 (0.53%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Scarlet fever			
subjects affected / exposed	1 / 203 (0.49%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Roseola			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Suspected COVID-19			
subjects affected / exposed	0 / 203 (0.00%)	1 / 190 (0.53%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	11 / 203 (5.42%)	10 / 190 (5.26%)	13 / 203 (6.40%)
occurrences (all)	12	11	14
Urinary tract infection			
subjects affected / exposed	1 / 203 (0.49%)	0 / 190 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Viral infection			
subjects affected / exposed	2 / 203 (0.99%)	0 / 190 (0.00%)	3 / 203 (1.48%)
occurrences (all)	2	0	3
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 203 (0.99%)	2 / 190 (1.05%)	1 / 203 (0.49%)
occurrences (all)	2	2	1
Sinusitis bacterial			
subjects affected / exposed	0 / 203 (0.00%)	0 / 190 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 203 (0.00%)	2 / 190 (1.05%)	0 / 203 (0.00%)
occurrences (all)	0	2	0
Decreased appetite			
subjects affected / exposed	71 / 203 (34.98%)	60 / 190 (31.58%)	71 / 203 (34.98%)
occurrences (all)	206	138	192

Non-serious adverse events	VNS_Med Group		
Total subjects affected by non-serious			

adverse events subjects affected / exposed	165 / 195 (84.62%)		
General disorders and administration site conditions Administration site erythema subjects affected / exposed occurrences (all) Administration site pain subjects affected / exposed occurrences (all) Administration site swelling subjects affected / exposed occurrences (all) Injection site bruising subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 23 / 195 (11.79%) 33 65 / 195 (33.33%) 82 11 / 195 (5.64%) 16 0 / 195 (0.00%) 0 48 / 195 (24.62%) 91		
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all) Milk allergy subjects affected / exposed occurrences (all) Food allergy subjects affected / exposed occurrences (all) Seasonal allergy subjects affected / exposed occurrences (all)	 1 / 195 (0.51%) 1 0 / 195 (0.00%) 0 0 / 195 (0.00%) 0 0 / 195 (0.00%) 0		
Reproductive system and breast disorders Genital rash subjects affected / exposed occurrences (all)	 0 / 195 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders			

Asthma				
subjects affected / exposed	2 / 195 (1.03%)			
occurrences (all)	2			
Wheezing				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			
Rhinorrhoea				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			
Rhinitis allergic				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			
Respiratory tract congestion				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			
Respiratory disorder				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			
Productive cough				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			
Oropharyngeal pain				
subjects affected / exposed	1 / 195 (0.51%)			
occurrences (all)	1			
Bronchial hyperreactivity				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			
Cough				
subjects affected / exposed	4 / 195 (2.05%)			
occurrences (all)	4			
Epistaxis				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			
Nasal congestion				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			

Psychiatric disorders Irritability subjects affected / exposed occurrences (all)	 94 / 195 (48.21%) 278		
Investigations Influenza A virus test positive subjects affected / exposed occurrences (all)	 1 / 195 (0.51%) 1		
Injury, poisoning and procedural complications Arthropod bite subjects affected / exposed occurrences (all) Contusion subjects affected / exposed occurrences (all) Fall subjects affected / exposed occurrences (all) Foot fracture subjects affected / exposed occurrences (all) Head injury subjects affected / exposed occurrences (all) Torus fracture subjects affected / exposed occurrences (all)	 1 / 195 (0.51%) 1 0 / 195 (0.00%) 0 0 / 195 (0.00%) 0 0 / 195 (0.00%) 0 0 / 195 (0.00%) 0 0 / 195 (0.00%) 0		
Nervous system disorders Somnolence subjects affected / exposed occurrences (all)	 68 / 195 (34.87%) 170		
Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all) Iron deficiency anaemia	 1 / 195 (0.51%) 1 		

subjects affected / exposed occurrences (all)	2 / 195 (1.03%) 2		
Macrocytosis subjects affected / exposed occurrences (all)	0 / 195 (0.00%) 0		
Ear and labyrinth disorders Excessive cerumen production subjects affected / exposed occurrences (all)	0 / 195 (0.00%) 0		
Ear pain subjects affected / exposed occurrences (all)	0 / 195 (0.00%) 0		
Cerumen impaction subjects affected / exposed occurrences (all)	0 / 195 (0.00%) 0		
Eye disorders Conjunctival hyperaemia subjects affected / exposed occurrences (all)	0 / 195 (0.00%) 0		
Gastrointestinal disorders Abnormal faeces subjects affected / exposed occurrences (all)	0 / 195 (0.00%) 0		
Constipation subjects affected / exposed occurrences (all)	0 / 195 (0.00%) 0		
Diarrhoea subjects affected / exposed occurrences (all)	4 / 195 (2.05%) 4		
Flatulence subjects affected / exposed occurrences (all)	0 / 195 (0.00%) 0		
Nausea subjects affected / exposed occurrences (all)	1 / 195 (0.51%) 1		
Regurgitation			

subjects affected / exposed	0 / 195 (0.00%)		
occurrences (all)	0		
Teething			
subjects affected / exposed	1 / 195 (0.51%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	3 / 195 (1.54%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 195 (0.00%)		
occurrences (all)	0		
Dermatitis			
subjects affected / exposed	1 / 195 (0.51%)		
occurrences (all)	1		
Idiopathic urticaria			
subjects affected / exposed	0 / 195 (0.00%)		
occurrences (all)	0		
Eczema			
subjects affected / exposed	1 / 195 (0.51%)		
occurrences (all)	1		
Dermatitis diaper			
subjects affected / exposed	7 / 195 (3.59%)		
occurrences (all)	7		
Dermatitis contact			
subjects affected / exposed	2 / 195 (1.03%)		
occurrences (all)	2		
Urticaria			
subjects affected / exposed	0 / 195 (0.00%)		
occurrences (all)	0		
Rashes, eruptions and exanthems NEC			
subjects affected / exposed	64 / 195 (32.82%)		
occurrences (all)	329		
Rash scarlatiniform			

subjects affected / exposed	1 / 195 (0.51%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	2 / 195 (1.03%)		
occurrences (all)	2		
Miliaria			
subjects affected / exposed	0 / 195 (0.00%)		
occurrences (all)	0		
Dermatitis atopic			
subjects affected / exposed	1 / 195 (0.51%)		
occurrences (all)	1		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	1 / 195 (0.51%)		
occurrences (all)	1		
Cellulitis			
subjects affected / exposed	0 / 195 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	1 / 195 (0.51%)		
occurrences (all)	1		
Bronchiolitis			
subjects affected / exposed	2 / 195 (1.03%)		
occurrences (all)	2		
Acute sinusitis			
subjects affected / exposed	0 / 195 (0.00%)		
occurrences (all)	0		
Candida nappy rash			
subjects affected / exposed	0 / 195 (0.00%)		
occurrences (all)	0		
Herpangina			
subjects affected / exposed	0 / 195 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	3 / 195 (1.54%)		
occurrences (all)	3		

Hand-foot-and-mouth disease				
subjects affected / exposed	1 / 195 (0.51%)			
occurrences (all)	1			
Gastroenteritis viral				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			
Gastroenteritis				
subjects affected / exposed	1 / 195 (0.51%)			
occurrences (all)	1			
Exanthema subitum				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			
Ear infection				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			
Croup infectious				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			
COVID-19				
subjects affected / exposed	2 / 195 (1.03%)			
occurrences (all)	2			
Laryngitis				
subjects affected / exposed	2 / 195 (1.03%)			
occurrences (all)	2			
Conjunctivitis bacterial				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			
Conjunctivitis viral				
subjects affected / exposed	1 / 195 (0.51%)			
occurrences (all)	1			
Laryngotracheitis obstructive				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			
Mastitis				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			

Mastoiditis				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			
Metapneumovirus infection				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			
Nasopharyngitis				
subjects affected / exposed	3 / 195 (1.54%)			
occurrences (all)	3			
Otitis externa				
subjects affected / exposed	1 / 195 (0.51%)			
occurrences (all)	1			
Otitis media				
subjects affected / exposed	1 / 195 (0.51%)			
occurrences (all)	2			
Otitis media acute				
subjects affected / exposed	6 / 195 (3.08%)			
occurrences (all)	6			
Otitis media chronic				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			
Parainfluenzae virus infection				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			
Pharyngitis				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			
Pharyngitis streptococcal				
subjects affected / exposed	2 / 195 (1.03%)			
occurrences (all)	2			
Pneumonia				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			
Pneumonia viral				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			

Respiratory syncytial virus bronchiolitis				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			
Respiratory syncytial virus infection				
subjects affected / exposed	1 / 195 (0.51%)			
occurrences (all)	1			
Respiratory tract infection viral				
subjects affected / exposed	1 / 195 (0.51%)			
occurrences (all)	1			
Rhinitis				
subjects affected / exposed	1 / 195 (0.51%)			
occurrences (all)	1			
Rhinovirus infection				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			
Skin candida				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			
Sinusitis				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			
Scarlet fever				
subjects affected / exposed	0 / 195 (0.00%)			
occurrences (all)	0			
Roseola				
subjects affected / exposed	1 / 195 (0.51%)			
occurrences (all)	1			
Suspected COVID-19				
subjects affected / exposed	2 / 195 (1.03%)			
occurrences (all)	2			
Upper respiratory tract infection				
subjects affected / exposed	6 / 195 (3.08%)			
occurrences (all)	6			
Urinary tract infection				

subjects affected / exposed	0 / 195 (0.00%)		
occurrences (all)	0		
Viral infection			
subjects affected / exposed	2 / 195 (1.03%)		
occurrences (all)	2		
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 195 (0.00%)		
occurrences (all)	0		
Sinusitis bacterial			
subjects affected / exposed	0 / 195 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 195 (0.00%)		
occurrences (all)	0		
Decreased appetite			
subjects affected / exposed	57 / 195 (29.23%)		
occurrences (all)	131		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 October 2021	This amendment at the request of CBER to add early safety time point checks, to exclude participants with a history of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection who remain symptomatic, to exclude susceptible high-risk individual members of the potential participant's household, to clarify that varicella-like-rash includes injection site varicella-like rash, to include holding rules for the first 200 study participants enrolled and to revise the grading to assess the severity of the varicella-like rash.
15 November 2021	The amendment was primarily to reflect the expansion of the study to the countries other than the United States of America (US). Outside of the US, participants will have the same vaccination schedule but will be co administered Prevnar 13 only if the pneumococcal conjugate vaccine is recommended at 12-15 months as per national immunization schedule. Also, the storage conditions for Varivax were updated with the country-specific details, and corrections were made to the temperature excursions for study vaccines. Additionally, this amendment conditionally allowed administration of a second dose of Varivax and/or Havrix in non-US countries (not part of the study procedures).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported